EFFECTS OF COVID-19 ON THE DIAGNOSIS OF BRAIN METASTASES. A RETROSPECTIVE ANALYSIS

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EFFECTS OF COVID-19 ON THE DIAGNOSIS OF BRAIN METASTASES. A RETROSPECTIVE ANALYSIS (Abstract): Delays in cancer diagnosis and treatment can significantly impact patient survival and quality of life. The COVID-19 pandemic intensified these challenges by limiting access to medical services and postponing essential oncologic interventions. This study **aimed** to evaluate the effects of such delays on the diagnosis and management of brain metastases in neuro-oncology patients during the pandemic period. **Materials and methods**: A retrospective analysis was conducted on 100 patients who underwent surgical treatment for brain metastases at the Department of Neurosurgery, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iași, Romania. Patients were divided into two groups: the pre-COVID group (2018-2019, n = 57) and the COVID group (2020-2022, n = 43). Demographic, clinical, and pathological data were collected from medical records. Tumor volume, anatomical location, and histopathological characteristics were compared between groups. **Results**: The mean age of patients was 57.9 years, with a female-to-male ratio of 1.17: 1. The most common primary tumors were breast (27%), bronchopulmonary (20%), and gastrointestinal cancers (18%). Brain metastases were predominantly located in the supratentorial region (80%), especially in the parietal and occipital lobes. The median tumor volume was higher in the COVID group (16.8 cm^3) compared with the pre-COVID group (12.1 cm^3), suggesting delayed diagnosis and disease progression during the pandemic, although the difference did not reach statistical significance ($p = 0.11$). **Conclusions**: The COVID-19 pandemic contributed to diagnostic delays and increased tumor burden in patients with brain metastases, reflecting reduced access to timely healthcare. While demographic characteristics remained similar between periods, larger tumor volumes observed during the pandemic indicate that healthcare disruptions had tangible effects on disease progression. Continued research is necessary to assess the long-term impact of these delays on treatment outcomes and survival, as well as to develop adaptive strategies to ensure continuity of oncologic care during future healthcare crises. **Keywords:** COVID-19, BRAIN, METASTASES, TUMOR.

INTRODUCTION

Delays in cancer treatment can have significant implications for patient survival and quality of life. One of the most concerning consequences of such delays is the increased risk of mortality and disease

recurrence. Studies have demonstrated that timely diagnosis and early initiation of treatment are crucial for improving patient outcomes (1,2). When treatments are postponed, cancer has time to progress, which may render subsequent interventions more complex and less effective (3, 4, 5, 6). This situation underscores the importance of early interventions and close monitoring of disease progression.

Beyond biological risks, treatment delays can impose a substantial financial burden on patients. This may translate into additional long-term costs if the disease advances and requires more intensive and expensive therapies. Patients may face not only the financial strain of medical expenses but also economic losses caused by their inability to work or maintain daily activities. Thus, the consequences of delayed treatment extend beyond the medical sphere, affecting the socio-economic well-being of patients and their families.

The COVID-19 pandemic has amplified these challenges, placing significant strain on healthcare systems worldwide. Many institutions were forced to postpone elective cancer surgeries and reduce the use of systemic therapies as medical resources were reallocated to address the public health emergency. These measures have raised concerns about the long-term consequences of delayed treatment for cancer patients (2). Although it is evident that postponement negatively affected clinical outcomes, the lack of comprehensive data makes it difficult to precisely assess the impact of such delays on survival and disease progression.

Therefore, the need for high-quality data to evaluate the effects of treatment delays in oncology has become increasingly evident. Without such information, it is impossible to quantify the real impact of COVID-19 related preventive measures on cancer patients and on the healthcare systems that serve them. A deeper understanding of these effects could guide the development of more effective, patient-centered public health policies, ensuring timely interventions and optimal resource management.

Looking forward, the pandemic has served as a period of reflection for the medical community. It is essential for healthcare systems to reassess how they allocate and manage resources and to develop strategies that minimize delays in essential treatments. This requires not only better coordination among healthcare professionals but also a patient-centered approach that allows for the continuation of care even in times of crisis. Hence, future healthcare systems must be more flexible, adaptable, and better equipped to respond to emerging challenges, thereby ensuring improved outcomes for cancer patients.

In this context, our study focuses on the impact of COVID-19 in the field of neuro-oncology, emphasizing potential delays in the diagnosis of brain metastases. These metastases often present acutely, leading to new or progressive neurological deficits, symptoms of increased intracranial pressure, or seizures (7, 8, 9).

Delays in managing these conditions can have serious consequences, leading to a more severe decline in patients' health status. For example, delayed diagnosis may allow the disease to advance to a stage where therapeutic interventions become more complex and less effective, particularly in the context of heterogene-

ous molecular subtypes of brain metastases (3, 4, 5, 6). Many of these cases may require more sophisticated support and intensive management, which not only increases patient risk but also adds additional strain to the healthcare system.

