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Brain Metastases: Palliative and Supportive Care for Patients

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Abstract

Brain metastases (BMs), occurring in 10-30% of cancer patients, pose significant treatment challenges due to their complex nature, heterogeneity, and the limitations of crossing the blood-brain barrier (BBB). Lung, breast, melanoma, and renal cell carcinoma cancers are the most common sources. Palliative care for BMs focuses on improving patient quality of life by managing symptoms such as headaches, seizures, and cognitive impairments. Treatment approaches include surgery, radiation, and systemic therapies like chemotherapy, immunotherapy, and targeted medications, with a focus on individualized care to optimize quality of life (QOL) and survival. Imaging techniques such as MRI and neurocognitive evaluations play crucial roles in diagnosis and treatment planning. Symptom management, including controlling cerebral edema, seizures, and pain, is critical in palliative settings to enhance patient well-being. Advances in therapies and supportive care provide better management options, although long-term survival remains poor for many patients.

INTRODUCTION

OVERVIEW OF BRAIN METASTASES

Brain metastases (BMs) are tumors that originate from cancer cells that have spread to the brain from other parts of the body (Lin, 2012) and occur in approximately 10% to 30% of patients with cancer. Specifically, lung cancer patients have the highest risk, with brain metastases being found in up to 40% of such cases. For breast cancer patients, the incidence can range from 20% to 30%, while melanoma and renal cell carcinoma also contribute significantly to the prevalence of brain metastases, with varying rates depending on disease progression and other factors (Lin, 2012). BMs are the most frequent type of intracranial tumors in adults and can develop in various areas such as the brain tissue, leptomeninges, dura mater, and skull (Gavrilovic, 2005).

The primary cancers most commonly leading to brain metastases include lung cancer, breast cancer, colorectal cancer, melanoma, and renal cell carcinoma. These types of cancer are particularly prone to spreading to the brain, making them the most frequent sources of secondary brain tumors.

IMPORTANCE OF PALLIATIVE AND SUPPORTIVE CARE

Palliative care plays a crucial role in the management of brain metastases, focusing on improving patients' quality of life by addressing a range of needs. This approach involves effective symptom management, which includes alleviating issues such as headaches, seizures, nausea, and cognitive impairment. Pain control is another key aspect, with the use of medications and interventions to manage pain associated with brain metastases and its treatments. Additionally, palliative care provides essential psychosocial support, helping patients cope with emotional and psychological challenges, including anxiety and depression. Finally, it ensures coordination of care, facilitating seamless communication among healthcare providers to address the comprehensive needs of patients and their families. This integrated approach is vital for enhancing patient well-being and managing the complex symptoms associated with brain metastases (Km, 2001; Taillibert, 2005).

Treating brain metastases involves several significant challenges due to the complex nature of the condition and the unique characteristics of the brain. One major issue is the heterogeneity of tumors. Brain metastases can arise from various primary cancers, each with distinct biological behaviors and treatment responses, making a standardized approach difficult (Suh, 2020).

Additionally, the blood-brain barrier (BBB) presents a substantial obstacle, as it limits the effectiveness of many systemic treatments, including chemotherapy and targeted therapies, by preventing them from reaching the brain (Wilhelm, 2013). For treatments that can cross the BBB, such as radiation and certain chemotherapeutic agents, there is a risk of neurotoxicity, which can lead to cognitive and neurological side

effects (Dropcho, 2010). Furthermore, managing symptoms such as seizures, cognitive impairments, and increased intracranial pressure requires a multidisciplinary approach and careful balancing with the effectiveness of cancer treatments (Lauko, 2020). Finally, the need for individualized treatment plans is essential. Treatment must be tailored to each patient based on the type and location of the metastases, the primary cancer, and the overall health of the patient.

PATHOPHYSIOLOGY OF BRAIN METASTASES

CLINICAL PRESENTATION AND SYMPTOMS

For brain metastases that are left untreated, the median survival rate can be as short as one month (Langer, 2005). Some brain metastases are asymptomatic, while others cause symptoms typical of any intracranial space-occupying lesion due to brain compression and mass effect. Patients with brain metastases may experience headaches, seizures, cognitive decline, fatigue, and focal neurological deficits (Noh, 2018).

Headaches, which may be mild, are a symptom in up to 50% of patients with brain metastases, particularly those with multiple lesions or metastases in the posterior fossa. Papilledema, or optic disc swelling, is associated with headaches in about 15-25% of these

patients. Up to 40% present with focal neurological deficits like weakness or numbness, while seizures occur in 15-20% of cases. Additionally, 5-10% of patients have a sudden "stroke-like" onset of symptoms due to intratumoral hemorrhage, especially in tumors prone to bleeding, such as melanoma and renal cell carcinoma. Cognitive impairment or altered mental status is also frequent in patients with multiple metastases or increased intracranial pressure from mass effect, vasogenic edema, or changes in cerebrospinal fluid flow (Achrol, 2019).

Brain metastases can greatly affect a patient's daily functioning and overall prognosis. The development of these secondary tumors in the brain often results in neurological and cognitive impairments that can significantly interfere with everyday activities. As these impairments progress, patients may struggle to maintain their independence and require additional care and support. This decline in function not only diminishes the patient's ability to perform daily tasks but also negatively impacts their quality of life and overall autonomy.

Prognostically, the presence of brain metastases typically indicates a more advanced stage of cancer, often associated with a poorer overall outcome. The median survival for patients with brain metastases varies widely depending on factors such as the number and location of metastases, the type of primary cancer, the patient’s overall health, and the treatments received (Sperduto, 2013). The most common favorable clinical prognostic factors for brain metastases include a high Karnofsky Performance Status score (≥70), lower Recursive Partitioning Analysis (RPA) classes (I or II), absence of extracranial disease, and a low number of brain metastases (fewer than 2) (Mege, 2018).

DIAGNOSTIC APPROACHES

IMAGING TECHNIQUES

Advanced neuroimaging techniques can detect brain lesions, but they lack the specificity needed for a definitive diagnosis. Consequently, histopathological analysis of tissue obtained during surgical resection remains the gold standard for confirming the diagnosis (Usinskiene, 2016). Each imaging modality – MRI, CT, and PET scans – plays a specific role in identifying and characterizing these secondary brain tumors.

MRI is the preferred imaging technique for detecting brain metastases because of its superior contrast resolution and ability to provide detailed visualization of soft tissues. With the use of contrast enhancement, such as gadolinium, MRI is highly sensitive to detecting brain metastases, including small lesions and those located in challenging areas like the posterior fossa or near the skull base. This makes MRI especially useful for assessing the extent of metastatic disease, monitoring treatment response, and detecting recurrence (Sze, 1990). MRI excels at providing detailed anatomical images of brain metastases. On T1-weighted images, parenchymal metastases usually appear iso- to hypointense compared to the brain, and they can vary in intensity on T2-weighted images. These metastases generally have a roughly spherical shape. They are often accompanied by vasogenic edema, which appears as high signal on T2-weighted images and low signal on T1-weighted images. The edema can be extensive relative to the size of the tumor and is typically

confined to the white matter, leaving the overlying cortex relatively unaffected. If the cortex is involved, it may indicate the presence of other conditions, such as a primary brain tumor (Pope, 2018).

Advanced neuroimaging techniques are becoming more prevalent in the clinical assessment of brain metastases. Diffusion-weighted (DW)-MRI is particularly useful for evaluating ring-enhancing cerebral lesions. Diffusion is typically markedly restricted in abscesses, whereas it is less restricted in brain metastases, although regions of hypercellularity within tumors may show some diffusion restriction compared to normal brain tissue (Sparacia, 2016).

NEUROLOGICAL ASSESSMENT

Neurological assessment of brain metastases involves a thorough examination and the use of scoring systems to evaluate the impact of the disease on a patient's functional status and overall well-being. Key components of this assessment include neurological examinations and performance status scoring systems such as the Karnofsky Performance Status (KPS) and the Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG-RPA) classification.

Neurological Examination includes a comprehensive evaluation of motor function, sensory perception, cognitive abilities, and other neurological parameters. The examination helps in assessing the extent of neurological impairment caused by brain metastases and guides treatment decisions (Parsons, 2021).

The KPS is a widely used scoring system that evaluates a patient's functional status based on their ability to carry out daily activities. Scores range from 0 to 100, with higher scores indicating better performance and functionality. This scale helps in assessing the impact of brain metastases on a patient's quality of life and predicting prognosis (Timmermann, 2013). By evaluating a patient's performance status, the KPS helps clinicians gauge the impact of brain metastases on daily living, which is crucial for tailoring treatment plans and predicting patient outcomes. It also serves as a key component in various prognostic models and clinical trials, aiding in the stratification of patients based on their functional capabilities.

Neurological cognitive function (NCF) deficits are observed in 90% of patients with supratentorial brain tumors at different stages of their disease. Monitoring NCF in patients with brain tumors presents challenges due to the numerous neurological and medical issues that need attention during brief clinical visits. Brief screening tools, such as the Mini-Mental State Examination and the Montreal Cognitive Assessment, have limited sensitivity to subtle but significant changes in NCF experienced by these patients (Meyers, 2003). The gold standard for assessing NCF is a comprehensive neuropsychological evaluation. Multidisciplinary brain tumor clinics increasingly include neuropsychologists as part of the care team, providing access to detailed assessments. Neuropsychological evaluations may be abbreviated and tailored to individual needs and functioning levels but remain effective in detecting cognitive changes before they appear on brain imaging. These evaluations are also prognostic of overall and progression-free survival. Integrating neuropsychological assessments at key points in patient care helps guide treatment decisions and address multifaceted aspects of brain tumor management (Romero-Garcia, 2022).

Preoperative NCF assessments can be integrated with neurosurgical procedures to predict and minimize cognitive morbidity. Functional MRI and intraoperative mapping can benefit from preoperative cognitive evaluations, helping to identify issues that may affect mapping and predict the risk of cognitive decline post-surgery. For instance, patients with tumors involving the left temporal lobe who have no preoperative deficits in language and verbal memory may face a higher risk of surgically induced deficits in these areas (Kelm, 2017; Bookheimer, 2007).

Postoperative NCF evaluations are crucial for identifying subacute deficits that may benefit from treatment. The timing of these evaluations depends on individual patient needs, with assessments typically occurring after a recovery period. These evaluations help in identifying specific cognitive issues that may require outpatient treatment and are useful for planning support related to daily living activities and return to work (Bernstein, 1995).

TREATMENT MODALITIES

Current treatment strategies for brain metastases often involve a combination of modalities, including surgery, radiation therapy, chemotherapy, immunotherapy, and targeted medications. The choice of treatment depends on various factors, such as the size, location, number, and histopathology of the metastases, as

well as the characteristics of the primary tumor and any prior anticancer therapies. Surgery may be used for tissue diagnosis, cerebral decompression, and to extend survival when combined with adjuvant radiotherapy in select cases. Alternatively, radiotherapy can be used alone, and systemic therapies are often employed as well (Suh, 2020).

Despite the challenge of achieving curative outcomes in most cases of brain metastases, the goal is to tailor treatment plans to each patient to optimize quality of life (QOL) and overall survival. Increasingly, treatment decisions take into account factors such as anticipated survival, competing risks, and long-term toxicities, aiming to balance efficacy with the impact on the patient's long-term well-being.

According to the American Society for Radiation Oncology (ASTRO) guidelines, the management of brain metastases involves a multidisciplinary approach that emphasizes individualized care based on the patient's clinical status and tumor characteristics (Vogelbaum, 2022). In the management of brain metastases, stereotactic radiosurgery (SRS) is strongly recommended for patients with limited brain metastases and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. SRS provides precise, targeted treatment, reducing the risk of damage to surrounding healthy tissue, and is particularly effective for small- to medium-sized tumors. For patients with symptomatic brain metastases, immediate local therapy, such as SRS or surgical resection, is strongly recommended to alleviate symptoms and prevent further neurological deterioration.

Multidisciplinary discussion involving neurosurgeons is conditionally recommended for patients with tumors larger than 4 cm or those causing significant mass effect, as surgical resection may be necessary to relieve pressure within the brain. For asymptomatic patients eligible for systemic therapies targeting the central nervous system, a collaborative, patient-centered approach is advised to determine whether local therapies can be safely deferred, balancing the risks and benefits of intervention.

For patients who have undergone surgical resection of brain metastases, SRS is also recommended to enhance local control and reduce recurrence rates. Additionally, for those with a better prognosis undergoing whole-brain radiation therapy (WBRT), hippocampal avoidance (HA) and the use of memantine are strongly suggested to preserve cognitive function. On the other hand, for patients with poor prognosis, early palliative care is crucial for symptom management and providing support to caregivers. This ensures a better quality of life during advanced stages of disease progression Figures 1 and 2 are treatment algorithms based on the ASTRO Clinical Practice Guideline.

SURGICAL INTERVENTIONS

For patients with isolated, sizable, and surgically accessible brain metastases, neurosurgical resection is often the standard treatment approach. The primary advantage of surgery is its ability to rapidly alleviate symptoms. For patients with multiple brain lesions, if one dominant lesion causes a significant mass effect that threatens life or severely impacts quality of life, surgical intervention becomes a crucial component of treatment (Vogelbaum, 2022). One of the primary palliative roles of surgery is the alleviation of symptoms caused by brain metastases. These symptoms include headaches, seizures, cognitive impairments, and focal neurological deficits. By removing or reducing the size of a tumor, surgery can often provide significant and rapid relief from these symptoms, leading to improved functionality and comfort for the patient. For many patients, surgery can remarkably enhance the quality of life. By addressing the most symptomatic or life-threatening lesions, surgery can help restore the patient’s ability to perform daily activities and improve their overall functionality (Hatiboglu, 2013).

RADIATION THERAPY

Whole-brain radiation therapy (WBRT) has been the most commonly employed treatment for patients with multiple brain metastases due to its effectiveness in providing palliative care and its widespread availa-bility (Gao, 2015). By targeting the entire brain, WBRT helps manage multiple lesions simultaneously, which can lead to improved overall functional outcomes. This is particularly important for patients with widespread brain metastases who may otherwise experience progressive neurological decline. WBRT is used to control disease progression by targeting both visible and microscopic metastases throughout the brain. This broad treatment approach helps manage the disease more effectively when metastases are numerous and dispersed, reducing the risk of further neurological complications. The overall goal of WBRT in palliative care is to enhance the patients’ quality of life. By managing symptoms, controlling disease progression,

and preventing further decline, WBRT can contribute to a more comfortable and stable condition for patients facing advanced brain metastases (Dyer, 2014).

In recent years, as the cognitive side effects of whole-brain radiation therapy (WBRT) have become more apparent, stereotactic radiosurgery (SRS) has gained preference for treating patients with a small number of brain metastases (Brown, 2020). Acute side effects of WBRT typically include temporary hair loss, mild skin irritation, and fatigue, with less common side effects such as ear infections. High doses of radiation to the left hippocampus can lead to significant issues with verbal learning and memory. Additionally, radiation targeting the left hippocampus and other left-sided brain areas can impair verbal fluency, executive function, and processing speed, while radiation to the thalamus can also affect processing speed and executive function (Haldbo-Classen, 2020). SRS allows for precise, targeted treatment to the individual metastases in a single session, leading to significantly lower levels of cognitive dysfunction and fatigue compared to WBRT.

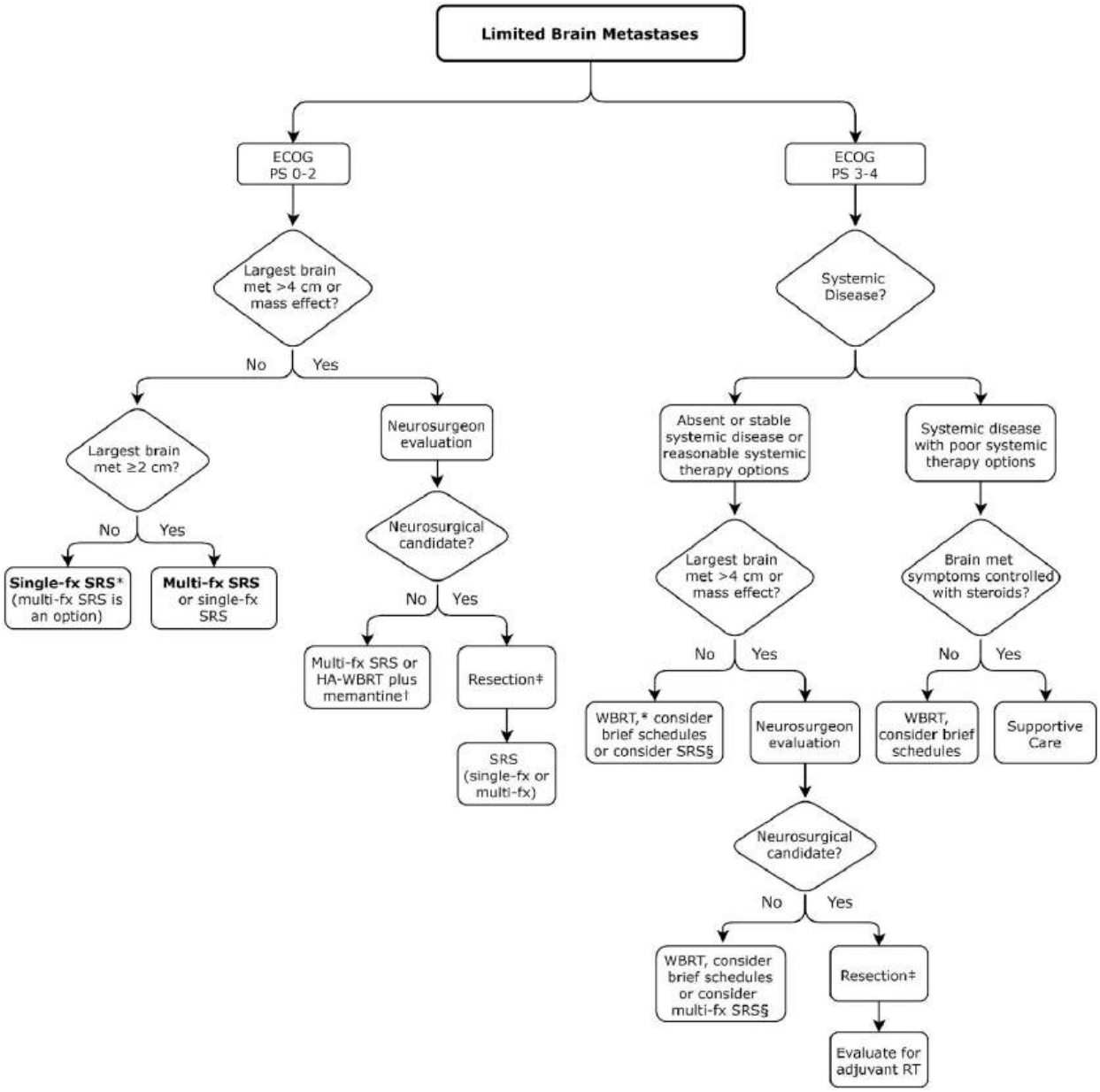

Figure 1. Treatment algorithm for limited BMs (Vogelbaum, 2022)

