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Analysis of the Structure of Deaths from Sporadic Metachronous Primary Multiple Malignant Neoplasms in a General Hospital

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ABSTRACT

Aim. To analyze the structure of deaths from sporadic metachronous primary multiple malignant neoplasms in 2017–2023 in a multidisciplinary inpatient facility.

Materials and methods. The study included 2,394 fatal cases of patients hospitalized in a multidisciplinary inpatient facility for emergency medical care. In 2017–2023, 29 metachronous primary multiple malignant neoplasms were identified, which was 1.3% of the total number of fatal outcomes and 11% of malignant neoplasms. The median age of patients was 72.0 (69.0–82.0) years. We examined the protocols of pathological studies of autopsy material of patients hospitalized in the inpatient facility of multidisciplinary clinics of Siberian State Medical University. In patients with metachronous primary multiple malignant neoplasms, the nosological structure, stage of the process, histological form of the neoplasm, the period between the diagnosis of the first and second malignant tumor, and the immediate cause of death were analyzed. Statistical processing of the results was carried out using the Statistica 10.0 software package.

Results. The first tumor was most often caused by squamous cell skin cancer (21%) or invasive ductal carcinoma of the breast (17.5%). The interval between the diagnosis of the first and second tumor was 72.0 (48.0–96.0) months. All patients received definitive treatment for the first tumor without progression. The second metachronous tumors were verified in an advanced stage in 72% of cases and caused the death of patients. Most often (17.5%) these were diffuse gastric cancer.

Conclusion. Metachronous primary multiple malignant tumors can occur long after the first ones (about 6 years), often in advanced forms (in this case, tumors verified exclusively postmortem – 69%), being the cause of death of patients. The most common first tumors in sporadic metachronous primary multiple malignant neoplasms are recurrent squamous cell skin cancer and ductal carcinoma of the mammary gland. The main target organ for the development of oncopathology is the stomach.

Keywords: sporadic, metachronous, primary multiple, malignant neoplasms

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Анализ структуры летальных исходов от спорадических метахронных первично-множественных злокачественных новообразований в стационаре общего профиля

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РЕЗЮМЕ

Цель. Провести анализ структуры летальных исходов от спорадических метахронных первично-множественных злокачественных новообразований (ПМЗНО) за период с 2017 по 2023 г. на примере стационара общего профиля.

Материалы и методы. Исследовались случаи летальных исходов 2 394 больных, поступивших в порядке скорой помощи в стационар общего профиля. В 2017–2023 гг. выявлено 29 метахронных ПМЗНО, что составило 1,3% от общего числа летальных исходов и 11% – от злокачественных новообразований. Медиана возраста больных соответствовала 72,0 (69,0–82,0) годам. Изучались протоколы патологоанатомических исследований аутопсийного материала пациентов, поступивших в стационарное отделение клиник общего профиля СибГМУ. В случаях с метахронными ПМЗНО анализировались нозологическая структура, стадия процесса, гистологическая форма новообразования, срок между диагностикой первой и второй злокачественной опухоли, непосредственная причина смерти. Статистическая обработка результатов проводилась с применением пакета программ Statistica 10.0.

Результаты. Первая опухоль чаще была представлена плоскоклеточным раком кожи (21%) или инвазивной протоковой карциномой молочной железы (17,5%). Временной промежуток между диагностикой первой и второй опухоли составлял 72,0 (48,0–96,0) мес. Все пациенты были радикально пролечены по поводу первой опухоли без прогрессирования. Вторые метахронные опухоли в 72% были верифицированы в запущенной стадии и являлись причиной смерти больных. Чаще (17,5%) они были представлены диффузным раком желудка.

Заключение. Метахронные ПМЗНО могут возникать через длительный временной промежуток (около 6 лет) после первых, часто в запущенных формах (в данном исследовании преимущественно посмертно – 69%), являясь причиной смерти больных. Наиболее частыми первыми опухолями при спорадических метахронных ПМЗНО являются плоскоклеточный рак кожи и протоковая карцинома молочной железы, а основным органом-мишенью для повторного развития онкопатологии – желудок.

