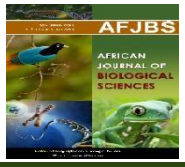
https://doi.org/10.48047/AFJBS.6.2.2024.1764-1774

AfricanJournalofBiological Sciences



ResearchPaper OpenAccess

An Overview about Whole brain irradiation Therapy

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Article History

Volume 6, Issue 2, April-June 2024

Received:1July2024

Accepted: 15July 2024

Published: 15July 2024

doi:

10.48047/AFJBS.6.2.2024.1764-1774

Abstract:Background: Whole brain irradiation (WBRT) includes treatment of the whole intracranial compartment (brain and brainstem) down to the foramen magnum or to the bottom of either the first or second cervical vertebrae, and it is a mainstay of treatment in patients with both identifiable brain metastases and prophylaxis for microscopic disease. WBRT has the ability to treat both gross and microscopic disease, preventing the development of new gross metastatic disease and its associated symptoms. The duration of response is highly variable. A relatively high rate of symptom improvement has been demonstrated, with 64–83% of patients benefiting in early studies. Brain irradiation has effects on brain vasculature as well as neuroglial cells and their precursors, including stem cells . In addition, inflammation and blood-brain barrier disruption, induced by radiation, may also cause or enhance direct or indirect cellular damage.

Keywords:*Whole brain irradiation Therapy.*

Introduction

WBRT includes treatment of the whole intracranial compartment (brain and brainstem) down to the foramen magnum or to the bottom of either the first or second cervical vertebrae, and it is a mainstay of treatment in patients with both identifiable brain metastases and prophylaxis for microscopic disease. Multiple dose fractionation regimens have been employed for WBRT, with no one schedule having been conclusively proven better than others, although single fraction therapy (ex. 10 Gy in a single fraction) has been shown to result in greater toxicity . Common utilized treatment schedules include 2.5 Gy in 14 or 15 fractions, or 3 Gyin 10 fractions. **(1).**

WBRT has the ability to treat both gross and microscopic disease, preventing the development of new gross metastatic disease and its associated symptoms. The duration of response is highly variable. A relatively high

rate of symptom improvement has been demonstrated, with 64–83% of patients benefiting in early studies **(2)**

Indications of WBRT: (3)

1-Whole brain radiation therapy **Noh et al., (3)** typically utilized in the palliative setting when treating patients with multiple brain metastases.

2-Less frequently, it is used in curative setting, as prophylactic cranial irradiation (PCI) for small-cell lung cancer and various high-risk or central nervous system (CNS) positive leukemias.

3-A part of the definitive regimen in some institutions for primary CNS lymphomas and medulloblastoma(cranio_spinal irradiation).

4-

Prophylactic Cranial Irradiation(PCI):

-Prophylactic cranial irradiation (PCI) is: a type of radiation therapy used to prevent the spread (metastasis) of tumer cells to the brain.It can be used for: small-cell lung cancer,various high-risk or central nervous system (CNS) positive leukemias and some trials explained the benefits of PCI in breast cancer., and the radiation dose is: far lower than that used to cure solid tumors but significantly higher than that used for imaging tests like computed tomography (CT) scans (**4**).

-Contraindications:

1-Because PCI can weaken blood vessels in the brain, it is never used in people with cerebrovascular conditions such as stroke, aneurysms, and vascular malformations. **(5).**

2- It is not used on people with epilepsy either, as it can increase the frequency and severity of seizures **(5).**

3-Should also be avoided in people with poor performance status, meaning those who are unable to take care of themselves. People who have a short life expectancy should also avoid PCI as it is likely to cause more harm than good. **(5).**

4-Not used in people with non-small cell lung cancer (NSCLC), the more common form of the disease, and it is increasingly avoided in people with extensive-stage SCLC **(6).**

***Prophylactic cranial irradiation in SCLC:**

-Lung cancer is the second most frequent cancer worldwide and the most common cause of cancer-related death **(7).**

-Small cell lung cancer (SCLC) is a neuroendocrine tumor closely related to smoking, of which about 1/3 are limited-stage SCLC (LS-SCLC) at diagnosis. After initial treatment, SCLC patients have a high propensity for relapse and metastases. Dissemination to the brain is a preferential pattern of relapse and metastasizing for patients with SCLC, and 50%–60% of SCLC patients will have brain metastases within 2 years after diagnosis **(8).**