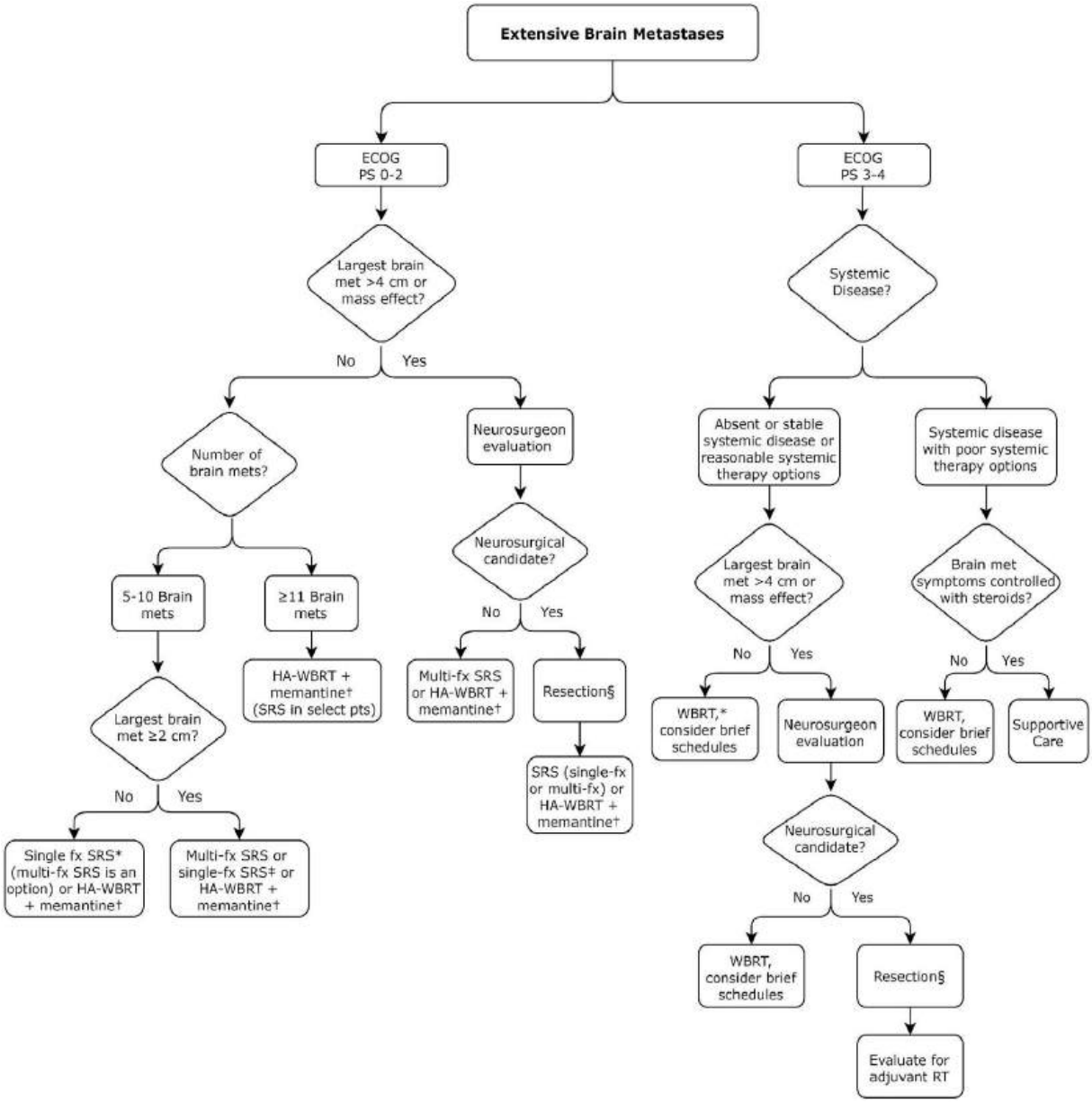

Figure 2. Treatment algorithm for extensive BMs (25)

SYSTEMIC THERAPIES

The role of chemotherapy in treating brain metastases has traditionally been limited due to the blood-brain barrier, which restricts the ability of many chemotherapeutic agents to reach effective doses within the brain (Arvanitis, 2020). However, certain chemotherapy drugs, like temozolomide and platinum-based agents, have shown some efficacy in treating brain metastases, particularly in combination with radiation therapy (Tian, 2017). Also anti-VEGF antibody bevacizumab has been utilized in combination with the HER2 inhibitors trastuzumab and lapatinib in a murine model of HER2-amplified breast cancer brain metastases (Tian, 2017). Chemotherapy is often considered for patients with brain metastases with systemic disease that is also responsive to chemotherapy, providing a dual benefit for both intracranial and extra-cranial disease control.

Targeted therapies have become increasingly more important in the treatment of brain metastases, especially for tumors expressing specific genetic mutations or alterations. Agents such as tyrosine kinase inhibitors (e.g., erlotinib, gefitinib for EGFR mutations in non-small cell lung cancer) and BRAF inhibitors have shown the ability to penetrate the blood-brain barrier and achieve meaningful intracranial responses (Long, 2012). These therapies offer a more focused approach, selectively targeting cancer cells with specific genetic alterations, which can lead to better outcomes and fewer side effects compared to traditional chemotherapy.

Immunotherapy, particularly immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab), has emerged as a promising option for treating brain metastases. Like targeted therapies, these treatments were initially tested in late-stage or previously treated patients. However, new data are now showing their significant potential for the long-term management of brain metastases. These therapies work by enhancing the body's immune response against cancer cells, including those in the brain (Di Giacomo, 2019). Immune checkpoint inhibitors, specifically those targeting surface proteins such as CTLA4 (ipilimumab) and PD-1 (pembrolizumab and nivolumab), as well as anti-PD-L1 agents (atezolizumab), have been developed and tested in patients with brain metastases from lung cancer (both NSCLC and SCLC) and melanoma (Berghoff, 2016). Immunotherapy's effectiveness in treating brain metastases is influenced by factors such as tumor type, genetic profile, and the presence of biomarkers like PD-L1 expression. These therapies can be used alone or in combination with treatments like radiation to improve outcomes and extend survival in patients with brain metastases. The choice of immunotherapy and its success rate can vary depending on the specific characteristics of the metastases and the patient's overall health condition (Zhou, 2023).

PALLIATIVE MANAGEMENT OF SYMPTOMS LIKE EDEMA, PAIN, AND SEIZURES.

SEIZURES

Seizures are a common symptom in patients with brain tumors, with their occurrence largely depending on the type of tumor. The incidence of seizures ranges from approximately 15% to 30% in those with brain metastases, while up to 80% of patients with grade 2 gliomas may experience seizures throughout their disease progression (Chan, 2017). Seizures appear especially in patients with multiple metastases (https://jnnp.bmj.com/content/78/4/342, 2024). Current guidelines advise against using antiseizure drugs (ASDs) as primary prophylaxis (Walbert, 2021). After a first seizure, non-enzyme-inducing ASDs are recommended due to fewer drug interactions (https://pubmed.ncbi.nlm.nih.gov/33293629, 2024). Levetiracetam is commonly used as the first-line ASD in brain tumor patients (Van der Meer, 2022). It has shown high efficacy in glioma patients, outperforming valproic acid in a large study, though it often causes psychiatric side effects. For patients with uncontrolled seizures, combining ASDs with different mechanisms is advised (St Louis, 2009). In the end-of-life phase, seizures often increase in frequency and are a common cause of hospitalization. Seizure medications should be maintained, and for patients with swallowing difficulties, alternatives such as oral solutions, subcutaneous levetiracetam, buccal clonazepam, or intranasal or subcutaneous midazolam can be considered (Koekkoek, 2016).

PAIN AND HEADACHES

Pain and headaches are common and significant symptoms in patients with brain metastases, particularly in the palliative care setting. These symptoms can result from tumor growth, increased intracranial pressure, and inflammation. Approximately 4%–62% patients with brain tumors are being affected (Walbert, 2014). Effective management of these symptoms is crucial for improving the quality of life in these patients .

Pain management is multimodal and follows a similar approach to that used for patients with systemic cancers, incorporating the World Health Organization's three-step analgesic ladder (Walbert, 2014). Neuropathic agents such as gabapentin and duloxetine should be continued as long as the patient can tolerate oral tablets. If swallowing becomes difficult, transitioning to liquid forms of these medications is recommended. As the disease progresses and oral intake becomes further compromised, liquid opioids, such as morphine, hydromorphone, or fentanyl, are commonly used. These opioids are selected based on patient tolerance and provider preference, with a combination of long-acting and short-acting agents often employed to manage both background and breakthrough pain (Sharma, 2021). It is important to avoid morphine in patients with renal failure, even for short-term use, due to the risk of accumulation and toxicity. In cases where the patient has both liver and renal failure, fentanyl is considered the most appropriate option because of its safer profile in these conditions.

INCREASED INTRACRANIAL PRESSURE. CEREBRAL EDEMA

Brain tumors and their treatments can compromise the blood-brain barrier, leading to the leakage of plasma fluid and proteins into the brain tissue, which causes vasogenic edema. This edema can result in increased intracranial pressure, contributing to significant morbidity in affected patients. The consequences of cerebral edema include various symptoms such as focal neurological deficits, seizures, nausea, vomiting, and headaches, all of which severely impact the patient's quality of life (Wick, 2004). Corticosteroids are commonly used

to treat cerebral edema, with dexamethasone being the preferred choice in neuro-oncology due to its high potency, long half-life, and minimal mineralocorticoid effects. However, prolonged use of dexamethasone can lead to significant adverse effects, including adrenal insufficiency, diabetes, immune suppression with an increased risk of opportunistic infections, myopathy, and neuropsychiatric issues. Therefore, its use should be minimized whenever possible (Dietrich, 2011). Temporary relief from acute symptoms can be achieved by techniques like lumbar puncture or external ventricular drainage, which reduce pressure by diverting CSF. For more chronic or recurrent cases, where long-term control of CSF buildup is needed, a ventriculoperitoneal (VP) shunt may be implanted. This surgical procedure involves placing a catheter into the brain's ventricles to divert excess CSF to the peritoneal cavity, providing sustained relief from hydrocephalus and preventing further neurological damage (Bander, 2021).

VP shunting offers a more permanent solution to symptomatic hydrocephalus by effectively managing the accumulation of CSF and restoring normal pressure dynamics in the brain. This can lead to improvements in both neurological function and overall quality of life for patients who are suffering from CSF-related complications. The procedure is especially beneficial in cases where other interventions fail to provide long-lasting relief (Bander, 2021).

NAUSEA

Managing nausea in patients with brain metastases involves several pharmacological options, each with specific benefits and potential side effects. Disintegrating ondansetron, at doses of 4–8 mg every 8 hours, is often the preferred choice due to its effectiveness, though it may cause constipation and headaches. Metoclopramide, dosed at 5–10 mg every 6 hours as needed, is particularly useful in patients with gastro-paresis, but it carries a risk of extrapyramidal side effects. Prochlorperazine and promethazine, dosed similarly at 5–10 mg and 6.25–12.5 mg respectively, are from comparable drug classes and offer alternative anti-emetic options. Additionally, lorazepam and olanzapine also have anti-emetic properties and can be considered in treatment plans. While liquid formulations are not available, orally disintegrating tablets (ODT) can be administered by placing them in the buccal mucosa for absorption, providing a practical alternative for patients who have difficulty swallowing (Sharma, 2021).

CONCLUSIONS

Brain metastases are a prevalent and severe complication in cancer patients, significantly impacting prognosis and quality of life. Effective management of brain metastases requires a multidisciplinary approach focused on palliative care to alleviate symptoms, including headaches, seizures, and cognitive impairments. Despite advancements in imaging, surgical interventions, radiation therapy, and the development of systemic therapies like immunotherapy and targeted treatments, the blood-brain barrier remains a critical challenge in delivering effective treatment.

While emerging therapies and personalized treatment plans offer hope for extending survival and improving patient outcomes, the prognosis for patients with brain metastases generally remains poor. Palliative care plays a vital role in maintaining patient comfort, addressing psychosocial needs, and improving overall quality of life. Ongoing research is necessary to further understand the biological mechanisms of brain metastases and to develop more effective therapies that can cross the blood-brain barrier, manage symptoms, and ultimately enhance survival rates.

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Polypharmacy in patients with terminal stage of cancer during palliative care

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ABSTRACT

This study reviewed the latest literature on polypharmacy as a therapeutic problem in palliative patients in the terminal stage of cancer. Analysis of dozens of publications allowed us to create a paper containing the most important information on the frequency of drug interactions and their impact on the comfort of palliative patients. Palliative treatment of advanced cancer involves the reduction of disease symptoms, especially those that most reduce the quality of life (e.g. pain, dyspnea, severe depression). In a patient with these symptoms accompanying cancer, polypharmacotherapy is most often used during palliative treatment. The analysis of adverse reactions occurring in this group of patients allows us to conclude that they are, in practice, due to unwanted drug interactions. Polypharmacy is a worldwide therapeutic problem, and despite the lack of a clear description of this phenomenon, the interpretation is always the incorrect use of pharmaceuticals. This significantly increases the risk of potentially serious drug-drug interactions (DDIs). During treatment planning, publicly available tools can be used: the Beers criteria, and STOPP/ START criteria, which will avoid therapeutic errors in the use of drugs. Polypharmacy is still a problem for the vast majority of patients in the terminal stage of cancer. Further research should focus on patients' quality of life, drug interactions, and adverse events.

Keywords: polypharmacy, palliative chemotherapy, advanced cancer, older adults

INTRODUCTION

Over the past few decades, there has been an increase in the average lifespan, resulting in a rise in the number of patients over the age of 65. These individuals constitute approximately 85% of all palliative care patients (NHPCO, 2020). Projections from the central statistical office (*Główny Urząd Statystyczny* – GUS) for Poland for the years 2015-2050 foresee a continuous increase in this aspect (GUS, 2015-2020). With the increase in life expectancy, the proportion of patients suffering from cancer, including malignant neoplasms, which are the second leading cause of death in Poland, has also increased (Rucińska, 2015). Changes in the demographic structure of the human population contribute to some extent to the increase in cancer incidence (and mortality) (Didkowska, 2011).

One of the key branches of palliative care is pain therapy. It is estimated that during anticancer therapy, this type of discomfort occurs in 30%-50% of patients, and in advanced stages of the disease, even up to 80% (Kotlińska-Lemieszek, 2004; Krawczyk, 2015). Despite treatment, this problem persists in up to 50% of patients (Nekolaichuk, 2013). Chronic pain treatment is often associated with the use of multiple medications, increasing the risk of polypharmacy, which is usually defined as the use of too many drugs or incorrect use of one or more drugs (Duława, 2015). This results in an increased risk of adverse effects of medications, which may result from interactions between medications or non-compliance with medical recommendations by the patient (Lee JQi, 2020).

To reduce the risk of polypharmacy, criteria such as Beers' and STOPP/START have been introduced. Beers was the first to notice that for safety reasons in patients with cancer, medications with a higher likelihood of adverse effects should be avoided if the chances of therapeutic benefits are lower (Beers, 1991; Beers, 1997). This criterion uses tables containing potentially inappropriate drugs for older adults, aiming to facilitate decision-making regarding specific therapeutic measures for individual patients. The use of these criteria has reduced the occurrence of polypharmacy in patients over 65 years of age (Fick, 2019; Cooper, 2015).

STOPP/START criteria consider aspects such as comorbidity, psychosocial status, independence, which is often low in patients in the advanced stage of cancer, and drug availability in various countries (Hamilton, 2011). The STOPP acronym refers to drugs whose use may potentially pose a threat, while START refers to those that are much more likely to bring therapeutic benefit (O'mahony, 2015). Using these criteria has reduced the occurrence of polypharmacy (O'mahony, 2015; Cooper, 2015; Hill-Taylor, 2016). It is worth noting that besides pain, patients with terminal cancer experience other problems such as dyspnea, which

worsens with the duration of the disease (Heyse-Moore, 1991), and psychiatric disorders such as depression and alcoholism, which are found in 4-28% of palliative care patients (Mercadante, 2015; Bruera, 1995). Regular alcohol consumption, as well as even occasional intake, affects the endogenous opioid system (Zale, 2015; Gianoulakis, 2001), which can lead to the phenomenon of hyperalgesia with continuous, chronic consumption, making effective pain treatment difficult (He, 2011; Becker, 2000). This example illustrates the complexity of palliative care patients' treatment and the importance of avoiding polypharmacy. Based on Cancer Pain Relief and Palliative Care: Report of a WHO Expert Committee, it is important to emphasize that such patients should be managed by a team of specialists, including, among others, a psychologist, a physiotherapist, and a physician.

SEARCH STRATEGY AND SELECTION CRITERIA

The process of creating this work involved a thorough literature review on palliative treatment in advanced cancer, considering key clinical aspects. To achieve this, databases such as PubMed, Elsevier, NCBI, and Google Scholar were searched, followed by analyzing literature available in both Polish and English. In total, 80 publications were analyzed. The literature review process utilized the following search terms: "polypharmacy", "polypharmacotherapy", "malignant neoplasms", "drug interactions", "elderly individuals", and "palliative chemotherapy". The scientific value of publications was verified by analyzing their content and relating them to current knowledge regarding the adverse effects of polypharmacotherapy. Research and review articles were included based on their relevance to the specific topic of managing cancer patients who may be taking more than one medication. Selection was made, and publications not meeting these criteria were excluded. After gathering enough publications, a critical analysis was conducted, followed by synthesis to obtain a broader perspective on the research problem.

REVIEW

DRUG INTERACTIONS MANAGEMENT IN PATIENTS WITH CANCER

Polypharmacy and its adverse effects are a problem in every patient group, not just in those suffering from cancer. However, a number of studies suggest that it is particularly common among individuals in the latter group. Many patients take a variety of medications and supplements for conditions unrelated to cancer, including medications for hypertension, cholesterol-lowering drugs, antiplatelet agents, anticoagulants, and bisphosphonates for fracture prevention (Cashman, 2010; Puts, 2009; Hanigan, 2008; Sokol, 2007; Werneke, 2004).

It is assumed that even half of individuals take contraindicated medications or doses not adjusted to their organ function before receiving a diagnosis of cancer (Puts, 2009). Some of these preparations are supplements, which can also contribute to polypharmacy resulting from polytherapy. It is observed that over 50% of individuals take supplements (Werneke, 2004), including St. John's wort (*Hypericum perforatum*), which is commonly known to interact with many medicinal preparations, including anticancer drugs such as imatinib, which is a tyrosine kinase inhibitor (Sokol, 2007). It is important to note that patients often do not report the use of supplements, including herbal preparations, to their physician, which, however, can significantly affect the metabolism of other drugs (Werneke, 2004). Therefore, a thorough medical history and patient education before starting chemotherapy are crucial to avoid adverse effects of treatment (Extermann, 2007; Maggiore, 2010; Delafuente, 2003). The negative impact of treatment may result from both direct adverse drug reactions, drug interactions, and increased therapy costs. Drug interactions account for 20-30% of adverse effects of treatment but have a significant impact on clinical condition even in 80% of individuals over 65 years of age (Beijnen, 2004). The risk increases with the number of medications taken (Blower, 2005; Delafuente, 2003).

However, it should be remembered that dietary supplements, including herbs such as the St. John's wort, as well as consumed food, fluids (e.g., grapefruit juice), patient's health and nutritional status, age, body mass, muscle and fat tissue content, comorbidities, and genetic factors, also affect drug metabolism (Beijnen, 2004). Chemotherapeutic agents are toxic drugs, so considering all variables seems to be crucial in utilizing their therapeutic potential and minimizing harmful effects (Beijnen, 2004; Blower, 2005). Improper patient management not only leads to ineffective therapy but also exposes the patient to additional costs, such as duplicated therapy, additional tests, or hospitalizations (Fulton, 2005; Riechelmann, 2009). Managing patients with cancer is a real challenge because, in addition to anticancer drugs, medications from other groups such as warfarin, glucocorticoids, antiepileptics, analgesics, antibacterials, antivirals, or antifungals

must be used. All these drugs can interact, making it extremely difficult to select the right polypharmacotherapy and avoid polypharmacy. Table 1 includes some of the drugs and their interactions relevant in a clinical setting, along with guidelines for management (Scripture, 2006; Kongkaew, 2008).

Table 1. Possible interactions between anticancer drugs and other medications

Drugs	Potential impact	Recommendations
Cisplatin with phenytoin	Decrease in phenytoin concentration – increased risk of seizures	Monitor phenytoin levels
Erlotinib with Carbamazepine	Decreased erlotinib concentration – reduced treatment efficacy	Maintain a 2-week interval between the use of these drugs
Erlotinib with ciprofloxacin	Increase in erlotinib concentration – increased risk of adverse effects	Monitor adverse effects and consider reducing the dose if necessary
Etoposide with warfarin	Increased anticoagulant effect – risk of bleeding	Monitor INR and adjust warfarin dose
Fluorouracil with warfarin	Increased anticoagulant effect – risk of bleeding	Monitor INR and adjust warfarin dose
Methotrexate with NSAIDs	Increased concentration – increased toxicity	Avoid co-administration

Source: based on (Lees, 2011).

PAIN MANAGEMENT

In cancer patients, "cancer pain" occurs. Although this term is not listed in the ICD-10, it is widely used in clinical practice. The first definition was proposed by John Joseph Bonica, and it stated: "cancer pain is any pain caused by cancer, cancer treatment, or both" (Kotlińska-Lemieszek, 2004).

