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MULTIPLE PRIMARY MALIGNANCIES – A STATISTICAL RETROSPECTIVE REVIEW

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RESUME

L'existence de cancers primitifs multiples chez un meme patient est rare. Elle a été décrite pour la première fois par Billroth en 1889. Les néoplasies malignes primitives multiples sont définies par l'existence de plus d'une tumeur primitive dans des organes différents, ou de deux tumeurs primitives ou plus développées à partir de différents types de cellules, au sein d'un même organe.

MOTS CLES*: tumeurs malignes primitives multiples, oncologie.*

1. Introduction

Multiple primary malignancies (MPM) comprise two or more primary cancers occurring in an individual that originate in a primary tissue and that are neither an extension, nor a recurrence or metastasis.

Theodor Billroth was the one who first established the criteria for diagnosing multiple primary lesions in 1879. In 1932, Warren and Gates proposed new criteria: [1] each tumor must present a definite picture of malignancy; [2] each tumor must be histologically distinct; and [3] the possibility that one is a metastasis of another must be excluded. Cancer incidence rises progressively during life span.

With advances in diagnostic and treatment techniques, the number of patients who develop multiple primary malignancies during long-term follow-up has been increasing.

Modern chemotherapy and radiotherapy have increased substantially the survival rate of patients with cancer. More patients survive long enough to develop subsequent primary tumors, whereas the development of more sophisticated diagnostic tools made possible the detection of synchronous occult tumors.

The mechanisms explaining the association of cancer and aging include: [1] time length of carcinogenesis (the longer a person lives the more likely it is that carcinogenesis will be completed and cancer will develop); [4] molecular changes of age (older tissues are susceptible to environmental carcinogenesis and undergo molecular changes similar to carcinogenesis); and [5] changes in the environment (aging is associated

with molecular changes in DNA signaling and body environment that may favor the development of cancer).

It is hard to separate out the exact cause of any one person's cancer, as mechanisms involved in MPM are not clearly elucidated.

Occurrence of two primary malignancies in the same individual may reflect the operation of numerous influences. Risk factors for the development of multiple primary cancers include an inherited predisposition to cancer; immunodeficiency, common carcinogenic or cancer-promoting aspects of lifestyle, hormonal, and environmental factors; treatment of the previous primary cancer; increased surveillance of cancer survivors, or the interaction of these factors. Through this study, we tried to show a few epidemiological aspects of multiple primary malignancies. We also reviewed literature in order to point out most important aspects of MPM and to compare our study's results with other similar studies. The discussions and conclusions of our work, although pointed out theoretically are of practical importance, that's why we gathered the main points of view found in the reviewed literature [6,7].

2. Materials and methods

We performed a single center analysis to assess the prevalence and the pattern of multiple malignancies in non-selected cancer patients with special focus on cancer-specific associations. We retrospectively reviewed records of patients with cancer who were admitted to the Radiotherapy Service of Clinical Emergency Hospital of Galati, from January of 2008 to December of 2009. Radiotherapy Service receives patients from four districts: Galati, Braila, Vrancea and Tulcea.

From a total number of 2254 patients who were admitted to Radiotherapy Department, 43 patients presented at least two primary malignancies that were confirmed by histopathological examination.

We performed subgroup analyses according to background, gender, age at the first and second cancer diagnosis, anatomic site of the first and second malignancy, cancers associations and elapsed time between the primary and second neoplasm. We also investigated histological type, treatment applied for the first cancer and follow-up data. We excluded malignancies of paired organs with the same histology, metastases or recurrences of the same cancer and patients without a clear histopathological confirmation of each tumor. For each patient, histology (also immunohistochemistry in some cases), stage at diagnosis, grading, were available. The malignancy-free survival period (MFSP) was measured from the date of the first diagnosis to the date of the second malignancy's histopathological diagnosis.

The limitation of our results is due to the small number of patients included in this study and by the fact that we have analyzed only patients admitted to the Radiotherapy Service (Surgery and Oncology Departments were not included).

3. Results and discussions

From a total number of 2254 patients who were admitted to Radiotherapy Department of Clinical Emergency Hospital, from January of 2008 to December of 2009, the prevalence of MPM was 1.9%.

