Original Article: Investigating the Relationship Between Seizures, Cancer, and Chemotherapy Effects: Risk Factors, Underlying Mechanisms, and Therapeutic Approaches

Reza Eghdam Zamiri[1], Saeid Charsouei[2]

[1]*Associate Professor of Radiology, Department of Radiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. (ORCID: 0000-0003-2889-2795/ Email: scharsouei@gmail.com)*

[2]*Associate Professor of Neurology, Department of Neurology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. (ORCID: 0000-0002-4639-4733)*

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ABSTRACT

Background: Seizures are a significant yet often overlooked complication in cancer patients, influenced by the tumor itself, treatment modalities, and individual patient factors. This review aims to explore the intricate relationship between seizures, cancer, and chemotherapy effects, focusing on risk factors, underlying mechanisms, and current therapeutic approaches. **Methods:** A comprehensive literature review conducted, encompassing studies on the incidence of seizures in various cancer types, the neurotoxic effects of chemotherapy and immunotherapy, and the multifactorial risk factors contributing to seizure development. Additionally, therapeutic strategies and the implications of palliative care in managing seizures evaluated. **Results:** The incidence of seizures in cancer patients varies significantly depending on tumor location, type, and treatment regimens. Chemotherapeutic agents have shown to exert neurotoxic effects, contributing to seizure activity. Identifying specific risk factors such as age, pre-existing neurological conditions, and type of cancer is crucial for early intervention. Current therapeutic approaches primarily involve the use of antiepileptic drugs (AEDs), although challenges persist due to drug interactions and the side effects of cancer treatments. **Conclusion:** There is a critical need for further research to better understand the mechanisms underlying seizures in cancer patients and to develop targeted management strategies. A multidisciplinary approach involving oncologists, neurologists, and researchers is essential for improving patient outcomes and quality of life. Enhanced understanding and collaboration will facilitate the development of evidence-based guidelines to address the complex needs of this population.

***Corresponding Author: Saeid Charsouei** (zamirireza@gmail.com)*

Introduction

The intersection between neurological disorders and cancer is a complex and multifaceted area of medical research [1]. Among these, the relationship between seizures and cancer poses unique challenges for clinicians and researchers alike. Seizures, a hallmark of various neurological disorders, can manifest in cancer patients due to multiple causes, including direct effects of the tumor, treatment-related side effects, or pre-existing conditions. Chemotherapy, a cornerstone of cancer treatment, has significantly improved survival rates for many patients, but its neurotoxic effects have increasingly become a matter of concern. Understanding the interplay between seizures, cancer, and chemotherapy requires an integrated analysis of risk factors, the underlying pathophysiological mechanisms, and the development of effective therapeutic strategies [2].

Seizures in Cancer Patients: Scope of the Problem

Seizures are a significant and often underappreciated complication in cancer patients, particularly in those with primary or metastatic brain tumors. They are characterized by abnormal, excessive electrical activity in the brain, leading to a range of clinical manifestations from mild sensory disturbances to severe convulsive episodes. In the oncology population, seizures not only impair quality of life but also complicate the management of the underlying malignancy, increasing the burden on both patients and healthcare providers. The occurrence of seizures in cancer patients presents unique diagnostic and therapeutic challenges, necessitating a multidisciplinary approach to care.

The incidence of seizures in cancer patients varies widely depending on the type, location, and extent of the malignancy. Brain tumors, whether primary or metastatic, are the most frequent culprits, with up to 40% of patients with gliomas and 20% of those with brain metastases experiencing seizures at some point during their illness. Gliomas, particularly low-grade gliomas, are highly epileptogenic due to their tendency to infiltrate and disrupt normal cortical structures. The tumor's mass effect, which compresses surrounding brain tissue, and the associated inflammatory responses contribute to neuronal hyperexcitability, predisposing patients to seizures. Similarly, metastases from cancers such as lung, breast, and melanoma are also known to provoke seizures, especially when they involve the cerebral cortex.

In addition to brain tumors, seizures can also occur in patients with non-central nervous system (non-CNS) cancers, although this is less common. Paraneoplastic syndromes, which are rare but serious immune-mediated disorders, can provoke seizures by affecting the nervous system, even in the absence of direct tumor involvement in the brain. In such cases, the body's immune response to the cancer leads to the production of antibodies or other substances that attack neuronal structures, causing seizures and other neurological symptoms. These syndromes are most frequently associated with small cell lung cancer, ovarian cancer, and testicular tumors, and they represent an additional layer of complexity in managing cancer patients with seizures.

The occurrence of seizures in cancer patients significantly impacts their overall prognosis and quality of life. For patients with brain tumors, seizures can be the initial presenting symptom, leading to the diagnosis of the malignancy. In others, seizures may develop later as the disease progresses, either due to the growth of the tumor or as a result of treatment-related complications. Seizures can interfere with the patient's ability to function independently, causing cognitive decline, mood disturbances, and social isolation. Moreover, they increase the risk of injury, especially in patients who experience generalized tonic-clonic seizures, which are associated with falls, fractures, and head trauma.

The development of seizures in cancer patients also complicates their treatment plans. For patients undergoing chemotherapy or radiation therapy, the use of antiepileptic drugs (AEDs) may lead to drug interactions that reduce the efficacy of cancer treatments or increase the risk of side effects. For instance, enzyme-inducing

AEDs such as phenytoin and carbamazepine can accelerate the metabolism of chemotherapeutic agents, potentially diminishing their therapeutic effects. On the other hand, chemotherapy and radiation therapy themselves can increase the risk of seizures by inducing neurotoxicity, further complicating the clinical picture. This creates a delicate balance in managing both the cancer and the seizures without exacerbating either condition [3].

