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# SUPPORTIVE AND PALLIATIVE CARE IN ONCOLOGY: CHALLENGES AND INTERVENTIONS

THESIS

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“Cancer”, “Difficulties”, “Challenges”, “Adverse Effect”, “Quality of life”,  
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## **LIST OF ABBREVIATIONS**

WHO	World Health Organization
NCDs	Non-Communicable Diseases
MASCC	Multinational Association of Supportive Care In Cancer
ESC	Enhanced Supportive Care
ESMO	European Society of Medical Oncology
ASCO	American Society of Clinical Oncology
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
NCCN	National Comprehensive Cancer Network
CRF	Cancer Related Fatigue
ICD	International Classification of Diseases
CP	Cancer Pain
SREs	Skeletal-Related Events
MM	Multiple Myeloma
ADT	Androgen Deprivation Treatment
BMD	Bone Mineral Density
EGFRIs	Epidermal Growth Factor Receptor Inhibitors, Respectively
MEKis	Mitogen-Activated Protein Kinase Inhibitors
HFS	Hand-Foot Skin Reaction
PPES	Palmar-Plantar Erythrodysesthesia Syndrome
5-FU	5-Fluorouracil
TKIs	Tyrosine Kinase Inhibitors
ADLs	Activities of Daily Living
SJS	Stevens-Johnson Syndrome

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<b>TEN</b>	Toxic Epidermal Necrolysis
<b>IV</b>	Intravenous
<b>BSA</b>	Body Surface Area
<b>CIA</b>	Chemotherapy Induced Alopecia
<b>CTCAE</b>	Common Terminology Criteria For Adverse Events
<b>CIPN</b>	Chemotherapy Induced Peripheral Neuropathy
<b>PN</b>	Peripheral Neurotoxicity
<b>DTR</b>	Deep Tendon Reflexes
<b>CSF</b>	Cerebrospinal Fluid
<b>PRES</b>	Posterior Reversible Encephalopathy Syndrome
<b>CNS</b>	Central Nervous System
<b>MTX</b>	Methotrexate
<b>IT</b>	Intrathecal
<b>ID</b>	Iron Deficiency
<b>OS</b>	Overall Survival
<b>FACT</b>	Functional Assessment of Cancer Therapy
<b>FN</b>	Febrile Neutropenia
<b>ANC</b>	Absolute Neutrophil Count
<b>ChT</b>	Chemotherapy
<b>G-CSF</b>	Granulocyte Colony-Stimulating Factor
<b>CINV</b>	Chemotherapy-Induced Nausea and Vomiting
<b>OHP</b>	Oncology Health Professionals
<b>PN</b>	Parenteral Nourishment
<b>BMI</b>	Body Mass Index
<b>GI</b>	Gastro Intestinal

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<b>NRS</b>	Nutrition Risk Screening
<b>MUST</b>	Malnutrition Universal Screening Tool
<b>SNAQ</b>	Short Nutritional Assessment Questionnaire
<b>MST</b>	Malnutrition Screening Tool
<b>BW</b>	Body Weight
<b>PS</b>	Performance Status
<b>IGF</b>	Insulin Like Growth Factor
<b>WCRF</b>	World Cancer Research Fund
<b>AICR</b>	American Institute For Cancer Research
<b>ONSs</b>	Oral Nutritional Supplements
<b>NSAIDs</b>	Non-Steroidal Anti-Inflammatory Medications
<b>ACS</b>	American Society
<b>HPA</b>	Hypothalamic Pituitary Adrenal
<b>CBT</b>	Cognitive Behavioral Therapy
<b>ACT</b>	Acceptance And Commitment Therapy
<b>MBSR</b>	Mindfulness-Based Stress Reduction
<b>BTAs</b>	Bone-Targeted Drugs
<b>SERMs</b>	Selective Estrogen Receptor Modulators
<b>RANKL</b>	Receptor Activator of Nuclear Factor-Kb Ligand
<b>RT</b>	Radiotherapy
<b>GnRHa</b>	Gonadotropin Releasing Hormone Agonist
<b>ATC</b>	Around-The-Clock
<b>TD</b>	Transdermic
<b>SC</b>	Subcutaneous
<b>OTC</b>	Over-The-Counter

<b>B. I. D</b>	Bis In Die Twice A Day
<b>TSH</b>	Thyroid Stimulating Hormone
<b>EXCAP</b>	Exercise For Cancer Patients
<b>ADT</b>	Androgen Deprivation Therapy
<b>PrBC</b>	Packed Red Blood
<b>ESA</b>	Erythropoiesis–Stimulating Agents
<b>RBC</b>	Red Blood Cells
<b>QoL</b>	Quality of Life
<b>G–CSF</b>	Granulocyte Colony Stimulating Factor
<b>HEC</b>	Highly Emetogenic Chemotherapy
<b>PEG</b>	Percutaneous Gastrostomy Tubes

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## General introduction

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Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs; the latter process is referred to as metastasis. It is the primary cause of death from cancer<sup>1</sup>.

According to World Health Organization (WHO) estimates, cancer is the top cause of death globally, accounting for about 10 million deaths in 2020.<sup>1</sup> Morocco is facing a significant transition in its epidemiological profile, with a growing burden of non-communicable diseases [NCDs], which now account for roughly 75% of all fatalities in the country including cancer<sup>1</sup>. Cancer's burden can be decreased with early identification, appropriate interventions and treatment, and mostly proper care for people who develop it. Many malignancies have a high possibility of being cured if detected early and addressed properly.

The panorama of cancer care is quickly shifting. Because of advancements in cancer therapy, a growing number of individuals, at various stages of their disease, are now living with cancer. They may be actively taking anti-cancer medicines for several years, or they may be off treatment, in remission, cured, or living with progressing illness<sup>2</sup>. Many of these patients, particularly those with advanced-stage cancer, will require the assistance of healthcare professionals who are experienced in dealing with a wide range of issues, whether related to the cancer itself or as a result of cancer treatment.

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There is emerging evidence that early supportive care can enhance these patients' quality of life, perhaps prolonging their longevity and lowering the need for severe therapies at the end of their lives<sup>3</sup>.

Supportive care is defined by the World Health Organization as an approach to improving the quality of life of patients and their families facing problems associated with life-threatening illness by preventing and alleviating suffering through early detection, accurate assessment, and treatment of pain and other physical, psychosocial, and spiritual problems<sup>4</sup>. When the Multinational Association of Supportive Care in Cancer (MASCC) defines it as "the prevention and management of the deleterious consequences of cancer and its treatment". This covers the full cancer treatment process and involves the participation and integration of most clinical disciplines. Optimal supportive care can help with proper diagnosis and management, which can lead to better results. This involves managing physical and psychological symptoms as well as side effects throughout the cancer journey, from diagnosis to treatment and aftercare. Support includes improving rehabilitation, secondary cancer prevention, survivorship, and end-of-life care<sup>5</sup>. On the other hand palliative care is a type of treatment that aims to alleviate rather than cure cancer-related symptoms and enhance the quality of life for patients and their families. Palliative care can make people's lives easier. It is especially important in areas where a significant number of patients are in late stages of cancer with little possibility of recovery. It can provide relief from physical, emotional, and spiritual concerns for more than 90% of cancer patients in advanced stage<sup>6</sup>.

Palliative care is a philosophy of caring as well as a well-organized, well-structured system for providing care. It includes aims like improving quality of life for patients and their families, maximizing function, assisting with decision-making, and giving chances for personal growth in addition to standard disease-model based treatments. As a result, it can be given alongside life-prolonging care or as the primary focus of attention<sup>7</sup>. Regardless of the stage of the disease or the necessity for other medicines, the goal of palliative care is to prevent and relieve pain while also promoting the highest possible quality of life for patients and their families, which require effective public health programs that include community and home-based care<sup>8</sup>.

The cancer care environment is quickly evolving, because of advancements in cancer therapy, a growing number of individuals, at all stages of their illness, are now living with cancer. They may be undergoing anti-cancer therapy, sometimes for a long period, or they may be off treatment, in remission, cured, or living with progressing illness<sup>9</sup>. Many of these patients may require the assistance of healthcare experts who are experienced in dealing with a variety of issues, whether they are caused by the disease or as a result of cancer therapy<sup>10</sup>.

The goal of this research study is to raise awareness of the difficulties that patients confront in oncology, whether it is adverse effects of anti-cancer therapy or due to the disease itself, or the changes in the quality of life coming along way. Our aim motivation is the hope that Enhanced Supportive Care (ESC) can be used across the entire cancer care continuum, that supportive care services can be integrated with oncology practice, including palliative care, pain medicine, interventional radiology, complementary therapy, psycho-oncology, spiritual care, and access to

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physiotherapy, dietetics, and occupational therapy<sup>10</sup>. Our plan is to roll out ESC in stages, starting with patients who have been diagnosed with cancer. Following that, ESC should be made available to patients with curable cancer, as well as cancer survivors, who are living with cancer as a chronic condition.

There is emerging evidence that early supportive care can enhance these patients' quality of life, allowing them to live as normally as a healthy human being, perhaps extending their lives and lowering the need for severe therapies at the end of their lives<sup>10</sup>. All with the aim of making enhanced supportive care a part of the whole cancer care process.

Furthermore, we aim to develop enhanced supportive care making it understandable and accessible to both medical professionals whatever their specialty is and patients. This was what motivated us to include different parameters in this one huge and pertinent subject of supportive care.

The aim of the research study is not only to give another research tool but also help integrate supportive care as an integral part of therapy that need its own surveillance and track of evolution.

All of this in the purpose of:

- Making the hospital a safe environment of trust and understanding where patients feel understood and supported by the caregivers and helping patients to easily cope with therapy.
- Helping health care givers in being more comfortable and confident in sharing informations with their patients and offering better solutions resulting in improving their quality of life and building a stronger caregiver–patient relationship.
- Ameliorating the prognosis and making the adverse effects controlable.

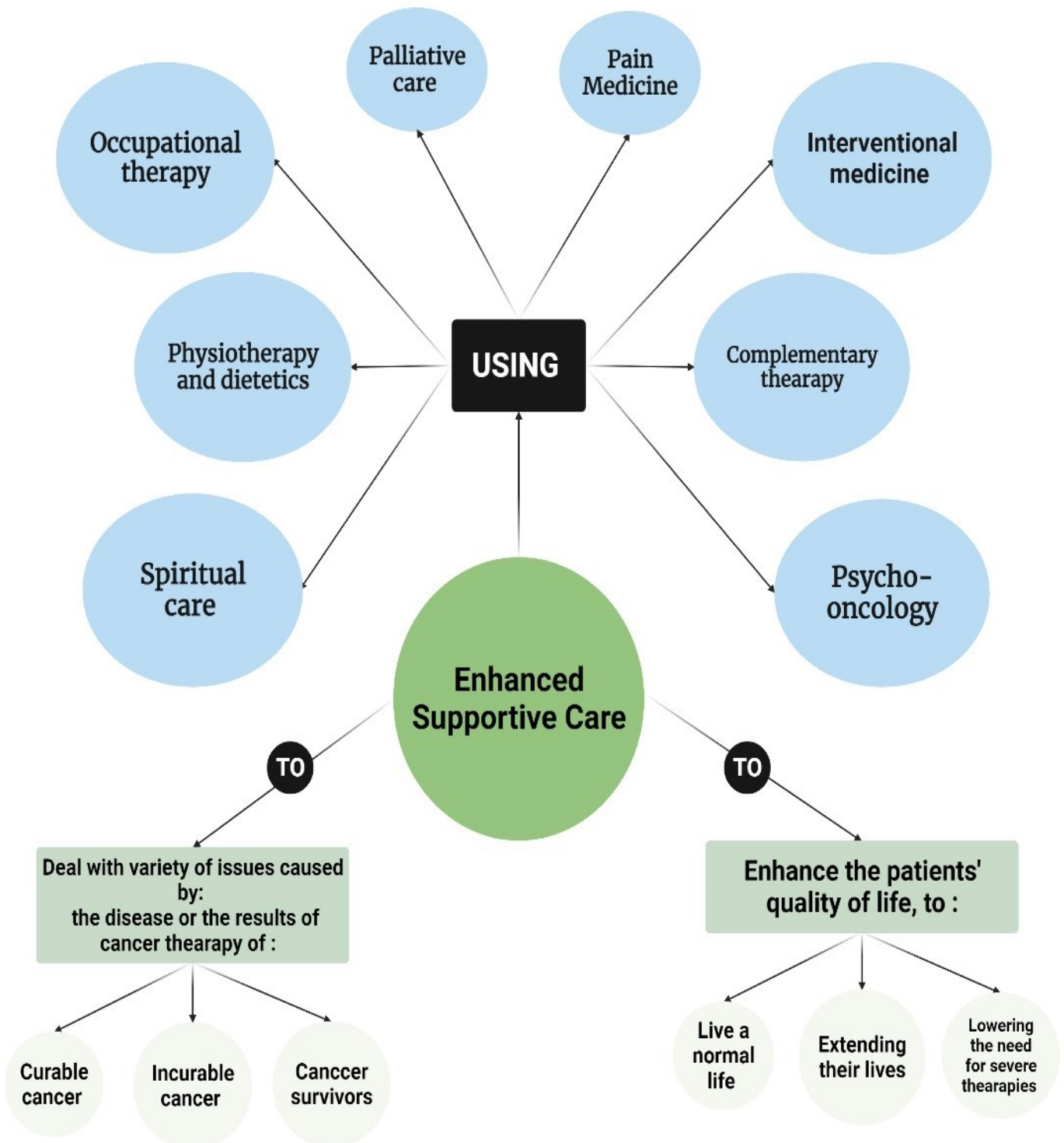


Figure 1: Enhanced Supportive Care: Parameters and Goals

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## Methods

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Our work is a literature search. The realization of the study lasted over 9 months, the first month was dedicated to protocol development which is the reading of multiple articles using mainly the two platforms:

-ESMO = European society of medical oncology

-ASCO = American society of clinical oncology

That gave us a clear vision about patient challenges after a cancer diagnosis, in order to cope with therapy and to increase the quality of life. After having a large idea about the subject and in the purpose of finding the different obstacles that patients face, and the interventions in the oncology spectrum our study topic was divided into two primary chapters.

-**Chapter I:** A large reviewing and detections of challenges of oncology in supportive care field.

-**Chapter II:** Reporting the solutions and interventions of the challenges.

While the primary criteria of selection was using the key words listed below, we selected potential publications by titles and abstracts and secondly we included other studies and publications after reading the whole article and mostly results. The first selection based on titles and abstracts was based mainly on pertinence and number of citations of the articles that enabled us to come up with more than 563 articles dated mostly between 2001 and 2021. After, and based on articles with significant population of patients and also the positive impact of the procedures applied on the quality of life, and the studies that led to guidelines, we came up to 195 articles. On the opposite, as exclusion criterias we eliminated articles and studies exposing the problems and challenges without proposing the alternatives and solutions, and duplicated records based on the title, authors, abstract and year of publication.

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## Databases and Keywords

Based on our study design we conducted a comprehensive literature search in PubMed, Google scholar, Microsoft academic and on the platform thesis.fr on two steps:

-The first step, to build up our first chapter, using the key word: “Oncology”, “Cancer” along with the words “Difficulties”, “Challenges”, “Therapy”, “Quality of life”.

-The second one, after making up the challenges we used a structured method (searching by segments) based on 9 challenges that represent equivalent sub-chapters we searched with applying these keywords in each segment:

- “Cachexia”, “Nutrition”, “Appetit”, “diets”
- “Physical activity”, “fatigue”, “exercicing”
- “Psychothearapy”, “CBT”, “ACT”, “depression”
- “Alopecia”, “chemothearapy”
- “Fertility”, “preservation”
- “Pain”, “cancer pain”, “analgesia”
- “Dermatological Oncology”, “dermatological toxicity”, “dermatological prevention”

Despite the wide range of keywords and the different combinations using “And” “Or”, it is possible that some potential studies have been missed. As the process of collecting articles is standardized based on keywords, we also used publications from other suggestions.



Figure 2: Methodology, inclusion and exclusion criteria

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## Chapter I: Challenges in oncology

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When a patient receives a cancer diagnosis, they are confronted with a slew of difficulties. Fear of death, disfigurement, suffering, handicap, infertility, reliance, abandonment, changed relationships, and financial hardship are all serious concerns, in addition to the medical and logistical considerations<sup>11</sup>.

The single largest source of psychological discomfort in people suffering from announcement of a diagnosis, the initial reaction is usually one of shock and denial, which lasts for a varying amount of time<sup>12</sup>. Emotional upheaval, such as worry, sadness, anger, sleeplessness, poor attention, and inability to operate, characterizes the second phase. Unless persistent uncertainty is intolerable, the patient generally returns to former coping mechanisms within 1 to 2 weeks, with the help of family, friends, and healthcare staff<sup>13</sup>.

This segment contains the different challenges that patients face to cope with their therapy after a cancer diagnosis, which can vary from one another due to different parameters, such as the announcement of the diagnosis itself, the severity of the disease, social context, patients' coping methods, the previous physical and moral state, and last and more importantly the supportive care system, most of the challenges will be listed below. Let's not forget due to the aging of the population and the consistent increase in cancer incidence with increasing age, the care of elderly cancer patients is becoming a serious public health concern in developed countries<sup>14</sup>

<sup>15</sup>.

Elderly cancer patients have a wide range of co-morbidities, physical reserve restrictions, and impairment, all of which necessitate unique therapeutic options<sup>16</sup>. Plus Treatment-related toxicity becomes more likely as people become older, and it can potentially lead to death. A thorough assessment of the patient's condition is now required.

It necessitates the assessment of multiple factors that influence an older adult's health, including physical, cognitive, affective, social, financial, environmental, and spiritual factors, which justifies the use of the comprehensive geriatric assessment (CGA) and the G-8 score, which has a high sensitivity and specificity (95% CIs)<sup>17</sup>.