In our series, the prevalence of MPM (1.9%) is similar to the one reported in literature (0.73% - 11%) (table 1, figure 1).

Table 1: *Number of MPM of all cancers admitted to Radiotherapy Service*

Year	Number of all neoplasm cases (per year)	Total number of cancers	Prevalence of MPM among all cancers
2008	1329	2254	1.9%
2009	925		

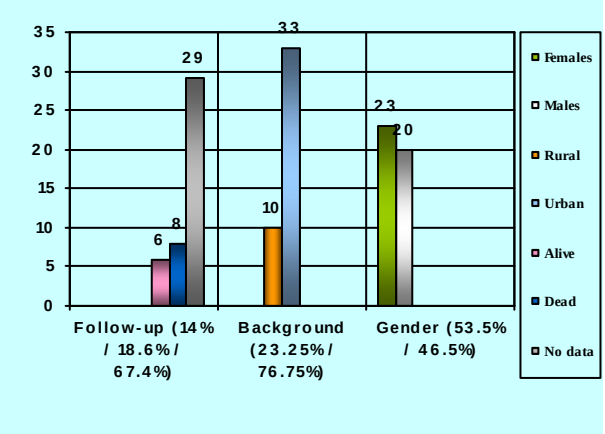

Figure 1. *Background, gender & follow-up*

At the time of performing this study, 8/43 (18.6%) patients with MPM died and 6/43 (14%) were alive. Low compliance of patients to follow-up could explain the reason why we don't have any data about most of them (29/67.4%).

Most of our patients were from an urban area (76.75%). This could be explained by a better access to medical healthcare but also by the higher number of risk factors that is specific to an urban area (figure 2).

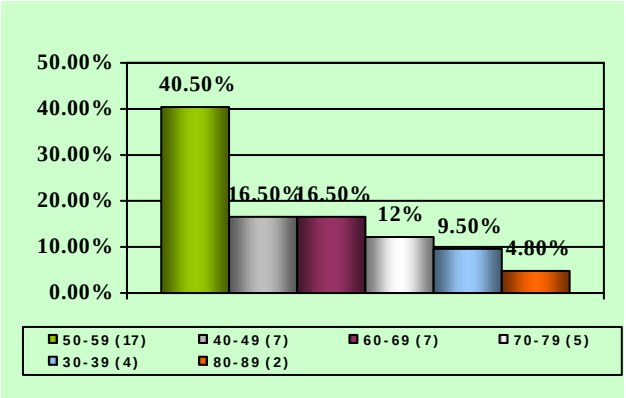

Figure 2. *Age at first cancer diagnosis*

In our group of study, 40.5% patients were between 50 and 59 years old at the moment of first cancer diagnosis, seven patients were between 40 and 49 years old and other seven patients were between 60 and 69 years old.

We can see that most of our patients were less than 70 years old when they were diagnosed with cancer for the first time (figure 3).

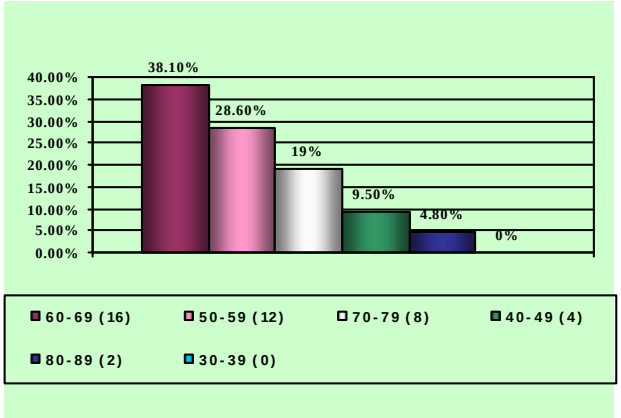

Figure 3. *Age at second cancer diagnosis*

38.1% of all patients were diagnosed for their second malignancy at an age between 60 and 69 and 28.6% patients were between 50 and 59 years old.

Two patients were between 80 and 89 years old at the time they were diagnosed with cancer for the second time, suggesting the importance of long-term follow-up of cancer patients (figure 4).

