The ESMO Handbook of Rehabilitation Issues During Cancer Treatment and Follow-Up is intended primarily to be read by physicians working in the field of medical oncology. The aim of this publication is to provide key information in the form of a comprehensive and well-arranged handbook that will help physicians gain better understanding of the issues surrounding patient rehabilitation.

This kind of book is currently lacking in the field of medical oncology and is envisioned to be an important and useful new resource for medical oncologists. This volume deals with clinical topics such as pain, fatigue and gastrointestinal sequelae and also discusses other aspects such as social and financial issues and lifestyle changes.
ESMO HANDBOOK OF REHABILITATION ISSUES DURING CANCER TREATMENT AND FOLLOW-UP
ESMO HANDBOOK OF
REHABILITATION ISSUES
DURING CANCER TREATMENT
AND FOLLOW-UP

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ESMO Press
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Introduction

Everybody wishes to enjoy a long and healthy life. To achieve this, one seeks to maintain a sound spirit and a healthy body. Once the diagnosis of cancer comes in, the whole picture changes in a horrible way. Cancer affects man’s well-being in many different ways. Physical activity is frequently reduced and it can be mentally hard to deal with the new situation. The partner and family members may be put under pressure. Disease symptoms or (late) adverse events delay the process of recovery during and after cancer therapy. The disease and its necessary treatment often undermine the employment process and raise financial issues. Inability to actively take part in the social process may lead to isolation and aggravate grief.

Medical professionals who are working within the field of oncology should have an open mind towards this continuous and complex process and help whenever and wherever possible. Being a good medical professional goes well beyond technical skills or a high scientific trial accrual. The term “personalised medicine” is currently used to point out that there could well be a tailored, targeted treatment regimen for every cancer patient in the near future. This term, however, has a second meaning: behind every disease there is a unique person who deserves personal guidance through his/her treatment and rehabilitation process. After reading this handbook, you will most certainly be able to comply with this personalised medicine goal.

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Introduction

Advances in early detection and treatment have improved survival rates of cancer over the past decades, with approximately 60% of patients living more than 5 years after diagnosis. Despite this longevity, cancer and its treatment are often associated with physical and psychosocial side effects, i.e. both long-term effects present during treatment and persisting afterwards, and late effects, which did not occur during treatment but appear later. In the process of destroying cancer cells, radiation therapy and chemotherapy also cause alterations to normal tissue and body functions, resulting in toxicities in many organs and body systems. Also, hormonal therapies such as androgen and oestrogen suppression, while highly effective for treating prostate and breast cancer, respectively, cause considerable side effects. While controlling the cancer, there is significant impact on the patient, including the cardiovascular, pulmonary, gastrointestinal, (neuro)endocrine, immune, and musculoskeletal systems. As a consequence, cancer survivorsa experience reduced cardiorespiratory fitness, reduced muscle mass and strength, increased

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aThe Centers for Disease Control and Prevention defined a cancer survivor as anyone who has been diagnosed with cancer, from the time of diagnosis through the rest of life.
fat mass, reduced bone health, and fatigue. Furthermore, many cancer survivors are at increased risk for anxiety, depression, sleep disturbances, reduced self-esteem, and lymphoedema. These adverse long-term and late effects severely impact the patient’s quality of life (QoL).

**Reduced Cardiorespiratory Fitness**

Cardiorespiratory fitness is determined by the transport of oxygen from the environment to skeletal muscles via several components of the pulmonary and cardiovascular systems including blood and blood vessels and by the capacity of skeletal muscle to utilise this oxygen. Cancer and its treatment may affect cardiorespiratory fitness via several mechanisms. For example, pulmonary mechanics and gas exchange may be disrupted by a tumour in the lungs, and anaemia may reduce the oxygen-carrying capacity. Systemic therapy may result in cardiac limitations. For example, anthracyclines could lead to atrial and ventricular arrhythmias, pericarditis, myocarditis, a reduced ejection fraction, and cardiomyopathy. Alkylating agents such as cisplatin may result in myocardial ischaemia/infarction, hypertension, heart failure, and arrhythmias. Chemotherapeutic agents may also reduce the muscle capacity for oxygen utilisation. Furthermore, radiotherapy in the chest area might cause cardiac or pulmonary limitations, such as angina, dyspnoea, heart failure, pericardial constriction, atherosclerosis, and mediastinal fibrosis, and may cause localised damage to muscle agents. In addition, androgen-suppression therapy results in considerable changes to the quantity and quality of skeletal muscle. Finally, low cardiorespiratory fitness levels may also result from reduced physical activity after cancer diagnosis, leading to a reduction in cardiac output, oxidative capacity, and muscle cross-sectional area.