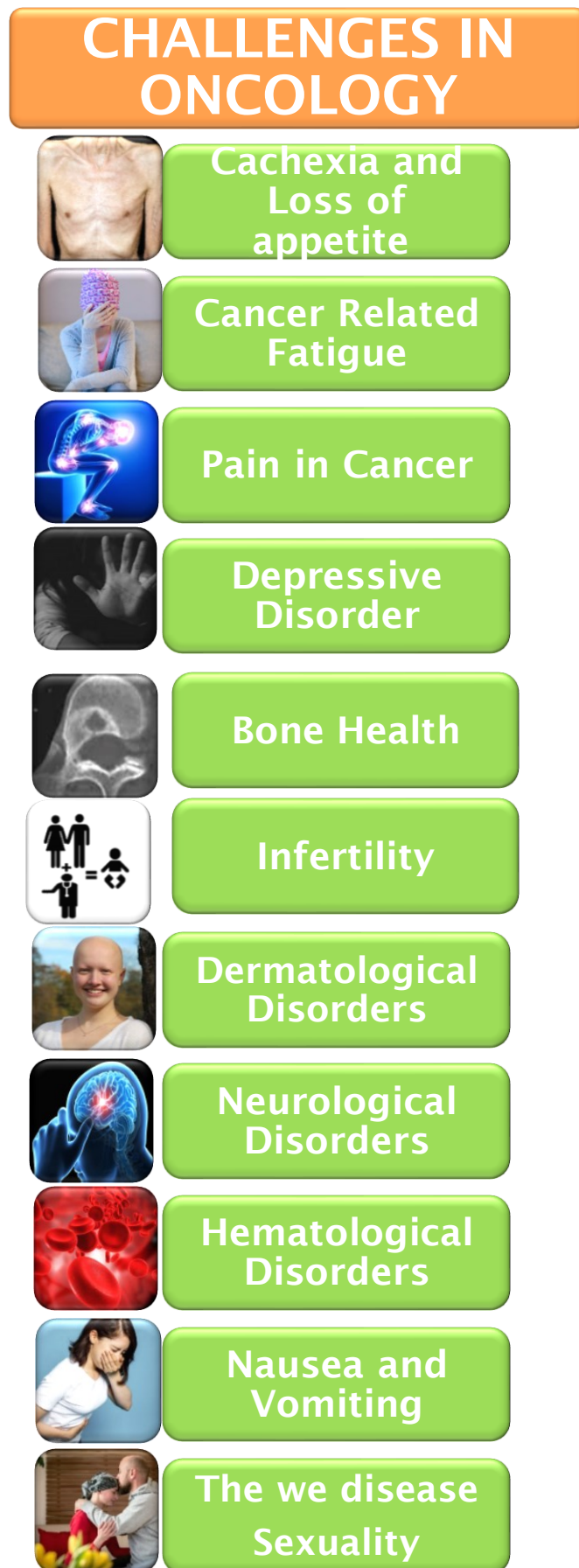


Figure 3: The list of challenges treated in our work

## I. Cachexia and Loss of appetite (Anorexia)

Cachexia has long been recognized as a side effect of cancer. Cachexia is weight loss with depletion of fat storage and muscle mass it is common in people with advanced cancer and may be the earliest indicator of a tumor<sup>18</sup>, is still an underdiagnosed and undertreated complex condition with objective and subjective components such as anorexia, early satiety, taste alterations, chronic nausea, distress, fatigue, as well as inadequate food intake, weight loss, inactivity, loss of muscle mass, and metabolic derangements, inducing catabolism. Cachexia affects almost half of all individuals with advanced cancer<sup>18</sup>.

Patients with limited resources are more likely to have anticancer therapy-related toxicity and a worse quality of life; toxicity leads to shorter treatment periods, lower dosage intensity, lower response rates, greater surgical complications, and higher death<sup>18,19</sup>.

The pathophysiology of cachexia is presently characterized as tumour interactions that shift metabolism and drive the brain to lower hunger, produce changes in taste and smell, affect gastrointestinal autonomic function, induce tiredness, and decrease daily physical activity<sup>18</sup>. While insufficient food intake is a primary cause of weight loss, metabolic changes and decreased exercise also play a role in muscle loss<sup>20</sup>.

All of this indicates that the ideal treatment is to prevent and cure cachexia before and during anticancer treatment, patients should be given all available nutritional therapeutic alternatives.

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## II. Cancer Related Fatigue

The National Comprehensive Cancer Network (NCCN), describes Cancer Related Fatigue (CRF) as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with functioning” it is one of the most comprehensive and commonly used definition<sup>21</sup>, CRF may be caused by abnormalities in the central (inflammation, hypothalamic–pituitary–adrenal axis) and/or peripheral neural systems (e.g., reduced energy metabolism)<sup>22</sup>.

The International Statistical Classification of Diseases and Related Health Problems 10th edition (ICD– 10) has specific diagnostic criteria for CRF inclusion and definition. The presence of specific symptoms such as lower energy, increased need to rest (which is disproportionate to changes in activity level), and linked symptoms across physical, emotional, and cognitive domains identify CRF as a syndrome according to the criteria<sup>23</sup>. Furthermore, fatigue has been linked to a lower rate of survival; tiredness at diagnosis and throughout survivorship has been linked to a greater rate of death<sup>24</sup>. Regardless of this, Unfortunately Even though clinical standards advocate comprehensive screening and care of CRF from diagnosis through follow–up, up to 50% of survivors reported not discussing, seeking advice, or receiving required help for CRF<sup>25</sup>.

### III. Pain in Cancer

Pain is frequent in cancer patients, especially in advanced stages of the disease, when the frequency is reported to be over 70%, resulting in poor physical and mental well-being<sup>26</sup>. Unrelieved pain is a major clinical issue and one of the most dreaded cancer side effects<sup>27</sup>.

Cancer pain is predicted to affect 30% to 70% of people with early-stage disease and 60% to 95% of individuals with late cancer<sup>28</sup>. During active anticancer therapy, the prevalence of cancer pain (CP) varies from 55 %, to 64 % in advanced illness<sup>28</sup>. When approximately 5%–10% of cancer survivors experience persistent severe pain that greatly limits their ability to function<sup>28</sup>. Increased survival with either life-prolonging or curative therapy leads to a rise in the number of people who suffer from chronic pain as a result of treatment, illness, or a mix of both<sup>29</sup>.

Cancer pain is regarded to be difficult to manage. Despite the existence of guidelines and a common knowledge of pain and pain management, more than half of patients are treated ineffectively<sup>30</sup>. It is reported when cancer pain is poorly managed it causes anguish and lowers quality of life, plus one-third of CP sufferers receive inadequate therapy<sup>28</sup>. Inadequate pain treatment appears to be the result of both professional and patient-related obstacles, its assessment and expertise are the most commonly stated hurdles among clinicians<sup>31</sup>. Patients frequently obstruct their own treatment owing to misunderstandings regarding analgesics and their adverse effects, noncompliance with treatment regimens, and poor communication with health care professionals about their pain problems<sup>31</sup>. Despite this, it has been suggested that successful pain therapy should be possible for 70% to 90% of cancer patients<sup>32</sup>.

## **IV. Psychological Disorders**

Regardless of the kind of cancer, the emotional effect of diagnosis, coping with therapy, concern about relapse, and confronting the potential of death can all lead to sadness and anxiety<sup>33</sup>. Other concerns are more oncology-specific. For example, it is the patient's perception of cancer as necessarily terminal, rather than the disease itself, that makes them feel worse. Chemotherapy and radiation, for example, can be particularly detrimental for young individuals who were previously physically active and healthy<sup>33</sup>.

Depression and anxiety are easily treated disorders, and failing to do so in cancer patients can have serious consequences. Depression and anxiety can affect a cancer patient's quality of life and social support, as well as lengthen hospitalization, negatively impact treatment compliance, and eventually diminish survival prospects. Therefore there is a compelling case for detecting and treating depression and anxiety in cancer patients<sup>33</sup>.

## **V. Bone health**

Cancer, as well as its treatment, can have a significant impact on bone health. Clinicians caring for cancer patients should be aware of the multimodal therapies available to reduce skeletal morbidity due to metastatic illness and to minimize cancer treatment-induced skeletal deterioration<sup>34</sup>.

## **1. Bone metastases**

Many patients with advanced cancer develop bone metastases, which, whether lytic or blastic in appearance, frequently result in skeletal problems known as skeletal-related events (SREs). Pathological fracture, the need for radiation to the bone, the necessity for surgery to the bone, spinal cord compression, and hypercalcaemia, albeit the latter may be of paraneoplastic origin, and can occur in the absence of bone metastases<sup>34 35 36</sup>.

Specific cancers, such as those of the breast, prostate, lung, and kidney, as well as multiple myeloma, are the most prevalent causes of metastatic bone disease (MM). The axial skeleton is the most prevalent location for bone metastases. The most prevalent skeletal occurrences are the requirement for radiation and pathological fractures, showing the burden of bone soreness and structural damage induced by metastatic involvement. The skeleton's metastatic involvement usually affects many places and generates pain and bone discomfort<sup>34 35 36</sup>.

## **2. Cancer Treatment-Induced Fractures**

Bone health can be harmed by cancer treatments, especially in women with breast cancer and men with prostate cancer. New issues in the maintenance of bone health in cancer patients have arisen as a result of recent advancements in adjuvant therapy for early-stage cancer. Aromatase inhibitors have shown to be more efficacious than tamoxifen in the treatment of breast cancer, but they are also linked to increased bone loss and the risk of fracture. Similarly, androgen deprivation treatment (ADT) has been linked to a reduction in bone mineral density (BMD) and an increased fracture incidence in men with prostate cancer.

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Both smoking and heavy alcohol use lower BMD, and alcohol consumption has been proven to lower BMD in males taking ADT for prostate cancer. ADT also promotes sarcopenia, which is aggravated in this patient group by a lack of exercise, resulting in reduced muscular strength and an increased risk of falls and fractures<sup>35</sup>

## VI. Cancer, Pregnancy and Fertility

Cancer is still a global public health issue that affects young people<sup>37</sup>. A considerable number of young patients are anxious about the potential influence of anticancer therapy on their fertility and future prospects of pregnancy at the time of diagnosis<sup>38</sup>. Given that cancer incidence rises with age and that survival rates for most cancers continue to improve, more women are either diagnosed with cancer during pregnancy or inquire about the feasibility and safety of pregnancy after a cancer diagnosis, all while dealing with the consequences of treatment-related late effects, making survivorship a critical topic<sup>39 40</sup>.

Infertility can result from the malignancy, surgery, or gonadotoxic treatments including chemotherapy and radiation<sup>41</sup>. Infertility difficulties, either permanent or temporary, are linked to worry, despair, sorrow, stress, and a lower standard of living<sup>42</sup>, and have been designated as "biographical disturbance"<sup>43</sup>. If these concerns are not addressed properly, it may have a detrimental impact on their treatment choices and adherence to the planned anticancer therapies, in light of the increased tendency of delaying childbirth in the last four decades<sup>44</sup>.

Due to an increase in the number of patients who have not finished their family planning at the time of diagnosis, demand for fertility preservation and information on the feasibility and safety of pregnancy after treatment completion is predicted to rise<sup>40</sup>.

## VII. Dermatological Toxicities

The skin, its appendages, hair, and nails all play a role in general health, aesthetics, and self-esteem. In cancer patients, these dermatological structures may be changed as a result of the illness (i.e. paraneoplastic dermatoses), as part of hereditary cancer syndromes, or as a result of anticancer treatments such as systemic drugs, therapeutic transplantation, radiation, and surgery<sup>45</sup>.

Systemic treatments are used in around 65% of all cancer patients, with cytotoxic chemotherapies, immunotherapies, biologics, targeted therapies, and endocrine drugs being the most commonly linked with dermatological side effects<sup>46</sup>. As a result, 76% and 32% of oncologists have reported dosage suspensions and discontinuations because to the acneiform rash caused by epidermal growth factor receptor inhibitors, respectively (EGFRIs)<sup>47 48</sup>.

Despite the fact that the majority of dermatological side effects are classed as grade 1 or 2 (Grade 1:Mild; Grade 2:Moderate; Grade 3:Severe; Grade 4:Potentially life-threatening)<sup>49</sup>, their chronicity, presence on cosmetically sensitive regions, and correlation with pruritus and pain sensations need the use of preventative or reactive therapy<sup>50</sup>.

## **1. Acneiform Rash (PAPULOPUSTULAR EXANTHEMA)**

Acneiform rash, also known as Papulopustular eruption, is characterized by papules and pustules that commonly occur on the face, scalp, upper chest, and back. It is one of the most common side effects<sup>48</sup> caused by drugs that target the human EGFR, such as erlotinib, cetuximab, and panitumumab, and has also been reported in individuals on sorafenib<sup>51</sup>. Mitogen-activated protein kinase inhibitors (MEKis), such as trametinib, binimetinib, and cobimetinib, all of which have been approved for the treatment of metastatic melanoma, have also been linked to the development of papulopustular eruption.

Within the first days to weeks after starting medication, 75%–90% of patients (all grades) and 10% to 20% of patients (grade 3/4) develop an acneiform rash. The occurrence and intensity of the rash have been linked to treatment response. Up to 38% of cases have been documented to develop (bacterial) colonisation or superinfections of the rash<sup>52</sup>.

## **2. Hand-Foot Skin reaction (HFS)**

Hand-Foot Skin reaction HFS, also known as palmar-plantar erythrodysesthesia syndrome (PPES), is characterized by redness, severe pain, swelling, and tingling in the palms of the hands or soles of the feet<sup>53</sup>. PPES is related with numerous cytotoxic chemotherapy drugs, including 5-fluorouracil (5-FU), capecitabine, doxorubicin, PEGylated liposomal doxorubicin, and cytarabine, and can cause grade 3/4 toxicity in 5% to 10% of cases<sup>52</sup>.

The hyperkeratotic hand/foot skin reaction (HFSR) differs from the classic HFS in that it has different clinical (well-defined painful hyperkeratosis) and histological patterns<sup>52</sup>; it is a painful complication seen most frequently during the first weeks of treatment with sorafenib, sunitinib, and pazopanib, as hyperkeratotic plaques formed mostly on pressure or friction points, these plaques can have substantial inflammation and xerotic hyperkeratosis, generally in a bilateral symmetric pattern, producing discomfort and debilitation that interferes with everyday activities<sup>54</sup>.

### **3. Maculopapular Rash**

This is the most prevalent adverse event that is Immunotherapy-related among rashes. It is a skin ailment distinguished by the presence of macules and papules lesions. It is one of the most common cutaneous adverse effects, typically affecting the upper trunk, spreading centripetally, and accompanied with pruritus<sup>55 51</sup>.

### **4. Paronychia/Periungual Pyogenic Granuloma**

Paronychia and/or pyogenic granulomas are caused by an infectious process involving the perionychium and are often encountered with EGFRi targeted therapy<sup>52</sup>, such as monoclonal antibodies or TKIs. This is a local condition that may not result in a life-threatening condition or death, however this might cause a limitation of instrumental or self-care ADLs<sup>51 56</sup>.

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## **5. Stevens–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)**

SJS and TEN are severe and sometimes deadly illnesses characterized by significant epidermal detachment and keratinocyte necrosis in mucosal and cutaneous tissue. The proportion of total body surface area affected by epidermal detachment is used to classify them. Stevens–Johnson syndrome is a condition in which the dermis is separated by less than 10% of the entire body surface area. Toxic epidermal necrolysis is a more severe condition in which the dermis separates by more than 30% of the entire body surface area. Gemcitabine and imatinib, among other cancer treatments, have been linked to these syndromes. There is usually a prodromal phase of flu–like symptoms before the rash appears. The trunk, neck, face, and limbs are commonly affected with erythematous dusky–red macules<sup>51 57</sup> .

**Table 1:** Skin and subcutaneous tissue disorder adverse events

CTCAEv4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<b>Rash acneiform</b>	Papules and/or pustules <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness.	Papules and/or pustules covering 10% to 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting daily activities.	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care daily activities; associated with local superinfection ; oral antibiotics are indicated.	Papules and/or pustules covering any BSA %, which may or may not be associated with symptoms of pruritus or tenderness and associated with extensive superinfection ; IV antibiotics indicated; lifethreatening consequences .	Death
<b>Hand-Foot Skin reaction (HFS) Palmar- plantar erythrodyse sthesia syndrome</b>	Minimal skin changes dermatitis erythema, edema, without pain	skin or (eg, hyperkeratosis) with pain; limiting instrumental ADL (Activities of Daily Living)	Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL	-	-

<p><b>Rash maculopapular</b></p>	<p>Macules/papules covering &lt;10% BSA with or without symptoms (pruritus, burning, tightness)</p>	<p>Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL</p>	<p>Macules/papules covering or less [30% BSA with or without associated symptoms; limiting self-care ADL</p>	<p>–</p>	<p>–</p>
<p><b>Pruritus</b></p>	<p>Mild localized; topical intervention indicated</p>	<p>Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL</p>	<p>Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated</p>	<p>–</p>	<p>–</p>
<p><b>Paronychia</b></p>	<p>Nailfold edema or erythema; disruption of cuticle</p>	<p>Localized intervention indicated; oral intervention indicated (eg, antibiotic, antifungal,</p>	<p>Surgical intervention or IV antibiotics indicated; limiting selfcare ADL</p>	<p>–</p>	<p>–</p>

			antiviral); nailfold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL
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			Skin sloughing covering <10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10%–30% BSA with associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment)	Death
Stevens– Johnson syndrome	–	–			

*Chen, Alice P.; Setser, Ann; Anadkat, Milan J.; Cotliar, Jonathan; Olsen, Elise A.; Garden, Benjamin C.; Lacouture, Mario E. (2012). Grading dermatologic adverse events of cancer treatments: The Common Terminology Criteria for Adverse Events Version 4.0. Journal of the American Academy of Dermatology, 67(5), 1025–1039. doi:10.1016/j.jaad.2012.02.010*

## 6. Alopecia (CIA)

One of the most debilitating side effects of chemotherapy is alopecia, the CIA most commonly manifests as diffuse grade 2 alopecia, this refers to hair loss that is more than 50% than usual for that individual and visible to others, affecting the whole scalp, although some patients may develop diffuse partial alopecia or patchy, unevenly distributed alopecia. It can affect the brows, eyelashes, and body hair in some cases<sup>58</sup>. Normally it occurs 1–3 weeks after starting therapy, its severity is determined mostly by the type of chemotherapy, dosage, route of delivery, and duration between infusions. Hair will begin to grow again 2–3 months after chemotherapy is completed, at a pace of around 1 centimeter each month<sup>48</sup>.

Hair loss is a dreadful experience for most cancer patients, and because of the symbolic value of hair, it has been shown that hair loss can lead to a sense of personality loss later on<sup>59</sup>. Because of the sudden and severe character of CIA, and since it is seen as a marker of cancer severity, it has the potential to have a significant emotional impact on patients<sup>58</sup> <sup>48</sup>. Even a grade 1 alopecia can have a significant psychological impact on patients, necessitating particular therapy<sup>48</sup>.

Table 2: Skin and subcutaneous tissue disorder adverse events

CTCAE (Common Terminology Criteria for Adverse Events)	Grade 1	Grade 2
Alopecia	Hair loss of \50% of normal for that individual that is not obvious from distance but only on close inspection; different hair style may be required to cover hair loss but it does not require wig or hairpiece to camouflage	Hair loss of \$ 50% normal for that individual that is readily apparent to others; wig or hairpiece is necessary if patient desires to completely camouflage hair loss; associated with psychosocial impact

*Chen, Alice P.; Setser, Ann; Anadkat, Milan J.; Cotliar, Jonathan; Olsen, Elise A.; Garden, Benjamin C.; Lacouture, Mario E. (2012). Grading dermatologic adverse events of cancer treatments: The Common Terminology Criteria for Adverse Events Version 4.0. Journal of the American Academy of Dermatology, 67(5), 1025-1039. doi:10.1016/j.jaad.2012.02.010*

## VIII. Neurological Disorders

Systemic cancer's neurological effects can be painful, debilitating, and even lethal. Cancer-related neurological problems can impact the brain in a variety of ways: diffusely, such as delirium or dementia, focally, for exemple hemiplegia or aphasia, or multifocally. Different neurological illnesses might appear with identical signs and symptoms, making diagnosis challenging. Furthermore, concomitant neurological diseases, which are frequent in older cancer patients, might make diagnosis more difficult. Early diagnosis and aggressive treatment can significantly improve a patient's quality of life and alleviate neurological symptoms<sup>60</sup>.

Systemic antineoplastic therapy causes central and especially peripheral neurotoxicity, which is a common and generally dose-limiting adverse effect<sup>61</sup>. The severity of these neurological effects not only makes it difficult for the patient to endure given the severity of the neurological symptoms in general, but it also necessitates suspending the therapy in question, necessitating knowledge on how to manage each of these side effects.

## 1. Chemotherapy Induced Peripheral Neuropathy (CIPN)

Symptoms normally appear within the first two months of treatment, progress throughout active anticancer therapy, and then settle down shortly after treatment is ended<sup>61</sup>.