The European Organization for Research and Treatment of Cancer (EORTC) trial in 2007 found that PCI also decreased the risk of BM and prolonged OS in -SCLC . However, although the findings of this study led to changes in guidelines and clinical practice, the effect of PCI was still subject to debate, as the patients in the EORTC study did not undergo routine brain MRI (**9**) ,

Another randomized trial in patients with -SCLC was performed and brain MRI was performed on every patient after initial CRT . The outcome showed that PCI had no benefit in prolonging OS in patients with SCLC (**10**).

-Furthermore, PCI benefits are reduced if SCLC patients are monitored by MRI and treated with stereotactic irradiation (SRI) **(11).**

***Prophylactic cranial irradiation in ALL:**

-The term “leukemia” covers a wide spectrum of blood disorders. Leukemia is classified into acute leukemia that advances quickly and chronic leukemia that progresses slowly and has got several obscure complications (**10**).

-In chronic leukemia, young blood cells are present, but only the mature ones produce functional cells. Whereas, acute leukemia occurs when white blood cells are produced out of control massively that the process causes unformed, partially developed cells to be released into the bloodstream **(8**).

-Acute leukemia is classified into two major classes based on a French–American–British (FAB) model, which is the most well-known classification model of leukemia: Acute Myeloid leukemia (AML) and Acute Lymphoblastic Leukemia (ALL). Then ALL is subdivided into T-cell lymphoblastic leukemia (T-ALL) and B-cell lymphoblastic leukemia (B-ALL).

-Cancer is the second most common cause of death in pediatrics and leukemia is the leading cause of death in pediatrics (**12**).

-Due to vital improvements in supportive care treatment outcome of pediatric ALL have improved significantly over the past decades. Retrospective studies show a dramatic elevation in overall survival and nowadays ten-year survival rate is almost 90% in improved countries for pediatrics **(12).**

-Standard treatment of acute lymphoblastic leukemia starts with four-week induction chemotherapy regimen. In order to prevent relapse, several intensive phases of chemotherapy over the course of several months, with a focus on Central Nervous System (CNS) relapse prophylaxis. Next step for the treatment is called intensification which consists of combination of chemotherapy drugs with higher doses eradicating as many blasts as possible. Final phase of chemotherapy treatment is termed maintenance, which consists of daily and weekly oral chemotherapy, monthly intravenous and oral chemotherapy, and periodic intrathecal chemotherapy. Duration of the therapy is roughly about two years for females and three years for males **(11**).

-Cranial irradiation was synthesized into ALL treatment after the risk for CNS relapse was recognized in the early 1980s. Although important advances in treatment outcome was grounded due to combination of intensive chemotherapy drugs, late complications associated with cranial radiotherapy are well-known for the world (**12**).

-Early trials for PCI in ALL utilized high-dose treatments, up to 24 Gy cumulative dose, that resulted in significant toxicity. Further experiments showed that lower-dose treatments (12–18 Gy) administered in smaller fractions provide equivalent benefit with lower neuro-toxicity (**13).**

***Prophylactic cranial irradiation in breast cancer:**

Breast cancer is the most common cancer in women and the second leading cause of cancer-related deaths after lung cancer. Brain metastases attack nearly 25% of advanced breast cancer patients, which greatly reduces their quality of life and overall survival (OS). **(14).**

The risk factors for the development of brain metastases are patient characteristics of younger age and ethnicity, tumor features of poorly differentiated, hormone receptor (HR)-negative and human epidermal growth factor receptor 2 (HER2)-positive, more than four metastatic lymph nodes and some genetic variations **(15).**

HER2-positive and triple-negative breast cancers (TNBC) are more likely to develop brain metastasis than luminal cancers. **(14).**

Approximately 15 percent of breast cancers overexpress human epidermal growth factor receptor 2 (HER2) **(14).**

Brain metastases (BMs):

-Epidemiology and etiology:

The exact incidence of brain metastases, which develop in nearly 30% of patients with solid tumours is unknown **(16).**

Cancers of the lung, breast and skin (melanoma) most frequently develop brain metastases and account for 67–80% of patients. Patients with small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC) have the highest rates of brain metastases at diagnosis, while those with melanoma have the highest risk of presenting with brain-metastatic disease. By contrast, cancers of the prostate, head and neck, skin (non-melanoma), and oesophagus rarely metastasize to the brain. **(17)**.