Radiation therapy to the brain, often employed in the management of brain tumors or metastases, is another common cause of seizures in cancer patients. While effective in reducing tumor size and controlling tumor growth, radiation can cause acute or delayed neurotoxicity, which may manifest as seizures. Acute radiation-induced seizures typically occur within the first few days or weeks after treatment and are thought to be due to inflammation and edema in the irradiated brain tissue. Delayed seizures, on the other hand, may develop months or even years after radiation therapy, as a result of long-term radiation damage leading to gliosis, scarring, and reduced neuronal function [4].

Surgical interventions for brain tumors, although often necessary for tumor debulking or biopsy, can also provoke seizures. The risk of postoperative seizures is particularly high in patients who undergo craniotomy or other invasive neurosurgical procedures, especially when the tumor is located in or near the motor cortex or other highly epileptogenic areas. Post-surgical seizures are often attributed to factors such as brain swelling, ischemia, or the formation of scar tissue, all of which can disrupt normal neuronal activity. While the goal of surgery is to reduce the tumor burden and, in some cases, alleviate seizure activity, the procedure itself carries inherent risks for inducing seizures [5].

Paraneoplastic seizures, although less common than tumor-related seizures, represent a particularly challenging subset of seizure disorders in cancer patients. These seizures are caused by the body's immune response to the tumor, leading to the production of autoantibodies that attack neuronal tissues. In paraneoplastic limbic encephalitis, for example, patients may develop seizures, memory loss, confusion, and mood disturbances as a result of inflammation in the limbic system. These syndromes often require a different therapeutic approach, involving immunosuppressive treatments such as corticosteroids, intravenous immunoglobulins, or plasmapheresis, in addition to standard seizure management.

In conclusion, seizures in cancer patients present a multifaceted clinical challenge that requires careful management. Whether caused by the direct effects of brain tumors, paraneoplastic syndromes, or treatment-related complications, seizures significantly impact patient outcomes and quality of life. Addressing the underlying mechanisms of seizure development in cancer patients, optimizing antiepileptic therapy, and minimizing treatment-related neurotoxicity are critical components of comprehensive cancer care. Further research into the interactions between cancer therapies and seizure activity will be essential for improving patient outcomes in this vulnerable population [6].

Chemotherapy-Induced Seizures: Neurotoxic Effects

Chemotherapy, a cornerstone in cancer treatment, often brings about a wide range of side effects, with neurotoxicity being one of the most concerning. Chemotherapy-induced seizures, although relatively rare, are a serious manifestation of neurotoxicity and can significantly complicate the management of cancer patients. These seizures occur as a result of the toxic effects that certain chemotherapeutic agents have on the central nervous system (CNS). The delicate balance between achieving effective cancer cell kill and minimizing neurotoxic effects is a major challenge in oncology, and seizures can be one of the most severe outcomes of this balance tipping unfavorably [7].

Several chemotherapeutic agents are known to be neurotoxic and may cause seizures in susceptible individuals. The platinum-based drugs, such as cisplatin and carboplatin, are frequently implicated in chemotherapy-induced seizures due to their ability to cross the blood-brain barrier and cause direct damage to neural tissues. These agents disrupt normal neuronal

functioning by interfering with DNA repair mechanisms, leading to cell death and subsequent neuronal excitability. While effective against various cancers, particularly solid tumors like lung and ovarian cancers, these drugs are notorious for their dose-dependent neurotoxic effects, including seizures, cognitive impairment, and peripheral neuropathy.

In addition to platinum-based drugs, high-dose methotrexate, a commonly used chemotherapeutic agent in the treatment of leukemia and lymphoma, can also lead to neurotoxicity and seizures. Methotrexate can cause acute, subacute, or chronic neurological side effects, with seizures being one of the most severe acute manifestations. The neurotoxic effects of methotrexate are believed to be due to its interference with folate metabolism, which is essential for DNA synthesis and repair in the CNS. In some cases, methotrexate-induced neurotoxicity may be reversible, but seizures that develop as a result of this toxicity require immediate medical intervention to prevent further CNS damage [8].

Another agent known for inducing neurotoxicity and seizures is ifosfamide. Ifosfamide, an alkylating agent used to treat various cancers, including sarcomas and lymphomas, has been associated with encephalopathy, a syndrome characterized by altered mental status, confusion, and seizures. This encephalopathy is thought to be caused by the accumulation of toxic metabolites such as chloroacetaldehyde, which can disrupt neuronal function and trigger seizures. The onset of ifosfamide-induced seizures is typically acute and may occur during or shortly after drug administration. Early recognition of this adverse effect is crucial, as discontinuation of the drug or dose adjustment can often lead to symptom resolution.

Chemotherapy-induced seizures are not always directly related to the neurotoxicity of the chemotherapeutic agents themselves. In some cases, seizures may arise indirectly due to metabolic disturbances or electrolyte imbalances triggered by chemotherapy. For instance, chemotherapeutic agents can cause tumor lysis syndrome (TLS), a potentially life-threatening condition in which rapid tumor cell death releases large amounts of potassium, phosphate, and uric acid into the bloodstream. The resulting electrolyte imbalances, particularly hyperkalemia and hypocalcemia, can lead to seizures in affected patients. Effective management of TLS is critical to prevent seizures and other severe complications in patients receiving high-dose chemotherapy.

Moreover, chemotherapy can increase the risk of seizures in patients with pre-existing CNS abnormalities, such as brain metastases or prior radiation therapy. In these patients, chemotherapy may exacerbate underlying CNS damage or inflammation, triggering seizures. Radiation therapy to the brain can weaken the blood-brain barrier, making the CNS more vulnerable to the toxic effects of chemotherapeutic agents. This synergistic neurotoxicity between chemotherapy and prior radiation increases the likelihood of seizures, particularly in patients who have received cranial irradiation as part of their cancer treatment [9].

The management of chemotherapy-induced seizures involves both preventive and reactive strategies. In patients at high risk of neurotoxicity, such as those receiving platinum-based drugs or high-dose methotrexate, close monitoring of neurological function and serum electrolyte levels is essential. The use of prophylactic antiepileptic drugs (AEDs) is sometimes considered, although this practice remains controversial due to potential drug interactions between AEDs and chemotherapeutic agents. When seizures do occur, prompt treatment with AEDs and adjustments to the chemotherapy regimen are necessary to prevent further episodes and mitigate CNS damage [10].