The first indicators of PN (peripheral neurotoxicity) in platinum-treated patients include a lack of Achilles reflex and diminished vibratory sensitivity in the toes, as well as numbness, tingling, or paresthesias in the fingers and toes. Long-term treatment may exacerbate symptoms and signs, resulting in a widespread loss of deep tendon reflexes (DTR) and proximal vibratory sensitivity impairment. The sensations of pins and temperatures, as well as joint position and mild touch sensitivity, are less affected. Loss of proprioception can lead to an ataxic walk in worst cases <sup>61 62</sup>.

-Toxicity most typically affects large sensory nerves in CIPN in a symmetrical length-dependent way. As a result, typical clinical symptoms are largely sensory, with acral pain and paraesthesia, as well as dysaesthesia, allodynia, and hyperalgesia as neuropathic "plus" traits. Sensory loss manifests itself in a 'glove and stocking' pattern, causing 'minus' symptoms such as numbness in the hands and feet, as well as reduced perception of light touch, vibration sensations, and hypoalgesia.

-Affection of the nerve terminals of fibers involved in temperature and pain perception is known as small fibre neuropathy. It causes a terrible burning feeling in the feet and/or hands as well as excruciating pain. Physical examination shows decreasing in pain perception and temperature sensitivity, in the painful parts described by the patient.

-Motor fibre involvement (associated with reduced or absent deep tendon reflexes or even distal weakness, atrophy of tiny foot muscles, tremor, cramps) or autonomic or cranial nerve symptoms are far less common than sensory impairment.

-Abdominal pain, constipation, postural hypotension, bladder problems, delayed stomach emptying, and reduced heart rate variability are all symptoms of autonomic involvement, which is common with vincristine and bortezomib use.

## **2. Central neuropathy**

### **a. Encephalopathy: Ifosfamide-induced acute encephalopathy**

Acute encephalopathy can manifest itself in a variety of ways, including paresis, speech difficulties, seizures, and cranial nerve dysfunctions. Its incidence has been linked to traditional chemotherapeutics. Changes in consciousness, from reduced attention to disorientation and delirium with psychotic symptoms, and changes in affect are both clinical characteristics of acute encephalopathy, like: apathy, anxiety, agitation. Differential diagnoses such cerebral bleeding or ischaemia in high-risk individuals, such as a history of thromboembolic event or current anticoagulation, as well as leptomenigeal illness, should be checked out radiologically. In the case of unexplained fever and meningeal irritation, a cerebrospinal fluid (CSF) investigation should be performed to rule out an infectious etiology<sup>61</sup>.

**b. Posterior reversible encephalopathy syndrome (PRES)**

The condition of posterior reversible encephalopathy (PRES) is uncommon, however it is becoming more common. Endothelial damage caused by sudden blood pressure shifts disrupts the blood–brain barrier, resulting in typical vasogenic oedema. 53 Because of limited sympathetic innervation and blood pressure autoregulation, the posterior areas of the brain are the most vulnerable to damage, causing: acute neurological abnormalities such as altered awareness, visual problems, blindness, migraines, and seizures are common in patients<sup>61</sup>.

**c. Acute Cerebellar Syndrome**

Patients receiving high–dose cytarabine (Cytarabine is mostly used to treat acute leukemia, particularly acute non lymphocytic leukemia), for example, may develop cerebellar syndrome. It causes dizziness, ataxia, dysarthria, vertigo, nausea, vomiting, and cerebellar or vestibule–cochlear eye movement problems, which generally appear 2 to 5 days after therapy begins. A T2–weighted MRI scan indicating cerebellar hyperintensities and CSF excluding central nervous system (CNS) infection, in addition to meticulous history–taking and neurological examination, will aid in the diagnosis<sup>61</sup>.

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d. Aseptic Meningitis

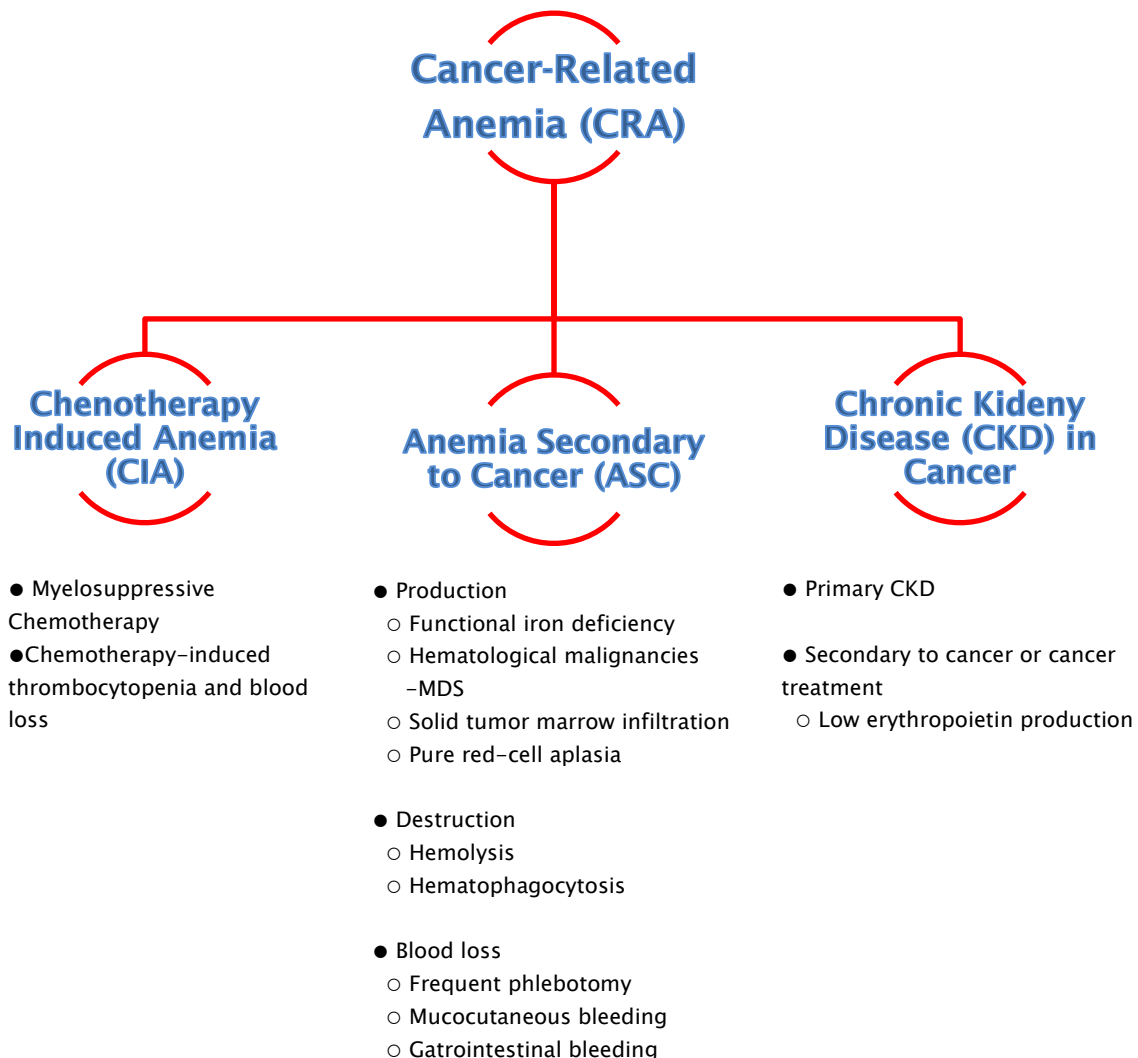
Aseptic meningitis is commonly connected with the use of intrathecal chemotherapeutics, and it can occur in 10% to 50% of patients receiving MTX, especially liposomal cytarabine. Meningeal irritation symptoms (headache, nuchal stiffness, vomiting, fever, and tiredness) normally appear within 2–4 hours following medication injection and remain for roughly 12 to 72 hours. Symptoms go away on their own after symptomatic therapy. CSF culture is used for differential diagnosis because it may reveal pleocytosis without other signs of bacterial illness. Concomitant administration of intrathecal corticosteroids (the most often used dose is 4 mg IT dexamethasone) to gradually avoid aseptic meningitis has gained significant clinical acceptance<sup>61</sup>.

## IX. Hematological Toxicities

Anticancer chemotherapies are linked to a slew of side effects. Hematological toxicity is one of the most common reasons for treatment cessation. These toxins reduce blood cell formation, resulting in anemia, neutropenia, and thrombocytopenia, all of which can be life-threatening to the patient. A reduction in bone marrow and blood cells is known as hematological toxicity, and it can lead to infection, bleeding, or anemia. Chemotherapy for cancer has two effects on cells: direct influence on proliferative cells and indirect effect on the bone marrow microenvironment and hematopoietic growth factor. Depending on the medicine, dosage, and timing, the duration between drug administration and the beginning of this toxicity might range from 12 hours to 8 weeks<sup>63</sup>.

## 1. Anemia

Anemia and iron deficiency (ID) are common cancer consequences that affect 30% to 90% of patients<sup>64</sup>. They are more common in individuals with solid tumors or hematological malignancies, with anemia developing in 50% of patients treated with chemotherapeutic drugs<sup>65</sup>. All of the causes are clarified in the figure below, including the myelo-suppressive effects of chemotherapy and radiation treatment<sup>66</sup>, as well as additional causes such as dietary inadequacies, marrow infiltration, and blood loss.



**Figure 4: Types of Cancer-Related Anemia**

Gilreath, J. A., Stenejem, D. D., & Rodgers, G. M. Diagnosis and treatment of cancer-related anemia. *American journal of hematology*. 2014;vol. 89, no 2, p. 203–212. doi: 10.1002/ajh.23628

Anemia is frequently linked to tiredness, cognitive impairment, physical function impairment, and a lower quality of life<sup>67</sup>. Even if a causative direct association has yet to be proved, anemia's consequences may include a diminished response to cancer therapy and overall survival (OS). Anemia is a common cause of morbidity and has been linked to an increased risk of death<sup>68</sup>.

You may assess tiredness and other anemia-related symptoms, with the FACT measuring system. It's a valuable measure of quality of life in cancer therapy, concentrating on the problem of fatigue-related anemia<sup>69</sup>.

The kind of cancer, the criteria of anemia, the stage of the disease, and whether or not patients have been treated all influence the prevalence numbers which range from (9g/dL vs. 11g/dL)<sup>70</sup>.

## **2. Febrile Neutropenia (FN):**

Neutropenia is regarded as an oncology emergency that can have catastrophic repercussions, including infection problems and mortality<sup>71 72</sup>. FN is associated with significant morbidity, as 20–30% of patients experience problems that necessitate in-hospital treatment, with a total in-hospital death rate of 10%<sup>73</sup>. The number of people who die from FN has continuously decreased, yet it is still a substantial cause of death.

An oral temperature of  $>38.3^{\circ}\text{C}$  or two consecutive readings of  $>38.0^{\circ}\text{C}$  for 2 hours and an absolute neutrophil count (ANC) of  $0.5 \times 10^9/\text{l}$ , or projected to decrease below  $0.5 \times 10^9/\text{l}$ , are considered febrile neutropenia (FN)<sup>73</sup>.

Despite significant breakthroughs in prevention and treatment, FN is still one of the most common and dangerous side effects of cancer chemotherapy (ChT). It is a major cause of morbidity, healthcare resource consumption, and therapeutic effectiveness compromise as a result of ChT delays and dosage reductions. Most standard-dose ChT regimens cause neutropenia for 6–8 days, and FN is seen in about 8 per 1000 cancer ChT patients. FN is associated with significant morbidity, as 20–30% of patients experience problems that necessitate in-hospital treatment, with a total in-hospital death rate of 10%<sup>73</sup>.

Other than ChT, various variables have been identified as contributing to the increased risk of FN and associated consequences. Age plays a significant role among them, with older patients having a larger chance of FN after ChT, as well as poorer morbidity and death rates. Other elements that play a comparable function include:

- Advanced illness,
- Previous episode of FN,
- No antibiotic prophylaxis or use of granulocyte colony-stimulating factor (G-CSF),
- Mucositis,
- Low performance status, and/or cardiovascular disease<sup>73</sup>.

The existence of a suspected infection focal site such as pneumonia, abscess, cellulitis, exacerbates the situation. The Multinational Association of Supportive Care in Cancer (MASCC) prognostic index predicts a mortality rate of less than 5% if the MASCC score is  $\geq 21$ , but as high as 40% if the MASCC score is  $< 15$ <sup>73</sup>. As a consequence of the adoption of suitable antibiotic therapy, preventative measures, risk assessment methods, and adequate patient care strategies, the morbidity and death rates of FN have reduced over time. However, FN, which is mainly linked to complex infections, is still a serious hazard and an oncological emergency. The threat is heightened by the continued appearance of antibiotic-resistant bacteria, which cause difficult-to-treat diseases and result in the deaths of millions of people throughout the world<sup>73</sup>.

## X. Nausea and Vomiting

Nausea and vomiting are among the most unpleasant and upsetting side effects of chemotherapy, according to patients, but it can also be caused by the disease itself due to obstruction of the the digestive tract. Significant advancements in our understanding of the pathogenesis of this frequent consequence of antineoplastic treatment have occurred during the previous two decades. Chemotherapy-induced nausea and vomiting (CINV) may develop within hours after receiving chemotherapy medications or may not appear until after the first 24 hours and last for many days and become chronic<sup>74</sup>.

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According to patients, the most disabling side effects of chemotherapy are nausea and vomiting. Inadequate management of these symptoms causes physiologic debilitation and psychologic distress, which leads to the patient being medically unable to continue therapy or becoming noncompliant, as well as a reduction in short-term quality of life. Effective management of chemotherapy-induced emesis is an important part of oncologic patients' overall care, as it improves patient compliance and increases the therapeutic index of chemotherapy regimens, lowering overall cancer therapy morbidity and mortality<sup>75 76</sup>.

## **XI. The we-disease and sexuality**

There is growing understanding of the impact of cancer and cancer treatment on couple relationships, which has been labeled as the "we-disease": Psychosocial discomfort experienced by cancer patients and their spouses is reported to be higher than that of the general population<sup>77</sup>. There is a link between patient and partner discomfort, implying that couples may react as an "emotional system." Couples who collaborate to address cancer-related stress, on the other hand, report improved psychological well-being, coping mechanisms, relationship satisfaction, and illness adjustment<sup>78</sup>. As a result, cancer researchers and doctors have prioritized researching therapies to lower psychological suffering and promote partner coping<sup>79</sup>.

Cancer may have a variety of direct and indirect effects on a person's sexuality and self-image<sup>80</sup>. Cancer (particularly testicular, prostate, penile, bladder, or gynecological malignancies), as well as therapy, can affect physical structures required for sexual function; this is one of the most prevalent and severe side effects of cancer and its treatment<sup>80</sup>.

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Changes in body image and self-esteem, cancer-related exhaustion, pain or mental issues, or stress in sexual partner relationships all play a role<sup>81 82</sup>. Illness has an impact on a person's physical well-being, as well as their self-image, desire, emotional and sexual closeness with their partners, and reproductive choices. It has been proven that sexual dysfunction has a substantial detrimental impact on one's quality of life<sup>83 84</sup>. However, oncology health professionals (OHP) are often hesitant to talk to patients about these difficulties<sup>80</sup>.

Sexuality appears to become less essential for some patients in the face of a life-threatening condition, whilst it becomes more vital for others by emphasizing residual pleasure, liveliness, and emotional connectedness. Medical treatment (hormonal therapy, erection aids, reconstructive surgery, etc.) as well as educational and counseling treatments can be used to help patients. Sexual or couple therapy may be necessary at times. Although multimodal therapy regimens have been created with considerable effectiveness, there is still a scarcity of data<sup>85</sup>.

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## Chapter II: Interventions and recommendations

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## I. Nutritional Intervention

Nutrition is a crucial component of supportive, rehabilitative, and palliative care. The primary objective is to address the patient's physiological and psychological requirements. This involves supplying energy, nutritional substrates, and anabolic stimulation, as well as compassionate assistance to treat eating dysfunctions related to emotional and social elements. The goal of nutritional assistance is to guarantee enough energy and nutrient intake by allowing the patient to consume regular food, enjoy eating, and engage in meals with others as part of social life. Dietary counseling, pharmaceutical medicines, and parenteral nourishment (PN) are all examples of nutritional and metabolic therapies<sup>18</sup>.

### 1. Risk screening

Nutritional risk screening should be performed on a regular basis in all cancer patients having anticancer therapy. To detect nutritional problems at an early stage, we propose that nutritional intake, weight change, and BMI be evaluated on a regular basis, starting with cancer diagnosis and continuing depending on the clinical situation's stability. We advocate objective and quantitative examination of nutritional intake, nutrition effect symptoms, muscle mass, physical performance, and the degree of systemic inflammation in individuals with abnormal screening. An evaluation of elements that are limiting or may interfere with sustaining nutritional status should include an analysis of:

–Nutrition has an effect on symptoms such as anorexia, nausea, changes in taste and smell, mucositis, constipation, dysphagia, chronic pain, abdominal discomfort, and diarrhea, as well as components of GI function that may be responsible for these symptoms.

-Tiredness, physical activity, shortness of breath, and psychological anguish<sup>86</sup>.

The assessment should concentrate on adjustable factors that may be addressed through intervention. The systematic use of a nutritional impact checklist has been proven to prompt more therapeutic actions, resulting in improved symptom management and, as a result, improved nutritional intake<sup>87</sup>.

Based on these findings, a personalised intervention may be initiated, including nutritional advising, reducing nutritional impact variables, and focusing on any other issues that may be limiting optimal nutrient intake.

One of the tools proposed for malnutrition screening is shown in the table below:

**Table 3: Malnutrition: Definition and criteria**

<b>Malnutrition</b>	<b>Defined by three criteria: a positive malnutrition screening test combined with one phenotypical and one aetiological criterion:</b>	
	<b>Mandatory Screening</b>	Malnutrition risk predicted by a validated screening test, e.g. NRS-2002, MUST, SNAQ, MST or other
	<b>Phenotypical criteria</b>	Loss of or low body mass as defined by at least one of the following: A1: weight loss >5% in 6 months A2: body mass index below 20 kg/m <sup>2</sup> A3: low muscle mass
	<b>Aetiological criteria</b>	Reduced food availability (B1) and/or increased catabolism (B2) B1 (starvation type): reduction in food availability B1a: food intake <50% for >1 week B1b: any reduction in food intake for >2 weeks B1c: chronic malabsorption B2 (cachexia type): increased acute or chronic systemic inflammation

*MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool; NRS- 2002, Nutrition Risk Screening 2002; SARC-F, Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls; SNAQ, Short Nutritional Assessment Questionnaire.*

## 2. Nutritional status:

To guarantee that all patients have access to proper nutritional and metabolic care, we recommend that all patients having anticancer treatment should be screened for nutritional risk, at regular intervals, the following aspects of nutritional status should be critically examined when assessing nutritional status:

- Body mass (BW).
- Weight gain or loss in the preceding months.
- Body composition with an emphasis on muscle mass.
- Food consumption with a focus on calories and protein.
- Performance Status (PS)
- Details on the existence and severity of systemic inflammation<sup>19 86</sup>.

Patients who are found to be at no immediate risk of malnutrition by screening should be re-screened at regular intervals, typically every 3 months or at anticancer treatment staging or, if anticancer treatment has a high risk of inducing malnutrition prophylactic nutritional support should be considered. All patients who are identified as at risk after malnutrition screening should be referred to a nutrition specialist for an assessment of nutritional and metabolic status, as well as an examination of food intake impairment and GI function.