Ключевые слова: спорадические, метахронные, первично-множественные, злокачественные новообразования

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

One of the relevant problems of modern oncology is the steady increase in multiple primary malignant neoplasms (MPMN). The prevalence of primary multiple malignant tumors in the world ranges from 2 to 17% [1]. In 2015–2023 in Russia, the number of MPMN diagnosed in the reporting year increased from 39,195 to 77,433, the percentage of MPMN from the number of newly diagnosed malignant neoplasms is from 6.7 to 11.5%, and the MPMN rate per 100,000 people ranges from 26.8 to 52.8. As of the end of 2023, 288,345 patients who were under follow-up monitoring had MPMN, which amounted to 6.9% of the total number of patients registered in cancer institutions [2].

MPMN may be hereditary and non-hereditary [3–7]. Detection of genetic disorders possibly associated with hereditary syndromes is an effective tool for early diagnosis of MPMN and selection of optimal treatment tactics [8]. However, about 70% of MPMN are cases of sporadic metachronous malignant tumors diagnosed after six or more months from the moment of verification of the first neoplasm [8, 9]. The steady increase in their number is explained by the improved methods of early diagnosis and therapy of malignant neoplasms and, as a consequence, an increase in the survival rate of cancer patients, environmental and biological factors, and an increase in the overall life expectancy of the population [10–12]. However, there is still no unified concept in understanding the key mechanisms of development of sporadic metachronous MPMN, and the nosological structure and mortality from sporadic metachronous MPMN are yet to be properly analyzed.

The study of clinical morphological and molecular genetic structures with the aim of implementing these principles, as well as the analysis of the structure of fatal outcomes from sporadic metachronous MPMN can become a platform for the development of a system for early detection of the second tumor with subsequent modern definitive treatment, which will lead to an improvement in the quality of life, overall survival increase and a decrease in mortality in patients with widespread metachronous MPMN.

The aim of the study was to analyze the mortality structure from sporadic metachronous multiple primary malignant neoplasms in 2017–2023 using the example of a multidisciplinary inpatient facility.

MATERIALS AND METHODS

The study included 2,394 fatal cases of patients hospitalized for emergency care in multidisciplinary inpatient facility of Tomsk in the period from 01.01.2017 to 31.12.2023, including 264 cases of malignant neoplasms. We examined the protocols of pathological studies of autopsy material. Histological preparations stained with hematoxylin and eosin were examined by light microscopy using an Axio Lab.A1 microscope (Carl Zeiss, Germany). In cases with metachronous MPMN, the following parameters were analyzed the nosological structure, stage of the process, histological form of the neoplasm, the period between the diagnosis of the first and second malignant tumor, and the immediate cause of death.

Statistical processing was carried out using the Statistica 10.0 software package. Basic statistical data and nonparametric criteria were used. The frequency of detection of features was determined by the descriptive statistics method. Comparison of the frequency of detection of features was carried out using the Student's t-test. Differences were considered statistically significant at $p < 0.05$.

The study complies with the standards of the Declaration of Helsinki and was approved by an independent Ethics Committee of Siberian State Medical University of the Ministry of Healthcare of the Russian Federation, protocol No. 5600 dated 23.10.2017.

RESULTS

In 2017–2023, 29 sporadic metachronous MPMN were identified, accounting for 1.3% of all deaths and 11% of deaths from malignant neoplasms. The median age of patients with MPMN was 72.0 (69.0-82.0) years. The most common type was squamous cell carcinoma of the skin (21.0%) or invasive ductal breast cancer (17.5%). Other localizations were less common (Table 1).