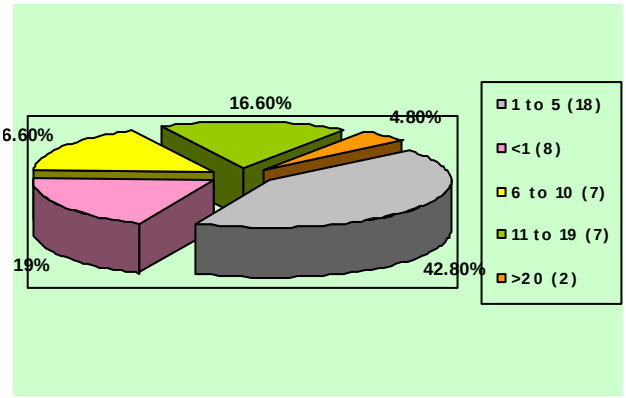

Figure 4. *Elapsed time between first and second diagnosis (years)*

The longest period of elapsed time between first and second cancer diagnoses was of 20 years (2 patients), while most of patients (42.8%) were diagnosed for their second malignancy after 1 to 5 years. Short elapsed time between diagnoses can indicate that there were premalignant lesions that haven't been explored enough,

while long elapsed time suggests again how important long-term follow-up is in cancer patients (figure 5).

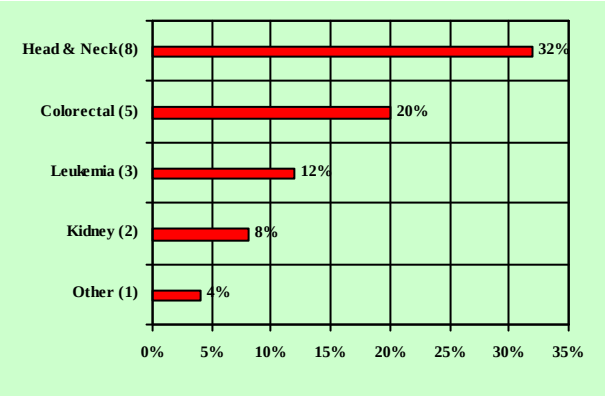

Figure 5. *Most frequent cancer locations at first diagnosis (males and females)*

The most common first diagnoses were head & neck cancers, followed by colorectal ones and leukemia (32%, 20% and 12%, respectively) (figure 6).

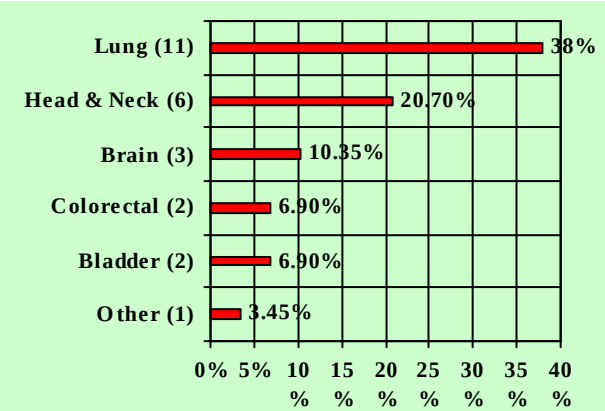

Figure 6. *Most frequent cancer locations at second diagnosis (males and females)*

The most frequent cancer locations for the second cancer diagnosis were lung (38%) and head & neck (20.7%) ones. Other less frequent locations included brain (3), colorectal and bladder [2] (figure 7).

The main neoplasm associations in the female subgroup were colorectal (initial diagnosis)/cervix cancer (3 patients), cervix/breast cancer [3], endometrial/breast cancer [3] and cervix/lung cancer (2 cases) (figure 8).