The best direct measurement of cardiorespiratory fitness is the peak oxygen uptake (peakVO\(_2\)). A review by Steins Bisschop and colleagues showed that most studies of cancer survivors reported reduced peakVO\(_2\) levels (between 16 and 25 mL/min/kg). Lower peakVO\(_2\) values in cancer survivors compared to the healthy population indicate decreased cardiorespiratory fitness levels and, consequently, are an indication for physical exercise training. Moreover, screening for cardiac, pulmonary,
or musculoskeletal limitations before the start of an exercise programme is recommended. Low peakVO$_2$ has also been shown to be related to an increased risk of premature death.

PeakVO$_2$ can be measured during a cardiopulmonary exercise test (CPET) with continuous gas exchange analysis during incremental exercise, which is generally conducted on a cycle ergometer or treadmill and is considered feasible and safe. It can be used to monitor individual cardiorespiratory fitness and allows exercise programmes to be tailored to individual fitness levels by using either a percentage of peakVO$_2$, a percentage of the peak heart rate, or the heart rate at the anaerobic threshold to guide exercise intensity.

Exercise during or after cytotoxic cancer treatment was found to be associated with significant improvements in peakVO$_2$ compared to a non-exercise control group. Larger improvements were found in patients who participated in an exercise programme after completion of cancer treatment. This suggests that exercise during adjuvant therapy is of primary importance to maintain cardiorespiratory fitness.

**Reduced Muscle Mass and Strength**

Muscle wasting is present in approximately 50% of cancer survivors, contributing to decreased responsiveness to cancer treatment and severe dose-limiting toxicities, in turn contributing to poor prognosis and increased morbidity and mortality. Because muscle strength is related to muscle mass, muscle wasting also contributes to weakness and reduced functional ability and independence. In addition, due to its mediating role, muscle wasting may have serious consequences on glucose metabolism and chronic low-level systemic inflammation. Muscle wasting results from an imbalance between the rate of muscle protein synthesis and degradation and, in particular, from accelerated muscle protein degradation. Mechanisms underlying muscle protein degradation include tumour- and treatment-related increases in pro-inflammatory cytokines and proteolysis-inducing factors, as well as testosterone suppression, reduced food intake, and low physical activity levels.
Increased Fat Mass
Cancer and its treatment are commonly associated with changes in body composition. The specific detrimental changes in total weight, lean body mass, and fat mass differ by cancer and treatment types. An increase in fat mass is common during adjuvant treatments, for example for breast, colon, prostate, and gynaecological cancer, which has a significant impact on the risk of type 2 diabetes, asthma, chronic back pain, osteoarthritis, metabolic syndrome, and cardiovascular disease. In addition, obesity has been associated with a poorer overall and cancer-specific survival.

Reduced Bone Health
Hypogonadism and the subsequent oestrogen deficiency associated with cancer treatment (chemotherapy, hormone therapy) can result in an imbalance between function of the osteoblasts and osteoclasts, resulting in greater bone resorption than formation. The result is a net loss of bone density and an increased fracture risk. Patients with breast or prostate cancer in particular are at increased risk for reduced bone health. Premenopausal women who are treated with alkalytic agents are at increased risk for cessation of ovarian function, which reduces oestrogen levels. Also, men treated with androgen-suppression therapy experience a decrease in oestrogen that parallels the reduction in testosterone. Furthermore, a high incidence of osteopenia and osteoporosis is observed in long-term survivors of Hodgkin’s and non-Hodgkin’s lymphoma treated with stem cell transplantation.

Exercise as Medicine in the Management of Cancer
Several reviews and meta-analyses demonstrate beneficial effects of physical activity and exercise\(^b\) in cancer survivors during and after treatment on physical and psychosocial outcomes. These include increased cardiorespiratory fitness, muscle mass and strength, reduced fatigue and depression, and improved QoL. The Physical Activity across the Cancer Continuum (PACC) framework proposes four time periods following

\(^b\)Exercise is a specific type of physical activity that is planned, structured, and repetitive and aims to improve or maintain physical fitness, performance, or health.
diagnosis during which physical activity can have an important role: pre-treatment, during treatment, survivorship, and end-of-life care.

The aim of exercise pre-treatment is to improve physical fitness (including cardiorespiratory fitness and muscle strength) prior to surgery or systemic therapy to enable patients to undergo treatment with fewer side effects or to enhance post-treatment recovery. In a systematic review of randomised controlled trials (RCTs) and non-RCTs, Singh and colleagues reported that the data available from patients with lung cancer, prostate cancer, and cancer of the abdominal area (e.g. colon, colorectal, liver) suggest that exercise – aerobic, resistance, or pelvic floor training alone or in combination – may have a positive effect on rate and duration of continence, functional walking capacity, and cardiorespiratory fitness. Some studies reported improved QoL and reduced length of hospital stay (which is an important prognostic variable for a positive surgical outcome), but findings were inconsistent, likely due to lack of power and differences in training duration prior to surgery.