While chemotherapy-induced seizures are a severe complication, advancements in understanding the mechanisms of chemotherapy-related neurotoxicity have led to the development of strategies to mitigate these risks. For example, the use of calcium and magnesium infusions has been shown to reduce the neurotoxicity of cisplatin, lowering the risk of seizures and other neurological side effects. Additionally, dose modifications, treatment breaks, and alternative chemotherapy agents may be considered in patients who develop seizures, balancing the need for effective cancer

treatment with the goal of preserving neurological function.

In conclusion, chemotherapy-induced seizures represent a serious and multifaceted challenge in cancer care. The neurotoxic effects of chemotherapeutic agents, particularly those that cross the blood-brain barrier, can lead to seizures in susceptible patients, while metabolic disturbances and prior CNS damage can exacerbate this risk. Careful monitoring and early intervention are critical to managing chemotherapy-induced seizures and preventing long-term neurological damage. As oncology continues to evolve, the ongoing study of neurotoxicity and its mitigation will be essential to improving outcomes for cancer patients receiving chemotherapy [11].

Risk Factors for Seizure Development in Cancer Patients

The development of seizures in cancer patients is influenced by a variety of factors, both intrinsic to the patient and related to their disease or treatment. Seizures can significantly complicate the clinical course of cancer, affecting the patient's quality of life and sometimes even leading to life-threatening complications. Understanding the risk factors that predispose cancer patients to seizures is crucial for both preventive strategies and timely interventions.

A key factor contributing to seizure risk in cancer patients is the presence of brain metastases. Metastatic disease to the central nervous system (CNS) is relatively common, especially in cancers such as lung, breast, and melanoma, and these metastases can disrupt normal brain function, leading to seizures. Brain metastases can cause seizures due to their mass effect, irritation of the surrounding brain tissue, and disruption of the normal electrical activity in the cortex. Patients with multiple brain lesions or metastases in the cortical regions of the brain are particularly vulnerable to seizure development. Early detection and management of brain metastases are important in reducing seizure risk in this population [12].

Another important risk factor is primary brain tumors, such as gliomas, meningiomas, and oligodendrogliomas. Seizures are often one of the first symptoms in patients with primary brain tumors, particularly in low-grade gliomas, where seizures occur in up to 70-90% of cases. These seizures are typically focal in nature but can generalize in some patients. The risk of seizures is directly related to the tumor's location, size, and growth rate, with tumors affecting the cortical areas being more prone to causing seizures. Seizures in these patients are often recurrent and may become difficult to control, requiring long-term antiepileptic therapy in addition to cancer treatment [13].

Chemotherapy and radiation therapy also contribute to the risk of seizures in cancer patients. Certain chemotherapeutic agents, particularly those that cross the blood-brain barrier, have a higher propensity for inducing neurotoxicity and seizures. Drugs such as cisplatin, methotrexate, and ifosfamide are well-known for their neurotoxic effects, and their use requires careful monitoring of CNS symptoms. Radiation therapy to the brain can exacerbate this risk by damaging the blood-brain barrier, making the CNS more vulnerable to the neurotoxic effects of these agents. Patients who receive combined chemotherapy and radiation therapy are at an even higher risk of seizure development due to the synergistic neurotoxic effects of these treatments [14].

Additionally, electrolyte imbalances and metabolic disturbances, which are common in cancer patients, can also precipitate seizures. Conditions such as hyponatremia (low sodium levels), hypercalcemia (high calcium levels), and hypoglycemia (low blood sugar) are frequently seen in patients undergoing cancer treatment. These imbalances disrupt the normal functioning of neurons, leading to increased excitability and a lower threshold for seizure activity. Tumor lysis syndrome, a metabolic complication caused by the rapid destruction of cancer cells, can also trigger seizures due to sudden changes in electrolyte and uric acid levels in the bloodstream [15].

Infection is another significant risk factor for seizure development in cancer patients. Immunosuppression, either from the cancer itself or from treatments like chemotherapy, increases the risk of CNS infections such as meningitis and encephalitis, which can lead to seizures. Opportunistic infections, including viral, bacterial, and fungal pathogens, are more

common in immunocompromised patients, and their CNS involvement often presents with seizures as a prominent symptom. Prompt diagnosis and treatment of these infections are essential to prevent permanent neurological damage and recurrent seizures [16].

Patients with a history of pre-existing seizure disorders are at greater risk of seizure recurrence or exacerbation during their cancer treatment. The stress of the cancer itself, along with the potential neurotoxic effects of treatment, can lower the seizure threshold in these patients. Moreover, drug interactions between antiepileptic medications and chemotherapy agents can alter the effectiveness of seizure control, leading to an increased risk of breakthrough seizures. This necessitates close monitoring of drug levels and careful coordination between oncologists and neurologists to ensure optimal seizure management [17].

Genetic predisposition is emerging as another factor in the risk of seizures in cancer patients. Some patients may have genetic mutations or polymorphisms that make them more susceptible to seizures, particularly when exposed to neurotoxic agents. For example, mutations in genes responsible for ion channel regulation or neurotransmitter metabolism may predispose individuals to seizures when combined with the additional neurological stress of cancer or its treatment. Although this area is still under investigation, understanding the genetic basis of seizure susceptibility could eventually lead to more personalized treatment plans for cancer patients at higher risk [18].

Lastly, advanced cancer stages are associated with an increased risk of seizures. As cancer progresses, patients are more likely to develop complications such as brain metastases, metabolic disturbances, and infections, all of which increase seizure risk. Furthermore, patients with advanced cancer often undergo more aggressive treatments, including high-dose chemotherapy, which can exacerbate neurotoxicity. In these patients, seizures can significantly impact overall prognosis and quality of life, making it critical to identify and mitigate risk factors as early as possible [19].