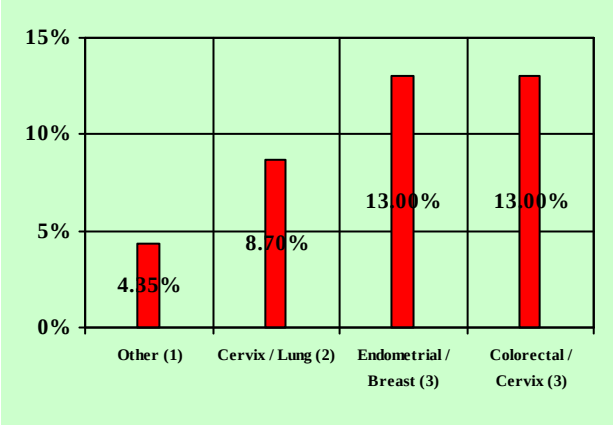

Figure 7. *Neoplasm associations in the female subgroup*

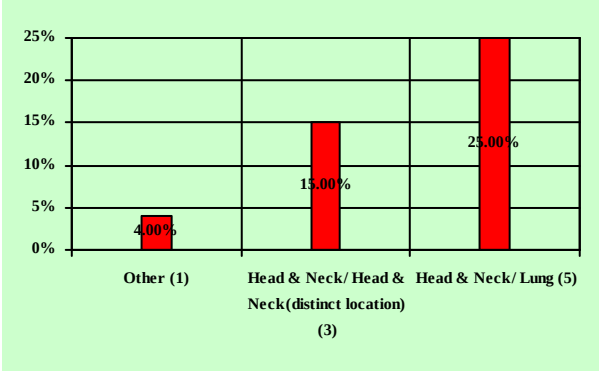

Figure 8. *Neoplasm associations in the male subgroup*

Among males smoking-related cancers, respectively head & neck/lung cancer [5] and head & neck/head & neck (distinct anatomic site) cancer [3], were the most frequent associations.(figures 9, 10,11)

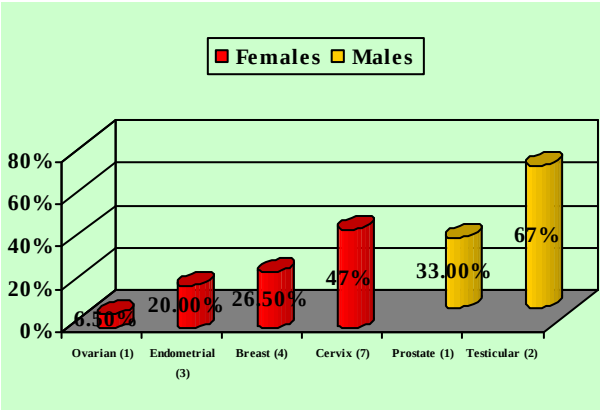

Figure 9. *Most frequent neoplasm locations at first diagnosis in the female and male subgroups*

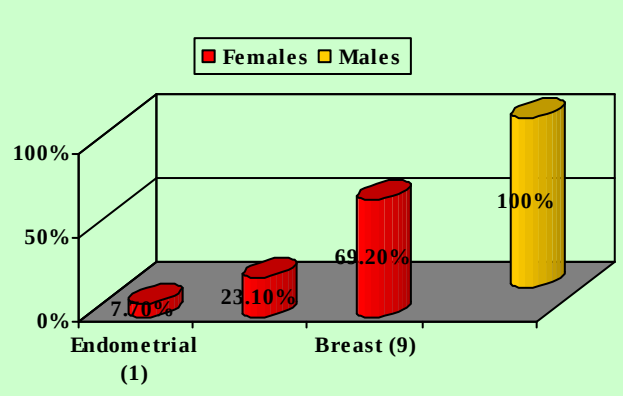

Figure 10. *Most frequent neoplasm locations at second diagnosis in the female and male subgroups*