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Patients identified as being at nutritional risk, we recommend an assessment of nutritional and metabolic status, which would include weight gain, weight loss, body composition, inflammatory state, nutritional intake, and physical activity, as well as an evaluation of the presence of factors interfering with the maintenance or improvement of this status, such as nutrition impact symptoms, gastro intestinal dysfunction, chronic pain, and psychosocial distress. Nutritional evaluations should be repeated at regular intervals, usually monthly, to help guide multicomponent anti-cachexia treatment<sup>86</sup>.

### **3. Nutritional requirements:**

The goal of nutritional treatments should be to meet energy and nutrient needs. Muscle exercise and measures to normalize metabolic status, reduce systemic inflammation, and relieve discomfort should be included<sup>86</sup>. Cancer patients have similar energy, nutritional, dietary needs to the general population, requiring around 25–30 kcal/kg/day, with a balance of calorie intake and expenditure, including the level of physical activity. Protein needs are estimated to be between 1.2 and 1.5 g/kg per day. These numbers should be adjusted based on the patients' renal function and any other metabolic abnormalities. The contribution of water and minerals should be investigated, particularly in cases when there are related hydroelectrolyte abnormalities. High amounts of vitamins and trace elements are not suggested unless there is a proven deficiency<sup>88 89</sup>.

–For patients who are able to eat we recommend the use of dietary counseling, assistance on choosing high-energy, high-protein foods, enriching foods (e.g by adding fat/oils, protein powder), and the use of oral nutritional supplements to provide nutritional support.

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-Patients who are able to eat and are malnourished or at risk, we recommend nutritional intervention to enhance oral intake, which includes dietary guidance, treatment of symptoms and derangements which are nutrition impact symptoms and that are responsible of the restriction of food intake, and the provision of oral nutritional supplements. If this is insufficient, tube feeding should be considered after making sure that the lower GI tract is functioning; otherwise, PN should be used. Separate feeding channels can be combined for maximum efficacy.

Concerning the modes of nutrition, if a patient is to be fed, enteral nutrition is recommended if oral nutrition remains inadequate after nutritional counselling and treatments, and parenteral nutrition is recommended if enteral nutrition is not sufficient or possible. If oral food intake has been substantially reduced for a long time, we recommend gradually increasing (oral, enteral, or parenteral) nutrition over many days and taking extra measures to avoid refeeding syndrome. The potentially catastrophic fluctuations in fluids and electrolytes that can occur in extremely malnourished individuals getting mechanical refeeding are known as refeeding syndrome, whether it is done enterally or parenterally. These changes are caused by feeding-induced hormonal and metabolic imbalances, and they can lead to major clinical issues such as cardiac and neurological problems. Hypophosphataemia is the most well-known biochemical hallmark of refeeding syndrome, although it can also include altered sodium and fluid balance, abnormalities in glucose, protein, and fat metabolism, thiamine insufficiency, hypokalaemia, and hypomagnesaemia.

## II. Dietary intervention

Table 4: Comparison of dietary interventions.

Dietary intervention	Benefits	Limitations
<b>Caloric Restriction</b>		
This nutritional intervention, defined as a 30% reduction in caloric consumption to enhance metabolic profile without inducing malnutrition <sup>90 91</sup> , resulted in a longer life span and a lower risk of chronic and age-related disorders, such as cancer, type II diabetes, and cardiovascular disease <sup>92</sup> .	<ul style="list-style-type: none"> <li>-Reduction in oxidative stress, inflammation, and growth factors (i.e. IGF-I and Ras/MAPK)</li> <li>-Improved insulin sensitivity and glucose tolerance</li> <li>-Decreased leptin levels</li> <li>-Promotes autophagy</li> <li>-Decreased angiogenesis</li> </ul>	<ul style="list-style-type: none"> <li>-Excessive weight loss</li> <li>-Risk of cachexia</li> <li>-Risk of malnutrition</li> </ul>
<b>Intermittent fasting</b>		
Involves a total calorie restriction for a period of time, usually 16 to 120 hours, followed by a refeeding interval. During the refeeding stage, a person's food intake is	<ul style="list-style-type: none"> <li>-Associated with improved chemotherapy-associated side effects -</li> <li>Improved insulin sensitivity and glucose tolerance</li> <li>-Decreased growth factors (i.e. IGF-I and Ras/MAPK)</li> </ul>	<ul style="list-style-type: none"> <li>-Excessive weight loss</li> <li>-Risk of cachexia</li> <li>-Risk of malnutrition</li> </ul>

not limited to certain food types or amounts<sup>93</sup>.  
–Decrease anabolic metabolism (termed differential stress resistance) –Increased AMPK

**Ketogenic diet**  
–Increased ketosis  
–Decreased inflammation  
**This diet has recently acquired popularity as a way to aid weight loss and lower the chance of developing different chronic illnesses it a moderate–protein, low–carbohydrate and high–fat diet<sup>94</sup>.**  
and growth factors (i.e. IGF–1)  
–Weight loss  
–Hypoglycemia, nausea, vomiting, and lethargy  
–Inhibition of tumorigenesis  
–Increase in serum cholesterol  
–Utilization of Warburg effect  
–Progressive bone loss  
–Selective increased oxidative stress in cancer cells

**Western diet**  
–Low nutritional density  
–Associated with prostate, breast, and colorectal cancer  
**Consisting of a high fat, processed meat, dairy, and carbohydrate consumption with a low fiber intake<sup>95</sup>.**  
None  
–Associated with chronic diseases

Gray, Ashley; Dang, Brian N; Moore, Theodore B; Clemens, Roger; Pressman, Peter (2020). A review of nutrition and dietary interventions in oncology. SAGE Open Medicine, 8(0), 205031212092687. doi:10.1177/2050312120926877

The Mediterranean diet has lately grown in popularity as a healthy way to lower cancer risk<sup>96</sup>. A Mediterranean diet is "convincingly" associated with a lower risk of weight gain, overweight, or obesity, according to the World Cancer Research Fund/American Institute for Cancer Research WCRF/AICR, whereas a "Western"-style dietary pattern is "probably" associated with an increased risk of these outcomes<sup>97</sup>. Provide a complete analysis of the MedD's alleged favorable benefits on overall cancer risk. In nations near the Mediterranean Sea, the mediterranean diet is quite frequent. It is characterized by a high intake of plant-based foods, whole grain products, vegetables, fruits, nuts, and legumes, as well as a regular diet of fish and shellfish, with red/processed meats and eggs being reduced. Olive oil is the most common type of fat. The Mediterranean diet lowers red meat consumption, which is pro-inflammatory and pro-oxidative<sup>96 98</sup>.

The presumed preventive benefits of the Mediterranean diet are attributed to the cumulative pattern rather than any particular dietary component. Inflammation, oxidation-reduction, and numerous metabolic processes are all affected by increased fruit and vegetable consumption, which may have anti-cancer benefits and improve healthy weight control<sup>99</sup>. Whole grains include phytic acids and fiber, which bind to carcinogens in the gastrointestinal system and neutralize them<sup>100</sup><sup>98</sup>. They have a foundation of mostly plant foods (such as non-starchy vegetables, whole fruits, whole grains, legumes, and nuts/seeds) and healthy protein sources (higher in legumes and/or fish and/or poultry, and lower in processed meats and red meat), as well as unsaturated fats, and are low in added sugar, saturated fats, and excess. In meta-analyses of observational studies, these healthy diet scores have also been linked to a decreased risk of colorectal cancer and overall cancer incidence<sup>101</sup>.

**Table 5:** Evidence for the Role of Weight Management, Physical Activity, and Diet for the Prevention of Cancer by Site

CANCER SITE	DIET
Breast	<ul style="list-style-type: none"> <li>• Dietary patterns rich in plant foods and low in animal products and refined carbohydrates lower risk (US Dietary Guidelines Advisory Committee 2015); the Mediterranean diet pattern lowers risk (Toledo 2015)</li> <li>• Consumption of nonstarchy vegetables and/or vegetables rich in carotenoids may lower risk for estrogen receptor–negative breast tumors (WCRFAICR 2018"); diets higher in calcium calcium–rich dairy may reduce risk (WCRF/AICR 2018)</li> </ul>
Colorectal	<ul style="list-style-type: none"> <li>• A healthy eating pattern with whole grains, higher fiber, and less added sugar lowers risk (WCRF/AICR 2018, US Dietary Guidelines Advisory Committee 2015'); consuming nonstarchy vegetables and whole fruits ole fruits probably lowers risk (WCRFAICR 2018)</li> <li>• Processed meat intake, even in small amounts, and red meat in moderate to high amounts, increases risk (WCRF/AICR 2018')</li> <li>• Consuming nonstarchy vegetables and whole fruits probably lowers risk (WCRFAICR 2018)</li> <li>• Consume diets higher in calcium/calcium–rich dairy foods (WCRF/AICR 2018*): supplemental calcium may lower risk (WCRFIAICR 2018)</li> <li>• Low circulating levels of vitamin D</li> </ul>
Lung	<ul style="list-style-type: none"> <li>• Consuming nonstarchy vegetables and whole fruits, including those high in vitamin C (especially for smokers), probably lowers risk (WCRFIAICR 2018)</li> <li>• Processed and red meat may increase risk (WCRF/AICR 2018)</li> <li>• High–dose B–carotene supplementation increases risk, particularly among smokers and those exposed to asbestos (WCRF/AICR 2018)</li> </ul>
Stomach/ Gastric	Regular intake of processed, grilled, or charcoaled meats increases risk for noncardia gastric cancer (WCRFTAICR 2018) Intake of nonstarchy vegetables and whole fruits, especially citrus fruits, probably lowers risk (WCRFIAICR 2018) Consumption of nonstarchy vegetables and whole fruits probably lowers risk (WCRFAICR 2018)
Liver	Consumption of fish may lower risk (WCRF/AICR 2018)

<b>Upper Aerodigestive</b>	Consumption of nonstarchy vegetables and whole fruits probably lowers risk (WCRFAICR 2018)
<b>Pancreas</b>	Processed and red meats as well as saturated fats in general may increase risk (WCRFAICR 2018) • Sugar-sweetened beverages may increase risk (WCRFAICR 2018)
<b>Prostate</b>	• Higher consumption of dairy products and calcium (>2000 mg/d) may increase risk (WCRFAICR 2018, Wilson 2015)

*Rock, Cheryl L.; Thomson, Cynthia; Gansler, Ted; Gapstur, Susan M.; McCullough, Marji L.; Patel, Alpa V.; Andrews, Kimberly S.; Bandera, Elisa V.; Spees, Colleen K.; Robien, Kimberly; Hartman, Sheri; Sullivan, Kristen; Grant, Barbara L.; Hamilton, Kathryn K.; Kushi, Lawrence H.; Caan, Bette J.; Kibbe, Debra; Black, Jessica Donze; Wiedt, Tracy L.; McMahon, Catherine; Sloan, Kirsten; Doyle, Colleen (2020). American Cancer Society Guideline for Diet and Physical Activity for cancer prevention. CA: A Cancer Journal for Clinicians, (), caac.21591-. doi:10.3322/caac.21591*

**Table 5: 2020 American Cancer Society Guideline on Diet and Physical Activity for Cancer Prevention**

Recommendations for individuals
<p><b>1. Achieve and maintain a healthy body weight throughout life.</b></p> <ul style="list-style-type: none"> <li>• Keep body weight within the healthy range and avoid weight gain in adult life.</li> </ul>
<p><b>2. Be physically active.</b></p> <ul style="list-style-type: none"> <li>• Adults should engage in 150–300 min of moderate–intensity physical activity per wk, or 75–150 min of vigorous–intensity physical activity, or an equivalent combination; achieving or exceeding the upper limit of 300 min is optimal.</li> <li>• Children and adolescents should engage in at least 1 hr of moderate– or vigorous–intensity activity each day.</li> <li>• Limit sedentary behavior, such as sitting, lying down, and watching television, and other forms of screen–based entertainment.</li> </ul>
<p><b>3. Follow a healthy eating pattern at all ages.</b></p> <ul style="list-style-type: none"> <li>• A healthy eating pattern includes: <ul style="list-style-type: none"> <li>o foods that are high in nutrients in amounts that help achieve and maintain a healthy body weight;</li> <li>o A variety of vegetables–dark green, red, and orange, fiber–rich legumes (beans and peas), and others,</li> <li>o Fruits, especially whole fruits with a variety of colors, and</li> </ul> </li> </ul>

- o Whole grains.
  - A healthy eating pattern limits or does not include:
    - o Red and processed meats;
    - o Sugar-sweetened beverages; or
    - o Highly processed foods and refined grain products.
4. It is best not to drink alcohol.
- People who do choose to drink alcohol should limit their consumption to no more than 1 drink per day for women and 2 drinks per day for men.

**Recommendation for Community Action**

- Public, private, and community organizations should work collaboratively at national, state, and local levels to develop, advocate for, and implement policy and environmental changes that increase access to affordable, nutritious foods, provide safe, enjoyable, and accessible opportunities for physical activity, and limit alcohol for all individuals.

*Rock, Cheryl L.; Thomson, Cynthia; Gansler, Ted; Gapstur, Susan M.; McCullough, Marji L.; Patel, Alpa V.; Andrews, Kimberly S.; Bandera, Elisa V.; Spees, Colleen K.; Robien, Kimberly; Hartman, Sheri; Sullivan, Kristen; Grant, Barbara L.; Hamilton, Kathryn K.; Kushi, Lawrence H.; Caan, Bette J.; Kibbe, Debra; Black, Jessica Donze; Wiedt, Tracy L.; McMahon, Catherine; Sloan, Kirsten; Doyle, Colleen (2020). American Cancer Society Guideline for Diet and Physical Activity for cancer prevention. CA: A Cancer Journal for Clinicians, (), caac.21591-.doi:10.3322/caac.21591*

**III. Cachexia management**

A disease-related malnutrition subtype identified using malnutrition screening, systemic inflammation, and at least one phenotypic criteria<sup>102 103</sup>:

**Table 6: Phenotypical criteria of cachexia**

<b>Phenotypical criteria</b>	Loss of or low body mass as defined by at least one of the following: <ul style="list-style-type: none"> <li>A1: weight loss &gt;5% in 6 months</li> <li>A2: body mass index below 20 kg/m<sup>2</sup></li> <li>A3: low muscle mass</li> </ul>
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*MST, Malnutrition Screening Tool; MUST, Malnutrition Universal Screening Tool; NRS-2002, Nutrition Risk Screening 2002; SARC-F, Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls; SNAQ, Short Nutritional Assessment Questionnaire.*

Changes in body resources and metabolic pattern, as well as impairment of physical function, are important goals in patients receiving anticancer therapy. Symptoms that are incapacitating, on the other hand, must be addressed. To ensure that all patients have access to proper nutritional and metabolic care, it is critical to detect at-risk patients by establishing a standardised screening method on a regular basis, and examine all at-risk patients for nutritional and metabolic health, as well as any deficits that may jeopardize this status<sup>18</sup>.

Cachexia screening should be integrated into standard cancer care, backed up by accountable clinicians, and connected to quick access to cachexia treatment options. Every cachexia patient should be provided therapies aimed at either improving or relieving the effects of cachexia, which necessitates a multimodal strategy focused at alleviating symptoms that affect food intake, guaranteeing appropriate energy and nutritional intake, reducing catabolic changes, promoting muscular exercise, and providing psychological and social support.

## **1. ONSs**

Food counseling using ONSs is generally helpful for generating weight gain and boosting dietary intake when it is required. Oral nutritional supplements are a well-balanced blend of macro- and micronutrients that come in the form of liquid feeds, puddings, and powdered formulations that may be reconstituted with milk or water. They come in a variety of presentations, flavors, and compositions, including fiber-rich and milk-, juice-, or yoghurt-like options<sup>104</sup>.

## 2. Corticosteroids

Corticosteroids are used to enhance appetite and have a high level of proof. We recommend using corticosteroids for a limited duration (1–3 weeks) to boost appetite in anorectic cancer patients with advanced illness, but be careful of the adverse effects such as muscle loss, insulin resistance, and infections<sup>86</sup>.

Methylprednisolone was given orally or intravenously to 402 individuals in three studies for 1–8 weeks at dosages of 32–125 mg per day. Significant improvements were observed in quality of life and appetite when compared to placebo, but not in body weight. Paulsen et al. has observed an improvement in appetite loss and fatigue after taking 32 mg of methylprednisolone per day for seven days in his study ‘Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer’<sup>105</sup>.

## 3. Progestins

Progestins may be used to boost appetite and BW in anorectic cancer patients with advanced illness, but they will not improve muscle mass, QoL, or physical function. Be warned that progestins (megestrol acetate and medroxyprogesterone acetate) might cause impotence, vaginal spotting, and thromboembolism when used. More than 30 randomized clinical studies have looked at progestins, and the data has been examined in various systematic reviews and meta-analyses<sup>106 107 86</sup>.

#### 4. Others

There is moderate evidence to support the use of olanzapine to manage nausea and appetite in advanced cancer patients. Androgens are not suggested because there is no proof of a favorable impact in terms of increasing muscle mass. The use of NSAIDs alone to treat cancer cachexia is not recommended due to a lack of evidence. The metoclopramide or Domperidone use alone to treat cancer cachexia is not recommended due to a lack of evidence. Plus there is inadequate evidence to support the use of medicinal cannabis or its derivatives to treat anorexia or early satiety<sup>18</sup>.

### IV. Physical Activity

#### 1. Should patients exercise during cancer treatment and recovery?

Exercise is safe and possible during cancer treatment; evidence strongly suggests that it might enhance physical functioning and different elements of quality of life. Exercise has been demonstrated to enhance cardiovascular fitness, muscle strength, body composition, exhaustion, and anxiety, as well as self-esteem, among those who exercise moderately. People who are already exercising but are getting chemotherapy or radiation therapy may need to exercise at a lower intensity and improve at a slower rate than people who are not receiving cancer treatment. Furthermore, resistance training regimens may be beneficial in slowing the onset of undesirable body composition changes such as sarcopenic obesity, a decrease of skeletal muscle mass is accompanied with a high amount of obesity, and osteopenia that can occur in some cancer patients receiving systemic treatment<sup>108 109 110 111 112</sup>,it can also attenuate systemic inflammation<sup>113</sup>.

The key objective should be to keep as much exercise going as possible. Despite strong evidence supporting exercising in the treatment of CRF, there is no specific exercise prescription for patients. Some observational and interventional studies have also shown that cancer patients who engage in at least 3 to 5 hours of moderate activity weekly may have better results and fewer adverse effects of anticancer treatment, such as tiredness. Current exercise prescription recommendations focus on the overall well-being of cancer patients<sup>114 23</sup>, ideally encouraging them to engage in regular physical activity in accordance with the ACS guidelines, specifically:

-Avoid inactivity and return to normal daily activities as soon as possible after diagnosis

-Aim for at least 150 minutes of moderate or 75 minutes of vigorous aerobic exercise per week and include strength training exercises at least two days per week, with an emphasis on strength training for women receiving adjuvant chemotherapy or hormone therapy<sup>115</sup>.

## **2. Are there special precautions patients should consider?**

Cancer patients' capacity to exercise may be restricted or prohibited due to a variety of factors. Some therapeutic side effects may raise the risk of exercise-related injuries and side effects. Physical activity should be avoided by patients with severe anemia until their condition improves, and patients with weakened immune systems should avoid going to public gyms and other community facilities until their white blood cell counts return to normal.

Radiation survivors should avoid swimming pools because chlorine might aggravate irradiated skin. Low-intensity exercises should be undertaken and gradually progressed for people who were sedentary prior to diagnosis.