During the pandemic, healthcare priorities were restructured, and resources were heavily burdened by the need to respond to the COVID-19 public health crisis. This situation led to delays in diagnosis and treatment, as well as decreased access to essential services for patients with neuro-oncological conditions. Therefore, it is crucial to analyze how these delays have affected clinical outcomes and to identify strategies for minimizing their negative impact, ensuring the efficient continuation of care.

Our study aims to provide a detailed analysis of these delays and to explore the so-called "therapeutic windows" that may arise in neuro-oncological treatment pathways. A comprehensive understanding of these aspects will not only contribute to improved management of patients in the future but will also aid in formulating more effective health policies that can meet patient needs during times of crisis. Investigating the impact of COVID-19 in neuro-oncology is essential not only for ensuring patient recovery but also for strengthening healthcare systems overall, enabling them to respond to emerging challenges with adaptable and effective solutions.

MATERIALS AND METHODS

We conducted a retrospective study of patients who underwent surgical treatment at the Department of Neurosurgery, Prof. Dr. Nicolae Oblu Emergency Clinical Hospital, Iași, Romania, during 2020-2022, and compared these findings with data from the pre-pandemic period (2018-2020).

Patients with newly diagnosed brain metastases were included, and the origin and type of primary tumors were recorded. Patients with multiple primary tumors who presented new manifestations of cerebral metastases were also included, as well as those with a syndrome of cancer of unknown primary origin.

We excluded patients with any diagnosis other than brain metastases. Patients with recurrent tumors were excluded, as were those unable to undergo MRI examination.

Patients were classified according to their access to medical care in:

- those treated during the pre-pandemic period with normal, unrestricted access (2018-2019; pre-COVID group), and
- those treated during the pandemic period with limited access to healthcare (2020-2022; COVID group).

The study analyzed 100 patients with brain metastases (57 in the pre-COVID group and 43 in the COVID group). Clinicopathological data were collected from electronic medical records and included demographic information and morphological characteristics of the cerebral metastases (location and cytopathological features).

The cytopathological examination was performed on intraoperative smears obtained from small biopsy samples collected during surgery. A small specimen (1-2 mm^3) was placed on the edge of a clean, dry, labeled glass slide and crushed gently using another labeled slide, applying sufficient pressure to spread the tissue into a

thin film on both slides. Both slides were immediately stained with 1% toluidine blue. In all cases, the cytological diagnosis confirmed the presence of brain metastases.

RESULTS

The analysis provides a detailed overview of the characteristics of patients with brain metastases included in the study, revealing valuable information about both their demographic profiles and disease progression.

A total of 100 patients were included, of whom 57 were treated before the pandemic and 43 during the COVID-19 period. This division allowed for comparison of potential differences in management and outcomes between the two periods.

The mean age of the patients was 57.9 years, with most individuals in their sixth and seventh decades of life. This suggests a higher incidence of brain metastases among middle-aged and elderly adults, consistent with the fact that such oncological complications typically occur at advanced disease stages in patients with long-standing primary malignancies. The median interval from initial cancer diagnosis to the development of brain metastases was approximately 34.42 months, indicating a substantial disease trajectory before cerebral involvement became clinically significant.

Gender distribution showed a female-to-male ratio of 1.17:1, indicating a slight predominance of women in the study population.

Regarding the patients' origin, nearly half came from rural areas (48%), while the remainder resided in urban areas (52%).

Educational level revealed a diverse profile: 62% of patients had completed secondary education, 36% held higher education degrees, and 4% had only primary education.

Overall, these data help outline a complex demographic and clinical profile of patients with brain metastases, including age, sex, education, and access to care.

The most common primary tumor was breast cancer (27%), followed by bronchopulmonary cancer (20%), and gastrointestinal tumors (18%) (fig. 1).

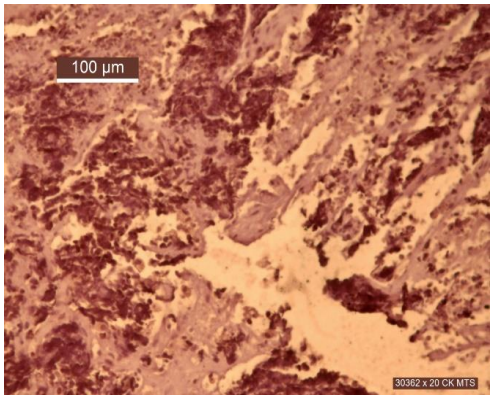

Fig. 1. Undifferentiated bronchopulmonary carcinoma metastasis.
(Immunodetection with cytokeratin, ×200)

In detail, among the gastrointestinal tumors, 5 patients were identified with esophageal cancer, 10 with colorectal cancer, 1 with pancreatic cancer, and 1 with peritoneal cancer. Other patients presented different types of malignancies: 7 were diagnosed with malignant melanoma, and 9 had renal tumors (fig. 2).