In a meta-analysis by Speck and colleagues, results of exercise during and after cancer treatment were presented separately. During treatment, small to moderate significant effects of exercise were reported for cardiorespiratory fitness, upper and lower body muscle strength, body weight, functional QoL, anxiety, and self-esteem. After treatment, large significant effects were found for upper and lower body muscle strength and breast cancer-specific concerns, and small to moderate significant effects for physical activity level, cardiorespiratory fitness, overall QoL, fatigue, insulin-like growth factor-1 (IGF-1), and symptoms and side effects. Similar effects were reported in other meta-analyses on this topic.

Resistance exercise is a potent stimulus of muscle synthesis, and consequently increasing muscle mass, endurance, and strength, thereby improving physical function and QoL. Exercise (aerobic, resistance, or a combination of both) during cancer treatment can improve upper and lower body muscle strength more than usual care. In a recent meta-analysis of RCTs evaluating the effects of resistance exercise during and after cancer treatment, Strasser and colleagues reported a significant increase in lower and upper body muscle strength and lean body mass.
Improvements in lower body muscle strength were greater in cancer survivors who completed an exercise intervention after cancer treatment, compared to those who exercised during cancer treatment. Whether there is a dose–response relationship remains unclear; however, the results suggest that exercise volume may be more important than exercise intensity in order to induce muscle protein synthesis.

Exercise and, in particular, resistance training and high-impact loading exercise can positively influence bone health by its osteogenic effects. Resistance exercises should be performed at sufficient intensity and should specifically load a target bone, thus both the hips and the spine. Weight-bearing activities such as jumping and skipping are more osteogenic than activities with lower impact forces; however, aerobic exercises using upper and lower body muscles and/or trunk rotation at sufficient intensity, such as aerobic dance, may also benefit patients with osteogenesis. Walking interventions generally have limited effect on bone health because the relatively low ground reaction force does not reach sufficient intensity to augment bone density.

The relative benefit of exercise versus pharmacological treatment is yet to be determined. Although exercise can be an effective non-pharmacological strategy for preserving bone health during and after cancer treatment, adequate calcium and vitamin D supplementation and treatment with pharmacological agents such as bisphosphonate and RANK-ligand monoclonal antibody may also be important. These agents are, however, associated with considerable side effects.

Few studies have examined the effects of physical activity in palliative cancer patients. The few case reports and uncontrolled trials available suggest that the role for physical activity is promising, as it may maintain physical function, independence in activities of daily living, and overall QoL. It is therefore recommended to encourage palliative cancer patients to consider a physical activity intervention under the specific direction and guidance of their attending medical team.
Physical Activity and Cancer Outcome

Sufficient levels of physical activity may also be important to improve disease-free and overall survival. Observational studies showed that higher levels of moderate-to-vigorous physical activity were associated with lower mortality risk in survivors of breast, colon, and prostate cancer, with physically active survivors having approximately 50% lower mortality. However, to establish a causal relationship between physical activity and survival, additional RCTs are needed.

RCTs evaluating the effects of physical activity on biomarkers related to cancer prognosis have recently been summarised by Ballard-Barbash and colleagues. The results suggest that exercise may result in beneficial changes in circulating levels of insulin, IGF-1, and IGF-1 binding proteins in breast cancer survivors. There is also evidence that exercise leads to beneficial changes in circulating levels of C-reactive protein and in natural killer cell cytotoxic activity in cancer survivors, including breast, prostate, and gastric cancer. In prostate cancer survivors, there is consistent evidence that exercise does not increase prostate-specific antigen (PSA) or testosterone levels. Evidence for other biomarkers is limited or non-existent. Also, the mediating role of immune, endocrine, or musculoskeletal systems on the effects of exercise on cancer outcomes requires further investigation.

Furthermore, the interaction between physical activity and primary cancer treatment remains unclear. In the START trial, Courneya and colleagues found chemotherapy completion rates to be higher in patients who completed a resistance exercise programme during adjuvant chemotherapy treatment for breast cancer (89.8%), compared to a usual care control group (84.1%) or an aerobic exercise group (87.4%). This resulted in higher survival rates among the exercise groups compared to the control group.

In addition to observational data on survival and experimental data on biomarkers in cancer survivors, a few studies in animals suggested that exercise may inhibit tumour growth, but others did not. At present, further investigation on the effects of physical activity on chemotherapy completion rates and tumour growth is needed.
Physical Activity Guidelines

Given the increasing number of studies showing the safety and benefits of physical activity, exercise should be part of the standard care for all cancer survivors. Several evidence-based physical activity guidelines for cancer survivors have been published.