Special monitoring and attention should be given to older people and those with bone disease, such as skeletal metastases or severe osteoporosis, or major impairments such as arthritis or peripheral neuropathy, to limit the risk of falls and injury<sup>109 110 111 112</sup>.

### **3. How to prevent recurrence?**

Overweight and obesity have been linked to an increased incidence of many forms of cancer as well as a higher risk of recurrence in some malignancies, according to several studies, and physical exercise is an important part of maintaining and reaching a healthy body weight. Furthermore, physical activity aids in the prevention of cardiovascular disease, diabetes, and osteoporosis. As a result, cancer survivors should be encouraged to engage in physical activity<sup>109 110 111 112</sup>.

### **4. What if the disease or therapy needs bed rest for a length of time?**

If the condition or treatment involves periods of bed rest, reduced fitness and strength, as well as loss of lean muscle mass, might be predicted. Although Physical therapy is also recommended during bed rest to preserve strength and range of motion and to help fight the weariness and depression that are frequently encountered under these conditions<sup>109 110 111 112</sup>.

## V. Psychological Support

### 1. Diagnostic announcement

The announcement of a cancer diagnosis is a decisive step, sometimes the first, in the relationship between the doctor and his patient, a key moment that will seal the type of relationship and the trust between these two protagonists. However, this essential step in the patient's journey involves the communication of potentially traumatic information. Indeed, this announcement is not only about the diagnosis itself. It also involves the possible consequences of the disease, radically modifying the way in which the patient will project himself into the future, with a threat of death to come, either real or supposed <sup>116</sup>.

A poorly worded bad news announcement can have a negative impact on patients' perceptions of their clinical reality and the goal of treatments, decisions about treatment options, adherence to treatment, and psychological adjustment. A research found that announcing unpleasant news immediately increased patients' anxiety after the consultation <sup>117</sup>. Many factors can influence how bad news is experienced: factors related to the disease (type, context, severity), factors related to patients and their relatives (sociodemographic, emotional state, desire for information, desire to participate in decision-making...). As a result, while delivering terrible news, they must be considered <sup>118</sup>.

The announcement of bad news is further complicated when patients are accompanied by a loved one. According to studies, 16% to 75% oncological consultations take place in the presence of a loved one<sup>119</sup>. This is often the main patient caretaker: spouse, child, parent or sibling. During these consultations, the loved one can provide both emotional and informational support, allowing better understanding and retention of the information transmitted. However, both the patient and the loved one can be affected by the announcement of bad news. Indeed, a study has published that the increase in patient anxiety following these consultations to announce bad news is associated with the increase in anxiety of the relatives who accompany them<sup>120 118</sup>.

The announcement of bad news is a major issue in medicine and in oncology in particular, both for doctors and for patients and their relatives, the anxiety of the latter increases directly after this consultation, which makes the announcement more difficult to be performed when patients are accompanied by a loved one. The perception of this bad news depends on the type of cancer and factors specific to the patient: socio-demographic factors, emotional state, desire for information, willingness to participate in decisions and sometimes guilt due to the patient's previous lifestyle (smoking). During the announcement, the loved one can however provide both emotional and informational support, and facilitate the understanding and passing on of information. To minimize the negative impact of breaking bad news, communication should include assessment, information for personalized support. Training in these notification processes should be offered not only to medical specialists but also to other healthcare professionals (general practitioner, radiologists, nurses, etc.), at university level and in professional training<sup>118</sup>.

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We recommend that the diagnostic announcement has three phases: pre-announcement, announcement, post-announcement, these phases are interdependent and make it possible to provide appropriate information and support.

- During the pre-announcement phase, the doctor must visualize the cognitive and emotional state of the patient, trying to understand what the patient already knows, what he wants to know and his emotional state. The same is true for the relative if he is present during the consultation.

- The actual announcement must be made in a concise manner, with precise words, in order to avoid that the patient is overwhelmed by a flood of information that he is not in a position to process at the moment. At this stage, we must remain objective and avoid any strategy of reassurance, minimization and trivialization. We have to explain the medical term, we have to give the patient time to recover between two pieces of information, to show humanity and simplicity, to avoid hiding behind technical words.

- The third phase, the post-announcement phase, must provide informational and emotional support to the patient and his relatives. During the consultation, this announcement in three phases can be repeated several times depending on the different information to be transmitted concerning, for example, the treatment<sup>118</sup>. During the consultation, this announcement in three phases can be repeated several times depending on the different information to be transmitted concerning, for example, the treatment.

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**Table 7:** The three phases proposed by the Belgian experience.

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**The first phase:  
Pre-Announcement  
Phase**

This first phase is devoted to preparing the patient for the announcement and evaluation of the patient's situation.

Preparation involves briefly recalling the purpose of the consultation, to summarize the current medical situation and to introduce the announcement concerning the results of the examinations. During this phase, it is essential that the doctor assesses what the patient already knows, what he wants to know and his emotional state.

The patient's representations of his medical situation will have a direct impact on how the patient will experience the announcement of the bad news.

This assessment will provide the patient with adequate and appropriate information and support throughout the disclosure process.

During this phase, the doctor mainly has as communication tools the evaluation strategies (information search and clarification) that will allow him to represent the cognitive and emotional state of the patient.

If a loved one is present during the consultation, this first phase will also make it possible to assess their feelings related to the medical situation and to prepare them for the announcement.

The diagnosis must be announced concisely with precise words in order to prevent the patient from being overwhelmed by a flood of information that he is not, at the time, able to process.

**The second phase :  
Announcement Phase**

The bad news must also be announced in a precise manner (name the illness clearly). Care should be taken to avoid using overly specific medical terms that risk being out of reach for the patient and their loved ones, as well as reassurance, minimization and trivialization strategies that are not appropriate for this phase of the process.

It is of course necessary to avoid being moralistic during a possible transmission of information regarding the potential causes of the disease.

During this phase, the main communication tool will be the transmission of information which will allow the announcement to be understood by the patient and the loved one.

**The Third Phase:  
Post-Announcement  
Phase**

This phase is devoted to providing informational and emotional support to the patient and loved one according to their specific needs.

After the announcement, the doctor will make sure that the patient has understood the announcement. If he has a poor understanding of the situation, the doctor provides additional information to enable him to understand the news. The doctor will also assess his emotional state in

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order to provide him with support such as: recognition, empathy, reassurance. Indeed, the patient may show signs of psychological distress, state of shock, crying, anger, anxiety, etc.

While support is particularly important during this third phase, it should also be present throughout the announcement process.

If a loved one is present during the consultation, this phase will also make it possible to assess their understanding and their emotional state in order to be able to provide them the necessary support.

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Delevallez, F.; Lienard, A.; Gibon, A.-S.; Razavi, D. (2014). *L'annonce de mauvaises nouvelles en oncologie : l'expérience belge. Revue des Maladies Respiratoires, 31(8), 721-728.* doi:10.1016/j.rmr.2014.07.003

## **2. Psychosocial interventions**

Psychosocial interventions include things like psychosocial counseling, psychotherapy, and psychoeducation, as well as mind-body therapies<sup>114</sup>. The major aims of therapies are to assist patients in reorganizing their cognitive evaluation of CRF, changing their coping mechanisms and behavior, and addressing self-help or self-care measures. Relaxation methods, energy conservation, and stress management are all part of certain therapies. Individual and group psychosocial therapies are available for the majority of psychosocial interventions. Psychosocial therapies may be paired with physical exercise or training in some cases<sup>23</sup>.

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a. Psychoeducation

Several research have looked at the outcomes of psychoeducational programs, with results showing a meaningful reduction in CRF as well as an improvement in vitality<sup>121</sup>.

Psychoeducational therapies assist patients increase self-management, adaptability, and adjustment to their existing condition and treatments by focusing on CRF control. The most essential purpose of psychoeducational intervention is to assist the individual with cancer in self-care<sup>122</sup>. Given the strong link between emotional distress and exhaustion, psychoeducational therapies should concentrate on identifying coping mechanisms to improve the patient's capacity to cope with anxiety, depression, and psychosocial discomfort. It may be beneficial for patients to identify sources of psychological distress and, when feasible, minimize stressful activities<sup>23</sup>.

Another key aspect is to direct the patient's attention to tiredness patterns and achieving a balance between rest and activity throughout the day by grading each activity in terms of reported exhaustion. This strategy can assist the patient identify fatigue-inducing behaviors and establish particular techniques to avoid or alter them in order to set realistic objectives, prevent frustration, and engage in self-restorative activities<sup>123</sup>. Based on an assessment of the patient's fatigue patterns, an individual activity/rest program can be included, such as relaxation techniques or meditation, which may target underlying biological mechanisms and reduce cancer-related distress by decreasing activation of the hypothalamic pituitary adrenal (HPA) axis<sup>124</sup>.

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b. Cognitive behavioural therapy

Emotions, behaviors, and cognitive processes are all addressed in cognitive behavioral therapy (CBT) and applied to goal-oriented and systematic activities. CBT in CRF focuses on the individual and their pattern of psychological elements, taking into consideration the ideas and functional behaviors that are related to the condition. CBT is often utilized after treatment and for the long term, but it can also be used for patients who are still undergoing ChT and are experiencing acute exhaustion. CBT is commonly used to treat the following issues: dealing with cancer; fear of illness recurrence; dysfunctional ideas and beliefs about fatigue; sleep dysregulation; activity dysregulation<sup>125</sup>; low social support/negative social interactions<sup>23 126</sup>.

There have been various research on the effectiveness of CBT, but only a few of them have looked at exhaustion as a key goal. In these investigations, there was a clinically significant reduction in tiredness severity and functional impairment.

Several meta-analyses and systematic reviews have been published in the last 15 years on the efficacy of cognitive behavioral techniques, suggesting that CBT decreases depressive symptoms, reduces emotional distress, and improves quality of life at various stages of cancer treatment<sup>127</sup>.

c. Acceptance and Commitment Therapy

ACT therapies showed considerable benefits in quality of life and psychological flexibility, as well as decreases in discomfort, emotional disturbances, physical pain, and traumatic reactions. Overall, there is some evidence to support ACT as a beneficial psychotherapy strategy for cancer patients, despite the few published studies currently available. Since 1999, more than 100 ACT randomized controlled studies have been completed. ACT has also been popular in behavioral medicine for a number of chronic diseases and disorders, such as diabetes and chronic pain, as evidenced by these randomized controlled studies. People with chronic medical illnesses can benefit from ACT because it reduces distress and improves functionality.

The Society of Clinical Psychology of the American Psychological Association has approved ACT as having "high research support" due to its strong evidence and efficacy in the treatment of chronic pain (2016). One of the guiding principles of ACT is that suffering is an unavoidable aspect of human experience and that it could be handled by reacting to difficult life events with "psychological flexibility," which is defined as reaching the present moment as a fully conscious human being, fully and without unnecessary defense and changing a behavior in the service of chosen values.

When faced with obstacles such as cancer diagnosis, treatment, survivorship, or advanced disease, the ACT model articulates three key pillars of psychological flexibility: being present, opening up, and doing what counts. ACT, unlike CBT, is thought to be transdiagnostic, focusing on universal psychological processes that are thought to underlay psychological distress across illnesses and life circumstances. This minimizes the need on diagnosis-specific manuals, which are more commonly used with CBT. Above all, the transdiagnostic concept is highly adapted to dealing with the high levels of psychological and medical comorbidities that are common in cancer patients<sup>127</sup>.

Physical discomfort, unpleasant feelings, and disturbing thoughts, as an example, may be addressed concurrently and effectively using experiential exercises that develop the ability of acceptance, which can enhance mood, disease coping, and functioning even in relatively brief treatments. Patients are faced with life-changing decisions and worries not just after a cancer diagnosis but also throughout treatment, not only about their future but also the future of their family. Many patients must also face their own death<sup>127</sup>.

#### **d. Mindfulness-Based Stress Reduction (MBSR)**

MBSR was created to assist patients with chronic health disorders in dealing with challenging physical symptoms that did not improve with traditional medical therapy, with the early study focused on chronic pain<sup>128 127</sup>. As a result, rather than attempting to remove pain, the goal of MBSR is to promote self-regulation via the use of mindfulness, which is defined as paying attention, in the present moment, in a certain way; on purpose, and not judgmentally<sup>128 101</sup>.

Suffering may be alleviated by cultivating a neutral, open consciousness that allows for acceptance of pain sensations, as well as pain-related thoughts and emotions, without effort, rumination, or negative judgment. Committed mindfulness practice is linked to the dissociation of the sensory and affective/cognitive elements of pain, resulting in less suffering even while pain persists<sup>128 127</sup>. Because it focuses on coping with unpleasant, upsetting, and sometimes inevitable physical symptoms, MBSR is becoming more popular among cancer patients and has been shown to enhance psychological health and cancer adjustment<sup>128 127</sup>.

#### e. Art therapy

In 2006 a study that gathered 200 patients was conducted and the results were very significant, and showed that music has the power to change and move people emotionally. Individuals have been healed physically, psychologically, socially, emotionally, and spiritually using it. Music has been utilized for therapeutic purposes in hospice, palliative care, radiation treatment, chemotherapy, and medical procedures (such as port placement/removal or tissue biopsy). It has been linked to enhanced quality of life and spiritual healing, as well as symptom management such as pain and anxiety<sup>129</sup>.

Individual symptoms such as anxiety, sadness, pain, and shortness of breath improved clinically following music therapy intervention; however, there was no significant difference in patient scores based on whether or not the patient had a musical background. This demonstrates that music is a global language, and that no specific expertise is required to enjoy or profit from it. Anxiety, depression, discomfort, and shortness of breath were all considerably improved in patient ratings.

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As well as facial expressions, movement, and verbalizations all considerably improved<sup>129</sup>.

Music therapy is part of a complementary medicine program that is used in conjunction with medical treatment in supportive care. There are several advantages to using music therapy for cancer patients. Both interactive and receptive music therapy approaches (listening to recorded or live music, music) can be used to improve mood, reduce tension, anxiety, and boost relaxation. The therapy is an excellent way for cancer sufferers to get support during their treatment. It may also be necessary for developing successful rehabilitation programs that promote wellbeing, increase physical and emotional wellness, and improve overall quality of life. Music therapy can be utilized as a receptive and active intervention to decrease stress and anxiety associated with hospitalization as well as the unfamiliarity of the hospital setting<sup>130</sup>.

## **VI. Prevention and Management of Bone Health**

### **1. Lifestyle management**

Although the impact of lifestyle management on bone loss is difficult to assess, a few limited studies have shown that regular resistance training and weight-bearing activity can lead to modest increases in BMD as well as changes in bone metabolism biomarkers that indicate a reduction in bone metabolism. Patients should be encouraged and assisted in quitting smoking and drinking less alcohol, since these are known risk factors for fracture<sup>35</sup>.

## **2. Multidisciplinary management of bone metastases**

Treatment options differ based on the underlying condition. Endocrine therapies, chemotherapy, targeted medicines, and radioisotopes are all significant. In addition, structural issues such as bone loss or nerve compression may necessitate orthopaedic surgery<sup>35</sup>.

The function of bone-targeted medicines is to complement these therapies. In addition, structural issues such as bone loss or nerve compression may necessitate surgical intervention. To minimize morbidity and complement these therapeutic approaches, bone-targeted drugs (BTAs) are incorporated<sup>34</sup>.

## **3. Prevention of metastasis**

Bisphosphonates minimize bone metastases and enhance survival in postmenopausal women with breast cancer (natural or induced). Bisphosphonates have little effect on premenopausal women's illness outcomes. In castrate-resistant prostate cancer, denosumab prevents bone metastases<sup>35</sup>.

## **4. Prevention of treatment-induced bone loss**

Bisphosphonates help to prevent bone loss caused by ovarian suppression or aromatase inhibitors in early breast cancer, as well as androgen deprivation treatment in prostate cancer.

## **5. Management of Bone metastases**

To effectively treat metastatic bone disease, multidisciplinary management including skills in systemic therapies, radiation therapy, orthopaedic surgery, radiography, and supportive care, including palliative medicine, is essential.

- For the relief of localized bone pain, radiotherapy is the treatment of choice.
- Single fractions are just as effective for pain reduction as fractionated radiotherapy.
- Bisphosphonates and denosumab are osteoclast inhibitors that have become essential drugs in the treatment of metastatic bone disease due to their ability to prevent consequences, reduce symptoms, and enhance quality of life.
- Zoledronic acid is the most effective bisphosphonate for preventing metastatic bone disease morbidity.
- In the prevention of skeletal morbidity from solid tumors, denosumab is more effective than zoledronic acid.
- Bone-targeted treatment should be started as soon as metastatic bone disease is diagnosed.
- For metastatic bone disease, bone-targeted treatment should be continued forever and throughout the course of the illness.

## **6. Prevention of skeletal morbidity in metastatic bone disease**

Bisphosphonates and denosumab have proven themselves as useful additions to the current therapy options during the previous two decades. Multiple randomized controlled studies have shown that they are beneficial in lowering skeletal morbidity associated with metastatic cancer<sup>35</sup>.

- Risk factors that can be changed should always be addressed, including advice for bodyweight exercises, physical activity, and calcium and vitamin D supplements.



## VII. Fertility Preservation

### 1. Oncofertility counseling

Regardless of the kind or stage of cancer, all cancer patients of reproductive age should get comprehensive oncofertility counseling as early as feasible in the treatment planning process. This should include a discussion of the patients' current or future family plans, their health and prognosis, the disease's and/or proposed anticancer treatment's potential impact on their fertility and gonadal function, chances of future conception, pregnancy outcomes, and children, as well as an effective contraception in the context of systemic anticancer treatment if needed<sup>132 133</sup>.

Even if there is no interest in future children at the time of diagnosis, patients should be provided extensive oncofertility counseling to ensure that they completely understand the risk of treatment-related gonadotoxicity. When feasible, all patients should be given written information or access to resources, which should be noted in the medical record. All patients who may be interested in fertility preservation should be referred to a fertility doctor or a fertility facility as soon as possible<sup>134 133</sup>.

### 2. Fertility Preservation: Male patients

#### a. Gonadal shielding during RT

The germinal epithelium is protected by gonadal shielding during total-body radiation. In comparison to individuals who had testicular shielding, adolescent patients who did not get testicular shielding had a considerably reduced testicular volume in maturity<sup>135</sup>.

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**b. Sperm cryopreservation**

Before beginning anticancer therapies (ChT, RT, or surgery), sperm cryopreservation is standard of care and should be considered with every male cancer patient who is at risk of infertility. This approach is based on spermatozoa's ability to survive and fertilize after being frozen, usually in liquid nitrogen vapour or after controlled gradual freezing<sup>136 137</sup>.

The success rate for parenting with cryopreserved sperm from cancer patients is 49% [95% confidence interval (CI) 44 % -53 %]. Long-term cryopreserved sperm preservation is not linked to poor outcomes or thawed sperm quality<sup>138</sup>. Adults and teens in Tanner pubertal stages II-III are the indication and should consider sperm cryopreservation<sup>133</sup>.

**3. Fertility preservation: Female patients**

**a. Oocyte and embryo cryopreservation**

Before starting anticancer therapies, oocytes and embryos can be safely and effectively cryopreserved. Because oocyte cryopreservation may be done without a spouse, it is most post-pubertal women's preferred option. While embryo cryopreservation is a well-established and repeatable technique, it does necessitate the usage of sperm as well as the presence of a spouse or donor. Women who choose to preserve embryos made with their partner's sperm should be aware that the embryos will be the couple's joint property; if the relationship ends, it may be difficult to use the embryos<sup>139</sup>.