Accepting this definition, it can be assumed that pain may arise through direct effects of the disease, metastases, treatment, cachexia, or a combination of these factors. To properly select treatment and minimize the risk of polypharmacy, it is necessary to objectify the patient's sensations as much as possible. Visual-analog, verbal, and numerical scales can be used (Krajnik, 2013; Jarosz, 2007; Ciałkowska-Rysz, 2004). It is also important to emphasize that psychological aspects influence somatic pain sensations. Anxiety and mood disorders occur in 47% of cancer patients. Depression develops in 6% (De Walden-Galuszko, 2003; Araszkiewicz, 2004).

When it comes to pain management, medications should be used according to the analgesic ladder, which should be supplemented with drugs to minimize adverse effects and other disease symptoms such as tonic-clonic seizures or vomiting (Kotlińska-Lemieszek, 2011; Christie, 2021).

First-line drugs should be acetaminophen and NSAIDs, but caution must be exercised regarding interactions. When using NSAIDs, particular attention should be paid to patients concurrently treated for psychiatric disorders with SSRIs, venlafaxine, clomipramine, and duloxetine, as these drugs have antiplatelet effects and, when combined, may lead to bleeding complications (Siwek, 2016). In such patients, the addition of proton pump inhibitors to minimize the occurrence of complications is recommended. NSAIDs also affect kidney metabolism, so special attention should be paid to patients treated with lithium, as NSAIDs reduce its elimination by the kidneys, increasing its concentration and toxic effects (Hansten, 2010; Malec--Milewska, 2017).

In case of insufficient therapeutic effect, opioid use may be considered, as they have a lower risk of drug interactions due to their lesser impact on cytochrome P450 isoenzymes. This is because the therapeutic effect is mainly attributable to the parent drug and to a lesser extent to the metabolite (Hansten, 2010; Malec-Milewska, 2017). Morphine and oxycodone are recommended for use, with oxycodone being considered a first-line drug in the treatment of severe cancer pain (Dzierżanowski, 2010; Schmidt-Hansen, 2022). Compared to morphine, oxycodone has a stronger analgesic effect despite its lower affinity for κ and μ receptors, as it reaches about 6 times higher concentrations in the brain at the same blood level (Lalovic, 2006; Boström, 2008), lacks immunosuppressive effects, has better bioavailability, and less first-pass effect (Colucci, 2001; Pöyhiä, 1993; Beaver, 1978). It should be emphasized that there are no contraindications to the use of opioids in cancer patients, unlike in other populations (Jamison, 2015). However, it should not be forgotten that this group of drugs also interacts with, among others, psychotropic medications, which

can lead to serotonin syndrome (Jyrkkä, 2009) or malignant neuroleptic syndrome (Ware, 2018). It should be noted that patients taking antipsychotic medications may experience pain and spontaneous movements in the lower body due to changes in serotoninergic and dopaminergic neurotransmission in the CNS (dos Santos-Junior, 2017; Baxter, 2010). Tiapride is worth noting among patients requiring neuroleptics, as it also has an analgesic effect but can lead to addiction (Malec-Milewska, 2017). Other drawbacks of opioid drugs include fever when concurrently used with MAO inhibitors, sedation, CNS depression, and synergistic effects with P2Y12 antagonists, reducing their effectiveness in anticoagulant protection (Mao, 2002).

POLYPHARMACY AS A RESULT OF NON-ADHERENCE PHENOMENON

The deterioration of the health of elderly individuals often results from not adhering to medical recommendations regarding medication intake. Many patients may not understand why they should take specific medications, leading to their improper use or premature discontinuation (Pasina, 2014). Studies show that a higher number of prescribed medications often correlates with a greater risk of non-adherence to usage recommendations (Gray, 2001).

When caring for elderly individuals, especially those in the terminal phase of chronic illness, it is also important to consider the appropriateness of the therapy being administered. Research shows that over half of patients with advanced dementia residing in long-term or palliative care facilities receive medications such as memantine, cholinesterase inhibitors, and lipid-lowering agents, the usefulness of which is questionable. Discontinuing such therapy can improve the quality of life of the patient without negatively impacting their lifespan (Winzelberg, 2005). Therefore, a conscious approach to prescribing medications to elderly individuals, considering their health status, potential side effects, and therapy appropriateness, is crucial. It is also important to educate patients and their caregivers about the necessity of adhering to medication intake recommendations and informing them about the purposefulness of the therapy being administered. This can improve the effectiveness of treatment and the quality of life of elderly individuals.

DEPRESSION AS A CHALLENGE IN CANCER THERAPY

Depression is a common mental disorder in elderly individuals, affecting over 7.5% of women and over 5.5% of men (McLaughlin, 2011). Anxiety and depression are psychological disorders commonly encountered in cancer patients (Pers, 2002).

A study from 2019 found an association between depression and polypharmacy, although no direct cause--and-effect relationship was established (Bazargan, 2019). However, a tendency for polypharmacy to develop in cases of depression was observed (Wongpakaran, 2018). This underscores the need for a thorough assessment of therapy administered to elderly patients with depression in cancer, considering the increased risk of medication interactions and their potentially negative impact on pharmacotherapy effectiveness (Kok, 2017).

Polypharmacy can lead to intensified adverse effects of anti-cancer drugs, which, in turn, can worsen daily functioning, and hospitalization requirements, and increased mortality (Sussman, 1995). Although there is no clear evidence that polypharmacy directly leads to depression, when prescribing end-of-life cancer therapy, possible adverse effects and potential drug interactions should be considered, given the increased psychological sensitivity of patients at the end of life.

PRACTICAL APPROACH IN THE CASE OF DETECTING POLYPHARMACY IN ONCOLOGY PATIENTS

Upon identifying polypharmacy, the physician should conduct an assessment of medication suitability for the patient's health status, medication dosages (e.g., depending on kidney and/or liver function), duration of use, repetition, drug-drug interactions, as well as interactions between drugs and diseases, and side effects. Additionally, the patient's ability to read medication intake instructions and their ability to organize medication intake should be assessed. The physician should also consider the pharmacological properties of the drugs, the patient's coexisting conditions, oncological prognosis, functional and cognitive status of the patient, as well as social, cultural, and economic factors (Hoel, 2021). In this way, the medication prescribing process considers the patient's care goals while maintaining their quality of life. In the case of identifying unnecessary and/or high-risk, but low-benefit medications, a medication discontinuation process should be carried out. Medication discontinuation is a systematic process of identifying and ceasing the use of medications in which current or potential harms outweigh current or potential benefits in the context of patient care goals, functional status, predicted lifespan, values, and preferences (Scott, 2015). There are

many challenges associated with successful medication discontinuation, including patient complexity, limited consultation time, fragmented care, uncertainty about benefits and harms, and emotional attachment of the patient to the medication.

DISCUSSION

Polypharmacy poses a significant challenge for physicians across many specialties, including oncologists. The ability to adjust doses in patients taking multiple drugs from various drug classes is crucial in oncology therapy, where overlapping side effects of medications often lead to decreased patient comfort and reduced effectiveness of cancer therapy. As noted by Justin P. Turner et al., nearly two-thirds of cancer patients take at least one drug that interacts with another therapy being used by the patient (Turner, 2014). It is the task of a geriatrician to effectively utilize the synergistic effects of drugs to reduce the doses of individual preparations, thereby minimizing the risk of side effects resulting from the use of a particular therapy. Among geriatric patients, particular attention should be paid to the function of organs responsible for drug elimination from the body and to select drugs that are eliminated by the more efficient organ.

Polypharmacy is particularly pronounced in elderly patients and cancer patients. As L. Balducci et al. demonstrated, this phenomenon is more pronounced in the elderly (Balducci, 2013). Among cancer patients aged 70-79, polypharmacy occurred in 35% of patients, while in those aged 90-99, it was already present in 41%. Additionally, it was more pronounced in cancer patients compared to non-cancer patients in the appropriate age group. Proper therapy adjustment should be based on an analysis of the benefits and risks using Beers' criteria and STOPP/START criteria. Proper review of medications used, combined with an assessment of symptoms' severity, should be crucial in minimizing the side effects of therapies. Through appropriate medical intervention, polypharmacy in elderly patients can be significantly reduced (Zarowitz, 2005).

STOPP/START criteria are used in clinical practice to reduce polypharmacy. The STOPP (Screening Tool of Older People's Prescriptions) criteria, along with the START (Screening Tool to Alert to Right Treatment) criteria, are auxiliary tools that enable the reduction of the number of drugs used, leading to subsequent improvement in patients' health. Positive effects resulting from the use of STOPP/START criteria in clinical practice have been observed, including a reduction in hospitalization length and therapy costs (O'Connor, 2021).

Polypharmacy is particularly common in cancer treatment. F. Tian et al. observed an increased frequency of this phenomenon among cancer patients, resulting from the need for patients to take a larger number of drugs with a high risk of drug interactions, including analgesics and cytostatics. It is clearly more common in patients undergoing cancer therapy than in non-cancer patients in the corresponding age group (Tian, 2022). As noted by L. Balducci et al., the number of drugs taken by patients also increased six months before the cancer diagnosis, which may indicate the presence of prodromal symptoms of the disease in this group of patients, who try to treat them unaware of their actual cause (Balducci, 2013). Polypharmacy does not remain indifferent to the course of the disease, and a clear correlation is observed between increased risk of hospitalization and death in polypharmacy patients, not only in cancer patients (Chang, 2020). However, it also affects the quality of life of cancer patients, reducing it and exacerbating unwanted symptoms. One of the symptoms that particularly intensifies during cancer therapy is constipation, which results from both constipating opioids and other commonly used drugs in cancer therapy, including nonsteroidal anti-inflammatory drugs, antiemetic drugs, or especially cytostatic drugs. As T. Dzierżanowski et al. point out, intestinal disorders affect up to 75-90% of cancer patients treated with opioids. Alkaloids of the Madagascar periwinkle used in the therapy of testicular or breast cancers, as well as thalidomide used in the treatment of multiple myeloma, are strongly constipating cytostatic drugs (Dzierżanowski, 2010). The inability to defecate properly also affects the patient's mental attitude, lowering their well-being and negatively affecting their attitude in the fight against the disease. Other common factors that reduce the quality of life of cancer therapy patients include vomiting. Some of the most potent emetogenic drugs used in therapy include cisplatin and cyclophosphamide. The occurrence of this symptom is not only extremely burdensome for the patient but also often necessitates a change in therapy and the inclusion of antiemetic drugs, most commonly from the group of 5-HT_3 receptor antagonists (Theriot, 2018). Although these drugs are considered relatively safe, they can exacerbate constipation, which is frequently observed in this group of patients. As demonstrated by J. Theriot et al., this complication affects approximately 10% of individuals taking drugs from this group (Theriot, 2018). Therefore, in cancer patients undergoing therapy, this side effect may be particularly intensified by concomitant use of cytostatics.

SHORT CONCLUSION

Polypharmacy is a common and increasing problem among patients in the terminal stage of cancer. In our study, we discussed research dedicated to the relationship between polypharmacy and targeted or palliative treatment in this group of patients. In most cases, a correlation between the use of multiple drugs and the advancement of cancer was indicated, or groups of drugs causing symptoms worsening quality of life were identified.

Given the forecasts predicting an increase in the number of cancer patients in the coming years, conducting such research and developing precise guidelines regarding the issue of polypharmacy seems necessary. In our study, we point out available tools helpful in the daily practice of physicians dealing with polypharmacy among their patients. Disseminating knowledge about Beers' criteria, STOPP/START criteria, as well as providing patients with the opportunity to undergo consultations to assess the correctness of pharmacotherapy are simple yet effective steps that have already been implemented in many countries.

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Tertiary prevention strategies by comprehensive nutritional care in patients with digestive tract cancers

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Abstract

Introduction. Cancers of the digestive tract and their treatment are responsible for many side effects, e.g. decreased appetite, xerostomia, taste and smell disorders, nausea, vomiting, dysphagia, diarrhea, constipation, early feeling of satiety, malnutrition and cachexia. This requires appropriate nutritional strategies as tertiary prevention in supportive and palliative care in oncology. Aim of work was a review of the literature on the comprehensive dietary care in patients with digestive tract cancers to systematize nutritional knowledge and to indicate practical dietary solution that will be optimal for the patient.

Methods. A literature review was performed in databases: PubMed, Google Scholar, Research Gate, Science Direct and Scopus. Publications not older than 2014 were included. Keywords: digestive tract cancers, nutritional, supportive and palliative care, diet, oncology.

Tertiary prevention strategies. Dietary management regarding the side effects include: monitoring nutritional status, using an easily digestible diet, drinking fluids frequently in little doses, sucking ice cubes, pineapple slices and sugar-free sweets or gum, using food with a neutral smell and a mild taste, avoiding lying down while eating, appropriate consistency, aesthetics and food selection, using of products with a constipating or laxative effect and oral nutritional supplements in patients who require it, slowly eating small, more frequent meals rich in energy and nutrients.

Conclusion. The analysis of the literature confirmed the need to intensify activities related to nutritional strategies in patients with digestive tract cancers. The optimal solution for patients in supportive and palliative care seems to be comprehensive dietary care before, during and after hospitalization. Measurable effects may be achieved through a complex education including an interview, consultation, recommendations and practical dietary tips showed in interesting forms, focused on a specific patient, his condition and ailments.

INTRODUCTION

Malignant tumors are the second leading cause of mortality worldwide, significantly shortening average life expectancy and reducing quality of life. Regardless of the supportive or palliative nature of treatment, such tumors often diminish comfort and intensify pain during the terminal phase of the disease. This situation necessitates the implementation of adequate strategies, which are crucial elements of tertiary prevention (Arends, 2018).

Among all types of cancers, malignant tumors of the digestive tract are frequently diagnosed, including those affecting the upper (e.g. esophageal cancer) and lower digestive tract (e.g. colorectal cancer, stomach cancer, liver cancer and pancreatic cancer) (Bray, 2018; Ferlay, 2019; Kawakatsu, 2020; Sung, 2020). The increasing incidence of cancer, including digestive tract cancers, is likely attributable to rising life expectancy, advancements in civilization and a variety of individual factors, which is confirmed by numerous research (Buckland, 2014; Deng, 2016; Du, 2017; Fang, 2015; Ferro, 2018; Iyengar, 2016; Keum, 2016; Sung, 2018; Wang, 2017; Wang, 2018). These factors include sex, age, body weight, somatic and mental health status, comorbidities, inflammation, genetics, monitoring health, preventive activities, as well as environmental factors such as highly processed food, high-fat and high-carbohydrate diet, excessive stress, rushing life, lack of rest, lack of physical activity, use of stimulants and alcohol, and depression. All of these elements significantly increase the risk of carcinogenesis what the conducted research confirm (Bouras, 2022; Deng, 2021; Lee, 2022; Zhang, 2020).

The diagnosis of cancer, its ongoing progression, and the implementation of complex and exhausting therapeutic procedures can cause various side effects in patients, necessitating urgent interdisciplinary intervention, including nutritional intervention, in order to strengthen the body to cope with chronic disease and improve nutritional support. This intervention aims to strengthen the body to cope with chronic disease and improve nutritional status - an essential element for ensuring effective oncological therapy. Above all, it is important for alleviating pain and discomfort and improving the overall quality of life of patients,

which is a priority in the tertiary prevention of digestive tract cancers (Amano, 2019; Agarwal, 2017; Gouldthorpe, 2023). Tertiary prevention seeks to limit the complications associated with progressive disease and holistically enhance behavioral and therapeutic activities across various areas of health care, and monitor nutritional, exercise and psychological strategies (Minnaar, 2022; Miniotti, 2024; Scotte, 2023). Focusing on nutritional issues, monitoring of the nutritional status and diet of patients with digestive tract cancers is crucial at every stage of the disease, during all treatment methods and when side effects occur. Any disturbances in a patient's nutritional status exacerbate disease progression, complicate the therapeutic process and lead to a range of severe systemic disorders (Jankowski, 2021; Knight, 2022; Rucińska, 2022; Schuetz, 2019; Schuetz, 2021). The most common side effects and behavioral and nutritional problems faced by patients resulting from cancer and invasive oncological treatment are illustrated schematically in Figure 1. A detailed description of these identified problems and their possible solutions – particularly concerning comprehensive nutritional strategies as a complementary element of tertiary prevention in supportive and palliative therapy in oncology is provided in the "Review" section.

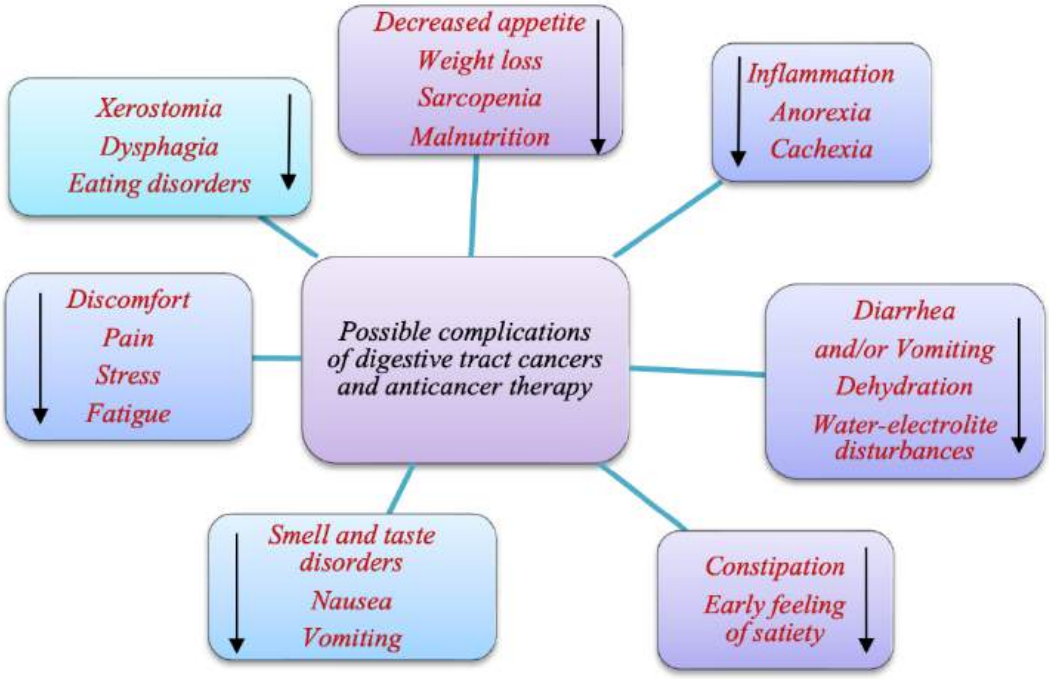

Figure 1. Most common possible complications of digestive tract cancers and anticancer therapy [own study]

This work aimed to review of the literature on the comprehensive dietary care in patients with digestive tract cancers for a tertiary prevention to systematize nutritional knowledge and to indicate practical dietary solution that will be optimal for the patient.

METHODS

This narrative review was designed and reported in accordance with the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA). The following databases: PubMed, Google Scholar, ResearchGate, ScienceDirect and Scopus were search using the terms: "digestive tract cancers", "esophagus cancer", "colorectal cancer", "gastric cancer", "liver cancer", "pancreatic cancer"; "nutrition in cancer"; "nutritional status of cancer patients" and secondary searches were conducted, adding the terms "nutritional care"; "supportive care"; "palliative care" to the previous terms. Due to the extensive literature, only the most relevant articles were selected, taking into account primarily the quality of the study, the most recent years of publication, and the variety of mechanisms and models studied.

The inclusion criteria were: 1) peer-reviewed articles in English, 2) full-text publications, 3) use of a clear study design (cross-sectional or observational studies, etc.), 4) studies published in the period January 1, 2014 – July 1, 2024. The exclusion criteria were: non-English articles, opinion pieces, scientific dissertations, abstracts. We also excluded studies of short duration (<2 weeks) and studies that focused on intercurrent medical conditions. Two independent reviewers conducted the search and selected the legal

acts and list of qualified articles, which we described. Reference lists from all selected articles were also examined for additional relevant studies.

Ethical Approval: This study did not require ethical approval as it is a narrative review of previously published studies.

TERTIARY PREVENTION STRATEGIES

Although a complete cure remains elusive for most advanced cancers, comprehensive supportive and palliative care is invaluable and justified. The authors of the research constantly emphasize that this type of care can significantly improve patients' daily functioning, alleviate symptoms and empower them to cope with chronic disease enabling better tolerance of long-term and aggressive anticancer treatments (Amano, 2018; Laviano, 2016; Lee, 2016). There is no single, universal diet for oncology patients due to various factors that can interfere with proper nutrition, such as metabolic disorders, increased catabolism, and systemic side effects that make it challenging for patients to eat and perform basic daily activities (Aapro, 2014; Arends, 2017). However, certain strategies and recommendations can assist patients in managing their ailments. It is essential to emphasize that these interventions should be tailored to each patient's specific conditions, taking into account clinical, mental, physical, and social factors (Mąkosza, 2024). Furthermore, it is crucial to ensure that the body receives all the necessary nutrients to support the fight against cancer and maintain the proper functioning of all organs and systems, while also enhancing patients' well-being and quality of life (Balstad, 2014; Maddocks, 2016; Mąkosza, 2024).