In 2010, the American College of Sports Medicine (ACSM) published physical activity guidelines for cancer survivors, which were based on extensive systematic review of the literature on adult survivors of breast, prostate, colon, haematological, and gynaecological cancers. The expert panel reported consistent evidence regarding the safety of exercise during and after cancer treatment (including intensive treatments such as bone marrow transplant) and beneficial effects on cardiorespiratory fitness, muscle strength, QoL, and fatigue. The ACSM recommends that cancer survivors should be as physically active as their abilities and conditions allow. Importantly, the recommendation is that cancer survivors should avoid being physically inactive regardless of cancer stage or treatment. Adult cancer survivors are advised to engage in either at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of both. Muscle-strengthening activities involving all major muscle groups are recommended at least two sessions per week. Several precautions for exercise should be taken into account, including arm and shoulder problems, skeletal fractures, infection risk, ostomy, and swelling or inflammation in the abdomen, groin, or lower extremity.

Lymphoedema is not a contraindication to exercise. A recent RCT showed that women with breast cancer-related lymphoedema can safely lift heavy weights during upper body resistance exercise, without fear of lymphoedema exacerbation or increased symptom severity.

Comparable physical activity guidelines have been published by the American Cancer Society (ACS), Exercise and Sport Science Australia, Comprehensive Cancer Center the Netherlands, the German Cancer Association, and the British Association of Sport and Exercise Science.
Current physical activity guidelines for cancer survivors are rather generic. Additional research is needed in order to develop more specific guidelines for a given exercise prescription (e.g. mode, frequency, intensity, duration), for a given cancer site at a particular phase of the cancer trajectory, and for specific outcomes. Future studies should focus on identifying clinical, personal, physical, psychosocial, and intervention moderators explaining “for whom” or “under what circumstances” interventions work. In addition, more insight into the working mechanisms of exercise interventions on health outcomes in cancer survivors is needed to improve the efficacy and efficiency of interventions. Existing programmes should also embrace the interests and preferences of patients to facilitate optimal uptake of interventions, and must take the principles of exercise training into account.

Declaration of Interest:
Dr Buffart has reported no conflicts of interest.
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Further Reading

Cancer Pain

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Introduction

Pain is a frequent and impacting symptom not only in advanced cancer but in any phase of the disease. Pain can be caused by cancer itself or comorbidities; it may result following surgery, radiotherapy (RT), chemotherapy (CT), targeted therapy (TT), supportive care treatments, and/or diagnostic procedures; or it may be unrelated to cancer. It is influenced by genetics, personal past history, mood, expectation, and culture. Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. The perception of the intensity of pain is not proportional to the type or to the extent of the tissue damage, but it is dependent on the interactions between nociceptive and non-nociceptive impulses in ascending pathways, as well as the activation of descending pain-inhibitory systems. Pain is always a subjective sensation; it is what the patient says it is and may be affected by emotional, social, and existential components; thus it has been defined as “total pain”.

Pain has been defined as the fifth vital sign by the American Pain Society and its routine assessment is emphasised by international guidelines.

Cancer pain may be acute, chronic, or episodic (Table 1). Table 2 shows the most frequent chronic pain syndromes. From a pathophysiological point of view, pain can be classified as nociceptive (somatic and visceral), neuropathic (central, peripheral, sympathetic), or idiopathic (Table 3).
However, in the clinical setting, pain is more frequently a mixed pain and may involve multiple mechanisms, explaining the utility of combinations of different classes of analgesic drugs. Table 4 shows the semantic descriptors of neuropathic pain according to the International Association for the Study of Pain.

**Table 1** Temporal Classification of Pain in Cancer

- **Acute pain:** follows injury to the body and generally disappears when the body injury heals. It is usually due to a definable nociceptive cause. It has a definite onset and its duration is limited and predictable (i.e. pain related to surgery, biopsy, pleurodesis, pathological fracture, chemotherapy, radiotherapy, diagnostic and interventional procedures). It is often associated with objective physical signs of autonomic nervous system activity. Acute pain may also indicate a progression of disease and is often accompanied by anxiety.

- **Chronic pain:** due to the presence and/or progression of the disease and/or to treatments (i.e. chemotherapy-induced neuropathy and/or osteoporosis, post-surgery, post-radiotherapy). Chronic pain may be accompanied by changes in personality, lifestyle, and functional abilities and by symptoms and signs of depression. Chronic pain with overlapping episodes of acute pain (i.e. breakthrough pain) is probably the most common pattern observed in patients with ongoing cancer pain. This indicates the necessity for monitoring the intensity of pain and associated symptoms and the analgesic treatments. Furthermore, the appearance of acute pain, or progression of a previously stable chronic pain, is suggestive of a change in the underlying organic lesion and requires clinical re-evaluation.