A total of eight patients were classified as having cancers of unknown primary origin. This classification was necessary because these patients died during the COVID-19 pandemic, and the cause of

death was attributed to the virus, preventing accurate determination of the tumor's primary site.

These findings highlight the diversity of primary tumors that can lead to brain metastases and provide an overview of the distribution of cancer types within this patient group (fig. 3).

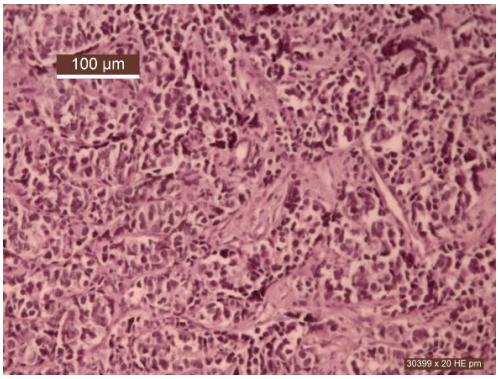

Fig. 2. Metastasis of moderately differentiated prostatic adenocarcinoma in a 68-year-old man. Preserved tubular structure is observed.

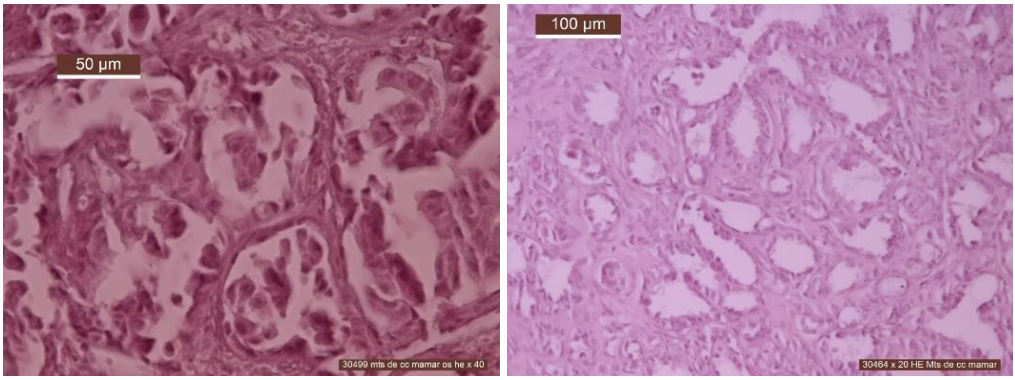

Fig. 3. Ductal carcinoma in a 60-year-old woman (HE staining, ×400). Tubular carcinoma in a 68-year-old woman (HE staining, ×200).

According to the results obtained, the distribution of brain metastases by anatomical location showed a predominance in specific brain regions. Thus, metastases were identified in the cerebellum in 20% of cases, in the right parietal lobe in 20%, in the left parietal lobe in 30%, in the right occipital lobe in 20%, and in the left occipital lobe in 10% of cases.

Regarding the distribution of brain regions, metastases were more frequently located in the supratentorial area (80%) compared with the infratentorial area (20%). This predominance in the supratentorial region is an important observation, as different areas of the brain can influence the symptomatology and clinical progression of patients with brain metastases.

These data indicate a higher tendency for metastases to localize in the parietal and occipital regions, which may have implications for treatment planning and follow-up strategies in such patients.

In this study, the majority of patients (92.6%) underwent surgical resection of brain metastases. This surgical intervention constituted an essential component of patient management, reflecting an aggressive therapeutic approach aimed at controlling metastases within the central nervous system (CNS).

From an oncological history perspective, 64% of patients had a previously diagnosed malignant neoplasm and were under regular surveillance without evidence of brain metastases before the study period. However, in 36% of patients, the brain metastasis represented the first manifestation of malignancy. These patients developed cerebral metastases without prior cancer symptoms; among them, 25 belonged to the pre-COVID group and 18 to the COVID group, suggesting a relatively balanced distribution between the two-time frames.

Analyzing the metastasis patterns, in 49% of patients the brain metastasis was the only secondary lesion identified outside the primary tumor, whereas in 51% of cases, brain metastases coexisted with metastases in other organs. This finding indicates a more aggressive systemic progression of the disease in the latter group.