Table 1

Localization and Morphological Type of the First Tumors of Deceased Patients with Multiple Primary Malignant Neoplasms, *n* = 29

Localization and histotype of the first tumor	Number of patients abs. (%)
Skin, squamous cell carcinoma of moderate differentiation	6 (21.0%), $p_{3,4,5,10,12} = 0.017$, $p_{8,9,11} = 0.047$
Breast, invasive ductal carcinoma	5 (17.5%), $p_{3,4,5,10,12} = 0.037$
Stomach, moderately differentiated adenocarcinoma	1 (3.5%)
Thyroid gland, papillary cancer	1 (3.5%)
Rectum, moderately differentiated adenocarcinoma	1 (3.5%)
Prostate gland, acinar adenocarcinoma	4 (14%)
Lung, invasive adenocarcinoma	3 (10.5%)
Colon, moderately differentiated adenocarcinoma	2 (6.5%)
Kidney, clear cell renal cell carcinoma	2 (6.5%)
Uterine body, endometrioid adenocarcinoma	1 (3.5%)
Bladder, high-grade urothelial carcinoma	2 (6%)
Salivary glands, adenoid cystic cancer	1 (3.5%)
Total	29 (100%)

Note. Here and in Tables 2, 3: abs. – absolute number.

Diffuse gastric cancer was most often detected as the second tumor in metachronous MPMN (17.5%) (Table 2).

Table 2

Localization and Morphological Type of the Second Tumor in Deceased Patients with Multiple Primary Malignant Neoplasms, *n* = 29

Localization and histotype of the second tumor	Number of patients abs. (%)
Breast, invasive lobular carcinoma	3 (11%)
Lung, small cell carcinoma	4 (14%)
Stomach, diffuse cancer	5 (17.5%) $p_{5,6,8,12} = 0.031$
Pancreas, low grade ductal adenocarcinoma	2 (6. 5%)
Thyroid gland, papillary cancer	1 (3.5 %)

End of table 2

Localization and histotype of the second tumor	Number of patients abs. (%)
Skin, squamous cell carcinoma of moderate differentiation	1 (3.5 %)
Rectum, low grade adenocarcinoma	2 (6.5%)
Liver, cholangiocarcinoma of the intrahepatic bile ducts	1 (3.5 %)
Colon, moderately differentiated adenocarcinoma	2 (6.5%)
Prostate gland, acinar adenocarcinoma	2 (6.5%)
Uterine body, high grade serous carcinoma	3 (11%)
Oropharynx, low grade squamous cell carcinoma	1 (3.5 %)
Ovary, high grade serous carcinoma	2 (6.5%)

Combinations of the first and second tumors were varied. Of the 29 cases of metachronous MPMN examined, 27 different combinations were identified. Only two sequences occurred more than once: skin – stomach and mammary gland – ovary (Table 3).

Table 3

Combinations of Localization of the First and Second Tumors in Deceased Patients with Multiple Primary Malignant Neoplasms, *n* = 29

Combinations of localization of the first and second tumor	Number of patients abs. (%)
Skin – mammary gland	1 (3.5 %)
Mammary gland – mammary gland	1 (3.5 %)
Stomach – lung	1 (3.5 %)
Thyroid gland – stomach	1 (3.5 %)
Mammary gland – pancreas	1 (3.5 %)
Rectum – thyroid gland	1 (3.5 %)
Skin – skin	1 (3.5 %)
Prostate gland - rectum	1 (3.5 %)
Prostate gland – liver	1 (3.5 %)
Skin – colon	1 (3.5 %)
Lung – prostate gland	1 (3.5 %)
Colon – prostate gland	1 (3.5 %)
Lung – uterine body	1 (3.5 %)
Skin – stomach	2 (6.25%)
Lung – colon	1 (3.5 %)
Sigmoid colon – uterine body	1 (3.5 %)
Right kidney – lung	1 (3.5 %)
Prostate gland – stomach	1 (3.5 %)
Kidneys – oropharynx	1 (3.5 %)
Uterine body – mammary gland	1 (3.5 %)
Bladder – rectum	1 (3.5 %)
Salivary gland – pancreas	1 (3.5 %)
Mammary gland – ovary	2 (6.25%)
The prostate gland – lung	1 (3.5 %)
Mammary gland – uterine body	1 (3.5 %)
Bladder – stomach	1 (3.5 %)
Skin – lung	1 (3.5 %)

The period between diagnosis of the first and second tumors was 72.0 (48–96) months (approximately 6 years). All patients received definitive treatment for the first tumor, and no progression was observed.