- **Breakthrough pain (episodic pain):** defined as
  a) **unpredictable** transient flares of severe or excruciating pain in patients already being managed with analgesics who have a controlled baseline pain. It is difficult to treat adequately due to its rapid onset and offset
  b) **predictable** episodic pain: caused by: (1) insufficient amount of opioids taken at regular intervals; (2) long intervals between analgesic drug administrations; (3) incident pain, for example due to the patient’s moving (bone metastases), swallowing (head & neck cancer), or coughing.

**Table 2** Chronic Pain Syndromes in the Cancer Patient

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<td>• Aseptic necrosis of femoral or humeral head</td>
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<tr>
<td>• Plexopathy</td>
</tr>
<tr>
<td>• Raynaud’s phenomenon</td>
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<table>
<thead>
<tr>
<th>Postradiation pain syndrome</th>
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<tbody>
<tr>
<td>• Radiation myelopathy</td>
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<tr>
<td>• Mucositis</td>
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<tr>
<td>• Radiation necrosis of bone</td>
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<tr>
<td>• Radiation-induced peripheral nerve tumours</td>
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<tr>
<td>• Radiation fibrosis of brachial or lumbosacral plexus</td>
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<tr>
<td>• Radiation enteritis and proctitis</td>
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<tr>
<td>• Burning perineum syndrome</td>
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<table>
<thead>
<tr>
<th>Chronic pain associated with hormonal therapy</th>
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<tbody>
<tr>
<td>• Gynaecomastia with hormonal therapy for prostate cancer</td>
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<table>
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<tr>
<th>Pain directly related or unrelated to cancer</th>
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</thead>
<tbody>
<tr>
<td>Paraneoplastic syndrome</td>
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<tr>
<td>Myofascial pain syndrome</td>
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<tr>
<td>Postherpetic neuralgia</td>
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<tr>
<td>Debility, constipation, bed sores, rectal or bladder spasm, gastric distension</td>
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<tr>
<td>Osteoporosis</td>
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</tbody>
</table>
Despite the availability of several effective treatments including non-opioids, opioids, adjuvant drugs, invasive management of refractory pain and updated guidelines from authoritative learning societies, undertreatment is still too frequent. Lack of pain control and poor relief is still documented in several publications across all types of primary cancers, solid and haematological malignancies, stages of disease, and settings of care.

The presence of comorbidity, older age, social conditions, and disparities may further complicate the management of pain, requiring a more holistic approach to assure an adequate and personalised treatment.
Personalised Assessment of Pain

Poor pain assessment is the greatest barrier to effective cancer pain management. To be adequately treated, cancer pain needs to be identified, assessed, classified, and managed with a multistep approach that includes, as reported in the recent review by Hui & Bruera (2014): “systematic screening, comprehensive pain assessment, characterisation of pain, identification of personal modulators of pain expression, documentation of personalised pain goals, and implementation of multidisciplinary treatment plan with subsequent customised longitudinal monitoring” (Figure 1; Tables 5 and 6). Predictive factors for cancer pain can be assessed with different tools which help physicians to identify patients with more difficult to control pain syndromes. Observation of pain-related behaviours and discomfort is indicated in patients with cognitive impairment to assess the presence of pain. After the comprehensive assessment of pain during the first visit, a close monitoring of pain and opioid-related adverse effects (nausea, vomiting, constipation, drowsiness) is paramount. For this purpose a simple symptom assessment tool should be considered as routine clinical practice in all stages and phases of cancer diagnosis and treatments. The Edmonton Symptom Assessment System (ESAS) is a 10-item patient-rated symptom assessment tool. It was developed and validated for cancer populations in different languages and cultures, and also indicated as a screening tool for anxiety and depression.

Table 5 Assess and Re-assess the Pain, the Symptoms, and Comorbidities

- Causes, temporal onset, type, site and radiation, duration, intensity, relief and temporal patterns, number of breakthrough episodes, pain syndrome, pain at rest and/or moving, somatisation
- Acute pain and/or chronic pain; predictable pain; incident pain
- Presence of the trigger factors and the signs and symptoms associated with the pain (sleep, anxiety, depression, delirium, appetite, existential/spiritual suffering, well-being)
- Needs for counselling
- Chemical coping, alcoholism, nicotine use, history of addiction, opioid misuse
- Presence of relieving factors
- Use of analgesics and their efficacy and tolerability
- Concomitant medications
- Require the description of pain quality
- Treatment-related and/or cancer-related pain or unrelated to cancer or its treatments
- Post-surgery pain
Validated assessment tools for the assessment of pain

Visual analogue scale

10cm

no pain worst pain

Verbal scale pain

- No pain 1
- Very mild 2
- Mild 3
- Moderate 4
- Severe 5
- Very severe 6

Numerical scale

no pain 0 1 2 3 4 5 6 7 8 9 10 worst pain

Figure 1  Validated and most frequently used pain assessment tools. From Ripamonti Cl, et al. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol 2012; 23(Suppl 7): vii139–vii154. By permission of Oxford University Press on behalf of ESMO.