DECREASED APPETITE → BODY MASS LOSS → SARCOPENIA → MALNUTRITION → ANOREXIA → → CACHEXIA

One of the primary challenges faced by cancer patients undergoing treatment is reduced appetite. Scientists report in original and review works that without immediate nutritional intervention, this can result in serious consequences, including malnutrition and cachexia (Cederholm, 2015; Deutz, 2016). Approximately half of patients with advanced cancer experience loss of appetite as an initial symptom, and this condition tends to worsen in about three-quarters of those individuals as the disease progresses (Soeters, 2017). According to observations and results of conducted studies the desire to consume food is often diminished due to the loss of both fat and lean body mass. Significant loss of lean mass can lead to sarcopenia, frequently triggered by a systemic inflammatory response (Vanhoutte, 2016). As described by Wu et al., this syndrome promotes catabolic processes and contributes to the degradation of proteins in skeletal muscles (Wu, 2024). Furthermore, systemic inflammation, which is commonly associated with chronic fatigue during cancer progression, weakens anabolic pathways. As a result, there is a reluctant supply of energy, nutrients, minerals, and vitamins to the body. When combined with insufficient physical activity, this situation often leads to further muscle atrophy (Cruz-Jentfort, 2019). Consequently, these factors can culminate in uncontrollable anorexia and irreversible cachexia. Both sarcopenia and malnutrition, as well as anorexia and cachexia, are associated with significantly negative clinical outcomes in cancer treatment, ultimately diminishing patients' life expectancy and adversely impacting their quality of life (Zhang, 2022). Therefore, it is essential to undertake comprehensive monitoring, preventive measures, and therapeutic interventions, particularly regarding well-planned nutritional management (Argilés, 2019; de Las Peñas, 2019; Gyan, 2018). Prioritizing screening tests to assess the nutritional status of cancer patients is crucial. International clinical guidelines emphasize the importance of identifying malnutrition or the risk of malnutrition. These screening tests should be conducted for every patient during hospitalization and at each outpatient visit. They must be easy and quick to administer, reliable, credible, and conducted by authorized personnel. There are several tools available for the professional assessment of nutritional status, including:

- Malnutrition Universal Screening Tool *(MUST*);
- Mini Nutritional Assessment (*MNA*);
- Nutrition Risk Screening (*NRS*);
- Subjective Global Assessment (*SGA*) (Cao, 2021).

These questionnaires can be used in full or shortened versions. They cover patients' aspects relating primarily to their qualitative and quantitative way of absorbing food, drinking fluids, anthropometric measurements, including data on recent weight loss, general health condition, comorbidities, polypharmacy, chronic stress, social conditions, as well as their own assessment regarding their nutritional status. If the screening test result

is interpreted as inconsistent with the desired one, suggesting malnutrition or a risk of its occurrence, it requires further, in-depth preventive and treatment procedures.

As shown by Muscaritoli et al., a robust nutritional strategy is absolutely essential in this case, as its neglect could significantly worsen the patient's clinical condition (Muscaritoli, 2019). First and foremost, the patient is advised to adopt an easily digestible diet tailored to relieve stress on the gastrointestinal tract. The goal of such a diet is to enhance the patient's nutritional status through improved digestion and absorption of nutrients. An easily digestible diet should be customized according to the patient's individual needs and preferences (Mąkosza, 2024). To support the nutritional status of cancer patients, it is important to increase the energy and nutrient density of the meals consumed. This can be achieved, for instance, by fortifying the diet with additional fats such as butter, oils, olive oil, and ground nuts to prevent unintentional weight loss (Muscaritoli, 2019). Food for special medical purposes, such as oral nutritional supplements, can also be introduced (Muscaritoli, 2021). These supplements serve as concentrated sources of energy and nutrients, available in liquid, ready-to-drink forms or as powders that can be dissolved in water. They can function as either independent sources of nutrition or as supplements to regular meals. The selection of these preparations must consider the patient's clinical condition and any comorbidities. Consuming smaller, more frequent meals throughout the day (ideally 6-8 meals) is also a valuable strategy, as long as they are properly balanced, especially in terms of high protein content (Deutz, 2016). It is also important to serve small meals on large plates filled with colorful, appetizing, and aesthetically pleasing foods to encourage the patient's consumption. Meals should be enjoyed in a relaxed atmosphere and, if possible, outdoors. It is advisable to avoid distractions such as watching TV or using electronic devices during mealtime.

In cases of eating disorders such as lack of appetite, malnutrition, sarcopenia, or anorexia-cachexia seasoning dishes with natural herbs and spices can be beneficial (Schoenberg, 2016). High-energy drinks can also be included in the diet but should be consumed after meals, rather than immediately before or during (Schuetz, 2019). Moreover, fostering a social eating environment is important so that the patient does not feel fear or loneliness but instead experiences support and joy while sharing meals with others.

Supplementation with omega-3 polyunsaturated fatty acids is recommended by Muscaritoli et al., as a daily intake of 2 grams in patients undergoing chemotherapy has yielded several measurable therapeutic benefits, such as improved appetite, increased energy levels, and gains in body weight and muscle mass (Muscaritoli, 2019; Muscaritoli, 2021). Furthermore, increasing the level of daily physical activity through light exercise or walks outdoors can stimulate appetite (Schoenberg, 2016; McTiernan, 2019). Physical exercise should be tailored to the patient's condition, capabilities, and preferences.

SYSTEMIC INFLAMMATION

According to common knowledge, chronic systemic inflammation is a concern associated with ongoing cancer process, including cancer cell proliferation, as well as malnutrition, sarcopenia, anorexia and cachexia (Cotogni, 2021). It creates a favorable microenvironment for further tumor growth and is one of the key characteristic of malignant tumor development (Piotrowski, 2020). According to Arends et al., tumors often resemble non-healing wounds, and inflammatory mediators can enhance the inflammatory response within the cardiovascular system, initiating and intensifying systemic inflammation (Arends, 2018). Chronic inflammation in the body disrupts energy intake by activating the immune system, leading to changes in metabolic processes (Argilés, 2015). This imbalance results in predominance of catabolic reactions over anabolic ones, as well as insulin resistance, and an increased risk of malnutrition associated with the anorexia--cachexia syndrome and chronic fatigue (Arends, 2018). The progression of generalized inflammatory response syndrome is challenging; it negatively affects various aspects of daily functioning in cancer patients, including the initiation of severe eating disorders. The reports of Hopkins et al. confirm the repercussions include lowered well-being, diminished self-acceptance, reduced daily efficiency and productivity, strained relationships, communication issues with family and friends, decreased physical activity, hindered independence, and increased anxiety (Hopkinson, 2014). For these reasons, it is essential for multidisciplinary therapeutic teams to implement practical solutions to mitigate further detrimental effects on the clinical condition of patients. Given that intense inflammation during cancer is often triggered by malignant tissues, effective anticancer therapies, combined with multidirectional diet interventions, can alleviate the distressing symptoms experienced by patients (Arends, 2018).

Undoubtedly, the thesis put forward by Aderson et al. is justified – to reduce the intensity of the inflammatory process and alleviate accompanying ailments, proper nutrition is a vital therapeutic component (Anderson, 2020). Nutrition should be rich in antioxidant and anti-inflammatory compounds, which will support the immune system and help patient's body combat chronic illness and multiple side effects associated with both the primary disease and systemic treatments. Following the report by Żyła et al., effective nutritional management for individuals with cancer should incorporate nutrients with scientifically proven immunomodulatory effects, primarily glutamine, arginine, omega-3 fatty acids (EPA and DHA), and beta-glucans (Żyła, 2021). A thoughtful integration of these nutrients, including the selection of appropriate proportions and the timing of their inclusion in the diet, can contribute to a milder disease course and enhance the likelihood of remission.

FATIGUE

Chronic fatigue is one of the most common symptoms of cancer and its treatment. Inflammation, hormonal disorders, psychoemotional disorders, and nutritional deficiencies, especially protein deficiency, contribute to the feeling of weakness and deterioration of somatic and mental performance (Chia-Chien, 2021). Adapting dietary recommendations and properly planned increase in physical and social activity of cancer patients may improve their quality of life, positively influencing the effectiveness of anticancer treatment. Researchers confirm that chronic fatigue syndrome often correlates with anorexia, lack of appetite, gastrointestinal symptoms, pain, poor well-being and poorer performance (Inglis, 2019). This is equivalent to difficult food intake, increasing aversion to food leading to complete anorexia, increasing the risk of malnutrition and cachexia, thus intensifying already existing metabolic disorders. This has a very negative impact on the results of treatment and the quality of life of patients. Cancer-related fatigue is defined as a subjective, persistent feeling of fatigue that is related to the development of cancer or its treatment and lasts longer or is more severe than would be expected as a result of the patient's current physical activity (Kuhnt, 2019). It is so intense that it causes discomfort and interferes with normal functioning. Cancer patients describe fatigue as reduced physical capacity, weakness, and a great need for rest. This is accompanied by loss of energy and fatigue even after rest – sleep (Baguley, 2019). Fatigue is particularly severe in elderly people, treated with various methods and with comorbidities. What is more, at the time of cancer diagnosis, approximately 40% of patients report fatigue, and during chemotherapy and/or radiotherapy as many as twice as many – 80-90% of patients (Wang, 2014). Besides, the researchers made very important observations: in approximately 1/3 of diagnosed cases, chronic fatigue may persist for up to several years in remission (Kang, 2023). Fatigue and decreased performance usually accompany sarcopenia, which is characterized by an unintentional reduction in lean body mass, mainly muscle tissue (Stobäus, 2015). The weakening of muscle strength results from the predominance of catabolic processes and the intensification of the systemic inflammatory response associated with the development of cancer (Thong, 2020). Metabolic disorders leading to a reduction in muscle mass associated with negative energy and protein balance, reduced myosin synthesis and increased apoptosis may also contribute to lower physical performance and the feeling of constant fatigue (O'Higgins, 2018). Similarly, decreased food intake, often accompanied by increased basal energy expenditure, may deepen feelings of exhaustion in cancer patients (Maschke, 2017).

A proper nutritional strategy is crucial (Wilkes, 2018). The key to therapeutic success in the nutritional dimension is an individualized approach to each patient (Mąkosza, 2024). As a priority, nutritional management should begin with a very thorough, comprehensive nutritional and health lecture with the patient in order to learn as much as possible about him and his physical and mental health. Due to the most common symptoms coexisting with fatigue in oncological patients, it will probably be necessary to ensure a high-energy diet, with particular emphasis on the supply of protein, minerals, anti-inflammatory and antioxidant compounds. Therefore, it seems reasonable to increase the consumption of fruit, vegetables, whole grain products, fatty sea fish and other sources of omega-3 polyunsaturated fatty acids, including rapeseed oil, flax, linseed oil and nuts. It may be helpful to follow the principles of the Mediterranean diet with a predominance of products of plant origin (fruits, vegetables, whole grain products, legumes, nuts, seeds, olive oil), as well as moderate consumption of fish, cheese, yogurts, and only a small amount in the diet red meat. This nutritional model has an anti-inflammatory effect on the body and may reduce or prevent the severity of symptoms associated with chronic fatigue. It should be emphasized that each nutritional intervention should be considered individually and implemented only in the absence of any contraindications. Of particular importance in the diet is also an adequate supply of hematopoietic factors, including iron, folic

acid, vitamin B_{12}, and composing meals to increase the absorption of iron of plant origin (adequate intake of vitamin C, lower consumption of caffeine and theine). Fatigue may also increase dehydration, which is particularly undesirable in older patients, whose water content in the body and the feeling of thirst physiologically decrease. The estimated water requirement is approximately 30-35 milliliters per kilogram of body weight per day. In case of problems with food intake in order to meet the demand for particular nutrients, it is worth considering supplementing the food ration with oral industrial diets or introducing enteral and/or parenteral nutrition. It is also important to adapt the daily food ration to the capabilities, efficiency and mood of the patient who feels constantly exhausted. In patients with severe anorexia and insufficient body weight, it may be necessary to use therapy that stimulates appetite, e.g. in the form of megestrol acetate. In the case of patients with serious nutritional deficiencies, it is reasonable to implement supplementation under the supervision of a doctor and a dietitian. The proposed meals should be easy and quick to prepare, even by the patient himself, and encourage the patient to consume, e.g. soft-boiled eggs, dishes based on fruit, vegetables and dairy products, including jellies, puddings, mousses, sorbets, soups and cocktails. The atmosphere when eating food is crucial, as anxiety, stress, anxiety and negative emotions can disrupt their absorption. Patients should not feel forced to eat meals, they should do it freely and naturally when they feel like it. It is worth encouraging them to consume them when they feel better, taking into account the foods that are favorite and well tolerated by the patient. Reducing the severity of sleep disorders and improving effective rest may be facilitated by eliminating drinks containing caffeine, sweetened, carbonated and alcoholic beverages from the diet, as well as avoiding eating larger meals in the second half of the day, especially in the evening. Planning the breakfast well is particularly important because cancer patients usually tolerate meals better in the first half of the day. It is also worth dividing meals into several smaller, but served more often, e.g. drinks, sorbets, mousses with natural juices, fruits, vegetables, small groats, ground seeds and nuts, yogurt, buttermilk or kefir. Wholesome snacks may also be beneficial to increase the energy and nutritional value of the daily diet. Spices and herbs that are tolerated and accepted by patients may also be very beneficial, e.g. dill, basil, oregano, thyme, marjoram, ginger, parsley, and in the case of disturbances in the sense of taste and smell and/or pain, they may be helpful turn out to be food with a lower temperature. The taste of dishes can be enhanced by adding lemon juice, turmeric or ginger. Continuous dietary support for patients undergoing anticancer treatment gives significantly better results in reducing the severity of chronic fatigue and other troublesome side ailments resulting from the ongoing disease and systemic treatment (Zanetti, 2020).

INFLAMMATION OF THE ORAL CAVITY AND ESOPHAGUS → XEROSTOMIA → DYSPHAGIA

Post-treatment ulcers, swelling and atrophy, as well as esophagitis and stomatitis are a consequence of complex processes resulting from chemotherapy and radiotherapy (Bressan, 2016). The post-radiation reaction of the mucous membranes in the irradiated area manifests as pain, leading to the development of swallowing disorders. Difficulties in swallowing food result in nutritional deficiencies and, consequently, malnutrition, which significantly reduces the quality of life of patients (Bozorgi, 2020). Furthermore, a deterioration in nutritional status due to inflammation of the oral mucosa and esophagus may necessitate postponing chemotherapy, reducing the dosage of cytotoxic drugs, and may lead to infections as well as the need for enteral or parenteral nutrition (Jensen, 2019).

During oncological treatment of the head and neck area, it is essential to maintain proper oral hygiene. Teeth should be brushed with a soft toothbrush using specialized toothpastes, rinsed every two hours and kept moisturized. Healing processes of mucosa ulcers typically begin about two weeks after the chemotherapy/radiotherapy end, indicating that dietary recommendations should be followed for several weeks or even months. The WHO classification is employed to assess the degree of inflammation of the mucous membranes, which includes changes in the appearance, symptoms and functional alterations (Davies, 2021). This classification uses a five-point scale:

- grade 0 → there are no changes;
- grade I → redness, pain, discomfort, all functions are preserved;
- grade II → redness + ulceration, pain, discomfort, possible intake of solid food;
- grade III → redness + ulceration, pain, discomfort, possible intake of liquid food;
- grade IV → redness + ulceration, pain, discomfort, oral feeding impossible (Nuchit, 2019).

Dietary recommendations for patients with swallowing disorders primarily focus on modifying food consistency to ensure safe swallowing (Kristensen, 2020). The consistency of the diet is tailored to the severity of dysphagia, typically beginning with a basic diet and progressing through soft food, then pureed (very thick) food, blended (moderately thick) food, and finally liquid diets. For patients with stomatitis and esophagitis, the fundamental dietary guideline is to avoid spicy, sour, and hot foods, as well as those containing fruit acids, hard, and crunchy items that may irritate the oral mucosa. Instead, patients are encouraged to consume soft, moist, crushed, or blended foods, such as meals with thick sauces. In clinical practice, cancer patients facing these difficulties are advised to consume: blended meat and vegetable soups, cream soups, blended milk soups, sponge cakes soaked in milk, full-fat dairy products, puddings, jellies, milk and fruit smoothies, egg pastes, soft-boiled eggs, steamed scrambled eggs, and mild vegetable or fruit purees. Inflammation of the oral cavity and esophagus can lead to restricted food intake, resulting in unintentional weight loss. Therefore, a high-energy feeding model is recommended. To increase the energy density, it is beneficial to include products such as butter, rapeseed oil, linseed oil, olive oil, grated cheese, powdered milk, coconut milk, chocolate. These additions will enhance the energy and nutritional density of meals. Additionally, thickening dishes with wheat flour, potato flour, cereal flakes or egg yolk, can also enhance the energy and nutritional value of the meals. It is important to avoid foods that increase the risk of choking. Examples:

- with mixed consistency → soup with croutons;
- fibrous products → pineapple;
- bast products → green beans;
- dry products → crackers;
- round products → grapes;
- limp products → cucumber slice;
- styptic products → cocoa.

Additionally, products that are marinated in vinegar and high in salt, which can increase the burning sensation in the mouth, are also contraindicated. Examples:

- ready-made meat products;
- smoked fish and meat;
- canned meat and vegetables;
- marinades, pickles, spice mixtures, bouillon cubes, instant soups, all products with monosodium glutamate;
- processed and yellow cheeses.

Another complication following radiotherapy is damage to the salivary glands which can result in xerostomia (chronic dry mouth). Insufficient saliva production can make it difficult to form food bites, increase pain while swallowing, and elevate the risk of developing caries. Patients are advised against consuming fluids that can dry out and irritate the oral mucosa, as well as reduce saliva production. Therefore it is not recommended to drink strong coffee, tea infusions or carbonated beverages. It is essential to stay well-hydrated through the day, particularly by drinking water, but this should be done slowly and in smaller amounts rather than all at once. Soft, mild, moist, chilled and occasionally liquid foods are recommended to reduce pain. What is more to alleviate discomfort it is recommended to rinse the mouth with calendula infusions, sucking on ice cubes, pineapple slices, or sour candies and use sugar-free chewing gum, eat linseed porridge. Additionally, saliva-stimulating medications like pilocarpine, which are available at pharmacies without a prescription, can be beneficial.

Disturbances in the sense of taste and smell are often a consequence of anticancer therapy (von Grundherr, 2019). These treatments can damage the taste buds, resulting in a range of symptoms. Typically, this issue begins with a reduced sense of taste, followed by distortions in taste perception, and ultimately lead to a complete loss of the sense of taste (Crichton, 2019). These changes may be transient and reversible, often subsiding a few weeks or months after treatment ends, however, in some cases, they may be permanent

Patients most often report difficulties with the sensation of sour and bitter taste. These disorders can lead to decreased food intake, diminished quality of life and further systemic issues, primarily related to progressive weight loss and metabolic complications. Such problems may significantly worsen the patient's clinical condition and may also negatively affect their mental health (Webber, 2023).

In addition to the dietary recommendations detailed above in the event of problems with food absorption, several additional aspects are important:

- seasoning meals according to the patient's preferences, preferably using fresh herbs, lemon, lime, balsamic vinegar;
- in case of a metallic taste in the mouth, use non-metal cutlery;
- eating meat in a better tolerated form, e.g. in marinades with fruit, such as apple puree or cranberry sauce, as well as in marinades made of cream, coconut milk or lemon juice;
- to stimulate taste, including cold food products in the diet, such as fruit sorbets, cut and frozen banana pieces, as well as sucking cubes of frozen pineapple, watermelon or sucking frozen berries (e.g. blueberries, raspberries, strawberries) (Muscaritoli, 2021).