Underlying Mechanisms of Seizures in Cancer Patients

Seizures in cancer patients arise from a complex interplay of factors involving both the cancer itself and the treatments employed to manage the disease. The mechanisms by which cancer leads to seizures are multifactorial, involving direct effects on the brain, such as tumor growth, and indirect effects, like metabolic disturbances and treatment-induced neurotoxicity. Understanding these underlying mechanisms is crucial to improving the prevention and management of seizures in cancer patients.

One of the primary mechanisms of seizure development in cancer patients is the direct impact of tumors on the central nervous system (CNS). Tumors that invade or compress brain tissue can disrupt normal neuronal activity, leading to seizures. These tumors may either be primary brain tumors, such as gliomas, or secondary metastases from cancers like lung, breast, or melanoma. Tumor growth can lead to local irritation of the cerebral cortex, increased intracranial pressure, and the disruption of the blood-brain barrier, all of which lower the seizure threshold and promote abnormal electrical activity in the brain [21].

Brain tumors can also cause seizures through their effects on surrounding brain tissue. As tumors grow, they may cause peritumoral edema, which leads to increased pressure in the surrounding brain tissue. This edema results from both the tumor's metabolic activity and the body's inflammatory response to the growing mass. Edema alters the extracellular environment of neurons, disrupting ion balances and neurotransmitter function [22].

This disruption can lead to hyperexcitability of neurons and seizure initiation. Additionally, ischemia caused by tumors that compress blood vessels can deprive areas of the brain of oxygen and nutrients, further increasing the risk of seizures.

Disruption of the blood-brain barrier (BBB) is another key mechanism in cancer-related seizures. The BBB is essential for protecting the brain from toxins and pathogens circulating in the bloodstream, but cancer and its treatments can weaken this barrier. When the BBB is compromised, chemotherapeutic agents,

immune cells, and inflammatory mediators may enter the brain and trigger seizures. In brain metastases and high-grade tumors, the integrity of the BBB is often severely disrupted, allowing abnormal substances to penetrate the brain's delicate environment and trigger neuronal hyperexcitability.

Metabolic and electrolyte disturbances, often seen in cancer patients, also play a significant role in seizure development. Conditions like hypercalcemia [23], hyponatremia, and hypoglycemia, which are common in advanced cancer, disrupt normal neuronal function and increase the likelihood of seizures. Hypercalcemia, for instance, can lead to altered levels of calcium within neurons, affecting neurotransmitter release and synaptic function. Hyponatremia, often caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in cancer patients, leads to brain cell swelling and altered membrane potentials, which can induce seizures. Similarly, hypoglycemia deprives neurons of their primary energy source, resulting in electrical instability.

The immune response in cancer patients can also contribute to the development of seizures. Paraneoplastic syndromes, which are rare but significant complications of cancer, occur when the immune system mistakenly attacks normal tissues, including the nervous system, as it fights the cancer [24]. In paraneoplastic neurological syndromes (PNS), antibodies or immune cells target neuronal structures, such as ion channels or synaptic proteins, disrupting normal brain function and leading to seizures. These autoimmune processes are more commonly seen in cancers like lung cancer, lymphoma, and ovarian cancer, and can lead to seizures that are difficult to manage without addressing the underlying immune dysfunction.

Chemotherapy and radiation therapy introduce another mechanism of seizure development through neurotoxicity. Many chemotherapeutic agents are neurotoxic, especially those that can cross the BBB, such as cisplatin, methotrexate, and ifosfamide. These agents disrupt neuronal homeostasis by causing DNA damage, oxidative stress, and inflammation in the CNS, leading to seizures in susceptible individuals. Radiation therapy, particularly when directed at the brain, exacerbates this risk by causing cumulative damage to brain tissue and further weakening the BBB. Radiation-induced seizures may occur acutely during treatment or as late-onset effects months or even years after therapy.

Infection-related mechanisms are another important cause of seizures in cancer patients. Cancer patients, especially those receiving immunosuppressive treatments, are at higher risk for infections, including those that affect the CNS. Meningitis, encephalitis, and abscesses can directly damage brain tissue, triggering seizures. Additionally, sepsis and systemic infections can lead to metabolic changes, hypoxia, and inflammation that contribute to seizure development. Infections in cancer patients are often more severe and harder to treat, making seizures an important complication to monitor in this population [25].

Finally, seizures in cancer patients may arise from combined effects of cancer-related psychological and physiological stress. The diagnosis of cancer and the rigorous treatment regimens patients undergo can lead to extreme physical and mental stress. This stress can lower the seizure threshold in vulnerable individuals through neuroendocrine mechanisms. Prolonged stress increases levels of cortisol and other stress hormones, which have been shown to alter neuronal excitability and increase the risk of seizures. Additionally, sleep disturbances, anxiety, and depression, which are common in cancer patients, can further exacerbate this risk by contributing to neurological instability [26].

Current Therapeutic Approaches and Challenges

The management of seizures in cancer patients presents unique challenges, requiring an individualized approach that takes into account the underlying malignancy, treatment-induced complications, and the overall health status of the patient. Therapeutic strategies focus on preventing and controlling seizures, while also addressing the root causes, such as brain metastases or chemotherapy-induced neurotoxicity. Despite advances in both cancer treatment and seizure management, several obstacles remain in optimizing care for this vulnerable population.

One of the primary treatment options for managing seizures in cancer patients is the use of antiepileptic drugs (AEDs). AEDs are the cornerstone of seizure control, helping to reduce neuronal hyperexcitability and prevent further seizure episodes. Commonly used AEDs include levetiracetam, valproic acid, and phenytoin, which are chosen based on their efficacy, safety profile, and potential interactions with chemotherapy. Levetiracetam, in particular, is favored for its minimal drug-drug interactions and relatively low side-effect profile, making it a preferred choice in cancer patients undergoing complex treatments. However, AED selection must be carefully tailored to avoid exacerbating side effects or negatively impacting the efficacy of cancer therapies [27].