The second tumor was first detected when patients were admitted to the emergency care unit in a serious condition, often met the T4 criterion (48%) and was accompanied by distant metastases (72%) (Fig. 1). In 69% of cases, sporadic metachronous MPMN were histologically verified only postmortem. Certain difficulties arose when patients had a second (metachronous) tumor in the liver or lung. It was possible to differentiate it from possible progression of the first tumor with distant metastases to the lung or liver using conventional light microscopy on preparations stained with hematoxylin and eosin due to the different histotypes of the first and second tumors.

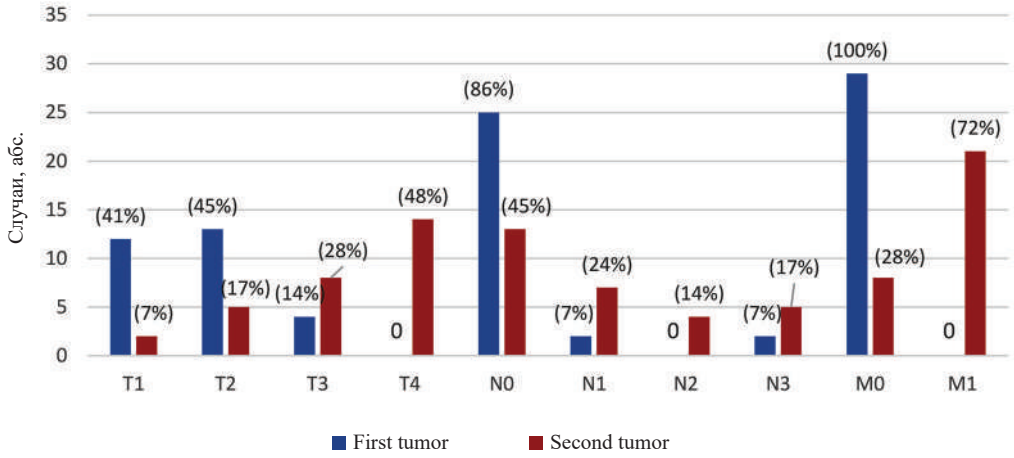

Fig. 1. TNM criteria for the first and second tumor in primary multiple malignant neoplasms, $n = 29$

In other cases, immunohistochemical examination would be necessary to differentiate between metastatic lesions and MPMN. A study of the localization of second tumor distant metastases showed that isolated massive metastatic lesions of the liver were observed more often (39%), isolated massive metastatic lesions of the lungs were observed less often (20%), and even less often – of the brain (4.5%), bones (4.5%) or generalized lesions with the involvement of several organs in the metastatic process in various combinations: lungs and liver (9.5%) and other variants of multiple metastasis – one case each (4.5%) (Fig. 2).