EARLY FEELING OF SATIETY

Early satiety in cancer patients can result from the disease itself and its treatments, limiting food intake and leading to unintentional weight loss and poor nutritional status (Hariyanto, 2021). This increases the risk of malnutrition, complications, and prolonged hospital stays, potentially delaying or halting treatment until the patient's condition improves. Early satiety is often associated with a loss of appetite, which can manifest as fasting. Patients may experience a sensation of stomach shrinking after prolonged periods without food (Zhou, 2017). Additional causes include disruptions in gastric motility, secretion of gastric juices, and psychosomatic factors such as stress related to diagnosis and treatment Grochowska, 2024). Surgical interventions, especially total gastrectomy in stomach cancer patients, can exacerbate these issues (Gharagozlian, 2020). Post-surgery, patients may suffer from early satiety, appetite disturbances, nausea, and constipation, with the digestive tract adapting over 3 to 6 months. Poor oral nutrition may necessitate temporary enteral feeding, significantly affecting quality of life and chemotherapy tolerance. Thus, treating early satiety depends on its underlying cause. Options may include proton pump inhibitors, prokinetics, or psychotropic medications if a psychosomatic issue is identified, necessitating consultation with a psychologist.

Effective nutritional management is crucial. Due to limited meal volumes, patients should consume high--energy-dense foods that are easily digestible and tailored to their preferences (Veeralakshmanan, 2020). Recommended foods include dumplings, pancakes, and pureed dishes – easily digestible sources of carbohydrates. Meals can even be partially ground (cocktails, mousses, purees, jellies, cream soups, pureed vegetables and fruits, very soft meatballs with a lot of sauce).. Fortifying meals with full-fat dairy, oils, and other energy-rich ingredients (full-fat milk, yogurts, fatty cottage cheese, mascarpone cheese, ricotta, mozzarella, feta, as well as butter, sweet cream, rapeseed oil, linseed oil, olive oil, milk coconut, walnut, coconut and almond flour) can enhance nutrition.

It is advisable for patients to eat 6 to 8 small meals daily, spaced every 2-3 hours, and to chew food thoroughly. They should avoid snacks, opting for calorie-free fluids like water instead. Presenting meals on larger plates can make portions appear smaller and more appealing. Patients should prioritize consuming nutrient-dense foods before vegetables and fruits (Surwiłło-Snarska, 2024).

As early satiety can lead to weight loss, additional nutritional support through specially formulated medical foods, available without a prescription, may be necessary. These products are balanced in energy and nutrition but should be monitored by healthcare professionals to prevent gastrointestinal complications.

NAUSEA AND VOMITING

Another common side effect of cancer and cancer treatment is nausea and vomiting. Alongside pharmacological agents, an appropriate nutritional strategy can significantly alleviate patients' symptoms while enhancing their well-being and quality of life (Marx, 2016).

Nausea and vomiting serve as important group of defense reflexes. They are common during oncological treatment, but can severely impair patient’s functioning. Nausea and vomiting can significantly obstruct food intake, potentially resulting in nutritional deficiencies and degrading nutritional status. These symptoms can also exacerbate the weakness, exhaustion, and apathy often experienced by cancer patients (Marx, 2017). Despite advancements in pharmacological therapies, nausea and vomiting, along with the administration of antiemetics during and after chemotherapy, may still persist in some patients. If left unaddressed, these symptoms often lead to the discontinuation of treatment. Antiemetic pharmacological treatment, on their own, may prove insufficient, especially for patients who metabolize drugs poorly and may suffer from

various side effects affecting multiple bodily systems, including renal, mental, metabolic, gastric, and immunological functions (Ravasco, 2019). Additionally, persistent constipation is a prevalent issue in clinical and dietary practice, requiring targeted dietary management distinct from that used for nausea and vomiting (Garutti, 2023). Therefore, dietary strategies appear to be essential in effectively addressing these challenges.

Dietary recommendations for the prevention and treatment of nausea and vomiting are based on eating food at room temperature, in ventilated rooms, with a mild taste and smell, and even chilled (Crichton, 2019). Hot and intensely scented meals stimulate the olfactory center in the cerebral cortex, thereby caused nausea and vomiting. It is advisable to consume food often, approximately every 2-3 hours, in small volumes while ensuring that the meals are rich in nutrients and energy (Garutti, 2023). Maintaining an upright position after meals can help prevent the regurgitation of food from the digestive tract. For oncological patients in cases of nausea, vomiting, or other ailments, it is crucial to consider the appropriate energy requirements of the diet (between 25-35 kilocalories per kilogram of body weight per day). Fats should be added to cold meals. The fat itself acts as a flavor carrier and will significantly increase the energy value of the complete dish. It is contraindicated to consume foods that irritate the gastric mucosa, including strong coffee, and it is also contraindicated to consume mint infusion, which causes the lower esophageal sphincter to dilate and thus may intensify vomiting (Mąkosza, 2024). Additionally, protein intake is recommended at a level of 0.8-1.5 grams per kilogram of body weight per day (Muscaritoli, 2019). A common challenge for cancer patients is meeting protein needs, as traditional sources like meat or fish may be poorly tolerated. Scrambled eggs and soft-boiled eggs are often the best tolerated protein sources. Among dairy products, fermented milk drinks like kefir and yogurt are beneficial, while raw milk can be consumed as pudding, adjusted in consistency according to preference (de Las Peñas, 2019).

It is crucial to consume easily digestible meals. In some cases, a liquid diet may be recommended, avoiding foods that can trigger nausea and vomiting, particularly those high in fiber, hard-to-digest vegetables, fatty or fried foods, and fast food. Pureed foods, such as potato and vegetable purées, mousses, and blended soups, can significantly improve intake for patients experiencing severe nausea. Carbohydrates should be consumed in refined forms, with options including white rice, wheat pasta, and boiled potatoes, while fatty foods like potato pancakes should be avoided. Allowed foods should be soft, cooked, and well-prepared. Fruits and vegetables should be cooked, pureed, or de-seeded, avoiding those that contribute to discomfort, such as cabbage, onions, and garlic. Cucurbits and starchy vegetables tend to be better tolerated. Adding a small amount of easily digestible fats, like butter or vegetable oils, can enhance flavor and energy content (von Grundherr, 2019).

One of the most critical nutritional strategies is to ensure proper hydration. The recommended fluid intake is approximately 2 liters per day. Adequate hydration is particularly vital, as dehydration can exacerbate nausea and prolong the time needed to metabolize medications (Bossi, 2018). It's important to drink fluids between meals rather than during them. During episodes of severe nausea and vomiting, fluids with antiemetic properties are recommended, such as ginger tea, ginger drinks, mineral water, or black tea without additives. It’s important to refrain from irritating foods, including strong coffee and mint infusions, which can exacerbate vomiting by relaxing the lower esophageal sphincter.

DIARRHEA → DEHYDRATION

Diarrhea is a common complication of cancer treatment that can lead to postponed therapy, reduced doses, or treatment discontinuation. It can result from chemotherapy, hormone therapy, immunotherapy, or radiotherapy, and is characterized by more than three unformed stools of over 300 ml per day lasting 5-14 days Chronic diarrhea persists for over two 2 months (Forde, 2017). Typically, it stems from impaired fluid and electrolyte transport in the intestines due to damage to intestinal mucosa cells or altered digestive anatomy. Various factors contribute to diarrhea, including cancer, mechanical obstructions, hormonal imbalances, inflammatory bowel diseases, infections, immunological reactions, medications, and dietary factors like food intolerances or high fiber intake (Garutti, 2023). In patients receiving abdominal or pelvic radiotherapy, secondary lactose intolerance often occurs due to enterocyte damage, impairing lactase enzyme secretion. Therefore, lactose-free dairy products are recommended from the start of therapy, as animal milk tends to be poorly tolerated. Sometimes fermented dairy products are better tolerated, and cheese and butter are quite well tolerated, because the lactose content in these products is negligible. In some patients with severe radiation enteritis, a gluten-free diet is additionally recommended (Bossi, 2018).

In addition to pharmacological treatment, dietary modifications are essential. Patients should avoid ingredients that aggravate diarrhea and include constipating foods. Probiotic and sodium butyrate supplementation may also be suggested. Dehydration and electrolyte loss are critical concerns, necessitating proper hydration and an easily digestible diet emphasizing constipating foods (McQuade, 2016). Patients should prioritize:

- Consume constipating fluids rich in electrolytes, such as black tea, dried berry infusions, non-carbonated mineral water, cocoa, vegetable broths, and oral rehydration solutions.
- Increase constipating solid foods like white rice, overcooked potatoes, semolina, stale bread, boiled carrots, unripe bananas, and jellies.
- Switch to lactose-free or plant-based milk alternatives (coconut, oat, almond, rice).
- Include potassium-rich foods like tomatoes and apricots, preferably in pureed forms (Garutti, 2023).

Patients should avoid:

- Laxative foods, including coffee, fruit juices, dried plums, and natural sweeteners (xylitol, erythritol, stevia).
- High-fiber foods, particularly raw vegetables and fruits, whole grains, and gassy foods like legumes and onions or garlic.
- Hot spices.

For persistent diarrhea, the BRAT diet (banana, rice, applesauce, toast) may be recommended short-term (Mąkosza, 2024). Post-symptom relief, reintroducing an easily digestible diet is essential, followed by a gradual return to balanced nutrition tailored to the individual's needs.

CONSTIPATION

Constipation frequently arises from cancer treatment. characterized by less than two bowel movements per week and difficult stool passage. It result from slowed large intestine peristalsis and excessive water absorption, often exacerbated by antiemetics, painkillers, antidepressants, low fiber intake, dehydration. To prevent constipation, dietary adjustments and laxative use can help, but it's crucial to first regulate bowel movement cycles with medication before introducing fiber to at least 25 grams per day (Sharma, 2021). A high-fiber diet for long-term constipation can risk intestinal obstruction (Muscaritoli, 2021).

Hydration is vital, with daily fluid intake recommended at 2-2.5 liters (8-10 glasses) from non-carbonated mineral water (rich in magnesium) and laxative-rich liquids. Patients can also include fruit juices like pear or plum compote, or tomato juice, sauerkraut or pickled cucumber juice as well as tea and coffee (if permitted). Natural sweeteners like erythritol, xylitol or stevia, and birch sugar may aid as well. Gradual fiber intake increase to 35 grams per day is advisable, focusing on whole grains, bran, coarse groats or finer groats (barley, millet), brown, wild or red rice, whole meal pasta cooked "al dente", raw vegetables and fruits with skin, dried plums and fermented products (Bellini, 2021).

To regulate digestion, enhancing physical activity tailored to the individual is essential. For constipation caused by obstruction, a liquid diet is recommended to avoid worsening the condition. Meal frequency should remain at 5-7 smaller meals rich in energy and nutrients (Bellini, 2021).

SHORT CONCLUSION

The analysis of the literature confirmed the need to intensify activities related to nutritional strategies in patients with digestive tract cancers.

The multitude of side effects resulting from progressive gastrointestinal cancer indicates the need to implement multidirectional, specialized nutritional strategies. This is crucial from the perspective of tertiary prevention in supportive and palliative care in oncology in order to ensure the full well-being of the patient, improve his clinical condition, quality of life and increase the effectiveness of the anticancer therapy used.

The optimal solution for patients in supportive and palliative care in oncology seems to be comprehensive dietary care before, during and after hospitalization due to essential role of tertiary prevention in digestive tract cancers patients.

Measurable effects may be achieved through a complex education including an interview, consultation, recommendations and practical dietary tips showed in interesting forms, focused on a specific patient, his condition and ailments.

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Role of radiotherapy in palliative care of patients with female genital tract cancers

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Abstract

The presented review concerns cancers of female genital tract which comprise a significant proportion of the cancer burden in women. We do not discuss palliative radiotherapy for breast cancer. Due to different reasons, even in developed heath care systems in which most of patients present early stage of disease during diagnosis and are suitable for radical treatment part of patients suffer from incurable cancers. The aim of the palliative radiotherapy in these patients, unlike radical is not to cure the patient but a disappearance or significant reduction of not only pain and bleeding, which are the most common, but also other symptoms like pressure or shortness of breath resulting from the mass of the tumor and/or its location. Achieving this goal improves the patient's quality of life. In some of them, the treatment also results in prolonged survival. Prolonged survival may applies both to patients who have a high loco-regional advancement of the cancer and who have distant metastases. The aim of this review is to discuss the following issues: the importance of estimating the patient's expected survival before choosing a palliative radiotherapy regimen, the efficacy of palliative radiotherapy in terms of symptoms from advanced and recurrent primary lesions and in terms of symptoms from metastatic lesions. Furthermore, the possibilities of using stereotactic radiotherapy in the oligometastatic phase of the cancer are also discussed.

INTRODUCTION

Cancer is associated with many somatic and psychological symptoms, the severity of which increases with the advancement of the disease. For patients with advanced, recurrent or metastatic cancer beyond the possibility of radical treatment, palliative treatment is the treatment of choice. Every patient qualified for any form of irradiation must express informed consent to this treatment. In justified situations, such consent may be given by the patient's legal representative. Additionally, cooperation with the patient is necessary to enable him to adopt a therapeutic position. The inability to adopt a repeatable therapeutic position means that the patient cannot be irradiated, independently from clinical situation. Patients qualified for palliative treatment can be divided into two groups. In the first group of patients, the focus is on achieving specific effects to alleviate symptoms such as pain, bleeding, pressure, and shortness of breath caused by the tumor mass or its location. This is accomplished through treatment methods used in radical cancer treatment, including surgical procedures, chemotherapy, and radiotherapy. These methods are complemented by a multidisciplinary approach that addresses the patient's physical, psychological, social, and spiritual needs. In recent years, attention has been paid to the fact that early implementation of integrated oncological treatment and palliative care improves the quality of life, reduces treatment costs, and in some cases extend patient survival (Smith, 2012). Palliative radiotherapy should be a cost-effective intervention which compared to radical radiotherapy is characterized by lower total and higher fractional radiation doses (named hypofractionated radiotherapy), shorter treatment duration, use of simpler irradiation techniques, minimal risk of poor tolerance and complications, and combined with palliative care, makes it possible to reduce or temporarily eliminate the symptoms that constitute the basis for qualification for this treatment, and in some cases it allows to extend the patient's survival. The percentage of patients receiving palliative radiotherapy at various times during oncological treatment ranges from 19 to 40%, according to literature data (Philpot, 2021; Murphy, 2013). The second group of patients receives palliative care without the use of radical treatment methods. The primary goal here is to minimize disease symptoms and optimize the patient's fitness and quality of life. Overall, the integration of palliative care into standard oncology care is emphasized as beneficial, leading to improved quality of life, reduced treatment costs, and, in some instances, prolonged survival. This review defines the role of radiotherapy in palliative treatment for gynecological cancer across various clinical scenarios.

PATIENT'S EXPECTED SURVIVAL

For patients with a short remain lifetime, the potential benefits of treatment should outweigh the expected side effects and burdens of treatment, and therefore palliative radiotherapy and/ or palliative care must be carefully considered. Kutzko et al. in meta-analysis including 42 studies and 88,516 patients with advanced cancer who received palliative radiotherapy in 14 different countries found that 16% of patients die within

30 days of treatment. Their finding can be used as a benchmark to establish a global quality metric for radiation oncology practice audits (Kutzko, 2022). The patient's expected survival time as assessed by the clinician, is a crucial factor in determining eligibility for palliative radiotherapy, as well as the treatment approach (e.g., fractionation method, treatment duration) (Fairchild, 2009; Gripp, 2010; Guadagnolo, 2013). Data suggest that is tendency to overestimate the patient's survival time before qualifying them for palliative treatment (Christakis, 2000; Glare, 2003). Prognostic models available in the literature, which consider various risk factors influencing life expectancy aim to provide a more objective estimate of patient survival. While they help minimize clinician subjectivity, limitations such as limited observation time and patient variability can still affect accuracy. Lam et al. suggested that among the available prognostic models, the one proposed by Chow et al. stands out for its simplicity and continued validation in recent years. This model considers only three risk factors, making it easy to use in clinical practice. These factors are: non breast vs breast cancer, site of metastases bone only vs other, KPS (Karnofsky Performance Scale) >60 vs ≤60 . Each of them are assigned the number 0 or 1. For group 1 (NRF(number risk factors) = 0–1): median estimated survival is 60 weeks; for group 2 (NRF = 2): median estimated survival is 26 weeks and for group 3 (NRF = 3): median estimated survival is 9 weeks (Lam, 2019; Chow, 2008; Krishnan, 2014; Zucker, 2018). Based on analysis of 68,505 patients treated with palliative radiotherapy Zaorsky et al. proposed another, more extensive model named METSS and based on metastases location, elderly (>65 years), tumor primary, sex, sickness/comorbidity, and site of radiotherapy (Zaorsky, 2021).

PALLIATIVE RADIOTHERAPY OF ADVANCED OR RECURRENT SYMPTOMATIC PRIMARY SITES

Due to anatomical location, typical symptoms of advanced cancer of the cervix, corpus, vulva or vagina include bleeding, vaginal discharge, pain and pressure on or infiltration of adjacent organs (bladder, rectum). In clinical practice, mainly external beam irradiation is used for these patients.

BLEEDING CONTROL

The most frequently used palliative irradiation regimens of total doses of 8-20-30 Gy given in 1-5-10 fractions respectively and repeated once a day, exert an early hemostatic effect through increased adhesion of platelets to endothelial cells, followed by vascular fibrosis. Radiotherapy regimens that involve the administration of more than one fraction of radiation are most effective in controlling bleeding. Another proposal is to administer three 8 Gy fractions of irradiation on days 0-7-21 (Zaorsky, 2021; Yan, 2011). The degree of bleeding control reaches 80-90% (Zaorsky, 2021; Sapienza, 2018; Elledge, 2020).

PAIN CONTROL

Local spread of gynecological tumors in the pelvic area may lead to infiltration of surrounding muscles and nerve roots and may cause nociceptive or neuropathic pain. The analgesic effect of palliative radiotherapy in the pelvis area includes reduction of tumor mass and modulation of pain signaling pathways (Seong, 2004). Hypofractionated radiotherapy given usually in 3-5 fractions as described above, together with pharmacologic helped control pain in 33- 78% of patients (Lonkhuijzen, 2011; Mishra, 2005; Kombathula, 2022; Aoshika, 2022).

ADVANCED RECURRENCE

Palliative radiotherapy for advanced local recurrence depends on the previous treatment. Patients who have not been irradiated and presented advanced local recurrence after surgery and who are not eligible for curative intent radiotherapy or surgery may be irradiated based on the schemes described above. There is no data on typically palliative radiotherapy in patients previously irradiated with a radical dose as a stand-alone method or as postoperative treatment. Due to the fact that we are talking about advanced local recurrence, administering a dose of e.g. 20Gy in 5 fractions external beam irradiation or brachytherapy will most likely have a negligible effect. Qualification for repeated radiotherapy, regardless of the intention of such treatment, requires consideration of, among others the current tumor volume and location based on imaging results, radiation dose received so far, the tumor's response after previous radiotherapy and the time that has passed since the previous irradiation. Taking these factors into account allows to estimate the risk of post irradiation complications. Few studies concern brachytherapy as a form of palliative radio-therapy, and in clinical practice it is a method used less often. (Kellas-Ślęczka, 2016).

PALLIATIVE RADIOTHERAPY OF METASTATIC SITES

VISCERAL ORGANS METASTASES

Patients with widely metastatic cancers are candidates mainly for palliative chemotherapy. Data on palliative radiotherapy in patients with metastases to the lung, liver, pancreas, or other visceral organs from female genital cancers are scarce. Whole liver radiation is an option for diffuse metastases from different primary lesions causing pain due to distension of the liver capsule, nausea or vomiting specially in patients, who no longer have any systemic therapy. Soliman and Dawson noticed after single irradiation with a dose of 7-8Gy improvements in symptoms in a substantial proportion of irradiated patients (Soliman, 2013; Dawson 2024). Suggestions regarding symptoms from thoracic metastases like hemoptysis, air obstruction are derived from palliative radiation of incurable lung cancer. Based on American Society for Radiation Oncology the following palliative radiotherapy regimens for metastatic lung lesions may be used in clinical practice:17Gy/2fractions, 10Gy/1fraction, 20Gy/5fractions, 30Gy/10fractions (Das, 2022). There are some case reports on palliative radiotherapy (Demirci, 2010; Kahvecioglu, 2023).