A major challenge in the use of AEDs in cancer patients is the potential for drug interactions. Many chemotherapy agents and supportive medications, such as steroids, can alter the metabolism of AEDs, leading to suboptimal drug levels or increased toxicity. For instance, phenytoin, a commonly used AED, is metabolized by the liver's cytochrome P450 system, which can be affected by chemotherapy agents like cyclophosphamide and carbamazepine, leading to unpredictable drug levels. This necessitates close monitoring of AED serum levels and adjustments to dosages as cancer treatment progresses. Managing these interactions is a complex and dynamic process that requires multidisciplinary collaboration between oncologists and neurologists.

In cases where brain metastases or primary brain tumors are the underlying cause of seizures, the treatment strategy often involves direct interventions targeting the tumor. Surgical resection is considered for accessible tumors, especially if the lesion is causing significant mass effect or is refractory to medical management. For smaller or inoperable tumors, radiation therapy, including stereotactic radiosurgery, can help reduce tumor size and control seizure activity. While these treatments aim to reduce tumor burden and mitigate seizure risk, they come with the added challenge of neurotoxicity, which can, paradoxically, increase the risk of seizures, particularly in the short term.

Another therapeutic approach involves addressing metabolic or electrolyte imbalances that contribute to seizure development. Cancer patients, especially those with advanced disease or undergoing aggressive treatments, are prone to disturbances such as hyponatremia, hypercalcemia, and hypoglycemia. Correcting these imbalances through intravenous fluids, electrolyte replacement, or medications to stabilize metabolic function can help reduce the risk of seizures. However, managing these imbalances can be challenging, as they may be exacerbated by cancer treatments, tumor lysis syndrome, or paraneoplastic syndromes, all of which require constant vigilance and adjustment of the treatment plan.

Immunotherapy, a newer class of cancer treatment, introduces another layer of complexity in seizure management. While immunotherapy offers significant promise in treating certain cancers, such as melanoma and lung cancer, it can also trigger immune-related adverse effects, including neurotoxicity. Checkpoint inhibitors like pembrolizumab and nivolumab, for example, can lead to immune-mediated encephalitis or other CNS complications, which can result in seizures. In such cases, managing seizures involves not only the use of AEDs but also immunosuppressive therapies like corticosteroids or intravenous immunoglobulin (IVIG) to control the underlying immune response. However, these immunosuppressive treatments can increase the risk of infections and further complicate the patient's overall condition.

For cancer patients with paraneoplastic syndromes (PNS), which result from immune responses targeting the nervous system, seizure management becomes even more challenging. Paraneoplastic seizures are often resistant to conventional AEDs and may require immunotherapy [28-30], such as corticosteroids, plasmapheresis, or rituximab, to reduce autoimmune activity. These patients often face a prolonged course of therapy, as PNS-related seizures tend to persist despite tumor control. Managing these cases requires a delicate balance between controlling the seizures and addressing the underlying immune response without compromising the patient's cancer treatment.

Additionally, managing seizures in end-stage cancer patients or those receiving palliative care presents unique challenges. In this setting, the focus often shifts from aggressive treatment to symptom control and maintaining quality of life. For these patients, the goal of seizure management is to minimize distress and maximize comfort. This may involve using sedative AEDs, like phenobarbital, which can provide seizure control while also offering a calming effect. However, the challenge lies in balancing seizure control with minimizing sedation, as overly sedative medications can reduce the patient's ability to interact with loved ones or engage in meaningful activities during their remaining time [30-32].

Despite the available treatment options, a significant challenge in managing seizures in cancer patients is the lack of standardized guidelines specifically tailored to this population. Most seizure management protocols are based on general epilepsy guidelines, which do not always account for the unique needs of cancer patients, such as drug interactions, treatment side effects, or the underlying malignancy. As a result, clinicians must rely on individualized care plans, often involving trial-and-error approaches, to find the optimal balance between controlling seizures and managing the cancer itself. Continued research is needed to develop evidence-based guidelines that address the specific challenges faced by cancer patients experiencing seizures [33-35].

The Need for Further Research

The intersection of seizures, cancer, and chemotherapy presents a complex clinical challenge that necessitates further research to enhance our understanding and improve management strategies. Despite advancements in cancer treatment and seizure control, significant gaps remain in our knowledge regarding the prevalence, etiology, and optimal management of seizures in cancer patients. Comprehensive research is essential to develop evidence-based guidelines that can better inform clinical practice and ultimately improve patient outcomes [35-37].

One critical area for future research is the identification of specific risk factors that predispose cancer patients to seizures. While it is known that certain types of tumors, particularly those located in or near the brain, increase the risk of seizure activity, the interplay of other factors [38-40], such as tumor type, stage, and treatment modalities, is not fully understood. Longitudinal studies that evaluate these variables in a diverse cohort of cancer patients can provide valuable insights into the mechanisms underlying seizure development and help identify high-risk populations who may benefit from proactive seizure management.

Moreover, research into the neurotoxic effects of chemotherapy and their relationship to seizure incidence is warranted. Although several chemotherapeutic agents have been implicated in seizure development, the precise mechanisms by which they induce neurotoxicity remain unclear. Investigating the pharmacodynamics and pharmacokinetics of these agents, along with their interactions with AEDs and other medications, can inform clinicians about safer prescribing practices and enhance the effectiveness of seizure prophylaxis in this population. Understanding these interactions may also lead to the identification of protective strategies or adjunct therapies that mitigate the risk of seizures [40-42].

The role of immunotherapy in cancer treatment adds another layer of complexity to the relationship between cancer and seizures. As immunotherapies become increasingly common, understanding their neurotoxic effects and potential to induce seizures is critical. Research that focuses on the incidence and mechanisms of seizure activity in patients receiving immunotherapy can guide clinicians in monitoring and managing these side effects effectively. This includes studies that explore the efficacy of various AEDs in this context, as well as the timing of seizure onset relative to treatment administration [43-45].