-Investigations:

BM detection in patients with cancer is important for accurate staging and optimal management. Symptomatic patients commonly receive a noncontrast-enhanced computed tomography (CT) scan of the head to rule out life-threatening conditions, which may suggest a diagnosis of BM, but it is not sensitive enough for staging. Thin-cut (≤1.5 mm), brain magnetic resonance (MR) imaging (MRI) with and without intravenous contrast is preferred for BM screening and has increased sensitivity compared with contrast-enhanced CT scans. For patients with contraindications to MRI, contrast-enhanced CT scans may be used.

These MRI characteristics, however, are not pathognomonic for BMs, and the differential diagnosis includes primary brain tumors, infection, demyelinating disease, and vascular abnormalities. Additional MRI sequences and other imaging modalities can be helpful in identifying and evaluating BMs to better differentiate them from other pathologies, such as MR spectroscopy, MR perfusion, and positron emission tomography (PET) **(18).**

-Prognostic assessment:

The prognostic classification of patients with brain metastasis has important implications for several aspects of patient management, including education, clinical management and treatment selection, and clinical trial stratification. These classification schema have evolved continuously over time. After a comprehensive analysis of a prospective clinical trial database containing data from 1,200 patients enrolled in one of three consecutive Radiation Therapy Oncology Group (RTOG) trials, it established three classes of patients with different survival estimates based on four key prognostic factors: age, Karnofsky performance status (KPS), evidence of control of the primary tumour and the status of extracranial metastases **(15).**

-Treatment:

.Aim of treatment: to achieve local control of the metastatic lesion, to improve life quality and to prevent death from neurological disease **(19).**

Early palliative care intervention improves overall survival , quality of life and especially benefits patients with significant symptom burden.

.The treatment options includes:

1. Corticosteroids: symptomatic BMs are managed adequately with corticosteroids (commonly dexamethasone) by reducing peritumoral edema and intracranial pressure. A common dexamethasone regimen is a 10-mg loading dose followed by 4 to 6 mg every 6 hours, although lower doses (4-8 mg daily) can achieve symptom control.
2. Antiepileptics: For patients who present with seizures, single-agent, standard, first-line antiepileptics should be used at the lowest effective dose to minimize medication toxicity. Antiseizure medication use for prophylaxis in patients without a seizure history is not recommended and is associated with more adverse effects **(20**).
3. Surgical resection: it exhibited to be beneficial for patients with one metastasis and good systemic condition, there is not enough evidence to evaluate the role of surgical resection for multiple brain metastases **(21).**

Advantages of surgical resection include providing histological diagnosis, avoiding long-term use of steroid, immediate amelioration of mass effect, and neurologic deficit **(19).**

4. Whole brain radiation therapy: is always used as an adjuvant therapy after surgical resection or for multiple metastases which is not suitable for surgical resection. The use of whole brain therapy was reported to further lengthen the median survival time to 4–6 months .

The most common WBRT regimen is 10 daily doses of 300 centigrays (cGy), although numerous dose and fractionation schemes have been reported **(22).**

Interestingly, an analysis of a recent phase 3 trial of WBRT in brain metastasis suggests that ten 300-cGy fractions may be superior to fifteen 250-cGy fractions. New approach was also designed to prevent neurological decline. Based on the rationale that hippocampal stem-cell injury during WBRT may contribute

to the memory decline, hippocampal avoidance WBRT (HA-WBRT) was applied to limit the injury to hippocampus. (**23**).

Stereotactic radiosurgery (SRS): It is another option to precisely deliver targeted high-dose radiation to the resection cavity, minimizing dose to the surrounding normal brain tissue, and potentially resulting in less adverse neurocognitive effects than WBRT. SRS is usually performed in a single session, up to a maximum of five sessions, using accelerator under the guidance of real-time imaging. (**24**).