BONE METASTASES

Most studies on palliative radiotherapy of metastatic lesions concern the skeletal and the central nervous systems. The skeletal system is the third most common site of metastasis for a wide range of solid tumors (Huang, 2022). Regardless of the location of the primary lesion, bone metastases cause pain, pose a risk of pathological fracture, and compression of the spinal cord. The following palliative irradiation regimens for metastatic bone lesions of comparable effectiveness are most commonly used in clinical practice: 8Gy/1fraction, 20Gy/5 fractions, 30Gy/10 fractions (Salamanna, 2021; Chow, 2014). On average, approximately 60% of patients observe at least a partial reduction in pain intensity 2-3 weeks after radiotherapy and 30% to 50% of patients noticed complete pain relief (Chow, 2012). Patients with bone lesions in addition to palliative radiotherapy may require analgesic treatment, steroids, medicines that inhibit the activity of osteoclasts responsible for bone resorption, or surgical stabilization. Surgical treatment, usually preceding radiotherapy, plays a very important role especially in cases of impending or completed fracture and compression of the spinal cord (Patchell, 2005; Lawton, 2019; Badhiwala, 2021).

BRAIN METASTASES

Estimated data indicate that globally between 8 and 10% of cancer patients may develop brain metastases (Arnaout, 2024). Clinical signs suggestive of brain metastases include headaches, balance disorders and seizures, nausea, vomiting and others (Kato, 2021). For patients with a single brain lesion combination of surgery and adjuvant radiotherapy (whole-brain or stereotactic irradiation) is associated with improved survival. In the case of multiple brain lesions radiotherapy with palliative intent and pharmacological treatment, mainly steroids is the treatment of choice. Typical whole brain irradiation regimens used in palliative setting are 30Gy in 10 fractions or less common 20Gy in 5 fractions (Gondo, 2022).

ADVANCED TECHNOLOGY IN METASTATIC CANCER

As mentioned earlier, the goal of palliative radiotherapy is to provide symptomatic relief that lasts for some time. Irradiation with one or few radiation fractions, preceded by planning based on CT imaging, is performed using three-dimensional techniques or more complexity techniques utilizes modulation of beams (termed intensity-modulated radiation) or arc radiation which allows for precisely deposit of a therapeutic dose of radiation in the volume of the neoplastic lesion while protecting the surrounding healthy tissues. The pinpoint radiotherapy technique termed stereotactic can be delivered to the body or the brain (then termed stereotactic radiosurgery) and may be used to treat target with high dose radiation with simultaneously rapid dose fall-off immediately adjacent. The technical details of each type of mentioned radiotherapy is beyond the scope of this manuscript, we want to draw the reader's attention to their clinical usefulness. Thanks to these techniques, the role of radiotherapy in an intermediate phase, between the localized metastatic and widely metastatic cancers (referred to as oligometastatic disease) has completely changed. The clinical implication suggests that in limited number of systemic metastatic lesions (generally less than five sites) and controlled primary site, local ablative therapy (surgery or stereotactic radiotherapy) may delay disease progression, the need for chemotherapy and reducing tumor burden. In systematic review of 667 patients treated with SBRT and median dose of 50,7Gy for recurrent or oligometastatic gynecologic cancers percentage of temporal local control exceeding 75% and 80% for abdomen and pelvis lesions

respectively. Above 50% of patients were ovarian cancer patients, lymph node metastases predominated. SBRT was well tolerated (Yegya-Raman, 2020). An another study reported comparable response rate with SBRT in oligometastatic ovarian cancer. The lymph node metastases predominated and radiation dose and number of fractions ranged from 36 to 60 Gy and from 4 to 8 respectively (Iftode, 2018). Cuccia et al. reported the results of 40 patients with multiple primary histology's, all presented extracranial oligometastases, lymph node metastases were the most common failure site. SBRT was delivered to a total median dose of 42 Gy (range, 24-70). The 2-year local control rate was 100% and the 2-year progression--free survival was 23% (Cuccia, 2021). Reddy et al. reported the results of retrospective analysis of 27 patients with oligorecurrence and oligometastatic cervical cancer. The authors noticed response in above 80% of patients and local progression-free survival rate of 75.9% was maintained at 3 years. Liver metastases were associated with a worse results (Reddy, 2020). The authors of a number of reports have noted a high rate of progression outside the field of stereotactic irradiation of metastatic lymph node(s), hence it seems advisable to irradiate the entire at-risk nodal echelon using conformal or intensity-modulated radiation therapy, and they also point to the importance of systemic treatment of oligometastatic disease. Appropriate qualification for stereotactic radiotherapy patients with brain metastases enables local control after a year in 80–95% of cases, and this technique, due to the small margin around lesion and rapid dose reduction in the healthy tissue is associated with a lower risk of late adverse events and serious neurological complications compared to whole brain irradiation. The benefits listed above have led to an increase in the use of stereotactic techniques in both the definitive treatment of single or multiple brain metastases and in adjuvant treatment and depending on clinical on situation total doses range from 21 to 36 Gy in 1-6 fractions (Jimenez, 2017; Masucci, 2018; Loo, 2021). Another area of ongoing exploration involves the stereotactic radiotherapy to metastases in liver, lung, and bone (Tree, 2013).

SUMMARY

The aim of palliative radiotherapy in patients not suitable for radical treatment is to achieve the disappearance or significant reduction of symptoms such as pain, bleeding, pressure, shortness of breath resulting from the mass of the tumor and/or its location. Palliative radiotherapy is characterized by lower total doses and a few, higher than in conventional radical radiotherapy fraction doses, shorter treatment duration, and minimal risk of poor tolerance and complications. In combination with palliative care improves the quality of life of patients and in some cases allows to extend the survival.

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Retropharyngeal space anatomy and the overview of non-traumatic illnesses in this region

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ABSTRACT

The aim of the article is to review of the anatomy and diseases of retropharyngeal space. It is defined as a part of peripharyngeal space and contains lipid tissue and lymph nodes. In clinical point of view, several ailments are significant in this area, such as metastasis, fluid collection or primary lesions. In the case of retropharyngeal infections, most of the illnesses are concentrated on the abscesses. Main symptoms are as follows: neck pain, dysphagia and odynophagia. Other complaints are metastases of several carcinomas, such as nasopharyngeal carcinoma, oral cavity squamous cell carcinoma or hypopharyngeal squamous cell carcinoma, where the first one is the most often.

INTRODUCTION TO THE RETROPHARYNGEAL SPACE ANATOMY

Retropharyngeal space (RS, lat. *spatium retropharyngeum*) is an odd part of the peripharyngeal space (*spatium peripharyngeum*), which is also formed by even parapharyngeal space (*spatium parapharyngeum*). It is limited by following structures:

- superiorly by the base of the cranium;
- anteriorly by the posterior wall of the pharynx and esophagus;
- from the bottom by the mediastinum;
- sideways it is connected with the parapharyngeal space.

Moreover, RS is located anteriorly to the prevertebral muscles and buccopharyngeal fascia bounds it in anterior border. In the posterior direction RS is bounded by the prevertebral fascia.

RS can be devided into two parts, danger and true, where the true part is located anterior to the danger space and starts on the base of skull and ends at around thoracic spine T1-T6 vertebrae. The danger space is formed inferiorly to the true RS and leads to mediastinum (Mnatsakanian et al., 2022). This link between the pharyx and the mediastinum is a potential way for various infections (Tomita et al., 2016; Debnam, Guha-Thakurta, 2012).

Other topographic division of the RS is based on the hyoid bone location. According to this, suprahyoid and infrahyoid parts can be described. The infrahyoid component contains mainly lipid tissue (Debnam, Guha-Thakurta, 2012; Gervasio et al., 2010). In the suprahyoid some lymph nodes are observable. In some types of diseases, these nodes are indicated to the surgical dissection. In that cases, the identification of the alar fascia, which is known as an orientation point, is necessary (Ozlugedik et al., 2005). This fascia can be detected by the occurence of superior sympathetic ganglion, cervical sympathetic trunk and superior laryngeal nerve.

Retropharyngeal lymph nodes are located in the medial direction to the internal caroid artery. In general, they are divided into two groups:

- medial group;
- lateral group, also known as nodes of Rouvière.

Research have shown, that in medial group some atrophies during the childhood are raported, while the lateral group is more susceptible to the development of cancers in adulthood.

The blood supply of RS depends on the pharyx vessels and delivery. Particularly, lesser palatine arteries, ascending pharyngeal artery, superior thyroid artery and inferior thyroid artery are important. Another blood supply of this region is performed by carotid sheath, which contains common carotid artery, internal carotid artery, vagus nerve and internal jugular vein.

It should be noted, that there are no nerves inside the RS, but its walls are supplied by pharyngeal nerve plexus on buccopharyngeal fascia. It is formed by branches from some cranial nerves (IX, X, XI) with both motor or sensory fibers. In addition, recurrent laryngeal nerve innervates the most of intrinsic muscles of the larynx.

CLINICAL ASPECTS OF THE RETROPHARYNGEAL SPACE

Epidemiologic research have shown that almost 20%-50% of oropharyngeal, hypopharyngeal or cervical oesophagal carcinomas are correlated with the metastasis of retropharyngeal lymph nodes (Tanaka et al., 2014; Hallak et al., 2019). In that case, this anatomical region and its abnormalities can be approved as symptoms of various diseases. In the course of neck pain, severe issues in RS can be detected. According to this, RS examination should be performed.

In some cases, the dissection of retropharyngeal lymph nodes may be indicated, for instance, in tonsil cancer (Moore et al., 2013). Another clinical issue taking place in RS is abscess, which also need a surgical treatment (Ojiri et al., 1998). It is known, that most common causes of RS abscesses are peritonsillar abscesses and pyogenic lymphadenitis. Other examples of surgical purposes are as follows (Mnatsakanian et al., 2022):

- Metastasis (Abdelrahman et al., 2022; Pan et al., 2021): primary spinal tumors, ethesioneuroblastoma, papillary thyroid carcinoma, melanoma, lymphoma, squamous cell carcinoma, nasopharyngeal carcinoma;
- Fluid collection (Bhatt, 2018): hematoma, angiodema, RS lymphadenitis, Kawasaki disease, pyriform sinus, COVID-19 (Steehler et al., 2022), acute calcific tendinitis of the longus colli muscles;
- Primary lesions (Alnami et al., 2022): synovial sarcoma, lipoma, liposarcoma.

RETROPHARYNGEAL INFECTIONS AND ITS COMPLICATIONS

It was indicated, that the most common cause of retropharyngeal space infections are from upper aerodigestive tract fragments, especially sinusitis (Gianoli et al., 1991). Significant symptoms of these affairs are as follows:

- Fewer/chills;
- Odynophagia;
- Neck stiffness;
- Sore throat;
- Dysphagia;
- Neck pain.

Moreover, certain signs can co-occur in these infections: neck swelling, temperature >38.2, respiratory distress, airway obstruction, nausea/vomiting, pharyngeal bulge, drooling or diaphoresis. That kind of infections can have serious complications, such as descending necrotizing mediastinitis. It requires complex diagnostics, which include clinical and radiological tests. Treatment is surgical or empirical broad spectrum antibiotic therapy (Brajkovic et al., 2022). In younger children, methicillin-resistent Streptococcus aureus deep neck infections are more often (<15 months; Cheng, Elden, 2013).

In addition to mediastinitis, possible complications of infections in this area include aspiration pneumonia, common carotid artery aneurysm and internal jugular vein thrombosis. In the case of retropharyngeal abscess, recurrences can occur after healing. Depending on the characteristics of the abscess, surgical drainage or parenteral antibiotic therapy may be undertaken (Daya et al., 2005). If a secondary aneurysm or pseudoaneurysm develops in the internal carotid artery, then neurological complications such as Horner's syndrome or cerebral ischemia can occur (Ruff et al., 2017).

Retropharyngeal abscesses can be defined as deep neck space (DNS) infections, which have differentiated ways to manifest and potential lethal complications (Reilly, Reilly, 2012). It should be noted, that other inflammatory issues can be misdiagnosed with abscess, for instance acute calcific tendinitis of the longus colli muscle (Ko-Keeney, Fornelli, 2022). It can also exhibit similar symptoms, such as dysphagia and neck pain (Langer et al., 2020). In addition to laboratory tests, an imaging study should also be performed. Moreover, in some cases patients with suspected abscess will not respond to antibiotics. Here again, incorrect diagnosis may be the cause. Such a cause with similar symptoms may be Kawasaki disease (KD), which is a systemic inflammatory ailment, mainly in young children. Its symptoms are concentrated the

most in head and neck (for example cervical lymphadenopathy; Sliman et al., 2023). In adults rare abscesses have been caused by the tuberculosis (Kamath et al., 2007; Al Soub, 1996). For that type of abnormality, itraoral aspiration and antitubercular chemotherapy are good options (Menon, Baruah, 2014). Large masses can also cause displacement of the cervical vertebrae C5-C6. Often significant foregin bodies present in the oral area can migrate and consequantly cause retropharyngeal abscesses (Das et al., 2022). Infrequent cases have been described after Salmonella species infections (Su et al., 2003).

Aside from bacterial infections, retropharyngeal abscesses can develop during fungal invasion in patients with decreased immunity, for example cryptococcus neoformans. Typical symptoms then appear, like odynophagia and sarcoidosis (Das et al., 2010). Interestingly, retropharyngeal abscess may may occur after COVID-19 infection (Wang et al., 2021). It is probably, that its occurrence is influenced by many factors and predisposition to the development of such an abscess.

Recent research have shown the risko of the application of selective immune modulation biological agents for rheumatoid arthritis. In rare cases, some neck infections with that kind of therapy can be observed, especially as retropharyngeal abscess (Kakarala et al., 2010). Symptoms include neck pain and odynophagia. If the size of this abscess is large, it may be advisable to make an transcervical incision and drainage, apart from antibiotic therapy.

RETROPHARYNGEAL METASTASES

It was considered, that retropharyngeal lymph nodes (RLN) are important structures in the development and metastasis of head and neck cancer. In the case of oral cavity squamous cell carcinoma, especially I, II and III levels are areas of metastasis and may require surgical resection, but there are rare situations (Abdelrahman et al., 2022; Shah, 1990). Attack on RLN is highly associated with the poor prognosis of recovery (Paleri et al., 2016). Hovewer, in the course of mentioned carcinoma, there are low (at around 1%) reported cases of metastasis to RLN (Oikawa et al., 2019). The most amount of metastasis was indicated in the nasopharyngeal carcinoma (69%; Ho et al., 2012). It is related with the stage of the disease – in heavily developed and aggressive cancers, such metastasis will be more likely, which also depend on the modifications in lymphatic drainage (Nishida et al., 2005).

In the nasopharyngeal carcinoma, the N1 stage was coded as in high risk to RLN metastasis (Edge, Compton, 2010). This means very rapid involvement of these lymph nodes. More recent retrospective studies have also maintained this stage as a key one (Pan et al., 2021). However, it can be different in individual populations.

Nasopharyngeal carcinoma can be characterized by specific metastatic pathway. It passes in an orderly way down of the neck (Tang et al., 2007; Sham et al., 1990). Knowledge of this feature can be helpful in assessing the stage of the disease development.

It is also important to list other tumor masses moving through RLN. Some rare conditions should be mentioned, for instance olfactory neuroblastoma, which is malignant neoplasm from the olfactory epithelium (Kim et al., 2006). The prognosis in its case is poor and metastasis can be unusual and distant. Other reports indicated the option of metastasis of papillary thyroid carcinomas by RLN. The transcervical removal of these nodes should then be considered (Kainuma et al., 2011).

Other research have indicated the RLN metastasis from the hypopharyngeal squamous cell carcinoma. It is known, that in this case also the prognosis becomes worse (An et al., 2021). The situtation is similar for oral cancer, where metastasis to RLN is rare, but the prognosis then becomes poor. To increase survival in this entity, surgical excision of these metastases is recommended (Oikawa et al., 2019).

CONCLUSIONS

- RS is a part of peripharyngeal space; it contains lipid tissue and lymph nodes;
- Significant non-traumatic clinical problems within RS include the following complaints: metastasis, primary lesions and abscesses;
- In RS infections, several main symptoms can be indicated: neck pain, odynophagia or dysphagia. Moreover, certain pathogens can infect RS: Streptococcus aureus, Salmonella species and Cryptococcus neoformans;
- The most common RLN metastases are formed by nasopharyngeal carcinoma. Other cancers metastasize there less frequently, for instance oral cavity squamous cell carcinoma or olfactory neuroblastoma.

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Anti-inflammatory diet in cancer disease

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ABSTRACT

Cancer risk factors include internal, individual characteristics (i.e. chromosome abnormalities, gene mutations, age, clinical conditions, hormone unbalance), and external causes (i.e. diet, tobacco smoke, use of alcohol, pollutants, exposure to radiation, infections). Most of external reasons of cancer are associated with some form of chronic inflammation. Pathogenesis of up to 20% of human tumors is associated with pathogens and infection-driven inflammations, 30% of cancers can be linked to tobacco smoking and inhaled pollutants (such as silica and asbestos), and 30-50% cancers onset can be avoided due to change of alimentary habits including diet. The relationships between inflammation and cancer are varied and complex. On one hand we have chronic inflammation caused by the external triggers, on the other hand we have cancer-related inflammation which is an essential component of the tumor microenvironment. This leads to amplification of inflammation processes promoting cancer cells proliferation, degradation and remodeling of the extracellular matrix, weakening of vascular barriers and to the immunosuppression associated with malignant disease. All of this enable cancer progression. There is growing evidence linking diet and modulation of the inflammatory response. Anti-inflammatory potential of diet can be reflected by indicator called the Dietary Inflammatory Index. Researches on possible effect of diet on inflammation and cancer revealed that consumption of meals with high Dietary Inflammatory Index was associated with higher risk of colorectal cancer, breast cancer, and prostate cancer. In this review, we will focus on current evidence of the pathways connecting inflammatory conditions with neoplastic transformation and progression. We also provide an overview on anti-inflammatory effects of diet in field of reducing cancer incidence and improving cancer therapy outcome.

INTRODUCTION

According to The Global Burden of Disease (GBD) study 2019, cancer is one of a leading causes of death worldwide, second after cardiovascular diseases (Roser, 2015, updated 2019). The number of cancer new cases and cancer deaths is growing year by year. Moreover, these numbers are growing faster than the birth rate of the world population (11%) over the same period. At the same time, in 9 years (2010-2019), number of new cancer cases increased by 26% from 18.7 million (95% UI: 18.0-19.3 million) to 23.6 million (95% UI: 22.2-24.9 million) and number of total cancer deaths increased by 20.6% from 8.3 million (95% UI: 7.89-8.57 million) to 10 million (95% UI: 9.36-10.6 million) (Global Burden of Disease 2019 Cancer Collaboration, 2019). Majority of cancers (90-95%) is caused by external, environmental, and lifestyle factors (Rasnic, 2020; Tsaousis, 2019). The main environmental factors responsible for the development of malignant neoplasia are pathogens, air pollutants, ultraviolet and ionizing radiation. Cancer risk factors arising from human life style are tobacco smoking, excessive alcohol consumption, diet, and physical activity (Hatta, 2021; Liu, 2021; Jurdana, 2021; Rasnic, 2020; Lewandowska, 2019). The evidence indicates that smoking is a leading cause up to 30% of cancer-related deaths (Hecht, 2006). It is estimated that 30-50% of all cancer cases could be prevented by changes in alimentary habits (Mentella, 2019; Donaldson, 2004). The link between diet and cancer was revealed in various types of cancer. Interestingly, in the top ten cancer types (total burden of disease measured in Disability-Adjusted Life Years (DALYs) per 100,000 individuals from all cancer types) listed in GBD study 2019, there is eight cancers which etiology may be connected with nutrition. Listing from the top (the highest burden rate) there are lung cancer, colon and rectum cancer, stomach cancer, breast cancer, liver cancer, esophageal cancer, pancreatic cancer, and prostate cancer (Liu, 2021; Global Burden of Disease 2019 Cancer Collaboration, 2019). Numerous studies has demonstrated the presence of an inverse relationship between high Mediterranean diet (MD) adherence and various cancer types incidence (Mentella, 2019). The study of Van den Brandt et al. showed 40% decrease incidence of breast cancer in post-menopause women with high MD adherence in comparison to women with low MD adherence ($HR_{MD\ high}$ vs. $_{MD\ low}$ = 0.60, 95% CI: 0.39-0.93) (van den Brandt, 2017). Another study estimated the odds ratios (ORs) of breast cancer through a Mediterranean Diet Score (MDS), summarizing the major characteristics of the Mediterranean dietary pattern and ranging from 0 (lowest adherence) to 9 (highest adherence). It appeared that the ORs for breast cancer were 0.86 (95% CI: 0.76-0.98) for a MDS of 4-5 and 0.82 (95% CI: 0.71-0.95) for a MDS of 6-9 (p for trend = 0.008) (Turati, 2018). Furthermore, current evidence indicate that consuming whole fruits, vegetables, legumes, olive oil, nuts, and fish (components characteristic for Mediterranean diet) and avoiding red and processed meat, refined grains, sweets, caloric drinks, juices, convenience food, and sauces (components characte-

ristic for Western diet) might reduce colorectal cancer risk (Castello, 2019; Rosato, 2016). It was noted that the OR for a 1-point increment in the MDS was 0.89 (95% CI: 0.86-0.91) (Rosato, 2016). A 1-point increase in the MDS was also associated with a decreased risk of gastric cancer of 5% (95% CI: 0.91-0.99) (Buckland, 2011). Diet based on regular consumption of vegetables (especially garlic, onion, leeks, tomatoes, carrots, pumpkins, and cruciferous vegetables, as cabbages, broccoli, cauliflower, brussels sprouts) and fruits is likely to decrease at least a 60–70% risk of breast, colorectal, and prostate cancers, and 40-50% risk of lung cancer (Donaldson, 2004). This protective role of diet on listed cancer types onset is associated with high intake of nutrients like fiber, antioxidants such as the carotenoids (α-carotene, β-carotene, lycopene, lutein, cryptoxanthin), folic acid, selenium. The protective effect of olive oil consumption on risk of breast, gastrointestinal, upper aerodigestive and urinary tract cancer (Markellos, 2022; Moral, 2022), bladder cancer (Brinkman, 2011) was also confirmed.