The mean volume of brain metastases was 19.7 cm^3, with significant interindividual variability (±18.1 cm^3), the median being 13.5 cm^3, and ranging from 0.3 to 69.4 cm^3. When comparing the pre-COVID and COVID groups, the mean tumor volume was higher in patients treated during the pandemic, with a median of 16.8 cm^3, compared to 12.1 cm^3 in the pre-COVID period. Although this difference was not statistically significant ($p = 0.11$, Mann-Whitney U test), it may suggest a potential impact of the pandemic on early diagnosis and management of these patients.

These findings provide a complex overview of the clinical and pathological characteristics of patients with brain metastases, highlighting aspects related both to disease history and to management across different time periods (pre-COVID vs. COVID).

DISCUSSION

In malignant tumors, delayed initiation of treatment is a critical factor that significantly worsens prognosis. Studies show that even a four-week delay can have a measurable impact on morbidity and mortality among cancer patients, regardless of the treatment modality (1, 2). Such delays adversely affect all therapeutic options, though the degree of impact varies: the risk of disease progression increases by an estimated 6-8% for surgical interventions, 9% for radiotherapy, and 13% for systemic therapies such as chemotherapy and immunotherapy (1, 8, 9).

Before the COVID-19 pandemic, treatment delays in oncology were primarily determined by two categories of factors: patient-related and systemic/institutional (1, 2). Among patient-related factors, the most common obstacle was lack of financial resources, affecting approximately 28% of cases. This difficulty reflects challenges in covering the costs of treatment, transportation, and accommodation in specialized centers (3). Additional factors, such as distance from treatment facilities (12.7%), dependence on others for support (9%), and delayed presentation due to symptom neglect (16%), also contributed to treatment postponement (2, 6).

From a medical standpoint, delays of-

ten occurred when patients were initially diagnosed outside major specialized centers, where access to modern equipment and multidisciplinary teams was limited (4,7). In such cases, the time required for diagnosis and referral to an appropriate facility prolonged treatment initiation, negatively influencing prognosis and survival outcomes (3, 5).

During the COVID-19 pandemic, the impact of these factors intensified, amplifying treatment delays among oncology patients (2, 8). Pandemic restrictions including reduced treatment capacity in cancer centers, reallocation of medical resources to COVID-19 care, and isolation measures-further limited access to therapy (2, 8). As a result, delays caused by the pandemic compounded existing healthcare challenges, exacerbated the prognosis for many patients with malignant diseases (1, 2, 8).

The reduction in the number of surgical procedures and oncologic therapies, as well as the rescheduling and postponement of cancer treatments, became a global concern during the pandemic (6, 7). These disruptions affected most medical centers worldwide and interfered with supply chains, including the availability of medical personnel, which decreased by up to 79% in some institutions (6). This reduction in human resources had a major impact on hospitals' capacity to maintain standard treatment flow for oncology patients (8, 9).

However, the impact of COVID-19-related disruptions on cancer patients was not uniform. The final effect of these restrictions varied depending on multiple factors, including age, comorbidities, type of treatment required, and disease stage (5, 6). For instance, elderly patients or those with multiple comorbidities faced a higher risk of complications due to delayed care, while patients with aggressive tumors were particularly affected by postponement of essential therapies such as surgery and systemic treatments (3, 7).

These pandemic-induced changes highlighted the vulnerability of healthcare infrastructure during global crises and underscored the urgent need for adaptation strategies to ensure continuity of essential care for patients with severe conditions like cancer (1, 2, 8). The pandemic forced many oncology centers to reprioritize cases by severity and to develop innovative solutions to minimize the negative effects of restrictions on cancer patients (2, 9).

CONCLUSIONS

The present study provides relevant data on the impact of the COVID-19 pandemic on the diagnosis of brain metastases, contributing to a better understanding of how this global health crisis influenced the evolution and management of cancer cases involving the brain. Comparative analysis of patients diagnosed before and during the pandemic revealed no significant demographic differences between the two groups, suggesting that age, sex, and area of residence were not influenced by the pandemic period.

However, a statistically significant difference was observed in the median tumor volume, which was higher in patients diagnosed during the pandemic. This increase in tumor size suggests that diagnostic delays-caused by reduced access to health-care services during the pandemic-led to patients presenting with more advanced disease stages and larger brain lesions. Such situations complicate treat-

ment planning, as larger and more advanced tumors typically require more complex interventions and are associated with a less favorable prognosis.

To fully assess the long-term impact of diagnostic delays on treatment outcomes and survival among patients with brain metastases, this study will continue. The future objective is to analyze in greater detail how diagnostic delays, determined by pandemic-related constraints, affected treatment efficacy and overall disease progression.

Continuing this research will enable a more comprehensive understanding of the pandemic's consequences on oncologic care and provide valuable insights for optimizing healthcare system responses for similar crises in the future.

CONFLICT OF INTEREST AND FUNDING

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