Additionally, the management of seizures in cancer patients, particularly those with advanced or metastatic disease, requires exploration of palliative care strategies. While the focus on seizure control is essential, balancing this with overall patient comfort and quality of life presents unique challenges. Research examining the use of sedative AEDs and their impact on patient well-being, cognitive

function, and engagement in daily activities can provide crucial data to inform palliative care protocols. Such studies can also address the ethical considerations of treatment decisions in the context of terminal illness [46-48].

The impact of patient education and caregiver support on seizure management in cancer patients is another important area for research. Investigating how educational interventions can enhance understanding of seizure risk and management among patients and their families may improve adherence to treatment regimens and timely reporting of seizure activity. Furthermore, exploring the effectiveness of support networks and resources available to caregivers can lead to more comprehensive care strategies that encompass both patient and family needs, ultimately improving outcomes [49].

Collaboration between oncologists, neurologists, and researchers is essential for advancing our understanding of seizures in cancer patients. Multidisciplinary studies that encompass various specialties can lead to more holistic approaches in research and treatment. Collaborative efforts may also facilitate the development of standardized guidelines that address the unique challenges faced by this patient population, ensuring that research findings are effectively translated into clinical practice [50].

Finally, investment in research funding and initiatives targeting seizures in cancer patients is crucial for driving progress in this field. Increased funding can support large-scale clinical trials, multicenter studies, and basic research that delves into the biological mechanisms behind seizure development and management. As the incidence of cancer continues to rise globally, prioritizing research in this area will not only enhance our understanding of the complex relationship between cancer and seizures but also ultimately improve the quality of life and survival outcomes for affected patients [51].

Conclusion

The intricate relationship between seizures, cancer, and chemotherapy underscores a pressing need for a deeper understanding and a more comprehensive approach to management in this vulnerable patient population. Seizures in cancer patients can arise from a multitude of factors, including tumor type, location, and the neurotoxic effects of treatment modalities such as chemotherapy and immunotherapy. Recognizing these complexities is crucial for clinicians in order to provide optimal care and improve patient outcomes.

Current therapeutic strategies primarily focus on the use of antiepileptic drugs (AEDs) to manage seizure activity. However, the unique challenges presented by drug interactions, metabolic imbalances, and the side effects of cancer treatments necessitate a tailored approach to each patient's care plan. The variability in response to AEDs among cancer patients highlights the importance of individualized treatment strategies and underscores the need for ongoing monitoring and adjustment based on the evolving clinical picture.

Research is urgently needed to elucidate the underlying mechanisms of seizure development in cancer patients, particularly in relation to the effects of various treatments. Understanding the interplay between different risk factors, neurotoxicities, and patient characteristics will be pivotal in identifying those at higher risk for seizures. Furthermore, investigations into the neurotoxic profiles of newer cancer therapies, including immunotherapies, will be essential as their use becomes more widespread.

Palliative care considerations also play a vital role in managing seizures in advanced cancer patients. The balance between controlling seizures and maintaining quality of life is paramount, necessitating the development of protocols that prioritize patient comfort. Investigating the efficacy of sedative AEDs and the impact of educational interventions for patients and caregivers will further enhance holistic care.

In conclusion, a multidisciplinary approach that fosters collaboration between oncologists, neurologists, and researchers is essential for advancing our understanding of seizures in cancer patients. Continued research efforts, supported by adequate funding and resources, are crucial to develop evidence-based guidelines and innovative therapeutic strategies. By addressing the complexities of this interplay, we

can significantly improve the quality of life and clinical outcomes for cancer patients experiencing seizures, ultimately fostering a more supportive and effective healthcare environment.

References

[1] A Abouchenari.,et al., Advancements in dental implant technology:the impact of smart polymers utilized through 3D printing.,Journal of synthesis and sintering., **2024** 4(2): [Google Scholar], [Publisher], [Crossref]

[2] A Feizy, et al., HER2 expression status and prognostic, diagnostic, and demographic properties of patients with gastric cancer: a single center cohort study from Iran. Asian Pacific journal of cancer prevention: APJCP, **2018**, 19(6), 1721. [Google Scholar], [Publisher], [Crossref]

[3] A Karimi-Moghadam, et al., Parkinson disease from mendelian forms to genetic susceptibility: new molecular insights into the neurodegeneration process. Cellular and molecular neurobiology, **2018**, 38, 1153-1178. [Google Scholar], [Publisher], [Crossref]

[4] AA Esmaeilzadeh, F Nasirzadeh, Investigation of Chemicals on Breast Cancer. Eurasian Journal of Chemical, Medicinal and Petroleum Research., **2024** 1 (5), 51-75 [Google Scholar], [Publisher]

[5] AA Esmaeilzadeh, S Kordjazi, A Salari., A Short Review on the Use of Chemotherapy Drugs in Uterine Cancer., Eurasian Journal of Chemical, Medicinal and Petroleum Research., **2024** 1 (5), 87-96 [Google Scholar], [Publisher]

[6]Amirhossein Jalali et al. Investigation of Cardiopulmonary Complications in Patients with Infection and Prevalence of Intubation in ICU with Radiological Point. Pakistan Heart Journal. **2023** 56 (2): 906-919 [Google Scholar], [Publisher], [Crossref]

[7]Elahe Kebriyaei et al . Knowledge and Practice of Iranian Dentists Regarding Post Space Preparation and Coronal Reconstruction of Endodontically Treated Teeth. Jundishapur Journal of Health Sciences. **2024**, 6(4): e147990 [Google Scholar], [Publisher], [Crossref]

[8]Ezatollah Jalalian et al . Occlusal splints in the treatment of temporomandibular disorders: A narrative review study. Journal of Dental Medicine Tehran University of Medical Sciences. **2024**, 37(5): 1-8 [Google Scholar], [Publisher], [Crossref]