Summarizing, there is a growing evidence that certain nutrients and dietary patterns have significant impact on the causes and the prevention of cancer (Markellos, 2022; Moral, 2022; Mentella, 2019; Turati, 2018; Rosato, 2016; Donaldson, 2004). In this review we describe the links between diet and cancer taking into consideration anti-inflammatory, anti-oxidative, and immune-modulatory properties of food. It is due to the fact, that chronic inflammation is a one of the cancer hallmarks, playing imperative role in the development and progression of neoplasia. The inflammation processes may be the result of chemical factors (carcinogens), physical factors like ultraviolet radiation, chronic infections (i.e. HPV, EBV, *Helicobacter pylori*, *Opisthorchis viverinni*) and lifestyle factors (i.e. obesity, alcohol, tobacco, diet). Finally, there is also cancer-driven chronic inflammation in the tumor microenvironment (Muresancu, 2022; Wen, 2022; Liu, 2021; Hatta, 2021; Zhao, 2021; Khandia, 2020; Multhoff, 2012; Whiteside, 2008). The variety of cells in tumor microenvironment (i.e. cancer cells as such, macrophages, neutrophils, lymphocytes, dendritic cells, natural killer cells, fibroblasts, adipocytes, endothelial cells) produce many inflammatory mediators, including cytokines, chemokines, growth factors, free radicals, prostaglandins and proteolytic enzymes. These factors fuel prolonged inflammation what favors tumor cell survival and proliferation, immunosuppression and angiogenesis, while at the same time promoting the accumulation of oncogenic mutations (Maiorino, 2022; Wen, 2022; Zhao, 2021; Multhoff, 2012; Whiteside, 2008). In this paper, we attempt to elaborate current knowledge about pathways of anti-inflammatory effect of certain food and nutrients and we want to present the latest scientific evidence supporting anti-inflammatory dietary intervention in cancer.

SEARCH STRATEGY AND SELECTION CRITIERIA

The extensive literature search was conducted online and the following databases were used: PubMed (NCBI), Google Scholar, Scopus. We searched through the most relevant studies including randomized controlled trials (RCTs), in vivo and in vitro experimental studies, and literature reviews and meta-analyses published between 2000 to 2023.

The main key words were: cancer causes, cancer risk factors, cellular mechanisms of carcinogenesis, molecular mechanisms of carcinogenesis, biology of cancer, chronic inflammation, chronic inflammation in disease, chronic inflammation in cancer, diet in cancer, anti-inflammatory diet, anti-inflammatory diet in cancer, dietary inflammatory index, anti-inflammatory nutrients.

CANCER AS A DISTURBANCE OF THE BODY'S HOMEOSTASIS

A cancer (neoplasia) is an abnormal tissue that arises from a single "diseased" cell in the body. It grows as a result of uncontrolled cell divisions, combined with a simultaneous disruption of the differentiation of the resulting cells. The body loses control over the process of cell proliferation as a result of mutations of various genes that encode proteins that play an important role in the cell cycle. Such genes are called protooncogenes and anti-oncogenes. The newly formed cancer cells do not differentiate into typical tissue cells, they form tumor – abnormal mass of tissue (Kontomanolis, 2021; Patterson, 2018; Cooper, 2000). A tumor may be classified as benign or malignant depending on the multiple characteristic. Benign tumors grow in size in their primary location, they don't invade surrounding normal tissue nor spread to distant parts of the body. In contrary, malignant tumors are capable to spread throughout the body via the circulatory or lymphatic systems (metastasis). They usually also invade the tissues around them. Only malignant tumors should be properly referred as cancer. Cancer can metastasize anywhere in the body including the breast, lungs, liver, brain, intestines, reproductive organs, blood, or skin. The differences between benign

and malignant tumors are also related to their treatment and recurrence. A benign tumor can usually be completely treated with surgery, although some may be treated with radiation therapy or chemotherapy. Malignant tumors apart from surgery mostly require chemotherapy, radiation therapy, or immunotherapy medications to eliminate a tumor cell that still remains after treatment or to treat secondary tumors present at other parts of the body (distant metastases) (Kontomanolis, 2021; Patel, 2020; Leemans, 2011; Cooper, 2000). Benign and malignant tumors are classified and grouped according to the type of cell from which they start. The following six main categories indicating the origin of cancer cells are:

- carcinoma – malignancies of epithelial cells covering or lining on surfaces of organs, glands, or body structures (i.e. adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, melanoma, and transitional cell carcinoma) (Cooper, 2000);
- sarcoma – solid tumors of connective or supportive tissues such as bone, cartilage, fat, muscle, tendons or blood vessels (i.e. osteosarcoma, chondrosarcoma, Ewing's sarcoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma) (Miwa, 2023);
- leukemia – blood cancer, which arise from impairment of the hematopoietic system (i.e. acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, myelodysplastic syndromes) (Kantarjian, 2021; Juliusson, 2016);
- lymphoma – a heterogeneous group of lymphoid malignancies (i.e. Hodgkin lymphomas, non-Hodgkin lymphomas) (Jiang, 2017);
- myeloma – originates in the plasma cells of bone marrow (Rajkumar, 2016);
- central nervous system cancers – they starts from the cells of brain and spinal cord (i.e. gliomas, glioneuronal tumors, neuronal tumors, ependymal tumors, choroid plexus tumors, pineal tumors, cranial and paraspinal nerve tumors, meningiomas (Luis, 2021).

Carcinogenesis is a multistage process that is extremely complicated and refers to many different levels of regulation. Etiologically it involves mutations in genes that play role in maintaining the balance between cell proliferation and apoptosis. There are environmental, exogenous and endogenous factors, as well as individual factors, including age, and genetic predisposition which contribute to the development of cancer. However, it is worth to notice, that an inherited predisposition to cancer is found in about 5-10% of all cancer cases. Individuals who carry a mutation in any of genes called cancer predisposition genes have an increased susceptibility to cancer (Rasnic, 2020; Tsaousis, 2019). The majority of cancers are sporadic, they result from genetic changes which are induced by various factors which are presented in Figure 1 (Muresancu, 2022; Liu, 2021; Hatta, 2021; Jurdana, 2021; Lewandowska, 2021; Golemis, 2018; Blackadar, 2016). If the DNA damage is not repaired or the cell does not die by apoptosis, the process of neoplastic transformation is initiated. This single mutated cell begins to proliferate. Additional mutations followed by selection for more rapidly growing cells within the population then result in progression of the tumor and malignancy. Proliferation of cancer cells and their differentiation results in the formation of a cancerous tumor. In the final stage the tumor acquires the ability to infiltrate tissues and form metastases (Golemis, 2018; Paterson, 2018; Leemans, 2011; Cooper, 2000). A tumor is not simply a group of cancer cells, but rather is composed of heterogeneous and interactive populations of cancer cells and cancer stem cells along with infiltrating and resident multiple types of host cells, secreted factors, extracellular matrix and tumor-associated stroma. Tumor cells stimulate significant molecular, cellular and physical changes within their host tissues to support tumor growth and progression. They create so called tumor microenvironment which also contain blood vessels, lymphatic vessels, immune cells, fibroblasts and extracellular matrix. Together they form a specific microenvironment that plays an important role in tumor progression, metastasis, and escape from immune surveillance (Wen, 2022; Pan, 2020; Gupta, 2018; Whiteside, 2008).

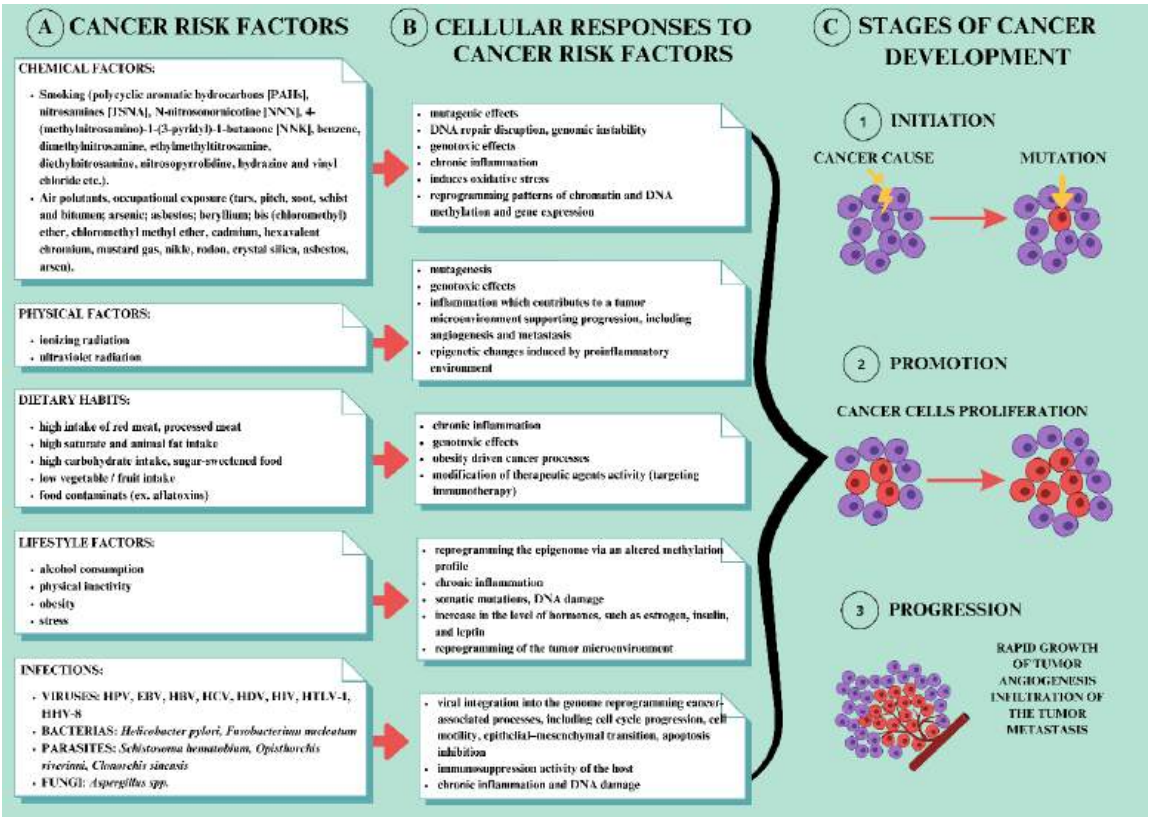

Figure 1. Multiple factors involved in carcinogenesis (Panel A) and mechanisms for the carcinogenicity of particular cancer causes (Panel B); stages of cancer development (Panel C); own study based on (Muresancu, 2022; Liu, 2021; Hatta, 2021; Jurdana, 2021; Lewandowska, 2021; Golemis, 2018; Blackadar, 2016)

CHRONIC INFLAMMATION – FRIEND OR FOE?

Inflammation is the body's natural defense mechanism that accompanies infections caused by such factors as pathogenic microorganisms, tissue damage, burns, ischemia or internal factors. If the immune system works properly then it recognizes the source of the problem and eliminates it without damaging its own tissues. In acute stages of inflammation, pathogen-associated molecular patterns (PAMPs) are recognized by local tissue macrophages or dendritic cells, activating the secretion of pro-inflammatory mediators like cytokines, chemokines, vasoactive amines, reactive oxygen species (ROS), and eicosanoids. This initial phase leads to the recruitment of neutrophils, than monocytes and lymphocytes accumulating in the inflammation site to neutralize harmful molecules. The recruitment of monocytes and their differentiation into macrophages at sites of inflammation are key events in determining the outcome of the inflammatory response and initiating the return to tissue homeostasis (Maiorino, 2022; Wen, 2022; Greten, 2019; Feehan, 2019; Gupta, 2018; Headland, 2015). So, under normal conditions, at the final stage the inflammatory response is alleviated and full tissue repair occurs. Inflammation can become chronic if the cause of the inflammation persists or certain control mechanisms in charge of shutting down the acute inflammation process fail. In contrary to its acute phase, in chronic inflammation, tissue destruction occurs faster than cellular regeneration, causing pathological fibrosis. The tissue's function can be reduced or even lost. In chronically inflamed tissue, the stimulus of the immune system is persistent. Chronic inflammation has been found to mediate a wide range of diseases, including autoimmune diseases, cardiovascular diseases, diabetes, arthritis, neurodegenerative diseases, and cancer (Rohm, 2022; Rajesh, 2022; Jin, 2022; Konig, 2020; Khandia, 2020; Multhoff, 2012).

If we look deeper at the cancer factors outside of germline mutations, most of them are associated with some form if chronic inflammation. Starting from the chronic infections (i.e. *Helicobacter pylori* and gastric cancer, human papilloma virus and cervical cancer, Epstein-Barr virus and Burkitt's lymphoma, *Schistosoma haematobium* and bladder cancer), through ultraviolet radiation, tobacco smoking, and chemical pollutants (i.e. tobacco and bronchial lung cancer, pancreatic cancer, or esophageal adeno-carcinoma, asbestos fiber and mesothelioma, ultraviolet light and melanoma), finishing on dietary factors

and obesity as such (i.e. red meat and processed meat and colorectal cancer, alcohol and hepatocellular carcinoma, or breast cancer (Muresancu, 2022; Liu, 2021; Hatta 2021; Golemis, 2018, Multhoff, 2012). The connection between tumorigenesis and inflammation is mediated via intrinsic and extrinsic pathways (Mantovani, 2008). The incristic pathway is activated by cancer-initiating genetic alterations causing inflammation and neoplasia. There are mutation-driven proto-oncogene activation, chromosomal rearrangement/ amplification, and inactivation of tumor suppressor genes causing recruitment and activation of inflammatory cells secreting inflammatory mediators and thus generate an inflammatory microenvironment. Tumor-extrinsic inflammation can be triggered by many factors like bacterial and viral infections, chemicals, ultraviolet radiation, alcohol, obesity, autoimmune disease etc.

The majority of infiltrating inflammatory cells in chronic inflammation are macrophages and leukocytes. They generate high levels of reactive oxygen (ROS) and nitrogen species (RNI), which induce mutations. Thus, systemic inflammation can lead to increased mutagenesis, predisposing to accumulation of mutations in normal tissue and activation of oncogenic pathways. For example, accumulation of mutations in Tp53, KRAS, APC and other cancer-related genes in intestinal epithelial cells can trigger colorectal cancer formation (Canli, 2017; Roobles, 2016). What's more, cytokines (i.e. interleukin 6 (IL-6), tumor necrosis factor alfa (TNF-α), and IL-1β) produced by inflammatory cells activates epigenetic changes resulting in modulation of expression levels of oncogenes, genes controlling DNA stability, and tumor suppressors (Grivennikov, 2013).

This new transformed malignant cells need to growth to create tumor. Both inflammation pathways – intrinsic and extrinsic, induce the activation of several transcription factors such as nuclear factor-kappa B (NF-κB), and signal transducer and activator of transcription 3 (STAT-3) that result in the formation of pro-inflammatory and immune-supressive factors including chemokines (IL-8), cytokines (i.e. IL-1, IL-6, IL-10, IL-22, IL-23, TNF-α), adhesion molecules (intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1)), epidermal growth factor (EGF), and prostaglandin-endoperoxide synthase 2 (PGHS-2). NF-κB and STAT-3 interact at multiple levels, they are key players in a communication between cancer cells and their microenvironment, especially with inflammatory/immune cells that infiltrate tumors (Zhao, 2021; Fan, 2013; Multhoff, 2012; Aggarwal, 2009). Functional interactions between NF-κB and STAT-3 in immune cells control the production of pro-inflammatory cytokines that maintain inflammation and stimulate tumor growth by activating NF-κB and STAT-3 in cancer cells. What's more, NF-κB and STAT-3 control the expression of anti-apoptotic, pro-proliferative and immune response genes in premalignant and cancer cells. In other words, they are responsible for inflammation-promoted tumor growth and spread. The presence of constitutively active NF-κB, and STAT-3 was found in hepatocellular carcinoma, colon, breast, ovarian, pancreatic, prostate, and brain tumors, leukemia, lymphoma, and multiple myeloma (Kuo, 2017; Gong, 2017; Weichert, 2007; Pikarsky, 2004; Greten, 2004).

Once the tumor grew it creates and shapes its own tumor microenvironment. Various immune effector cells are recruited to the tumor site, their anti-tumor functions are downregulated, largely in response to tumor-derived signals. They favor tumor survival, boost the inflammation and promote the tumor growth and metastasis. The tumor milieu is infiltrated by immune cells mediating adaptive immunity, T cells, dendritic cells, as well as effectors of innate immunity, macrophages, polymorphonuclear leukocytes (Maiorino, 2022; Wen, 2022; Greten, 2019; Multhoff, 2012; Whiteside, 2008). Macrophages present in tumors are known as tumor-associated macrophages (TAMs). They are re-programmed to inhibit lymphocyte functions through release of inhibitory cytokines such as IL-10, prostaglandins or reactive oxygen species. TAMs express a variety of cytokines that stimulate tumor cell proliferation and survival, including EGF, platelet-derived growth factor (PDGF), tumor growth factor (TGF-β1), hepatocyte growth factor (HGF), and epithelial growth ligands of the factor receptor (EGFR) family and basic fibroblast growth factor (BFGF). They are involved in angiogenesis of tumor, as they release the angiogenic molecules and express a series of enzymes – metalloproteinases (MMP) involved in the regulation of angiogenesis, including MMP-2, MMP-7, MMP-9, MMP-12, and cyclooxygenase-2 (COX-2) (Maiorino, 2022; Pan, 2021; Martinez, 2008). Myeloid suppressor cells accumulating in human tumors promote tumor growth and suppress immune cell functions through copious production of an enzyme involved in l-arginine metabolism, arginase 1 (increase superoxide and NO production), inducible nitric oxide synthase (iNOS), TGF-β, IL-10, COX-2, and indoleamine 2, 3-dioxygenase (IDO) (Maiorino, 2022; Ochoa, 2007; Tsai, 2007). Tumor-associated dendritic cells are usually immature and they have ability to stimulate antigen-reactive effector immune cells, primarily T cells and B cells (Maiorino, 2022).

REVIEW OF ANTI-INFLAMMATORY NUTRIENTS

There is growing evidence showing a significant association between a high pro-inflammatory diet and increased cancer risk. The Western diet has been identified as strongly pro-inflammatory. This diet is characterized by the consumption of high-energy and processed foods rich in simple sugars, saturated fats, which contains few vegetables and fruits, but is rich in red meat, refined grain products, salty and sugary snacks, sweetened beverages or fast food. Low consumption of vegetables and fruits is associated with insufficient intake of vitamins, minerals, antioxidants and dietary fiber. What's more, an imbalance in the intake of fatty acids (saturated to unsaturated) leads to the formation of pro-inflammatory eicosanoids (Christ, 2019; Furman, 2019; Seaman, 2002). Purified cereal products, sweets, confectionery are sources of simple carbohydrates, have a high glycemic index and are poor in vitamins, minerals and dietary fiber. When consumed, they cause a rapid rise in blood glucose levels, which also leads to an increase in insulin, which when secreted in excessive amounts is a pro-inflammatory factor. A diet rich in high glycemic index foods has been shown to be closely associated with higher levels of serum inflammatory markers, such as IL-4, IL-6, CRP, TNF-α (Shivappa, 2017; Shivappa, 2014; Sears, 2011; Galland, 2010).