Table 6  Characteristics of An Effective Pain-Relieving Therapy

- Prevent the onset of pain: for this purpose drugs are not administered “as required” but rather “by the clock”, taking into account the half-life, bioavailability, and duration of action of the different drugs

- Be simple to administer: thus easy to manage for the patient himself/herself and his/her family, especially when the patient is cared for at home. The oral route appears to be the most suitable to meet this requirement, and, if it is well tolerated, must be considered as the preferential route of administration

- Be individualised: the dosage, the type, and the route of drugs used must be administered according to each patient’s needs. Individualised pain management should take into account the stage of disease, concurrent medical conditions, characteristics of pain, and psychological and cultural status of the patient
Procedural-related Pain

Electrodiagnostic testing, imaging, and/or laboratory testing as well as therapeutic procedures (tracheal suction, wound drain removal, wound dressing, medication of skin ulcers) can provoke acute pain and discomfort. Diagnostic endoscopic examinations with or without visceral dilatation and digital examination can cause discomfort or overt pain. Fine needle aspiration cytology, biopsy of masses and nodules, percutaneous liver biopsy, transrectal ultrasound-guided prostatic biopsy, venipuncture, arterial puncture, lumbar puncture, percutaneous or central venous catheter placement, thoracentesis and pleurodesis are examples of procedures associated with pain. Local anaesthetic and/or systemic analgesics (non-steroidal anti-inflammatory drugs [NSAIDs] plus opioids) or nerve blocks are necessary, depending on the type of procedure. However, only a minority of patients receive any medication before or during a specific procedure. Bone marrow biopsy or aspiration (BMBA) is treated with various pharmacological interventions: local anaesthetic (with low efficacy when administered alone), intravenous sedation with benzodiazepine and/or opioids or with inhaled nitrous oxide, and premedication with opioids.

Lumbar puncture is frequently associated with post-dural puncture headache developing from hours to days after the procedure. The use of an atraumatic needle may reduce pain. Hydration, bed rest, and analgesics can resolve the symptoms in a few days.

Often, procedural pain is not considered a major problem by the physician, because of the prevalent importance of obtaining a specific cancer diagnosis. The importance of recognising and pre-empting pain induced by medical procedures should be stressed, to avoid the development of central sensitisation, a phenomenon causing an increase in the area and the response to noxious stimuli and a reduction in pain threshold.

In many circumstances premedication with local or intravenous anaesthetics and/or analgesic drugs is mandatory. No guidelines are available on the assessment and treatment of pain caused by diagnostic and/or therapeutic procedures and more research in this setting is necessary.
Treatment-related Pain

All cancer treatment modalities have the potential to cause pain. Data in the literature show that about 59% of patients on anticancer treatments, and 33% of patients after curative treatments, present with pain. Moreover, 5% to 10% of survivors have pain that interferes with functioning. Thirty per cent of breast cancer survivors report pain 10 years after treatment.

Patients should be informed about pain onset and pain management during the anticancer treatment to avoid discontinuation of therapies. In addition patients should be encouraged to take an active role in their pain management.

Pain syndromes related to cancer surgery are well described. The most frequent are breast cancer pain (from wide local excision, lumpectomy, axillary dissection, conserving surgery, radical mastectomy, breast implants/reconstruction, lymphoedema, frozen shoulder), post-radical neck dissection pain, post-thoracotomy pain, post-surgical pelvic floor myalgia, phantom limb pain, and neuroma pain. Modern, less invasive surgical techniques such as lumpectomy and axillary dissection and/or reconstruction do not always result in less post-surgery pain. Acute pain following surgery requires the administration of an opioid analgesic or the implementation of more specific strategies such as regional anaesthetic techniques. Patient-controlled analgesia (PCA) can be delivered intravenously or through an epidural catheter. Post-surgical pain may become a chronic pain syndrome (Table 2).