5- Systemic Treatment of Brain Metastases:

Some argue that upfront systemic therapy in these patients addresses patients' intracranial and extracranial disease while also potentially sparing them from the neurotoxic effects of radiation therapy (RT) until intracranial disease progression. Others maintain that the risk of neurotoxicity from SRS is low and that BM-directed therapy earlier in the course of treatment or, in the case of immunotherapy, combined with systemic therapy may result in better outcomes (**25**).

Medulloblastoma (MB):

-Epidemiology and Incidence:

Medulloblastoma (MB) is the most common malignant pediatric brain tumor , where it accounts for around a quarter of all intracranial neoplasms and around half of posterior fossa tumors. The majority of MB arise in children with a median age of 9 years, and a peak in incidence between the ages of 3 and 7 years . However, a second peak is seen in adults accounting for around 25% of cases. The 5-year overall survival for MB is approximately 75%, however, long-term therapy-related morbidity remains a significant concern **(26).**

Median age of presentation is 5-6 years in children and 25 years in adult, the ratio is 2:1 for males to females. 30-40% of patients have craniospinal fluid (CSF) spread at the time of diagnosis **(27).**

-Clinical Presentation:

Patients with medulloblastoma commonly present with symptoms evolving over a period of weeks to months. A combination of signs and symptoms of cerebellar dysfunction and increased intracranial pressure are frequently encountered. Classic symptoms of increased intracranial pressure include irritability, lethargy, nausea and vomiting, morning headaches, anorexia, and behavioral changes.(**28**).

-Workup:

The combination of brain/spine imaging and lumbar cerebrospinal fluid cytology is more sensitive than either test alone; therefore, both are recommended as part of the extent of disease evaluation **(29**).

- Classification:

The diagnosis is made, dependent on the integration of tissue-based information available to the pathologist . The newest classification scheme separates MB into two separate general designations, MB, histologically defined and MB, genetically defined**.** The updated 2021 World Health Organization (WHO) central nervous system tumor classification combined the four histologic subtypes into a single type, “Medulloblastoma, histologically defined.” The 2021 WHO classification further elaborated the medulloblastoma molecular subtypes: the SHH subgroup was divided into four groups, and the Group 3 and 4 subtypes (non-SHH, non-WNT) into eight groups **(30).**

Complications of WBRT:

Brain irradiation has effects on brain vasculature as well as neuroglial cells and their precursors, including stem cells . In addition, inflammation and blood-brain barrier disruption, induced by radiation, may also cause or enhance direct or indirect cellular damage.The primary factors influencing the developing of complications include the volume of normal brain tissue treated, the total radiation dose, and the fractionation schedule. (**31).**

Radiation-induced toxicities are classified according to the time of occurrence after the treatment:

1-acute complications develop during or up to 1 month after irradiation.

2- early delayed or subacute effects occur 1–6 months after irradiation.

3- late delayed effects refer to complications that occur ≥6 months after radiation exposure and are often irreversible.

***Acute Complications:**

1-Fatigue:

-The most common acute complication of brain RT is fatigue, which is encountered in >50% of patients (**32**).

-Symptoms typically begin within 2 weeks of the start of RT, peak at approximately 6 weeks, and may persist for several months, with gradual improvement **(33).**

-Many factors have been correlated with the occurrence of fatigue, such as the type of cancer, or the duration of the radiation treatment course.Furthermore, results of recent studies indicate that the disruption of pathways that interconnect the basal ganglia, cerebellum, and higher cortical centers or a hormonal imbalance due to pituitary gland irradiation may play an important pathophysiologic role in the occurrence of fatigue after RT**(33).**

2-Alopecia and Dermatitis:

-Total or partial alopecia is extremely common after cranial irradiation and may be permanent with higher radiation total doses. Alopecia occurs only where the radiation beams traverse the scalp**. (33).**

-The severity and permanence of alopecia is directly related to dose. Lower doses of radiation cause partial hair thinning. With higher doses, complete patches of alopecia may occur. **(34)**

-Radiation dermatitis is usually mild and may be treated with soothing moisturizers. Skin/scalp mild erythema commonly occurs three to five weeks after RT, largely dependent on dose to skin and occurring one to two weeks after alopecia has started. **(34)**

3-Loss of appetite:

-Anorexia is a common symptom with cranial irradiation, occurring in more than half of patients undergoing fractionated cranial RT. Patients typically feel well but have less desire to eat **(2).**

4-Nausea and vomiting:

-may occur occasionally as a side effect of cranial irradiation. This is far less common than simple loss of appetite. Antiemetics or corticosteroids are used to prevent symptoms. **(2)**

5-Headaches:

-Mild headaches may occur at any time during cranial irradiation and are often mild enough or transient enough that patients do not require medication. The headaches are often related to direct irradiation and inflammation caused by radiation on irradiated tissues. For headaches that are more troublesome, acetaminophen is typically adequate to resolve the symptom. If not medically contraindicated, ibuprofen is also acceptable, especially if there are concerns about hepatic function and a desire to limit or avoid acetaminophen. A combination of both medications is also acceptable for more refractory headaches. **(34)**

6-Mucositis and Myelosuppression: **(35)**

-Among the complications related to craniospinal irradiation, mucositis and myelosuppression are relevant. The risk of their occurrence is significantly increased in patients who receive concomitant chemotherapy. Although these complications are temporary and usually resolve in less than a month.

- Pharyngeal mucositis is commonly associated with dysphagia, secondary malnutrition, and increased complication rates.

-Recently, a model to identify patients at high risk for the need of artificial nutrition has been proposed, and it could help the clinician to optimally select patients who could benefit from prophylactic percutaneous endoscopic gastrostomy tube insertion .

Early Delayed Complications:

1-Pseudoprogression:

-is frequently found in patients with high-grade gliomas (HGGs), which occur in roughly 15%–30% of patients treated with RT and concomitant temozolomide chemotherapy and this complication most likely occurs because of endothelial damage and the increased permeability of the tumor vasculature induced by chemoradiation treatment, which leads to tissue hypoxia.**(36).**

-pseudoprogression is a mild and self-limited form of necrosis and appears earlier on MR imaging. Pseudoprogression is characterized by contrast enhancement on MR imaging **(36).**

2-Somnolence Syndrome and Neurocognitive Deficits:

-Somnolence syndrome (SS) is an early delayed complication that usually occurs during the second month after irradiation and lasts for approximately 2 weeks. It is mainly diagnosed in children, especially after prophylactic cranial irradiation for acute lymphoblastic leukemia (**37**).).

-As suggested by its name, the main symptom of this syndrome is excessive sleepiness, often accompanied by drowsiness, a low-grade fever, and anorexia.

-the etiologic mechanism that explains its development is still unknown;

-Treatment is usually not required, but steroids may be useful for symptomatic relief and for prevention as well (**37**).

3-Transient Myelopathy:**(38)**

-it is characterized only by the Lhermitte phenomenon, an electrical sensation that runs down the back and, frequently, into the limbs.

-The symptom may be elicited by neck flexion and usually resolves after several months. The remainder of the neurologic examination is normal, and, on MR images, there are no specific findings.

-Transient radiation-induced demyelination of the posterior columns has been proposed as the cause of the phenomenon.

***Late Delayed Complications:**

1-brain tissue necrosis:

-Treatment-induced brain tissue necrosis (also referred to as radiation necrosis) is a serious complication that typically develops one to three years after radiation, although the range is quite broad and cases have been reported more than 10 years after radiation **(39).**

-Tissue necrosis typically develops at or adjacent to the original site of tumor, the location that received the highest radiation dose **(39).**

-Tissue necrosis can also develop in part of the normal brain parenchyma that was included in the treatment field of a tumor originating outside the brain, such as temporal lobe necrosis that develops in some patients treated for nasopharyngeal cancer or clival chordoma, and in this setting, brain tissue necrosis typically results in new focal neurologic signs, and imaging studies such as CT or MRI may show an enhancing mass lesion with edema **(39).**

-Symptoms produced by localized brain necrosis depend upon the location of the lesion and can include focal neurologic deficits or more generalized signs and symptoms of increased intracranial pressure. Approximately 20 percent of patients have seizures . Brainstem necrosis can produce severe clinical sequelae, including gait and balance problems, as well as multiple cranial neuropathies.