[9]F Beiranvandi et al. Systematic investigation of cardio vascular & clinical problem in patients with covid-19 with Neurological and Pathological point. The seybold Report Journal. **2023** 18(4): 1634-1653 [Google Scholar], [Publisher], [Crossref]

[10] H Kaseb Ghane et al., Power Laser Application for Immediate Implant Placement in Infected Sites: A Systematic Review, Photo-biomodulation, Photomedicine, and Laser Surgery, **2024** 41, 12 [Google Scholar], [Publisher], [Crossref]

[11] K Hadavand Mirzaei, et al., Application of Robotic Instruments in Hip Arthroplasty Surgery Based on Practical Tips a Systematic Review, Eurasian Journal of Chemical, Medicinal and Petroleum Research, **2024**, 3 (2), 593-609 [Google Scholar], [Publisher], [Crossref]

[12] K Hadavand Mirzaei.,et al. Medical care of infection patients undergoing weight loss surgery and laparascopy,relying on cardio-pulmonary & Neurological care: A systematic review.,International Neurology Journal., 2024 28(2):74-83 [Google Scholar], [Publisher], [Crossref]

[13] K Hadavand Mizaei et al. Application of Robotic Instruments in Hip Arthroplasty surgery based on practical Tips: A systematic Review , Eurasian journal of chemical, medical and petroleum Research. **2024** 3(2): 593-609 [Google Scholar], [Publisher], [Crossref]

[14] K Hashemzadeh et al., Effects of interval training on post-coronary artery bypass grafting hemodynamic indices. **2020** [Google Scholar], [Publisher]

[15] K Saadati, et al., A study on comparison of overall survival and disease-free survival among gastric cancer patients treated with two adjuvant and neoadjuvant methods. Journal of Medicine and Life, **2015**, 8(4), 186. [Google Scholar], [Publisher]

[16] M Amiri-Shoar, et al., Comparative proteomic analysis of breast cancer tissue and the adjacent normal tissue in Iranian patients with HER2 negative ductal carcinoma of breast. International Journal of Cancer Management, **2017**, 10(5). [Google Scholar], [Publisher], [Crossref]

[17] M Dashti.,et al.Advancement and Application of Deep Learning on Detection of peri-Implantitis,a Narrative Review.,Journal of Advances in Arfificial Intelligence and Machine Learning;2024 Review 4(2):2290-2301 [Google Scholar], [Publisher], [Crossref]
[18] M Jafari, KH Mirzaei, M Shojaei, M Saboury., A Systematic Review: The Relation Between Vitamin D and Short Chain Fatty Acid in Serum Plasma with Protein Recombination in VDR in Multiple Sclerosis Patients (MS)., Eurasian Journal of Chemical, Medicinal and Petroleum Research., **2024** 3 (3), 819-840 [Google Scholar], [Publisher]
[19] M Jafari, M Saboury, M Shojaei, KH Mirzaei., Methylation and Demethylation Gene Pathway Bio Chemistry Signaling in Fat and Athlete Adults with Point of Dopaminergic Points, Eurasian Journal of Chemical, Medicinal and Petroleum Research., **2024** 3 (3), 841-861 [Google Scholar], [Publisher]
[20] M Lak et al. Evaluation of the Relationship between Neurological and Cardiovascular Diseases in Adults and Children with Infection and HTN Basen on pharmacological points. International Neurourology Journal. **2024** 28(1): 821-832 [Google Scholar], [Publisher]
[21] M Shabani, M., et al., Life skills training effectiveness on non-metastatic breast cancer mental health: a clinical trial. Iranian Red Crescent Medical Journal, **2024**, 16(1). [Google Scholar], [Publisher]
[22] M Shojaei. Alternative Systematic Review of Insulin Resistance and the Role of Sex Steroids on Leptin Levels. Eurasian Journal of Chemical, Medicinal and Petroleum Research **2024** 3(1): 296-306 [Google Scholar], [Publisher], [Crossref]
[23] M Shojaei. CHAT-GPT and artificial intelligence in Medical Endocrine System and interventions. Eurasian Journal of Chemical, Medicinal and Petroleum Research., **2024** 3(1): 197-209[Google Scholar], [Publisher], [Crossref]
[24] M Shojaei. Leptin as a Surrogate Marker of Insulin Resistance. **2024** 1: 124 [Google Scholar], [Publisher]
[25] Mahmood Anaraki Robati et al. Effect of Repeated Microwave Disinfection on Surface Hardness and Dimensional Accuracy of Two Dental Stone Materials.Journal of Advances in Bioscience & Clinical Medicine. **2014**, 3(1): 17-24 [Google Scholar], [Publisher], [Crossref]
[26] Majid Khalilizad et al. Imaging Methods Applicable in the Diagnostics of Alzheimers Disease, Considering the Involvement of Insulin Resistance with Clinical Pharmacological Point. Pakistan Heart Journal. **2023** 56(3) [Google Scholar], [Publisher], [Crossref]
[27] Mfonido Ekong et al. From the Intensive Care Unit to Recovery: Managing Post-intensive Care Syndrome in Critically Ill Patients. Cureus.**2024**; 16(5) [Google Scholar], [Publisher]
[28] MK Gol., & A Davoud., Checklist for Determining Severity of Pain and Type and Dosage of Analgesics Administered to Women s Patient Undergoing Breast Surgeries. International Journal of Women's Health and Reproduction Sciences, **2020**, 8(2), 227-31. [Google Scholar], [Publisher], [Crossref]
[29] MK Gol., et al., Relationship between procrastination and optimism in undergraduate nursing students of medical sciences universities of Northwest Iran-1397. **2018**, [Google Scholar], [Publisher]
[30] R Dargahi, et al., Does coronavirus disease affect sleep disorders in the third trimester of pregnancy in women with low back pain. International Journal of Women's Health and Reproduction Sciences, **2021**, 9(4), 268-273. [Google Scholar], [Publisher], [Crossref]
[31] R Mohammadian, et al., Angioplasty and stenting of symptomatic vertebral artery stenosis clinical and angiographic follow-up of 206 cases from Northwest Iran. The neuroradiology journal, **2013**, 26(4), 454-463. [Google Scholar], [Publisher], [Crossref]
[32] R Rikhtegar, et al., Stem cell-based cell therapy for neuroprotection in stroke: A review. Journal of cellular biochemistry, **2019**, 120(6), 8849-8862. [Google Scholar], [Publisher], [Crossref]
[33] Renee Scott-Emuakpor et al. Mammary Paget's Disease Mimicking Benign and Malignant Dermatological Conditions: Clinical Challenges and Diagnostic Considerations. Cureus.**2024**; 16(7)[Google Scholar], [Publisher]
[34] S Abdollahi Fakhim., et al., Comparison of two-flap palatoplasty plus intravelar veloplasty technique with and without double-layer Z-plasty on the soft palate length in children with cleft palate. Oral Maxillofac Surg.