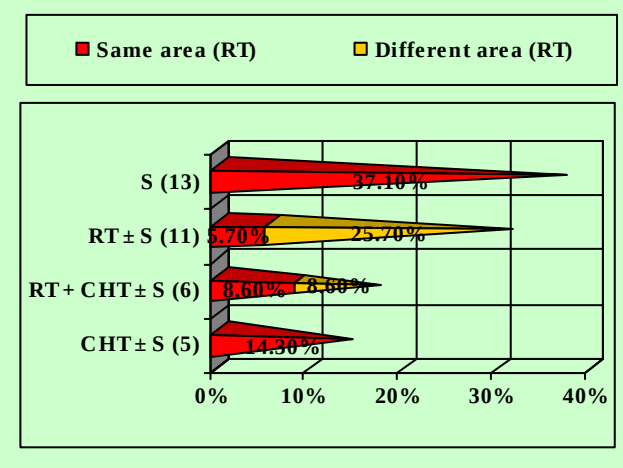

Figure 11. *First cancer treatment*

In our study, surgery alone was applied as a therapeutic method for the first cancer in most cases (37.1%), surgery associated to radiotherapy was used in 25.7% of all cases. Other therapeutic methods that were used in our group of patients for treating the first cancer were surgery associated to radiotherapy and chemotherapy and surgery associated to chemotherapy.

As more becomes known about the influence of various treatment factors on second cancer risk, therapies may be modified to decrease the risk while maintaining equal levels of therapeutic effectiveness.

Survivors who were treated with radiotherapy have an increased risk of certain second cancers, so they should get careful follow-up. They will be watching for recurrence, be careful to follow screening recommendations for cancer to improve the chance of early detection.

The risk of developing a second cancer after radiotherapy depends on dose of radiation, treatment duration, age of patient, association with chemotherapy, smoking before and after first cancer treatment and other factors.

Treated area is also important, since these cancers tend to develop in or near the area that was treated with radiation. Certain organs, such as the breast and thyroid, seem to be more likely to develop cancers after radiation than others. More research will probably be done in the future to look at how genetics and radiation therapy interact, as well as the link between radiation therapy and other cancer-causing agents.

Our study illustrates the importance of obtaining an accurate history at the time of a patient's initial diagnosis and of performing appropriate analyses during the course of a patient's diagnostic work-up. An accurate recording of all patients' medical data is necessary for future studies. These actions help to identify important risk factors and prognostic indicators that assist in determining the most appropriate treatment strategies, taking into account possible side effects and the potential development of secondary neoplasm.

It is important to identify and remove factors that increase the risk of developing a second cancer. More than other risk factors, all patients should be encouraged to avoid tobacco smoke.

Short elapsed time between diagnoses suggests that there are premalignant lesions that haven't been explored. Detection of synchronous multiple primary cancers before treatment is very important when planning different types of cancer therapies.

Knowing the common sites of multiple primary cancers may be beneficial during evaluations before treatment for different cancer as a targeted prophylaxis.

The small number of patients that we have data about can be explained by the low compliance of patients to follow-up. There is a need of good communication

between patients and doctors in order for patients to be warned regarding the risk of developing secondary malignancies after the primary treatment and also about the occurrence of any new symptoms.

Each patient must be informed about the risk of developing secondary malignancies after the first treatment and about the importance of reporting any new symptom which might occur. Careful monitoring ensures an early detection for secondary tumors, and, subsequently, an appropriate management.

Multiplicity of primary malignancies itself does not necessarily indicate a poor prognosis as long as adequate diagnosis and management are performed.

4.Conclusion

Through this study we were able to show different statistical aspects and pointed out aetiology views on multiple primary malignancies.

Prevalence of MPM in our study was in the limits of the values we found in literature (between 0.73% and 11.7%).

Most of our patients were under 70 years old, not only for the first location, but also for the second neoplasm.

As reported in the literature, in our series, a secondary neoplasm seems to be a random phenomenon. We weren't able to conclude on some specific criteria, but only pointed out the most frequent neoplasm associations we found in our group of patients.

In our study, surgery alone was applied as a therapeutic method for the first cancer in most cases, suggesting that second cancer is not from radiation or chemotherapy. Treatment of first cancer is only one aspect of MPM.

There is a real need of scientific investigations and studies on cancer survivors in order to transform theoretical and suggestive views on MPM in concrete data that we can rely on in our daily practice, since MPM's prevalence has been increased lately. Such studies may serve as guidelines for rational follow-up programmes for cancer patients and to identify a potential surveillance protocol.

In addition, long-term follow-up and screening strategies are important

A long-term follow-up of cancer patients, not only for some years but for the rest of their lives, is important since second cancer can develop, as we have seen in this study, even after 20 years after the first cancer diagnosis.

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