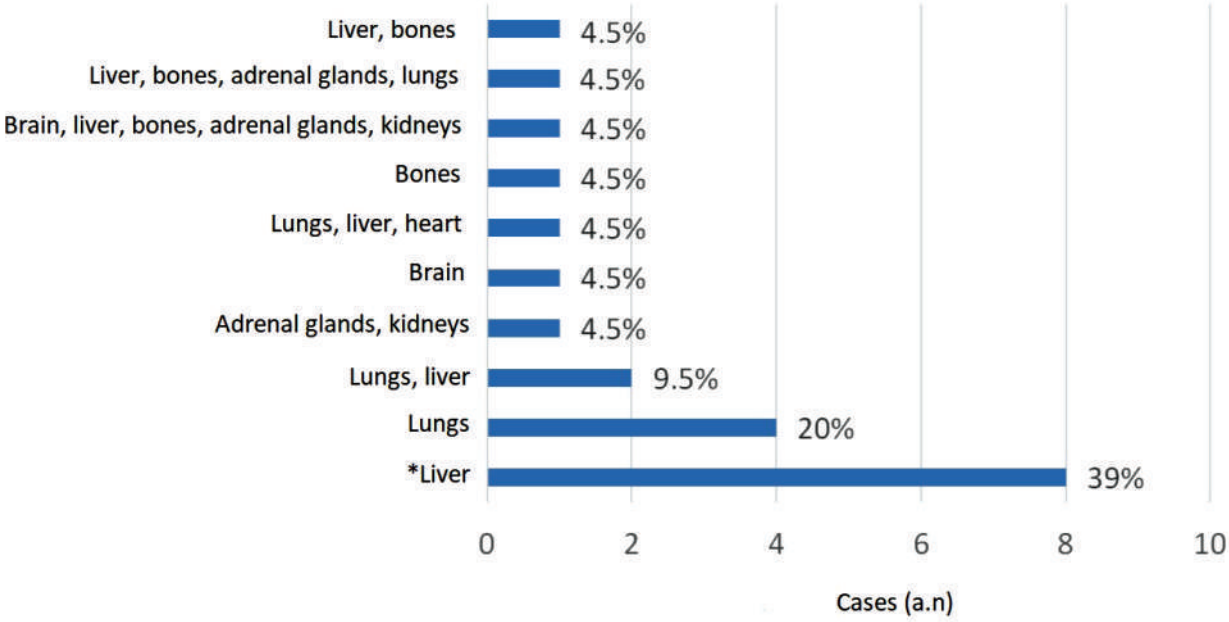

Fig. 2. Localization of distant metastases in primary multiple malignant neoplasms, $n = 21$: * $p_{1,5,6,7,8,9,10} = 0.003$, $p_2 = 0.011$

In metachronous MPMN, the most common causes of death are acute liver failure associated with massive metastatic liver disease (31%), acute terminal failure due to massive metastatic lung disease (21%), and peritonitis complicated by mechanical failure due to tumor stenosis (18%). In addition, in some cases, the following signs of death were diagnosed: a combination of acute liver and left ventricular failure (21%); acute renal failure; edema and dislocation of the brain; a combination of acute liver and renal failure; hemorrhagic shock (Fig. 3).

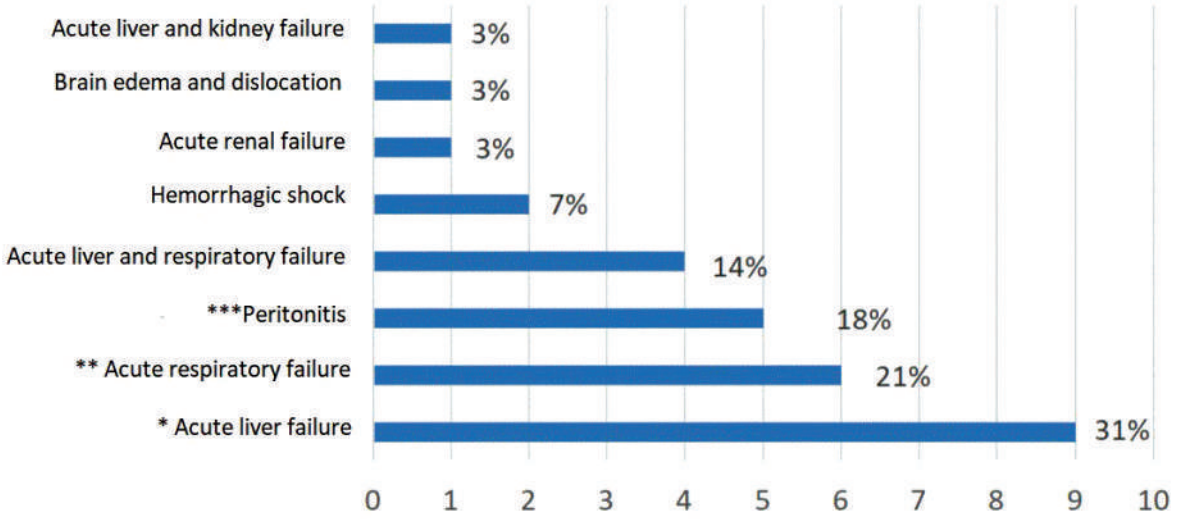

Fig 3. Causes of death in primary multiple malignant neoplasms, $n = 29$: * $p_{4,5,6} = 0.002$, $p_8 = 0.009$; ** $p_{4,5,6} = 0.017$; *** $p_{4,5,6} = 0.031$