Around 2 weeks of ovarian stimulation with gonadotropins is necessary for oocyte and embryo cryopreservation, followed by follicle aspiration. Ovarian stimulation can begin at any point throughout the menstrual cycle (referred to as "random start stimulation")<sup>140</sup>. However, timing is critical since the operation must be finished before any ChT can begin. Double stimulation can be considered in women with a poor ovarian reserve who do not need to start anticancer therapies right away; it takes 4 weeks and roughly doubles the number of oocytes recovered<sup>141</sup>.

Women under the age of 40 who will be subjected to gonadotoxic anticancer therapy and want to retain their fertility may consider oocyte or embryo cryopreservation. It is not recommended for women who have severe coagulation problems or are at a high risk of infection. In people who are unable or unable to undergo vaginal treatments, transabdominal monitoring and oocyte recovery may be an option. As a result, a well-established partnership between cancer and reproductive divisions is crucial<sup>133</sup>.

#### **b. Ovarian tissue cryopreservation**

Cryopreservation of ovarian tissue is an alternative to gonadotoxic therapies for sustaining fertility. Under general anaesthesia, biopsies of the ovarian cortex or unilateral ovariectomy are frequently performed via laparoscopy. Because no pretreatment is required, the process may be completed quickly and ChT can begin the next day if necessary<sup>142</sup>.

Although it is still deemed experimental in certain countries, the American Society for Reproductive Medicine recommends that it should be considered a standard technique that should be administered to carefully chosen individuals<sup>143</sup>. The key factor impacting success rate, as with oocyte and embryo cryopreservation, is age: women who are younger at the time of cryopreservation had better reproductive results following ovarian tissue transplantation than older women, with just a few pregnancies reported in women over 36 years of age<sup>144</sup>. Another risk factor is that the procedure should not be recommended to patients who have a high surgical/anaesthesia risk due to their disease, because ovarian tissue collection and transplantation are usually done via laparoscopy, and should ideally be done at the same time as other anesthetic procedures. Another important risk is transmission after transplantation owing to remaining neoplastic cells inside the ovarian cortex, which is especially dangerous in pelvic malignancies or systemic disorders like leukemia<sup>145</sup>.

**c. Ovarian transposition and gonadal shielding during RT**

Another risk factor is that the procedure should not be recommended to patients who have a high surgical/anaesthesia risk due to their disease, because ovarian tissue collection and transplantation are usually done via laparoscopy, and should ideally be done at the same time as other anesthetic procedures. Another important risk is transmission after transplantation owing to remaining neoplastic cells inside the ovarian cortex, which is especially dangerous in pelvic malignancies or systemic disorders like leukemia<sup>146</sup>.

Oocyte retrieval from transposed ovaries may be done safely. Ovaries can be restored to their original place following RT in some situations. Patients undergoing surgery and RT had a 65% chance of retaining ovarian function. Ovarian transposition carries the same surgical risk as other gynecological operations (risk of bowel and vessel injury). A transposed ovary has a very low risk of developing ovarian cancer<sup>147</sup>. Gonadal shielding, which does not need surgery, might be a viable alternative to ovarian transposition<sup>133</sup>.

#### **d. Medical gonadoprotection**

The goal of medicinal gonadoprotection during ChT is to lessen the risk of primary ovarian insufficiency and the reproductive and endocrine implications that come with it. This method could be useful for people who don't want to get pregnant and aren't interested in preserving their fertility. Its applicability for premenopausal patients of all ages, non-invasive nature, minimal health risk, and potential usage in combination with fertility-preservation treatments are all potential benefits<sup>148</sup>.

The sole technique that has entered clinical usage is temporary ovarian suppression during ChT accomplished by giving a GnRHa at the beginning at least 1 week before the onset of systemic cytotoxic treatment and continuing for the length of therapy. Temporary ovarian suppression with a GnRHa during ChT should be regarded a conventional option for ovarian function preservation in premenopausal breast cancer patients receiving (neo) adjuvant systemic cytotoxic treatment, according to the existing data . Despite the limited available evidence, usage of a GnRHa may be explored in premenopausal women with other malignancies who are candidates for ChT, due to its other possible medical benefits, such as menstrual cycle regulation and avoidance of menometrorrhagia risk. Importantly, temporary ovarian suppression with a GnRHa during ChT should not be viewed as a substitute to cryopreservation procedures for patients interested in fertility preservation<sup>133</sup>.

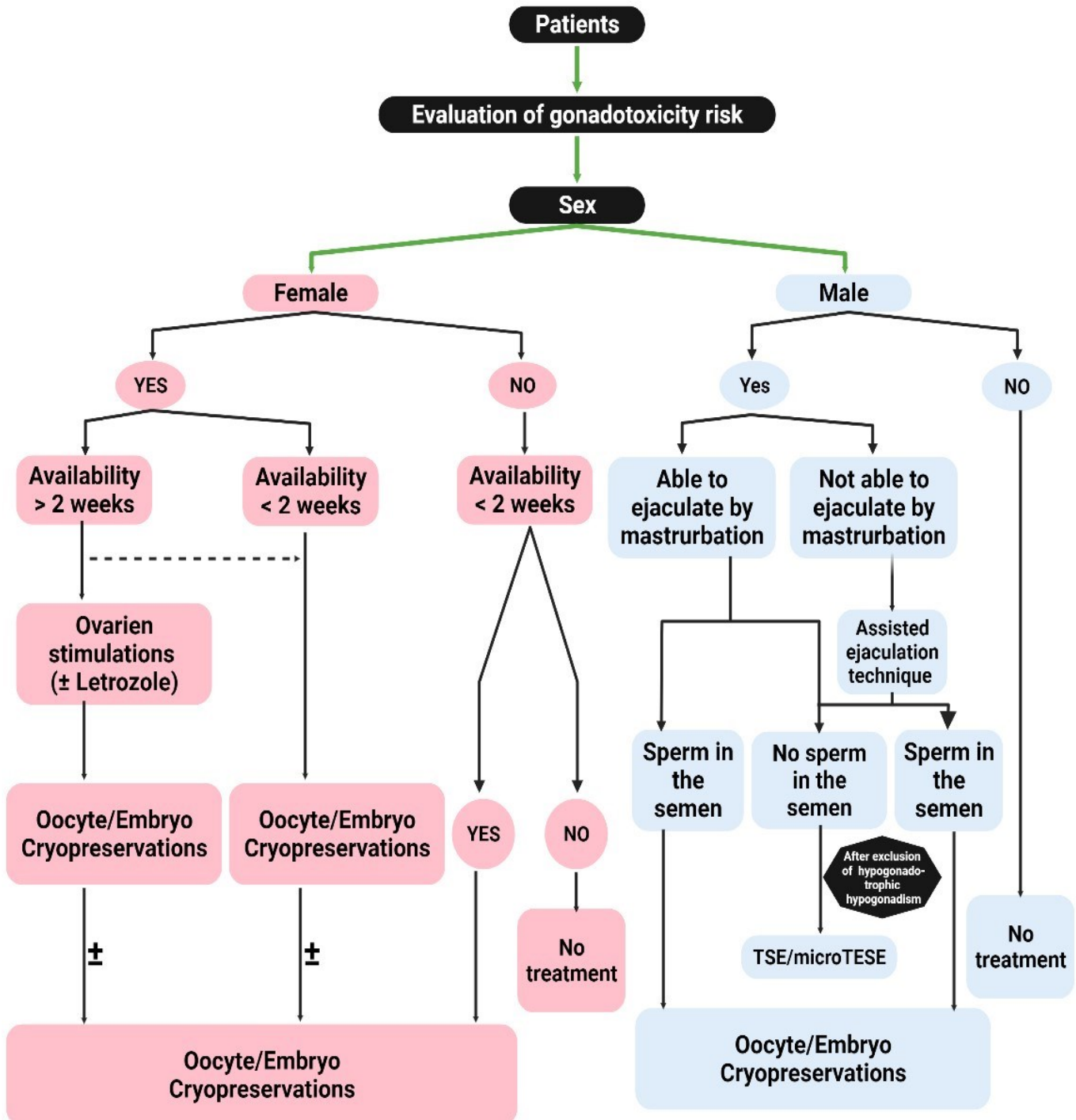


Figure 5: Decision Tree for preservation of fertility for both sexes

## VIII. Management of pain

### 1. Pain screening and assessment

Every contact should include a pain screening and an initial complete pain evaluation. This evaluation should describe the pain, determine its etiology, and draw conclusions regarding pathophysiology (pain descriptors, associated distress, functional impact, and related physical, psychological, social, and spiritual factors), as well as information on cancer treatment history and comorbid conditions, psychosocial and psychiatric history (including substance use), and previous pain treatments. A physical examination should be done in conjunction with the history, and diagnostic tests should be done if necessary<sup>149</sup>. Clinicians should assess if other health specialists are required to offer complete pain treatment to individuals with complicated requirements. If it is thought essential, the doctor should assign responsibility for each area of treatment and send patients as needed<sup>149</sup>.

### 2. Recommendations of Nonpharmacologic Interventions

Clinicians can prescribe or refer patients to other specialists to offer the therapies listed in the table below to help cancer survivors manage chronic pain and improve pain-related outcomes. Pre-existing illnesses and comorbidities must be considered in these therapies.

**Table 8: Disciplines and Interventions for Chronic Pain**

Disciplines	Possible Interventions
<b>Psychological approaches</b>	Cognitive behavioral therapy, distraction, mindfulness, relaxation, guided imagery
<b>Physical medicine and rehabilitation</b>	Physical therapy, occupational therapy, recreational therapy, individualized exercise program, orthotics, ultrasound, heat/cold
<b>Interventional therapies</b>	Nerve blocks, neuraxial infusion (epidural/intrathecal), vertebroplasty/kyphoplasty

Paice, J. A.; Portenoy, R.; Lacchetti, C.; Campbell, T.; Cheville, A.; Citron, M.; Constine, L. S.; Cooper, A.; Glare, P.; Keefe, F.; Koyyalagunta, L.; Levy, M.; Miaskowski, C.; Otis-Green, S.; Sloan, P.; Bruera, E. (2016). *Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology, (), JCO.2016.68.5206-*. doi:10.1200/JCO.2016.68.5206

### 3. Recommendations of Pharmacologic Interventions

It is crucial to provide a therapy that patients and families can handle on their own. If well tolerated, the oral route should be regarded the preferable mode of delivery. Patient participation in pain treatment promotes both communication and pain reduction through improving patient understanding as well as physician evaluation and prescription<sup>150</sup>.

The start of pain should be avoided by administering medications around-the-clock (ATC), taking into consideration the half-life, bioavailability, and duration of action of various pharmaceuticals<sup>150</sup>.

The pain intensity influences the kind and amount of analgesic medications, which must be quickly modified to achieve a balance between optimal pain relief and minimal adverse effects<sup>150</sup>.

The WHO suggests a method for cancer pain therapy based on a three-step analgesic ladder, from non-opioids to mild opioids to powerful opioids, dependent on pain severity. In practice, this means starting with paracetamol and non-steroidal anti-inflammatory medications (NSAIDs). Opioid analgesics are the cornerstone of analgesic therapy and are categorised according to their capacity to manage pain, which ranges from mild to moderate intensity in the second step, to moderate to severe intensity in the third step<sup>150</sup>.

**a. Treatment of mild pain**

At any step of the WHO analgesic ladder, paracetamol and NSAIDs are unanimously approved as part of the management of cancer pain. Several systematic evaluations on the efficacy of paracetamol and NSAIDs for cancer pain treatment, either alone or in conjunction with opioids, are available<sup>150</sup>.

**b. Treatment of mild to moderate pain**

Weak opioids like tramadol, dihydrocodeine, and codeine can be used in conjunction with non-opioid analgesics to treat mild to moderate pain. Low doses of strong opioids might be used as an alternative to weak opioids. Although this proposal is not part of WHO guidelines currently, there is no evidence that using low-dose strong opioids instead of weak opioids causes an increase in adverse effects<sup>150</sup>.

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c. Treatment of moderate to severe pain

In the treatment of moderate to severe cancer-related pain, strong opioids constitute the basis of analgesic therapy, and precautions should be taken and opioid dosages must be adjusted, in case there is a renal insufficiency, because when toxic metabolites build up in the body, confusion, sleepiness, and hallucinations can occur<sup>150</sup>.

- Oral morphine is the first-line opioid for moderate to severe cancer pain.
- Oral to intravenous morphine has a relative potency ratio of 1:2 to 1:3.
- In individuals with chronic renal disease stages 4 or 5 (estimated glomerular filtration rate 30 mL/min), fentanyl and buprenorphine (through the TD or IV route) are the safest opioids.
- The SC route is straightforward and effective for administering morphine, diamorphine, and hydromorphone, and it should be the first-choice alternative route for patients who are unable to receive opioids orally or intravenously.
- When SC administration is contraindicated (peripheral oedema, coagulation problems, poor peripheral circulation, and the necessity for high volumes and dosages), IV infusion should be explored.
- When pain treatment is required quickly, IV administration is an alternative for opioid titration.
- In individuals with chronic renal disease stages 4 or 5 (estimated glomerular filtration rate 30 mL/min), fentanyl and buprenorphine (through the TD or IV route) are the safest opioids.
- The SC route is straightforward and effective for administering morphine, diamorphine, and hydromorphone, and it should be the first-choice alternative route for patients who are unable to receive opioids orally or intravenously.

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-When SC administration is contraindicated (peripheral oedema, coagulation problems, poor peripheral circulation, and the necessity for high volumes and dosages), IV infusion should be explored.

-When pain treatment is required quickly, IV administration is an alternative for opioid titration<sup>150</sup>.

## **IX. Dermatological interventions**

### **1. Acneiform Rash**

#### **a. Preventive management**

To avoid (papulopustular exanthema) acneiform rash:

-Avoid frequent washing with hot water (hand washing, showering, and bathing).

-Avoiding skin irritants such as over-the-counter (OTC) acne medicines, solvents, and disinfectants.

-Alcohol-free OTC moisturising creams or ointments used to the body on a daily basis, ideally with urea-containing (5-10%) moisturisers.

-Avoid excessive sun exposure.

-Apply SPF 15 sunscreen to exposed regions of the body and every 2 hours when outside.

-Oral antibiotics for 6 weeks at the beginning of therapy, with or without application of a low/moderate potency steroid to the face and chest<sup>52</sup>:

-Because of their antibacterial and anti-inflammatory qualities, well-established pharmacological preventative methods are based on prophylactic treatment with oral tetracyclines [doxycycline 100 mg (b.i.d) bis in die or minocycline 100 mg once daily].

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-The use of oral tetracyclines can reduce the occurrence of grade  $\geq 2$  rash. The prevention can be done with or without the use of topical corticosteroids (e.g. low-potency corticosteroids such as hydrocortisone 2.5% or alclometasone 0.05 % b.i.d.) to the face or chest, since their usefulness is still debatable<sup>151 52</sup>.

### **b. Therapeutic management**

-First, if an infection is suspected, for example, due to failure to respond to gram-positive antibiotics, the presence of painful skin lesions, pustules in arms, legs, and trunk, yellow crusts, or discharge, a bacterial culture must be obtained, and antibiotics must be administered for at least 14 days based on sensitivities.

-For grade 1 and 2 rash, it is advisable to start or increase the potency of topical corticosteroids and to start oral tetracycline antibiotics for at least 6 weeks: Oral antibiotics for 6 weeks at the commencement of therapy, with or without b.i.d. application of a low/moderate potency steroid to the face and chest.

-A brief course of systemic corticosteroids (e.g., prednisone 0.5–1 mg/kg body weight for 7 days with a tapering dosage over 4–6 weeks) is recommended for the therapy of grade 3 rash, coupled with suspension of EGFRis until the rash is grade 1<sup>152 52</sup>.

**Table 9: Acneiform Rash: grading and interventions**

Grading	Intervention
Grade 1 and 2	–Oral antibiotic for 6 weeks (doxycycline 100 mg b.i.d. OR minocycline 50 mg b.i.d. OR oxytetracycline 500 mg AND – Topical low/moderate steroid
Grade $\geq 3$	Oral antibiotic for 6 weeks (doxycycline 100 mg b.i.d. OR minocycline 50 mg b.i.d. OR oxytetracycline 500 mg b.i.d.) AND _ Topical low/moderate steroid _ Systemic corticosteroids (e.g. prednisone 0.5–1 mg/kg body weight for 7 days)

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## 2. Hand–Foot Skin reaction (HFS)

### a. Preventive management

- Avoid hand and foot irritation, lengthy walks, hard lifting without protection.
- Treat predisposing conditions before beginning anticancer treatment.
- The use of urea 10% cream three times per day dramatically reduced the occurrence of all–grade HFSR.
- In particular, for taxane–based treatment, employ skin cooling gloves or stockings.
- For capecitabine–based treatment, a personalized strategy to each patient is recommended for celecoxib 200mg b.i.d.

**b. Therapeutic management**

- Keratolytics (e.g., topical creams or ointments containing salicylic acid 5%– 10% or urea 10% –40%) are used to treat hyperkeratosis.
- Skin irritation is treated with topical corticosteroids with high potency (e.g., clobetasol proprionate 0.05%).
- Antiseptic solutions (e.g., silver sulfadiazine 1 percent, polyhexanide 0.02% –0.04%) can be used to treat erosions and ulcerations.
- Lidocaine 5% cream or patches may be used for analgesia on sore parts of the feet and hands to allow everyday activities.

Table 10: Hand-Foot Skin reaction: grading and interventions

Grading	Intervention
Grade 1 and grade 2	<p>Continue drug at current dose and monitor for change in severity</p> <ul style="list-style-type: none"> <li>_ Topical high-potency steroid b.i.d.</li> <li>_ Lidocaine 5% patches or cream</li> </ul> <p>Reassess after 2 weeks</p>
Grade 3 or intolerable grade 2 treatment	<p>Interrupt treatment until severity decreases to grade 0-1;</p> <p>and continue treatment of skin reaction with the following:</p> <p>Continuation or initiation of:</p> <ul style="list-style-type: none"> <li>_ Topical high-potency steroid b.i.d.</li> <li>_ Lidocaine 5% patches or</li> <li>_ Possibly topical keratolytics (e.g. with salicylic acid 5%-10% or urea 10%-40%) cream</li> <li>_ Possibly antiseptic solutions (e.g. silver sulfadiazine 1%, polyhexanide 0.02%-0.04%) cream.</li> </ul> <p>Reassess after 2 weeks;</p>

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### 3. Maculopapular Rash

-Topical emollients, oral antihistamines, and/or modest dose topical corticosteroids can be used to treat Grade 1 symptoms.

-Topical emollients, oral antihistamines, and medium-to-high dosage topical steroids are used for grade 2 symptomatic therapy.

-Grade 3 necessitates the immediate cessation of checkpoint inhibition until they are returned to grade 1. Topical emollients, oral antihistamines, and high-strength topical steroids are used to treat the condition.

Depending on the severity of the symptoms, systemic corticosteroids of 0.5-1 mg/kg may be explored.

-In the rare occurrence of grade4 skin toxicity, checkpoint inhibitor medication should be discontinued, and patients should be hospitalised promptly and placed under the observation of a dermatologist. Intravenous (i.v.) (methyl)prednisolone 1-2mg/kg is administered, with decreasing when the toxicity settles to normal<sup>153</sup>.