Acute pain related to chemotherapy may be due to venous spasm, chemical phlebitis, vesicant extravasation at the site of infusion followed by desquamation and ulceration, and anthracycline-associated flare with local urticaria. Application of warm compresses or reduction of the rate of infusion can reduce pain due to chemical phlebitis caused by cytotoxic medications, as well as the infusion of potassium chloride and hyperosmolar solutions. Acute pain due to severe mucositis is a consequence of the myeloablative chemotherapy before bone marrow transplantation. It is frequently observed during radio(chemo)therapy for head and neck cancer. Continuous intravenous infusion of opioids plus PCA as on-demand bolus injections are adequate treatment in most cases; the use of transdermal opioids may be suggested where oral use is contraindicated.
Administration of paclitaxel generates a syndrome of diffuse arthralgias and myalgias in 10–20% of patients. The causes of the symptoms are unknown and there is no specific analgesic therapy. Steroids are the usual treatment. However, independent of the pathology, prolonged treatment with steroids or their abrupt discontinuation can provoke acute arthralgias and myalgias, a syndrome known as “steroid pseudorheumatism”.

Acute painful peripheral neuropathy resulting from cytotoxic chemotherapy such as vincristine, cisplatin, and oxaliplatin may persist over time. The syndrome usually is a sensory-predominant peripheral neuropathy with pain and dysesthesia that is most severe in the distal legs and sometimes extending to the hands and distal arms. Concomitant neurological deficit can worsen functioning.

Palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome) manifests as a painful erythematous rash in the palms and soles, often followed by bulla formation and desquamation after the administration of continuously infused 5-fluorouracil (5-FU), capecitabine (an oral 5-FU precursor), liposomal doxorubicin, and paclitaxel. It is usually self-limiting; however, symptomatic measures are required while treatment with pyridoxine induces resolution of the lesions. In patients previously treated with RT, vinorelbine administration can provoke severe pain at the tumour site. Pre-treatment with ketorolac and morphine could reduce the occurrence of this symptom; otherwise, switching to oral vinorelbine is indicated.

In patients with haematological or lymphoproliferative malignancies and in those receiving immunosuppressive therapies, acute herpetic neuralgia is frequent and causes very distressing suffering and severe pain. This is a typical form of neuropathic pain and should be treated accordingly.

Table 7 shows the most frequent causes of targeted therapy-related pain and Table 8 shows the most frequent causes of radiotherapy-related pain. Although the analgesic therapy according to published guidelines is indicated to treat any type of pain, there is a strong need for well-conducted trials analysing pathophysiology, epidemiology, prevention, and treatment of TT-related pain and RT-related pain.
Hormonal Therapy-related Pain

Musculoskeletal symptoms, bone demineralisation with consequent osteopenia and osteoporosis, arthralgia, and myalgia are important side effects due to aromatase inhibitors (AIs) and are the causes of non-adherence to or discontinuation of the therapy. Recommendations for the management of joint symptoms include pharmacological and non-pharmacological interventions or the switch to a different hormonal

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**Table 7 Causes of Targeted Therapy-related Pain**

- Papulopustular rash
- Erythema
- Hand-foot skin syndrome
- Paronychia
- Fingertip fissures
- Radiation dermatitis
- Eyelashes growth distortion
- Oral mucositis
- Anal mucositis
- Abdominal discomfort with diarrhoea


**Table 8 Causes of Acute and Late Radiotherapy-related Pain**

<table>
<thead>
<tr>
<th>Acute phase</th>
<th>Late phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mucosal inflammation: stomatitis, pharyngitis, oesophagitis, enteritis, proctitis, etc.</td>
<td>Radiation fibrosis syndrome</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>Osteoradionecrosis of the jaw</td>
</tr>
<tr>
<td>Pain flare effect</td>
<td>Chest wall pain</td>
</tr>
<tr>
<td>Procedural pain: brachytherapy; implantation of “fiducial markers” in an organ for image-guided radiotherapy; passive mobilisation of bone metastatic patients during radiation treatment</td>
<td>Oesophageal stricture</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain due to bowel spasm</td>
</tr>
<tr>
<td></td>
<td>Urethral pain – dyspareunia</td>
</tr>
<tr>
<td></td>
<td>Anal stricture</td>
</tr>
</tbody>
</table>

therapy. NSAIDs, low doses of steroids for a short time, paracetamol, and duloxetine represent the most adequate analgesic approaches. Non-pharmacological approaches have been employed and need to be evaluated in well-conducted trials.

Supportive Therapy-related Pain

Acute phase reaction symptoms are commonly observed after intravenous administration of new-generation bisphosphonates in patients with bone metastases, as well as in patients with hormone-induced osteoporosis. The acute phase reactions are less frequent in patients treated with denosumab. Pain relief is generally achieved with the administration of NSAIDs and acetaminophen. For patients on regular analgesic opioid therapy, higher doses of these drugs should be prescribed. The intensity and incidence of pain caused by bisphosphonates may be reduced by pretreatment with acetaminophen or ibuprofen.