DISCUSSION

The problem of multiple neoplasm development is comprehensive and highly complicated. The literature mainly describes cases of multiple neoplasms of certain localizations [13, 14]. Issues of studying the multiple neoplasm development patterns in the population aspect are becoming more and more relevant. In addition to the accumulated hereditary burden, risk factors of the urbanized environment, habitual intoxications (alcohol, smoking), radio-chemotherapy of the first neoplasms, the increase in the incidence of multiple neoplasms is associated with the improvement of medical and diagnostic care, in particular oncological [6], which contributes to an increase in the life expectancy of cancer patients, and, consequently, the risk of tumor recurrence. The incidence of multiple neoplasms, in addition to the territorial features of the diversity of oncopathology, is affected by the quality of diagnostics and monitoring of oncopathology in the region [2].

This study, in which cases of fatal outcomes of patients hospitalized for emergency care were examined, demonstrates the problems of cancer patient follow-up: in 72% of cases, the second tumor was diagnosed in an advanced form with distant metastases, in 69% – postmortem. The high level of neglect [2] is alarming in the case of a newly diagnosed cancer and twice as alarming in the case of recurrent tumors. Under the existing federal rules for lifelong follow-up monitoring at special medical facilities with at least annual medical checkup of cancer patients, the detection of recurrent malignant tumors in an advanced form should be an exception.

The analysis showed that in the absence of topomorphological associations in most cases of MPMN, squamous cell skin cancer and ductal breast cancer should be considered as the most common first malignant neoplasm. Skin cancer was associated with the development of metachronous tumors of the mammary gland, skin, colon, lung and in two cases – stomach; breast cancer was associated with the development of tumors of the other mammary gland, pancreas, ovary and tumor of the uterine body.

This finding is close to the conclusions of some authors [5] based on follow-up examinations of patients who received definitive treatment, indicating the organs in which metachronous tumors most often occur: in skin cancer, these are the mammary gland, body of the uterus, stomach, and colon; in breast

cancer, these are the second mammary gland, body of the uterus, stomach, skin, and ovaries. The literature data [5] also correspond to the obtained data on the more frequent metachronous stage of malignant tumor in the stomach (17.5%). This circumstance identifies the importance studying gastric cancer as the second tumor in sporadic metachronous MPMN: its associative connections with certain cancer types.

The question of the approximate time frame for the development of the second tumor depending on the topomorphological characteristics of the first tumor and other risk factors remains open. In our study, it is about 6 years, but it is worth considering the manifestation of these events in an advanced form with multiple, mainly distant metastases.

CONCLUSION

Metachronous primary multiple malignant tumors can occur after a long period of time (about 6 years) after the first ones, often in advanced forms (in this study, they were diagnosed mainly postmortem – 69%), causing the death of patients. The most common first tumors in sporadic metachronous MPMN are squamous cell skin cancer and ductal breast cancer, and the main target organ for cancer relapse is the stomach.

It seems relevant to continue research into the patterns of MPMN development with the search for solutions aimed at developing methods for predicting second malignant tumors based on a combination of clinical, morphological and molecular genetic factors, as well as a monitoring system for this group of patients to early diagnose the second tumor and increase the effectiveness of antitumor treatment.

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Author contribution

Zavyalova M.V., Zhuikova L.D., Perelmuter V.M., Vtorushin S.V. – organization, conception and design. Pismenny D.S., Zavyalov A.V., Paderov Yu.M., Pikalova L.V. – collection and processing of material. Zavyalova M.V., Zhuikova L.D., Litvyakov N.V. – statistical data analysis. Zhuikova L.D., Vtorushin S.V., Pikalova L.V. – drafting of the manuscript. Grishchenko M.Yu., Paderov Yu.M., Pisenny D.S. – editing of the manuscript.

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