**Table 11: Maculopapular Rash: grading and interventions**

<b>Grading</b>	<b>Intervention</b>
<b>grade 1</b>	Symptoms can be treated with topical emollients, oral antihistamines and/or mild strength topical corticosteroids.
<b>Grade 2</b>	Symptomatic treatment consists of topical emollients, oral antihistamines and median-to-high strength topical steroids.
<b>Grade 3</b>	Immediate interruption of checkpoint inhibition, until these are back to grade1. Treatment includes topical emollients, oral antihistamines and high strength topical steroids [II, B]. Systemic corticosteroids 0.5-1 mg/kg can be considered, depending on the severity of the symptoms

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In the rare event of grade 4 skin toxicity, treatment with checkpoint inhibitors should be interrupted, and patients should be admitted **grade 4** immediately and be placed under supervision of a dermatologist. Treatment consists of intravenous (i.v.) (methyl)prednisolone 1–2 mg/kg with tapering when the toxicity resolves to normal .

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Haanen, J. B. A. G.; Carbone, F.; Robert, C.; Kerr, K. M.; Peters, S.; Larkin, J.; Jordan, K. (2017). *Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology, 28(suppl\_4), iv119-iv142.* doi:10.1093/annonc/mdx225

#### 4. Paronychia/Periungual Pyogenic Granuloma

##### a. Preventive management

- Preventive nail curvature correction with referral to a podiatrist if necessary.
- Avoiding repeated friction and trauma/excessive pressure.
- Cleaning with gloves.
- Avoiding trimming nails, or biting too short.
- Using antimicrobial soaks and washing with n cleansers and water.
- Regular nail trimming to ensure that they are straight and not too short;
- Daily application of topical emollients to the cuticles and periungual regions.
- Wearing cotton socks and fitting shoes<sup>52</sup>.

##### b. Therapeutic management

- If the lesions are self-limited, conservative treatment is recommended, such as high-potency topical corticosteroids alone or in combination with topical antibiotics, silver nitrate chemical cauterization, and stretchy tapes<sup>56 154 52</sup>.

-A controlled study found that topical povidone iodine 2% b.i.d. was beneficial for grade 1 and 2 paronychia.

-Anecdotal evidence suggests that oral antibiotics are beneficial. In eight patients treated with EGFRis, topical timolol (0.5% gel, b.i.d. under occlusion for 1 month) resulted in full eradication of toenail and fingernail paronychia and/or periungual pyogenic granulomas<sup>52 155</sup>.

-Surgical therapy with partial nail plate avulsion, or excision of a longitudinal section of the nail associated with the matrix, with physical elimination of excessive granulation tissue, is appropriate for unacceptable grade 2 or grade3 paronychia/pyogenic granuloma.

**Table 11: Paronychia/Periungual Pyogenic Granuloma: grading and interventions**

Grading	Intervention
<b>Grade 1</b>	Continue drug at current dose and monitor for change in severity Topical povidone iodine 2%, topical antibiotics/corticosteroids Reassess after 2 weeks
<b>Grade 2</b>	Continue drug at current dose and monitor for change in severity; obtain bacterial/viral/fungal cultures if infection is suspected. Topical povidone iodine 2%/topical beta–blocking agents/topical antibiotics and corticosteroids And/OR Oral antibiotics Reassess after 2 weeks
<b>Grade 3</b>	Topical povidone iodine 2%/topical beta–blocking agents/topical antibiotics and corticosteroids And/ OR Oral antibiotics OR Consider partial nail avulsion Reassess after 2 weeks;

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## **5. Stevens–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)**

Stevens–Johnson syndrome must be treated in the hospital, either in an intensive care unit or a burn unit<sup>156</sup>.

- Stopping the medicine that caused the condition is one of the treatments for Stevens–Johnson syndrome.
- Using intravenous (IV) fluids to replace electrolytes because skin loss can cause a large loss of fluid in the body, fluid replacement is an important element of therapy.
- Applying non–adhesive bandages to the skin affected.
- Using high–calorie meals to encourage recovery, maybe by tube feeding.
- Antibiotics are used as necessary to prevent infection.
- Administering pain relievers.
- Using dermatology and ophthalmology specialized teams (if eyes affected).
- IV immunoglobulin, cyclosporine, IV steroids, or amniotic membrane grafts may be used in some circumstances (for your eyes)<sup>157</sup>.

## **6. Management of alopecia**

The only technique that has been demonstrated to prevent CIA, at least to a certain degree, is scalp cooling. Vasoconstriction and decreased biochemical activity in the scalp and hair follicles caused by scalp cooling making hair shaft diameters shrink after scalp cooling, indicating only modest damage, healing, and continued hair growth. Scalp cooling generally begins 20–45 minutes before the ChT infusion and lasts for 20–150 minutes during and after the infusion<sup>48</sup>. Scalp cooling has been demonstrated to be beneficial in reducing the increasing severity of alopecia after subsequent cycles of ChT for both grade 1 and grade 2 CIA.

In seven out of eight randomized clinical studies that were conducted, scalp-cooled patients had a substantial benefit, with 50% to 65% of patients having grade 1 alopecia<sup>158</sup>. Furthermore, several observational studies and reviews have demonstrated the effectiveness of scalp cooling using gel caps or devices for a wide spectrum of cytostatics in patients with varied cancer stages<sup>159</sup>, the efficacy of scalp cooling is higher with taxane protocols<sup>48</sup>.

Haematological malignancies, cold sensitivity, cold agglutinin illness, cryoglobulinaemia, cryofibrinogenaemia, cold post-traumatic dystrophy, and whole-brain RT after chemotherapy are all contraindications to scalp cooling. A case of a patient with leukemia and a patient with cutaneous lymphoma were reported, where the appearance of a scalp skin metastasis as the first indicator of progression after scalp cooling has been observed<sup>160</sup>. Plus the only injuries caused by cold have been recorded after using frozen gel caps. Also, TSH, vitamin D, zinc, and ferritin serum levels should all be checked, and if required, a deficit has to be corrected.

Following cytotoxic ChT, topical minoxidil 5%, which is a solution against hair loss used to delay premature baldness as much as possible, can be used as a therapeutic intervention, and may help with hair regrowth. Individuals treated with minoxidil 5% daily demonstrated considerable improvement in 25% of cases and moderate improvement in 40% of cases in an uncontrolled trial of 41 patients<sup>161</sup>.

## **X. Management of Neurological toxicities**

### **1. Management of CIPN**

#### **a. Non-pharmacological prevention of CIPN**

##### **i. Exercise and functional training**

Exercise and functional training are suggested to be protecting against CIPN, in many data. Patients at risk of developing CIPN can benefit from medical exercise to increase muscular strength and sensorimotor functions, distal motor skills, body coordination, and balance (Exercise for Cancer Patients (EXCAP®)). In addition, exercise treatments for self-management should be included in the protocol. Before beginning any medical workout, as always, make sure there are no contraindications<sup>35 162</sup>.

Men taking ADT for prostate cancer should be urged to preserve bone health, muscular strength, and physical function by staying active as much as possible. Premature menopause and secondary amenorrhoea can be caused by cytotoxic cancer therapy, with menopause occurring on average 10 years sooner than usual. Premature ovarian failure is more common in women over the age of 40 at the time of treatment. The majority of research have found that bone loss in premenopausal women is caused by the endocrine effects of chemotherapy rather than direct cytotoxic damage to bone cells<sup>35 162</sup>.

##### **ii. Cryotherapy**

In small trials, cryotherapy using frozen socks or gloves showed some encouraging benefits<sup>15,16</sup>. There were some mixed outcomes in the largest randomised phase III research (n=180), with a high rate of dropout due to discomfort, although the prevention of CIPN with cryotherapy can be considered<sup>163 164</sup>.

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**b. Pharmacological treatment**

When individuals have persistent CIPN, treatment focuses on reducing or eliminating neuropathic pain. Sleep disturbance, anxiety, depression, and central sensitization of pain can all increase neuropathic pain, thus the treating physician should be aware of this<sup>150</sup>.

**i. Selective serotonin reuptake inhibitor**

In a major randomised trial, duloxetine was found to provide a moderate clinical benefit in individuals with painful CIPN, making it the sole medicine examined thus far in CIPN. Duloxetine was found to have a higher percentage of pain reduction than placebo in 231 individuals with CIPN (59% versus 38%)<sup>165</sup>. As a result, duloxetine is suggested for the treatment of neuropathic pain. Venlafaxine was also found to be effective in a small randomised trial (n=48) and could be used to treat neuropathic pain<sup>166</sup>.

**ii. Anticonvulsants and tricyclic antidepressants**

Based on what is known about managing neuropathic 'plus' symptoms in general, membrane stabilizing medications such as anticonvulsants (pregabalin, gabapentin) or tricyclic antidepressants can manage symptoms in individuals with CIPN. From a practical standpoint, it is critical to use all of the proposed medications for neuropathic pain for at least two weeks at the right dose before switching to another choice<sup>61</sup>.

**iii. Opioids**

Opioids may be used to alleviate neuropathic pain as a last resort. There is no strong evidence that one opioid is superior than another for neuropathic pain<sup>167 168</sup>.

**iv. Topical local intervention: Menthol**

A 1% menthol cream was given to the afflicted area in a phase II trial, and 31 of 38 assessable patients experienced significant pain alleviation with low harm. Topical low-concentration menthol cream might be tried because it is inexpensive and has had no known side effects<sup>169</sup>.

**v. Topical baclofen/amitriptyline/ketamine**

-In a randomized experiment (n=208), topical treatment with a baclofen/amitriptyline and ketamine-containing gel resulted in a non-significant improvement in sensory neuropathy<sup>170</sup>.

-A topical amitriptyline/ketamine mixture, on the other hand, was studied in 462 individuals in a randomized, controlled trial (RCT) and shown to have no effect on CIPN pain, numbness, or tingling.

-Patients with CIPN may benefit from capsaicin 8% patches<sup>61 171</sup>.

## **2. Central neurotoxicity**

### **a. Encephalopathy management**

The therapy is primarily symptomatic and comprises discontinuing the medicine that caused the problem, correcting electrolytes if they are out of balance, and symptomatic treatment with benzodiazepines, for example. A spontaneous complete remission can be found in practically all patients with no side effects<sup>61</sup>.

### **b. Posterior reversible encephalopathy syndrome Management**

When PRES is present, blood pressure must be closely monitored. In the case of seizures, treatment entails stopping anticancer and antiepileptic medications. Within two weeks, PRES is generally reversible with adequate supportive care. The decision to resume previous anticancer therapy must be made on an individual basis<sup>61 172</sup>.

### **c. Acute cerebellar syndrome Management**

Obviously, the antineoplastic medicine that is causing the cancer should be discontinued. Plus a voiding very high doses of cytarabine if appropriate especially in individuals with renal impairment<sup>61 173</sup>.

## **XI. Management of hematological toxicities**

### **1. Management of Anemia:**

The main goal of anemia management are to reduce or eliminate anemic symptoms, especially tiredness, resulting in enhancing the quality of life using the least intrusive treatment that corrects the underlying causes. Increased production of inflammatory cytokines owing to the underlying malignancy and/or toxicity of cancer therapy might result in underlying causes of anemia, primarily reduced erythropoietic function and disrupted iron homeostasis. Vitamin B12 and foalate deficiencies, on the other hand, are very uncommon causes of anemia in cancer patients<sup>174</sup>.

A hemoglobin level less than 11 g/dl in cancer patients should be explored, according to the NCCN (National Comprehensive Cancer Network). A reduction of more than 2g/dl should also be evaluated in individuals with a high baseline level. According to the NCCN, there are three types of anemia:

1. Asymptomatic anemia without major comorbidity, in which case surveillance and periodic reevaluation are recommended;
2. Asymptomatic anemia with comorbidity or high risk, for which transfusion should be considered;
3. Symptomatic anemia, for which transfusion should be conducted <sup>174</sup>.

Even if there are no symptoms or major comorbidities, transfusion may be necessary if the hemoglobin level drops after treatment. In patients who require quick correction of anemia, packed red blood cell (PrBC) transfusion is the sole therapy choice since it results in a 100% rise in Hb and haematocrit levels, as well as rapid alleviation in anemia-related symptoms. On the other hand , congestive heart failure,

bacterial contamination, viral infections, iron overload, and an increase in thrombotic events are among risks linked with PrBC transfusion<sup>174</sup>.

The new ESMO clinical practice recommendations offer advice on how to properly manage CIA using erythropoiesis-stimulating drugs, iron preparations for IV and oral administration, red blood cell, transfusion, and a combination of these therapies, as shown in the figure below<sup>175</sup>.

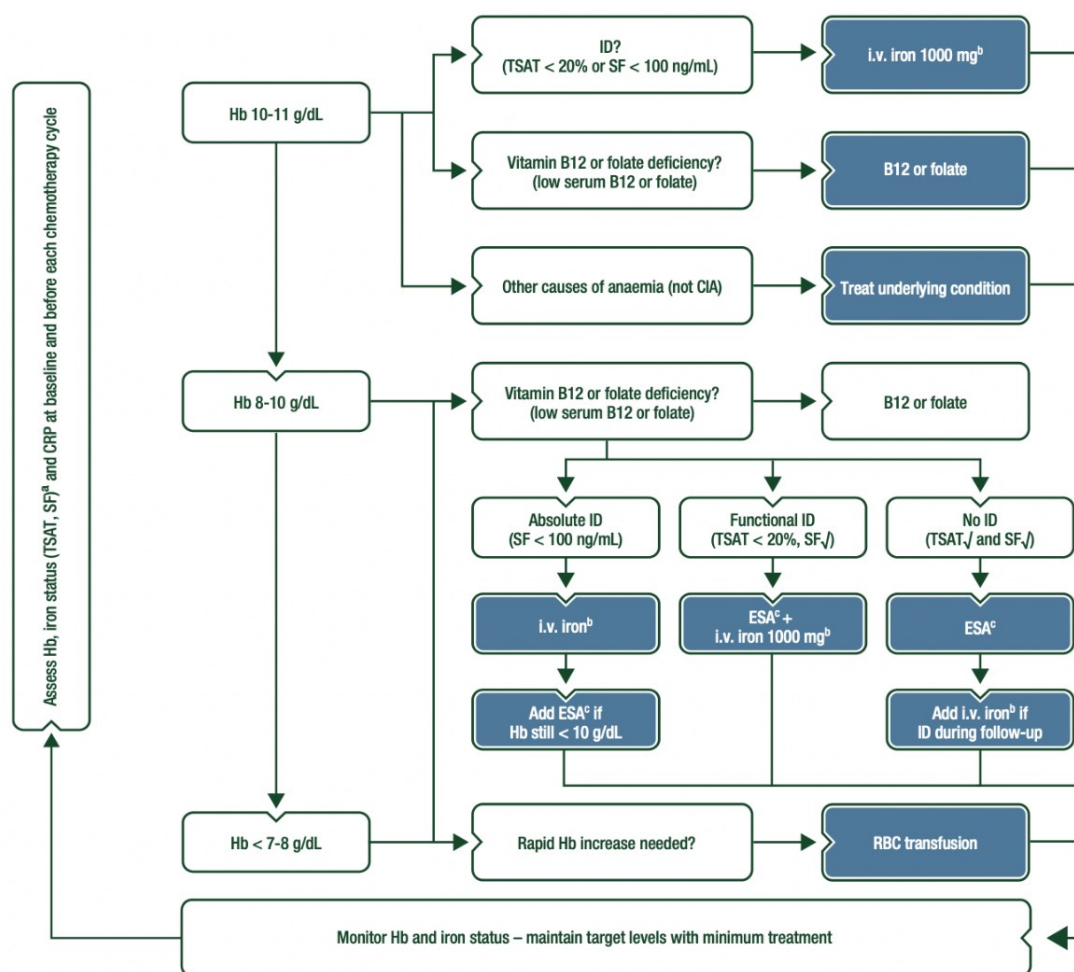


Figure 6: Management of chemotherapy induced anemia

Aapro M, Beguin Y, Bokemeyer C, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2018;29:iv96–iv110. doi:10.1093/annonc/mdx758

a. ESA erythropoiesis–stimulating agents

In patients undergoing ChT, therapy of anemia with an ESA should be explored following correction of Iron deficiency and other underlying reasons other than the malignancy or its treatment.

In cancer patients following chemotherapy, ESAs have been proven to boost Hemoglobin level and minimize the requirement for RBC transfusions. Those with symptomatic anemia who undergo ChT or combined RT–ChT and have a Hb level less than 10 g/dL, as well as patients with asymptomatic anemia who receive ChT and have a Hb level less than 8 g/dL, should receive ESA medication. Without RBC transfusions, the Hb objective is a steady level of 12 g/dL. Furthermore, when QoL parameters, fatigue–related symptoms, and anemia–related symptoms were combined in a meta–analysis of 23 trials that provided QoL outcomes and comprised 5584 patients, there was a statistically significant difference between patients treated with ESAs and controls. Also, because this medication is only effective in 60% of patients, it increases thrombotic events and death in patients undergoing no cancer therapy or only RT; consequently, ESA treatment is not indicated in patients who are not on ChT<sup>175</sup>.

### **b. Iron therapy**

Individual studies have also shown that IV iron has other advantages, such as improved QoL and a reduction in RBC transfusions and ESA dosages. In contrast to IV iron therapy, oral iron therapy did not produce improved results when compared to control groups who received no iron at all. The advantages of IV iron, on the other hand, were significant, with a much higher improvement in haematological response rate than oral iron. IV iron supplementation significantly enhanced the haematological response to ESA treatment compared to ESA alone in controlled clinical studies studying iron supplementation in ESA-treated anaemic cancer patients. Plus, patients may find that taking a single 1000 mg iron dosage is more convenient than taking numerous smaller doses<sup>175</sup>. Patients with active infections, on the other hand, should not undergo intravenous iron treatment <sup>174</sup>.

## **2. Management of febrile neutropenia**

Febrile neutropenia is a frequent dose-limiting toxicity of chemotherapy that has a major influence on the progression of cancer patients due to the possible development of major complications, death, delays, and a reduction in treatment intensity<sup>176</sup>.

In this section, we will give guidance for patient education, initial evaluation and investigations, outcome risk assessment, and ultimately prevention of febrile neutropenia with G-CSF (Granulocyte colony stimulating factor), all based on revised clinical guidelines.

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a. Patient Education and initial assessment and investigations

In order to successfully manage febrile neutropenia, it is necessary to recognize and react to probable infection as soon as possible. Outpatients must be instructed to monitor their symptoms, including body temperature, and given clear written instructions on when and how to contact the relevant department if they have concerns<sup>73</sup>.

A full history should be obtained, including the nature of the ChT provided, past prophylactic antibiotics, concurrent steroid usage, recent surgical operations, and the existence of allergies. To guide therapy, it is critical to review the clinical record for previous positive microbiology, particularly the presence of antibiotic-resistant organisms or bacteremia<sup>73</sup>.