As this certain dietary habits are well confirmed cancer cause, the logic step is to look at the possibilities and potential of food which have anti-inflammatory properties. So, the goal of the anti-inflammatory diet would be to alleviate the inflammatory processes that cause or develop during cancer. What is the definition of anti--inflammatory diet? In simple words, anti-inflammatory diet, is the one containing and combining various anti-inflammatory nutrients, and simultaneously is low in pro-inflammatory compounds. The greatest example is the Mediterranean diet, which is considered one of the most worldwide healthy dietary patterns thanks to a combination of foods rich mainly in antioxidants and anti-inflammatory nutrients. The health benefits of the Mediterranean diet are well documented and acknowledged in the literature (Dominguez, 2021; Mentella, 2019; Demini, 2017). Main nutrients of Mediterranean diet, that have confirmed anti-inflammatory properties are presented in Table 1.

Table 1. Main anti-inflammatory nutrients and their mode of action

ANTI-INFLAMMATORY NUTRIENTS	MECHANISMS OF ACTION	HEALTH BENEFITS	SOURCE IN DIET	REF.
monounsaturated fats (oleic acid)	inhibition of the activated NF-κB reduction of the pro-inflammatory eicosanoids production inhibition of TNF-α gene expression promotion of polarization of M2 macrophages, what therefore increase the secretion of anti-inflammatory IL-10	reduce the risk of cardiovascular disease, diabetes, Alzheimer's diseases, breast, colon, bladder, gastrointestinal, upper aerodigestive, urinary tract, and colon cancer	avocado, extra virgin oil, grapeseed oil, nuts, sesame, almonds	Markellos, 2022; Moral, 2022; Bangar, 2022; Pacheco, 2022; Riolo, 2022; Ravaut, 2020; Alkhalaf, 2019; Bhuyan, 2019
lutein, zeaxanthin	free radicals scavenger inhibition of the expression of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β)	improve the function of blood vessels, reduce the risk of breast and colon cancer	avocado, kale, spinach	Ahmed, 2022; Tramontin, 2020; Lara-Márquez, 2020; Alkhalaf, 2019; Bhuyan, 2019
sulforaphane	decrease of mitogen-activated protein kinases (MAPK) including p38, extracellular signal-regulated kinase (ERK) 1/2, and c-Jun N-terminal kinase (JNK), NF-κB increase the release of anti-inflammatory cytokines IL-4,IL-10 reduction of the cleavage of caspase-1 and caspase-3	reduces the risk of breast, colorectal, skin, oral, bladder, lung, prostate cancer, useful as a supplement to counteracting neurodegenerative diseases	broccoli, cauliflower, brussels sprouts, cabbages, kohlrabi, kale	Nandini, 2020; Ruhee, 2020; Schepici, 2020; Amjad 2015; Donaldson, 2004

	inducing glutathione S-transferases inhibiting expression of CYPs epigenetic modification of expression of genes allowing for enhanced expression of proteins such as p21 or Bcl-2-associated X protein significant changes in TGFβ, insulin signaling and EGF receptor pathways			
flavonols (quercetin, kaempferol, galandin, myricetin, catechin, epicatechin, procyanidins)	free radical scavenging due to a high oxygen radical absorbance capacity reducing the activation of NF-κB inhibiting the production and release of cytokines and chemokines attenuation the expression of inflammatory factors: ICAM-1, VCAM-1	chemopreventive agents against neurodegenerative diseases, cancer, heart disorders, reduce the risk of prostate, colon, liver, breast or lung cancer, among others	cocoa, black elderberries red cabbage, dark grape, green tea, apples	Ribeiro, 2023; Cinar, 2021; Alvarez-Cilleros, 2020; Sorrenti, 2020; Kopustinskiene, 2020; Maleki, 2019; Garcia, 2018
curcumin	inhibition of the activity of enzymes: COX-2, 5-LOX, MMP inhibition of the production of pro-inflammatory cytokines IL-1, IL-6, IL-8, TNF-α inhibition of activation of NF-κB	prevents arthritis, cardiovascular diseases, pancreatic cancer, breast cancer, digestive system	turmeric	Pivari, 2019; Sarkar, 2016; Girija, 2010
omega-3 fatty acids: DHA, EPA, ALA	inhibition of arachidonic acid metabolism active role as the precursors of potent, specialized pro-resolving mediators (SPMs), such as resolvins, protectins, and maresins	moderate- and low-certainty evidence suggests slightly reduces risk of coronary heart disease mortality and events, and reduces serum triglycerides, increasing ALA slightly reduces risk of cardiovascular events and arrhythmia, reduction of risk of brain breast, prostate cancer,	oily fish, flaxseed and flax oil, walnuts	Abdelhamid, 2020; Kwon, 2020
flavonoids, tannins, phenolic acids	reduction of the level of IL-1, IL-4, IL-5 increase in level of IL-10, IL-12, IL-1β, TNF-α, IFN-γ, IL-2 decreased amount of macrophages and neutrophils free radical scavenging due to a high oxygen radical absorbance capacity modulation of gut microbiota what results with the production of short-chain fatty acids (SCFAs)	reduce the risk of diabetes, neurological, cardiovascular diseases and various cancer, including colon cancer	red beans, blackberry leaves, blueberries, cranberries, strawberries, grapes	Golovinskaia, 2021; Pan, 2018

capsaicin	inhibition of the synthesis and release of TNF-α, IL-1β, IL-6, PGE2, nitric oxide inhibition of activated NF-κB, STAT3 modulation of gut microbiota what results with the production of short-chain fatty acids (SCFAs) free radical scavenging by enhancing FRAP (the ferric reducing antioxidant power), GSH level, PMRS activity (plasma membrane redox system), and ameliorating reactive oxygen species (ROS), MDA (malondialdehyde), and AOPP (advanced oxidation protein products) in the plasma	potentially reduce the risk of cancer of the digestive system, prostate and breast	chili pepper	Munjuluri, 2021; Rosca, 2020; Belenahalli Shekarappa, 2019; Mendivil, 2019; Buthani, 2007
lycopen	activating the antioxidant response element (ARE) associated with nuclear factor E2 (NFE2L2), what increases the amount of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px)) reduction of the growth of ROS and inhibiting oxidative stress suppression of inflammatory (TNF-α, IL-6, IL-8, and IL-1β), NF-κB, and apoptotic (caspase and Bbl-2) pathways regulation of mitogen-activated protein kinase (MAPK), inducible nitric oxide synthase (iNOS) inhibition of enzymes involved in the metabolism of arachidonic acid: COX-2 and 5-LOX	improves endothelial function, provides protection against atherosclerosis, reduce the risk of prostate, bladder, intestine and breast cancer	tomatoes, watermelon, pink grapefruit, apricots, rose hips fruit, papaya	Przybylska, 2022; Moran, 2022; Van Steenwijk, 2020
epigallocatehin 3-gallate	reduction of the production of IL-6, IL-8, TNF-α inhibition of the enzyme COX-2 participating in the synthesis of prostaglandins	reduces the risk of breast, prostate, gallbladder and biliary cancer, protects against cardiovascular disease and diabetes	green tea	Wang, 2021; Kochman, 2020

β-glucans	modulation of gut microbiota what results with the production of SCFAs enhancement of antimicrobial activity of macrophages, monocytes and neutrophils, by leading to maturation of these target cells increase production and release of inflammatory cytokines: TNF-α, CXC-chemokine ligand 2 (CXCCL2), IL-2, IL-6, IL-10, IL-12, IL-23 downregulation of IL-12 upregulation of programmed death receptor 1 (PD-L1) tumor expression	synergic effect with antitumor mAbs agents (potential therapeutic applications under investigation)	mushrooms algae, oats, cereals, barley, rye, wheat	Cognigni, 2021; Geller 2019
affeic acid phenethyl ester (CAPE)	inhibition of COX-2, COX-1, 5-LOX activity decreasing of JNK1, IkK, IkB phosphorylation lowering the activity of NF-κB decreasing of the release of LTB4, LTC4, and histamine decreasing of IL-1β, MCP-1, IL-8, IL-6, IL-6R, TNF-α the expression and production	potential therapeutic applications, that can be used in various diseases (including anti-viral, anti-bacterial, anti-cancer, immunomodulatory, and wound-healing activities) i.e.: CAPE potentiates gastric cancer cell sensitivity to doxorubicin and cisplatin, may be used as a chemopreventive agent, it protects normal cells against the cytotoxic effects of anti-cancer drugs	propolis	Batoryna, 2021; Tolba, 2013

EFFECTS OF ANTI-INFLAMMATORY DIET ON CANCER

Studies analyzing influence of diet on the occurrence of inflammation are most often based on the indicator called the Dietary Inflammatory Index (DII). DII was established in 2013 on the basis of numerous publications, which described the influence of 45 food components (consisting of whole foods, nutrients and other bioactive compounds derived from a much larger literature review), then included in the DII, on inflammation development. Dietary Inflammatory Index was validated against six inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein. The scoring algorithm of DII was based on the effects of each food parameter on the aforementioned inflammatory biomarkers. Each component of DII has given an individual positive or negative point value ("+1" or "-1" point). Positive values are assigned to ingredients and/or products that exhibit pro-inflammatory properties (i.e. saturated fatty acids, trans fat), while negative values were assigned to ingredients and/or products with anti-inflammatory properties (i.e. flavonols, MUFA, garlic). "0" was assigned when the food parameter had no effect on these six inflammatory biomarkers (Shivappa, 2014). Since DII was established, numerous studies examined and confirmed association between anti-inflammatory potential of diet and its impact on lowering the risk of cancer development. See Table 2 for summary of reviewed publications.

Table 2. Impact of anti-inflammatory diet on cancer – summary of reviewed studies with significant association between DII and different types of cancer

TYPE OF CANCER	STUDY CHARACTERISTICS	OUTCOME	REF.
Colorectal cancer (CRC)	case-control study N = 5040 age 30-75 years	positive association between CRC risk and energy-adjusted DII (E-DII): OR = 1.40; 95%CI: 1.16-1.68; Ptrend < 0.01) for the highest quartile E-DII compared with the lowest quartile after adjusting for potential confounders	Abulimiti, 2020
	prospective multiethnic cohort study N = 190963 age 45-75 years	more-proinflammatory diets (highest quartile compared with lowest quartile) were associated with an increased risk of CRC: HR = 1.21; 95%CI:1.11-1.32; when stratified by race/ethnicity, the association was significantly different between groups for men (P-interaction = 0.01), although not for women (P-interaction = 0.20) – significant associations with HRs ranging from 2.33 to 1.04 were observed in white, Japanese-American, and Latino men, and native Hawaiian women	Harmon, 2017
	prospective cohort study N = 489422 age 50-74 years	DII quartile 4 compared to 1 was associated with CRC risk among all subjects HR = 1.40; 95%CI:1.28-1.53, Ptrend < 0.01	Wirth, 2015
	prospective cohort study N = 34703 women age 55-69 years	higher DII score was associated with increased risk of CRC: HRcontinuous = 1.07;95%CI:1.01-1.15); HRquintile5vs1 = 1.16; 95%CI: 0.95-1.42	Shivappa, 2014
	prospective cohort study N = 152536 women age 50-79 years	higher DII scores were associated with an increased incidence of CRC: HRQ5-Q1 = 1.22; 95%CI:1.05-1.43; Ptrend = 0.02)	Tabung, 2014
Prostate cancer (PCa)	case-control study N = 652 age 64-75 years	increased risk for overall PCa risk was observed: when E-DII scores were categorized into tertiles the adjusted ORtertile2 = 2.63; 95%CI:1.61–4.37 and ORtertile3 = 3.35; 95%CI:2.06–5.53, Ptrend < 0.001; the adjusted OR for overall PCa = 1.25; 95%CI:1.12–1.40 for continuous E-DII scores	Hoang, 2019
	case-control study N = 462 age 48-89 years	higher DII scores were positively associated with PCa occurrence: the man having the most pro-inflammatory diet (tertile 3) had 50% higher odds of having PrCA compared to men having the most anti-inflammatory group (tertile 1) (ORtertile3vs1 = 1.50; 95%CI:1.24-1.80); what's more the odds of PCa were higher in obese men (ORtertile3vs1 = 1.81; 95%CI: 1.45-2.27), while no association was found among non-obese men (ORtertile3vs1 = 0.93; 95%CI:0.25-3.51)	Shivappa, 2018
	retrospective cohort study N = 726 age 46-74 years	among patients with Gleason score 7-10 PCa, DII was directly associated with both all-cause and PCa-specific mortality (HR highest vs. lowest DII tertile = 2.78; 95% CI: 1.41-5.48; and 4.01; 95%CI:1.25-12.86; respectively); no associations emerged among men with Gleason score 2-6 PCa	Zuchetto, 2016
Pancreatic cancer (PC)	prospective cohort study N = 450112 age 35-70 years	the inflammatory potential of the diet was measured by the inflammatory score of the diet (ISD) constructed on base of DII, subjects with a higher ISD presented a higher risk of developing PC, where each 1-point increment in the score's ISD increased PC risk by 11% (HR = 1.11, 95%:CI 1.02–1.22)	Cayssials, 2022
	case-control study N = 2573 age mean (SD): 66.7 (cases) and 65.4 (controls)	higher DII scores, reflecting a more proinflammatory diet, were associated with increased risk of PC (ORquintile 5vs1 = 2.54, 95%CI:1.87–3.46, Ptrend < 0.0001)	Antwi, 2016
	case-control study N = 978 median age: 63 (cases) and 62 (controls)	subjects with higher DII scores had a higher risk of PC, with the DII being used as both a continuous variable (ORcontinuous 1.24, 95%CI:1.11-1.38) and a categorical variable (subjects in 2nd, 3rd, 4th, 5th quintiles had increased risk of PC compared with the subjects in the lowest quintile of the DII, respectively: ORquintile2vs1 = 1.70, 95%CI:1.02-2.80; ORquintile3vs1 = 1.91, 95%CI:1.16-3.16; ORquintile4vs1 = 1,98, 95%CI:1.20-3.27; ORquintile5vs1:2.48, 95 % CI: 1.50-4.10; Ptrend = 0.0015)	Shivappa, 2015
Bladder cancer (BC)	case-control study N = 1355 age 25-80 years	subjects in the highest quartile of DII scores had a higher risk of BC compared to subjects in the lowest quartile (ORQuartile4vs1 = 1.97, 95%CI:1.28-3.03; Ptrend = 0.003); stronger associations between DII and BC risk was found among females (ORQuartile4vs1 = 5.73; 95%CI:1.46-22.44), and older ≥65 years (ORQuartile4vs1 = 2.45; 95%CI:1.38-4.34)	Shivappa, 2017

Ovarian cancer (OC)	case-control study N = 3442 median age: 56 (cases) and 57 (controls)	subjects in the highest quartile of DII scores had a higher risk of OC compared to subjects in the lowest (ORQuartile4vs1 = 1.47, 95% CI:1.07-2.01; Ptrend = 0.009);	Shivappa, 2016
Gastric cancer (GC)	case-control study N = 777 age 22-80 years	individuals with the most pro-inflammatory diet had a higher risk of GC compared to subjects with the most anti-inflammatory diet (ORQuartile4vs1 = 2.35, 95%CI:1.32-4.20; Ptrend = 0.004)	Shivappa, 2016
Breast cancer (BC)	case-control study N = 868 age 35-45 years	subjects in the highest quartile of DII scores had 1.5 times higher odds of BC than those with the lowest (OR = 1.56; 95%CI:1.04-2.35, Ptrend = 0.02)	Sasanfar, 2022
	case-control study N = 540 age 41-64 years	higher level of DII score was associated with a higher risk of developing BC after being adjusted for age OR = 2.11, 95%CI: 1.01–4.46, P = 0.04	Gholamalizadeh, 2022
Ovarian cancer (OC)	case-control study N = 1000 age 53-66 years	positive associations were observed between higher E-DII scores and OC odds, using both continuous DII scores (OR = 1.87; 95%CI:1.65-2.13) and by DII tertiles (ORtertile3vs1 = 7.04, 95%CI:4.70, 10.54, Ptrend < 0.001)	Tang, 2020
	case-control study N = 595 age > 25 years	significant association was observed between the most proinflammatory DII scores and OC odds among postmenopausal women (ORQuartile4vs1:1.89; 95%CI:1.02-3.52; Ptrend = 0.03)	Shivappa, 2018
Primary liver cancer (PLC)	prospective cohort study N = 103902 age 58-68 years	higher DII scores from food and supplement were found to be associated with higher risks of developing PLC (HRtertile3vs1 = 2.05; 95%CI:1.23-3.41; similar results were observed only for food	Zhong, 2020

PRACTICAL APPROACH – WHAT ANTI-INFLAMMATORY DIET SHOULD INCLUDE?

The main generic characteristic of Mediterranean diet, the great example of anti-inflammatory diet, is its plant-based composition and the inclusion of unprocessed foods. It is in opposite to Western dietary patterns, which are rich in processed and ultra-processed foods, high in calorie but low in nutrients (we call it commonly "empty calories"). It encompasses consumption of abundant seasonal various vegetables and fresh seasonal fruits. These are products that contain various types of vitamins (i.e. vitamin C, vitamin A, folic acid), minerals (i.e. magnesium), dietary fiber and other bioactive compounds such as polyphenols, carotenoids, isoflavones, flavonols, anthocyanidins which have antioxidant and anti-inflammatory properties (Finicelli, 2022; Gantenbein, 2021). A hallmark of Mediterranean diet is olive oil for cooking or seasoning (main fat source), and regular consumption of nuts and seeds (either as part of the recipes or as healthy snacks). They are the important sources of anti-inflammatory factors like vitamin E, selenium, zinc, polyunsaturated fatty acids (PUFA) with n-3 fatty acids and n-6 fatty acids, monounsaturated fatty acids (MUFA) (Ribeiro, 2023; Pacheco, 2022; Dominguez, 2021; Kwon, 2020; Pan, 2018; Cavicchia 2009; Steck, 2014; Serafini, 2016). Studies show that consumption of the above-mentioned nutrients with food is associated with lower levels of inflammatory markers (Mohseni 2019; Shivappa, 2013; Galland, 2010). Dietary patterns of Mediterranean diet are based on regular consumption of legumes several times weekly, whole cereals (mostly whole grains) daily, consumption of fish and seafood two to three times weekly, white meat two times per week, moderate consumption of eggs, dairy (yogurt, milk, cheese) several times per week. Red and processed meat may be included with utmost moderation in small amounts (max. twice a week). Very important part of this diet are herbs (i.e. basil, oregano, thyme) and spices (curcumin, chili, ginger), garlic and onion to flavor recipes and add more anti-inflammatory power to the dishes (Dominguez, 2021; Rosca, 2020; Mentella, 2019; Pivari, 2019). To identify major characteristics of Mediterranean diet model and to make it easy to follow its rules, an alimentary pyramid was created. It contains main foods of each specific kind of Mediterranean diet and their intake frequency per week (Mentelle, 2019).

Some other examples of dietary patterns meeting the anti-inflammatory diet criteria are: Dietary Approaches to Stop Hypertension (DASH diet), The MIND diet (a combination of the Mediterranean diet and the DASH diet), the Alternate Healthy Eating Index 2010 (AHEI-2010) or the Healthy Eating Index 2010 (HEI-2010), the Nordic diet (Yiannakou, 2023; Stefaniak, 2022; Mentelle, 2019; Al-Ibrahim, 2019; Galbete, 2018).

SHORT CONCLUSION

In conclusion, the current data have confirmed that some fruits, vegetables, spices, plant oils, nuts, cocoa and other food compounds display anti-inflammatory features, and application of anti-inflammatory diet has impact on inflammation state. Most studies concentrate on preventive role of anti-inflammatory diet in cancer and the results are very promising. On the other hand, the evidence on influence of anti-inflammatory diet on progress of cancer is very limited and it needs deeper investigation. Although it's important to notice, that anti-inflammatory diet should be considered as supplementary treatment of cancer, which makes it more difficult to evaluate its effectiveness. In spite of this, the current knowledge allows to postulate the anti-inflammatory diet as beneficial in modulation and counteracting of inflammation, thereby it may be the added value to cancer treatment.

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