-No specefic therapies have been established, and management is primarily symptomatic. The treatment decisions require a balance between the symptom control and avoidance of side effects. In some cases, tissue necrosis is an asymptomatic, self-limited process that can be managed conservatively without intervention. In patients who are symptomatic, we suggest initial treatment with a moderate dose of glucocorticoid,and in patients who do not achieve symptomatic response to glucocorticoids, or when glucocorticoids cannot be tapered without return of symptoms, a variety of other treatment options have been explored, including bevacizumab and laser interstitial thermal therapy (LITT) **(39**).

2-Leukoencephalopathy.:**(40)**

-The most common late delayed complication of cranial RT is leukoencephalopathy. It occurs within months to years after treatment, and the risk factors include a higher radiation dose, a large irradiated volume (eg, whole-brain RT), older age, and combined radiochemotherapy.

-This complication typically manifests as mild neurocognitive impairment; short-term memory and frontal functions are mainly affected. It is very common in children, who also manifest learning difficulties. Other

symptoms include seizure and motor abnormalities. Symptoms are usually irreversible and can either remain stable or slowly get worse.

3-Vasculopathy and ischemic stroke: **(41).**

-Children are probably more susceptible to radiation-induced vasculopathy than adults, and the supraclinoid region of the internal carotid artery and the circle of Willis seem especially vulnerable. Additional risk factors for neurovascular toxicity include administration of chemotherapy, young age at the time of radiotherapy, radiation dose (eg, whole brain radiation dose ≥24 Gy), and comorbid neurofibromatosis type 1.

4-Microbleeds and cavernous malformations: **(41).**

-Intracerebral microbleeds and cavernous malformations commonly develop after cranial irradiation with a median latency of several years, primarily in regions of the brain that have received >30 Gy .

5-Hypothalamic and pituitary endocrinopathies: **(41).**

- occur in up to 80 percent of adults following radiation therapy that includes these structures. Such injury may occur after doses as low as 20 gray (Gy) , and therefore patients who receive pituitary as well as nonpituitary cranial radiation are at risk.

-The time course of endocrine dysfunction after radiation to the hypothalamic and pituitary region is variable, with patients typically having abnormal serum hormone levels long before clinical symptoms develop. Abnormalities can develop as early as one year after completion of therapy, and the prevalence rises over time

6-Hypothyroidism:**(42)**

-It develops in 15 to 20 percent of adult patients after cranial irradiation. This may be a manifestation of either central hypothyroidism, due to irradiation of the pituitary through the cranial fields, or primary hypothyroidism due to irradiation of the thyroid from the spinal fields. Patients who have received cranial radiation should therefore undergo structured periodic monitoring of both thyroid stimulating hormone (TSH) and free T4.

7-Secondary tumer formation:**(43)**

-Following cranial irradiation, there is an increased risk of secondary meningiomas, malignant gliomas, nerve sheath tumors, and sarcomas; the risk of meningiomas and gliomas is proportional to the dose of cranial irradiation.

8-Mineralizing Microangiopathy:(**44**).

-It is characterized by dystrophic calcification, mainly within the basal ganglia (the putamen is particularly affected), the dentate nuclei, the cerebral gray-white matter junction, and sometimes in the cerebral cortex .

xerostomia:

- The poor prognosis traditionally associated with brain metastases previously limited interest in evaluating the long-term side effects of WBRT, as it was not expected that patients would live long enough to experience that late effects, however, the potential late effects of WBRT, including xerostomia, have become more important in overall survival achieved in patients with brain metastases,, as well as xerostomia can be induced during or shortly after radiation. **(45)**

-Saliva is an exocrine solution, consisting of 99% water. The remaining 1% consists of a variety of electrolytes and proteins, which are responsible for the various functions including speech, swallowing, and tasting **(45)**

-Its enzymes start the digestion of starches and fats in the mouth, and other salivary components, such as the epidermal growth factors, promote tissue growth, cell differentiation, and allow wound-healing . The antibacterial, antifungal, and antiviral agents in salivary fluid balance the oral biofilm, while the mineral components maintain the integrity of teeth, antagonizing demineralization processes **(45)**

-Definition of xerostomia:

Xerostomia (dry mouth), defined as a subjective feeling of oral dryness, and the term is derived from the Greek “xeros” , meaning “dry”, and “stoma” , meaning “mouth”. Xerostomia results in decreased salivary flow and changes in the composition of saliva **(46).**

-Causes of xerostomia:

The main causes of xerostomia are aging, radiation to the head and neck,autoimmune conditions, such as Sjögren's syndrome,rheumatic and dysmetabolic diseases, such as diabetes and the hepatitis C virus, however, the most common cause is drug-induced xerostomia, which is associated with more than 400 different drugs **(46).**

-Prevalence of Xerostomia:

The majority of the 550,000 patients who undergo radiation treatment for head and neck cancer annually and more than 4 million patients with Sjögren's syndrome worldwide suffer from salivary gland dysfunction **(47).**

More than 400 different drugs, including antidepressants, antipsychotics, antihistamines, antihypertensives, and others, are also major causes **(47).**

Aging itself is also a cause of xerostomia, but its incidence continues to increase as polypharmacy among the elderly increases **(47).**

-Symptoms and signs:

The most common symptom deriving from saliva alterations is dry mouth. The feeling is related to a poor protection of the oral tissues due to altered saliva. This situation leads the mouth to undergo ulcerations, aphthosis, mucositis, and infections, with a general sensation of pain and/or a widespread burning sensation (burning mouth). Burning is mainly localized at the tongue, together with the hard palate, due to a greater evaporation of the saliva in comparison to the other regions of the mouth. **(47).**

Sleep disturbances are also recurrent in xerostomia, due to the need to humidify the mucosa during the night; at which time, the saliva secretion is further reduced because of the circadian rhythm **(48).**

Furthermore, chewing and swallowing are negatively affected by the lower saliva, forcing patients to take continuous sips of water to facilitate food transit.

It mostly impairs neoplastic patients suffering from xerostomia, negatively impacting their survival by causing psychological anxiety and malnutrition. The latter is one of the major factors underlying the high morbidity experienced by these patients **(48).**

Additionally, the lowered pH of the viscous saliva leads to a bacterial shift that can occur in the oral biofilm, leading to the development of dysbiosis. This represents further opportunities to develop gingivitis, caries, and mucositis, with oral candidiasis in immunocompromised subjects being frequently represented **(48).**

Thus, xerostomia not only diminishes the quality of life in cancer patients, but also makes a major new health problem for them.

-Management of xerostomia:

The management of xerostomia remains a significant clinical challenge. Treatments have been mainly directed to increase the saliva flow using pharmacological treatments, while local salivary substitutes have been used to relieve the sensation of dryness and the compromised oral functions.However, there is no permanent solution approved by the US Food and Drug Administration for salivary gland hypofunction and resultant xerostomia **(49).**

Options of treatment include: para-sympathomimetic drugs that stimulate salivary secretion by means of the parasympathetic nervous system **(49).**

para-sympatholytic drugs that work in opposition to para-sympathomimetics inhibiting the secretion of saliva fluid. During radiotherapy, the inhibition of salivary secretion in animal testing evidenced it might protect the salivary glands from later damage **(49).**

cytoprotective agents that can be administered before or after cancer therapy, with the intent to prevent or reduce damage or toxicity to the normal tissues, without compromising therapeutic efficacy. Among them,(amifostine) is an organic thiophosphate that is indicated against the harmful effects of radiation or chemotherapy, including acute or late xerostomia. The cytoprotective mechanism involves free radical scavenging, DNA protection and repair acceleration, and induction of cellular hypoxia, antioxidant agents that ralated to the fact of oxidative stress is involved in the issue . Oxidation is implicated in the development of xerostomia in cases of Sjögren's Syndrome, radiotherapy patients, and systemic sclerosis**,** biological agents

that have been proposed in Sjogren's Syndrome patients, with the intent to antagonize the immunological disfunction evidenced by the infiltration of lymphocytic in exocrine and non-exocrine epithelia, and there is traditional medicine that WHO defines as a "medicine of long history that is the sum of the knowledge, skill, and practices based on the theories, beliefs, and experiences of different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness". **(50).**

Several studies have reported the capacity of traditional medicine in dry mouth symptoms, greatly referring to the use of herbal compounds **(50).**

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