The initial evaluation and investigations may be summarized in five key phases, which are as follows:

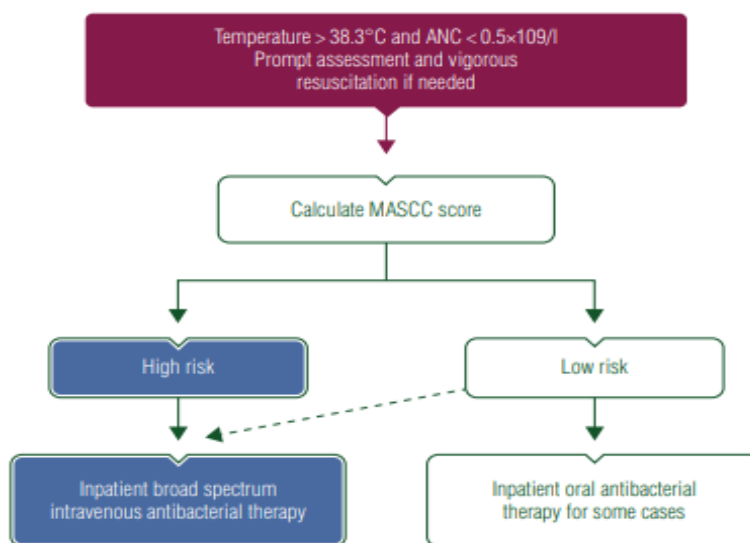
- 1– Make a note of the existence of indwelling intravenous catheters.
- 2– Symptoms or signs of an infection (respiratory system, gastrointestinal tract, skin, etc.)
- 3– Checking clinical records for past positive microbiological results
- 4– Routine examinations:
  - Urgent blood testing to assess bone marrow, renal and liver function
  - Coagulation screen
  - C-reactive protein
  - Blood cultures (minimum of two sets) including cultures from indwelling i.v. catheter

- Urinalysis and culture
- Sputum microscopy and culture
- Stool microscopy and culture
- Skin lesion (aspirate/biopsy/swab)
- Chest radiograph

5 –Further research (severe/prolonged neutropaenia/following allografts)

### b. Risk evaluation of the result

According to the most recent clinical practice recommendations, the great majority of FN patients treated using the method shown in Figure X respond quickly to empirical therapy.



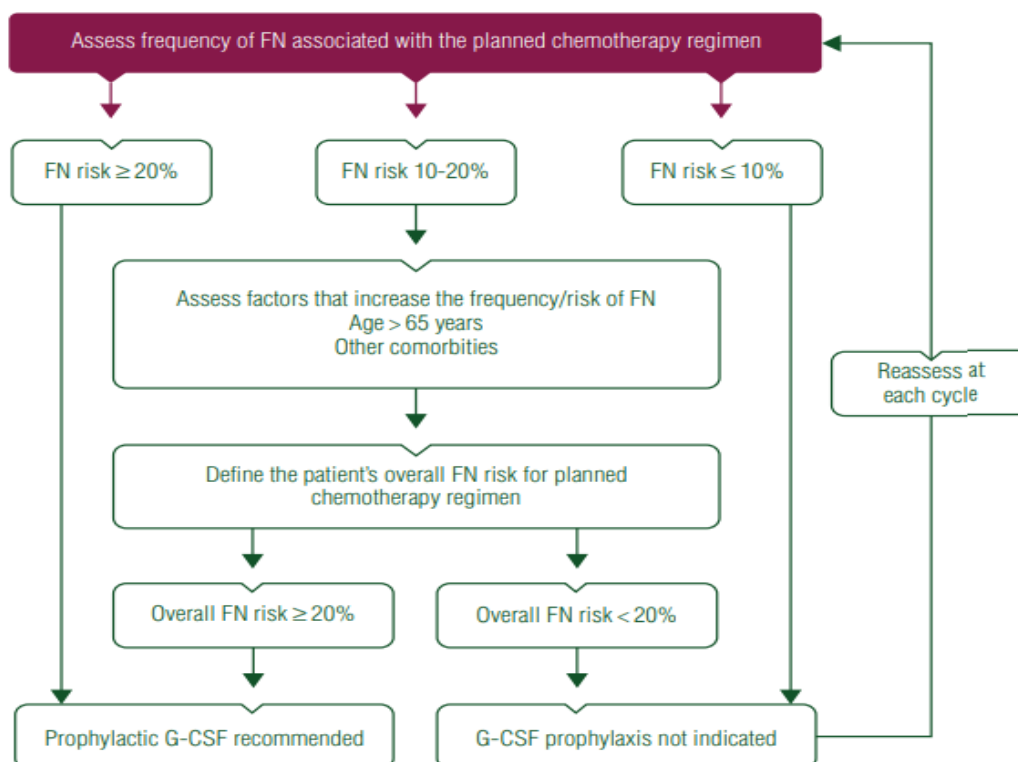
**Figure 7: Management of Febrile Neutropenia**

Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2016;27:v111–v118. doi:10.1093/annonc/mdw325

c. Prophylaxis of febrile neutropenia with G-CSF

Several meta-analyses demonstrate that primary G-CSF prophylaxis reduced the incidence of febrile neutropenia in patients with solid tumors by at least 50% without impacting tumor response or overall survival<sup>177</sup>. G-CSF should be supplied prophylactically if the risk of FN is more than 20% for all scheduled treatment cycles, according to most standards.

Figure below depicts an algorithm for making decisions on main prophylactic G-CSF usage based on risk classifications depending on the type of ChT. The algorithm is provided by the clinical practice guideline<sup>73</sup> and modified from recommendations developed by the European Organization for Research and Treatment of Cancer<sup>178</sup>.



**Figure 8:** Algorithm to manage febrile neutropenia

Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2016;27:v111–v118.

doi:10.1093/annonc/mdw325

## **XII. Management of Nausea and vomiting**

NCCN (National Comprehensive Cancer Network)<sup>179</sup>, ASCO (American Society of Clinical Oncology)<sup>180</sup>, and MASCC (Multinational Association of Supportive Care in Cancer)<sup>181</sup> have all released antiemetic recommendations. These principles serve as the foundation for CINV (chemotherapy induced nausea and vomiting) management recommendations. These updated recommendations are informed by research, ensuring the greatest quality evidence-based on clinical practice. The antiemetic medications that should be used to prevent CINV are highly precise recommendations in the antiemetic guidelines of several national and international associations; these are dependent on the emetogenicity of the individual chemotherapeutic agent being given<sup>182</sup>. A neurokinin-1 (NK1) receptor antagonist, a 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist, and dexamethasone are recommended for patients receiving highly emetogenic chemotherapy; a 5-HT3 receptor antagonist or dexamethasone is recommended for patients receiving moderately emetogenic chemotherapy. Various national and international recommendations currently prescribe olanzapine for the prevention of CINV in patients following highly emetogenic treatment<sup>183</sup>.

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## **1. Anticipatory therapy for CINV (Chemotherapy Induced Nausea and Vomiting)**

To avoid anticipatory CINV, patients should be counseled about their 'expectations' of CINV prior to starting therapy. Patients should be advised that very effective antiemetic prophylaxis will be administered, with 70–75 % of patients responding completely. To achieve the best management of CINV during the first course of chemotherapy, the most effective preventive antiemetic regimen for the patient's specific type of chemotherapy should be utilized prior to the first course of chemotherapy. If CINV is adequately controlled during the first cycle of chemotherapy, the patient is likely to have effective control during following rounds. If the patient has a bad CINV experience in the first cycle, following cycles may be more difficult to regulate, and resistant and/or anticipatory CINV may develop.

To achieve an optimal outcome and avoid anticipatory CINV, anti-anxiety drugs such as lorazepam or another benzodiazepine may be explored for excess anxiety prior to the first session of chemotherapy. Behavioral therapy may be used if anticipatory CINV develops despite the use of preventive antiemetics.

## **2. Treatment of Breakthrough CINV**

Breakthrough nausea and vomiting can be treated with phenothiazine, metoclopramide, dexamethasone, or olanzapine <sup>179</sup>. Unless a patient develops nausea and vomiting as a result of using a 5-HT<sub>3</sub> receptor antagonist as a prophylactic for chemotherapy or radiotherapy-induced emesis, a 5-HT<sub>3</sub> receptor antagonist may be beneficial. Patients who have nausea or vomiting after chemotherapy (days 1–5) despite appropriate prophylaxis should be treated with a 3-day oral olanzapine or oral metoclopramide regimen.

In patients receiving HEC (highly emetogenic chemotherapy) who developed breakthrough CINV despite using guideline-directed prophylactic antiemetics, a recently completed phase III study found that oral olanzapine (10 mg/day for 3 days) was significantly better than oral metoclopramide (10 mg three times daily for 3 days) in controlling both emesis and nausea<sup>184</sup>.

### **3. Refractory CINV**

Patients who acquire CINV during successive rounds of chemotherapy after antiemetic prophylaxis failed to manage CINV in previous cycles should have their prophylactic antiemetic regimen changed. A benzodiazepine such as lorazepam or alprazolam might be included to the preventive regimen if anxiety is a prominent patient factor in the CINV<sup>179</sup>.

### **4. Non-pharmacological treatments**

In palliative care, nondrug treatments are equally crucial in the management of nausea and vomiting<sup>185</sup>. It has been reported that the avoidance of external stimuli, such as sights, noises, or odors may have a beneficial effect . Foods that are fatty, hot, or heavily salty should be avoided also . Relaxation and distraction, for example, can help to reduce psychological agitation and anxiety<sup>185</sup>. In certain research, relaxation techniques using progressive muscle relaxation and guided visualization was beneficial in lowering chemotherapy-induced emesis <sup>187</sup>. However, there have been few studies on these interventions, and their effectiveness is still debatable and not scientifically validated.

Other non-drug therapies that practitioners are looking into as antiemetic adjuncts for patients with nausea are acupuncture, acupressure, and ginger and those have been shown to help with chemotherapy-induced emesis and anticipatory nausea but have not been evaluated in advanced disease nausea<sup>188</sup>. In patients with severe illness who are not amenable to surgery, draining percutaneous gastrostomy tubes(PEG), gastrointestinal stents, and other endoscopic methods may be used to relieve nausea and vomiting more rapidly and efficiently caused by bowel obstruction <sup>185</sup>.

Palliative care of an obstructive lesion in patients with locally advanced esophageal cancer comprises alcohol injection <sup>189,190</sup> laser therapy, argon plasma coagulation<sup>191</sup>, photodynamic therapy, and esophageal stent implantation. Nasogastric tubes, as alternative technique on the other hand, are less invasive than percutaneous endoscopic gastrostomy (PEG) tube but should not be used over an extended period of time. Nasogastric tubes pose the risk of repeated displacement, poor tolerability, and limits in ambulation and everyday activities. PEG tube maintenance is relatively simple, although it does need patient and caregiver's education.

Colonic decompression tubes, laser therapy, argon plasma coagulation, and self-expanding metal stents are all used in the treatment of malignant large intestinal obstruction. Colonic decompression tubes are frequently utilized to facilitate air (rather than stool) passage in patients who require clinical stabilization prior to surgery<sup>192</sup>. Self-expanding metallic stents are used to treat a major intestinal blockage.

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## Conclusion and perspectives

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Our literature search is about developing a strong Enhanced supportive Care through all the steps, from initial diagnosis and along the continuum of cancer therapy. This specific research was chosen to bring attention to this revolutionary subject on multiple levels, that is developing a strong Enhanced supportive Care, since it has shown improvement in quality of life, by eliviating symptom's burden, ameliorating survival, while also benefiting the health economy, which is why it should be an essential component of modern oncology treatment.

In order to accomplish this, we were able to develop two approaches in our research. The first consists of bringing up the challenges that both clinical practitioners and patients face to cope with therapy, and the second consists of demonstrating various solutions and management routes to each of these challenges.

The first chapter, entitled challenges in oncology, was about the most relevant problems and symptoms that reduce the quality of life, making coping with therapy a real challenge and patient's surveillance more difficult for caregivers during the continuum of cancer care. For this purpose, we defined challenges as the difficulties that are beyond the capacities of patients mostly and healthcare professionals. Furthermore, as we progressed in our work, we found out that each of these problems were correlated to one another, making each challenge the cause and the consequence simultaneously, these linked parameters can frequently lead to treatement discontinuation.

After discussing all of the challenges, we moved on to the second chapter, interventions and recommendations, where we were able to bring management plans tailored to the patient as well as professional healthcare, with the main goal of reducing, alleviating or eliminating the symptoms, contributing in ameliorating the quality of life. We provided some guidelines and recommendations to the issues described above, particularly because we discovered that some of the symptoms were underdiagnosed or were not given special attention, although the solutions are simple and achievable. In our research we relied on some studies that were carried out on a large number of patients, that have shown very significant results and brought radical changes in terms of treatment continuity, which pays in the good and the advantage of the patient, and which has after all always been our goal.

This work is an inevitable first step, involving a second, which is the concretization of this research, adapting it to our medical environment and system , in our case for our moroccan patients, aiming that it can see the light of the day, by the realization of a practical organization chart that can be carried out in our own work environment and hospitals, with the help and collaboration of a multidisciplinary team, to help our patients who are in desperate need to get out of that vicious circle.

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## **Abstract :**

Supportive and palliative care are the constitution of enhanced supportive care that is a strong component of cancer therapy. Since the cancer care environment is quickly evolving a growing number of individuals, at all stages of their illness, are now living with cancer, either undergoing anti-cancer therapy, off treatment, in remission, cured, or living with progressing illness. Based on the emerging evidence, early supportive care can enhance the patients' quality of life, allowing them to live as normally as a healthy human being, perhaps extending their lives and lowering the need for severe therapies.

Our aim is about developing a strong Enhanced supportive Care through all the steps, from initial diagnosis and along the continuum of cancer therapy, and helping health caregivers in being more comfortable and confident in sharing informations with their patients and offering better solutions resulting in improving their quality of life and building a stronger caregiver-patient relationship.

We relied on some studies that were carried out on a large number of patients, that have shown very significant results and brought radical changes in terms of treatment continuity, which pays in the good and the advantage of the patient, and which has after all always been our goal. Then we proceeded by developing two approaches in our research, the first consists of bringing up the challenges that both clinical practicers and patients face to cope with therapy, and the second consists of demonstrating multiple innovative management routes to each of these challenges.

This work is an inevitable first step, involving a second, which is the concretization of this research, adapting it to our medical environment and system, in our case for our moroccan patients, aiming that it can see the light of the day, by the realization of a practical organization chart that can be carried out in our own work environment and hospitals, with the help and collaboration of a multidisciplinary team, to help our patients who are in desperate need to get out of that vicious circle.

**KEYWORDS:**

“Cancer”, “Difficulties”, “Challenges”, “Adverse effects”, “Quality of life”, “enhanced supportive care”, “Management”

## Resumé :

Les soins de support et soins palliatifs constituent la nouvelle approche des soins de support qui est une composante importante de la thérapie contre le cancer. Étant donné que l'environnement des soins contre le cancer évolue rapidement, un nombre croissant de personnes, à tous les stades de leur maladie, vivent maintenant avec le cancer, qu'elles suivent un traitement anticancéreux, qu'elles ne soient plus sous traitement, qu'elles soient en rémission, guéries ou qu'elles vivent avec une maladie évolutive. D'après les preuves émergentes, les soins de support précoces peuvent améliorer la qualité de vie des patients, leur permettant de vivre aussi normalement qu'un être humain en bonne santé, prolongeant peut-être leur vie et réduisant le besoin de thérapies sévères.

Notre objectif est de développer des soins de support améliorés solides à toutes les étapes, allant du diagnostic initial et se prolongeant tout au long de la thérapie du cancer, et d'aider les soignants à être plus à l'aise et confiants dans le partage d'informations avec leurs patients et d'offrir de meilleures solutions résultant en une amélioration de leur qualité de vie et de construire une relation soignant-patient plus forte.

Nous nous sommes appuyés sur certaines études qui ont été menées sur un grand nombre de patients, qui ont montré des résultats très significatifs et apporté des changements radicaux en terme de continuité de traitement, qui paye dans le bien et l'avantage du patient, et qui a après tout toujours été notre objectif. Ensuite, nous avons procédé en développant deux approches dans notre recherche, la première consiste à évoquer les défis auxquels les cliniciens et les patients sont confrontés pour faire face à la thérapie, et la seconde consiste à démontrer de multiples voies de prise en charge innovantes pour chacun de ces défis.

Ce travail est une première étape inévitable, entraînant une seconde, qui est la concrétisation de cette recherche, l'adapter à notre environnement et système médical, dans notre cas pour nos patients marocains, visant à ce qu'elle puisse voir le jour, par la réalisation d'un organigramme pratique réalisable dans notre propre milieu de travail et nos hôpitaux, avec l'aide et la collaboration d'une équipe multidisciplinaire, pour aider nos patients qui en ont désespérément besoin de sortir de ce cercle vicieux.

**Mots clés :**

«Cancer» ,« difficultés », « défis », « Effets indésirables », « qualité de vie », « soins de soutien renforcés», « Prise en charge »

## ملخص:

الرعاية الداعمة والرعاية التلطيفية هي مكونات الرعاية الداعمة المعززة التي تعد مكونًا قويًا في علاج السرطان. نظرًا لأن بيئة رعاية السرطان تتطور بسرعة ، فإن عددًا متزايدًا من الأفراد ، في جميع مراحل مرضهم ، يعيشون الآن مع السرطان ، إما يخضعون للعلاج المضاد للسرطان ، أو خارج العلاج ، أو في حالة تعافي ، أو يتعافون ، أو يتعايشون مع المرض المتطور. استنادًا على الأدلة الناشئة ، يمكن للرعاية الداعمة المبكرة أن تعزز نوعية حياة المرضى ، مما يسمح لهم بالعيش بشكل طبيعي كإنسان سليم ، وربما يطيل حياتهم ويقلل من الحاجة إلى العلاجات الشديدة. هدفنا هو تطوير رعاية داعمة معززة قوية خلال جميع الخطوات ، من التشخيص الأولي وعلى طول السلسلة المستمرة لعلاج السرطان ، ومساعدة مقدمي الرعاية الصحية في أن يكونوا أكثر راحة وثقة في مشاركة المعلومات مع مرضاهم وتقديم حلول أفضل تؤدي إلى تحسين نوعية الحياة وبناء علاقة أقوى بين مقدم الرعاية والمريض. اعتمدنا على بعض الدراسات التي تم إجراؤها على عدد كبير من المرضى والتي أظهرت نتائج مهمة للغاية وأدخلت تغييرات جذرية من حيث استمرارية العلاج ، مما يعود بالفائدة على المريض ويفيده ، والذي كان ولا يزال في النهاية هدفنا. ثم شرعنا في تطوير نهجين في بحثنا ، الأول يتكون من طرح التحديات التي يواجهها الممارسون السريريون والمرضى للتعامل مع العلاج ، والثاني يتكون من إظهار طرق إدارة مبتكرة متعددة لكل من هذه التحديات. هذا العمل هو خطوة أولى حتمية ، تنطوي على خطوة ثانية ، وهي تجسيد هذا البحث ، وتكييفه مع بيئتنا الطبية ونظامنا ، بالنسبة إلينا لمرضانا المغاربة ، بهدف أن يتمكن عملنا هذا من رؤية ضوء النهار ، من خلال تحقيق مخطط تنظيمي عملي يمكن تنفيذه في بيئة العمل والمستشفيات الخاصة بنا ، بمساعدة وتعاون فريق متعدد التخصصات لمساعدة مرضانا الذين هم في حاجة ماسة للخروج من هذه الحلقة المفرغة.

## الكلمات الدالة:

"السرطان" ، "الصعوبات" ، "التحديات" ، "العلاج" ، "جودة الحياة" ، "الرعاية الداعمة المعززة" ، "طرق التدبير"



أطروحة رقم: 174/22

سنة 2022

## الرعاية الداعمة والمخففة في علم الأورام: التحديات والتدخلات

### الأطروحة

قدمت ونوقشت علانية يوم 27/04/2022

### من طرف

السيدة إيمان واحيدي

المزداة في 12/11/1996 بخريبكة

### لنيل شهادة الدكتوراه في الطب

#### الكلمات الأساسية:

"السرطان"، "الصعوبات"، "التحديات"، "العلاج"، "جودة الحياة"، "الرعاية الداعمة المعززة"، "طرق التدبير".

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