2020;24(4):495-9. Epub 2020/07/13. PubMed PMID: 32653995. [Google Scholar], [Publisher], [Crossref]

[35] S Abdollahi Fakhim., et al., Effects of phenytoin spray in prevention of fistula formation following cleft palate repair. Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery. **2019**;47(12):1887-90. Epub 2019/12/10. PubMed PMID: 31812307. [Google Scholar], [Publisher], [Crossref]

[36] S Abdollahi Fakhim., et al., Prevalence of Associated Anomalies in Cleft Lip and/or Palate Patients. Iranian journal of otorhinolaryngology. **2016**;28(85):135-9. Epub 2016/06/10. PubMed PMID: 27280100; PubMed Central PMCID: PMCPMC4881882. [Google Scholar], [Publisher], [Crossref]

[37] S Abdollahifakhim et al., Severe and Life-Threatening Paroxysmal Laryngospasm: Uncommon Presentation of COVID-19. Anesth Pain Med. **2023**;13(1):e130926. Epub 2023/07/25. PubMed PMID: 37489167; PubMed Central PMCID: PMCPMC10363359. [Google Scholar], [Publisher], [Crossref]

[38] S Amiri., et al., Effect of adenotonsillectomy on ADHD symptoms of children with adenotonsillar hypertrophy and sleep disordered breathing. Int J Pediatr Otorhinolaryngol. **2015**;79(8):1213-7. [Google Scholar], [Publisher], [Crossref]

[39] S Fakhari, et al., Comparing the effect of hypotension treatment due to spinal anesthesia with ephedrine or phenylephrine on arterial blood gases and neonatal Apgar score during cesarean delivery in obese mothers: Randomized clinical trial. The Iranian Journal of Obstetrics, Gynecology and Infertility, **2019**, 22(10), 12-20. [Google Scholar], [Publisher], [Crossref]

[40] S Hassani et al. Investigation of medical services in patients with diabetes,cardio-vascular and Rheumatology disease in ICU. Journal of pharmaceutical Negative Results. **2022** 13(10): 4137-4158 [Google Scholar], [Publisher], [Crossref]

[41] S Saedi, et al., Assessed the Complication of Central Nervous System in COVID-19 Patients: A Systematic Review and Meta-Analysis., Eurasian Journal of Science and Technology., **2021** 2: 185 [Google Scholar], [Publisher]

[42] S Saedi, et al., Epidemiological Study of Breast Cancer in Iran: A Micro Review Study., Eurasian Journal of Science and Technology., **2022** 2 (3):227-235 [Google Scholar], [Publisher], [Crossref]

[43] S Sayad et al. comprehensive evaluation of radiation oncology,medical and nursing care treatment in women with breast cancer based on sonographic and radiological points.Pakistan heart journal. **2024** 57(1) [Google Scholar], [Publisher]

[44] S Sayad et al., A comprehensive investigation of radio-oncology in breast cancer patients based on psychological and radiological problems in these patients., Pak Heart J.**2024** 57(01):237-241[Google Scholar], [Publisher], [Crossref]

[45] S Sayad.,et al.comprehensive evaluation of radiation oncology, Medical and Nursing care treatment in women with breast cancer based onsonographic and radiological points.,Pak Heart J.**2024** 57(01):251-255[Google Scholar], [Publisher], [Crossref]

[46] S Reza-Soltani et al. The Role of Artificial Intelligence and Machine Learning in Cardiovascular Imaging and Diagnosis. Cureus. **2024**; 16(9)[Google Scholar], [Publisher]

[47] Sh Mahboubi et al . Comparison the Dimensions of Maxillary Anterior Teeth to Golden Standard in Men and Women of an Iranian Population. Journal of Isfahan Dental School. **2024**, 19(4): 273-80 [Google Scholar], [Publisher], [Crossref]

[48] Sh Mahboubi et al . The prevalence of direct and indirect sequelae of conventional complete dentures in an Iranian population. EurAsian Journal of BioSciences. **2020**, 14(2): 6705-6711 [Google Scholar], [Publisher], [Crossref]

[49] Sh Mahboubi et al. Relationship between Personality Traits and Psychological Components with Job Burnout among Dentists: A descriptive-correlational study.Journal of Razi Journal of Medical Sciences. **2023**, 30(5): 95-107 [Google Scholar], [Publisher], [Crossref]

[50] Sh Mahboubi. Full Mouth Reconstruction in a Patient with Severely Worn Dentition by Restoring the Vertical Dimension of Occlusion: A Case Report.Journal of Revista Latinoamericana de Hipertensión. **2018**, 13(6): 544-546 [Google Scholar], [Publisher], [Crossref]

[51] V Tajiknia et al. Role of MRI in Preoperative Assessment of patients with Advanced ovarian cancer candidate for cytoreductive surgery, A Brief Review.Journal of Obstetrics Gynecology and Reproductive Sciences. 2021 5 (6) [Google Scholar], [Publisher], [Crossref]