Granulocyte-colony stimulating factor (G-CSF) and its long-term active form, pegfilgrastim, may induce bone pain that can result in discontinuation of the growth factor, reducing chemotherapy dose intensity, and consequently, the patient’s survival. Naproxen was shown to significantly reduce pegfilgrastim-induced bone pain by 22% over the whole 5 days of the course, with an absolute difference of 10%. Even with the preventive use of naproxen, more than 60% of patients still experienced some pain (19% severe pain).

Pharmacological Approaches in Treating Cancer Pain

In 1986 the World Health Organisation (WHO) published analgesic guidelines for the treatment of cancer pain based on a three-step ladder together with practical recommendations (Table 6). These guidelines serve as an algorithm (Figure 2) for a sequential pharmacological approach to treatment, according to the intensity of pain, reported by the patient. Non-opioid drugs such as NSAIDs or paracetamol are suggested for pain of mild intensity, moving on to opioids for more troublesome pain.
Opioid analgesics are classified according to their ability to control mild to moderate pain (i.e. codeine, dihydrocodeine, tramadol, dextropropoxyphene, tapentadol) (weak opioids) (Table 9) and those used for moderate to severe pain (morphine, methadone, hydromorphone, oxycodeone ± naloxone, fentanyl, diamorphine, buprenorphine, levorphanol, oxymorphone) (strong opioids) (Table 10). Opioid analgesics may be associated with non-opioid drugs (paracetamol or NSAIDs) and adjuvant drugs. The current recommended management of cancer pain consists of the regular administration of opioids and intermittent rescue doses of immediate-release opioids or NSAIDs for episodic pain. The treatment with opioids must be personalised according to the pharmacokinetics and pharmacodynamics of the drug, as well as the route of administration and the clinical condition of the patient. All opioids produce tolerance with chronic dosing and many patients require dose escalation to
accommodate their decreased sensitivity towards the drugs. This is not addiction and physicians must assess patients carefully to diagnose progression of the disease as early as possible.

Table 9  Opioid Analgesics for Mild to Moderate Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Pharmacology</th>
<th>Metabolism</th>
<th>Toxicity / Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>is an opium alkaloid</td>
<td>is a prodrug of morphine. The pharmacodynamic effects of codeine are largely due to the production of its active metabolite, morphine</td>
<td>is metabolised to active drugs within the body by CYP2D6. Poor metabolisers produce no CYP2D6 or undetectable levels of it. Without CYP2D6, codeine provides little or no analgesia.</td>
<td>A relevant accumulation of codeine has been reported in patients treated with codeine and undergoing haemodialysis when compared with normal subjects. Not indicated in presence of renal failure.</td>
</tr>
<tr>
<td></td>
<td>Commercially available in association with paracetamol</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dihydrocodeine</td>
<td>is a semisynthetic analogue of codeine</td>
<td>has an oral bioavailability of about 20% and the same analgesic potency as codeine when administered orally.</td>
<td>The CCK antagonist proglumide enhances the analgesic effect of dihydrocodeine</td>
<td>can produce severe toxicity when administered in patients with renal impairment. Oxidation of dihydrocodeine is reduced in patients with hepatic cirrhosis resulting in increased oral bioavailability caused by a reduced first-pass metabolism.</td>
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<tr>
<td>Tramadol</td>
<td>is a synthetic drug with opioid and non-opioid properties and thus a ceiling dose</td>
<td>agonist of the μ opioid receptor, also inhibits serotonin and norepinephrine reuptake.</td>
<td>After repeated oral administration the bioavailability is about 90–100%, the excretion is mostly via kidneys (90%).</td>
<td>The elimination time of the potent active metabolite is double in patients with hepatic or renal impairment. Not indicated in presence of renal failure. A severe serotonin syndrome may occur when tramadol is combined with drugs that increase serotonin activity.</td>
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</table>
### Table 9 (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Pharmacology</th>
<th>Metabolism</th>
<th>Toxicity / Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextro-propoxyphene (DPP)</td>
<td>is a µ agonist and a weak N-methyl-D-aspartate (NMDA) antagonist receptor</td>
<td>is a synthetic derivative of methadone</td>
<td>The analgesic effect of DPP hydrochloride in doses of 65 mg or more has been established in controlled studies</td>
<td>When it is administered regularly, plasma concentration gradually increases with a plateau after 2 to 3 days. It is metabolised in the liver to norpropoxyphene, which can accumulate in the body because of its long half-life (about 23 hours) and may produce central nervous system (CNS) toxicity.</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>New opioid, it binds to the µ opioid receptors and inhibits norepinephrine reuptake and thus has a ceiling dose</td>
<td>This characteristic reduces the risk of addiction</td>
<td>It seems to produce fewer GI adverse effects in respect to oxycodone</td>
<td>Comparative studies in large samples of cancer patients on chronic opioid use are necessary</td>
</tr>
<tr>
<td>Drug</td>
<td>Class</td>
<td>Pharmacology</td>
<td>Metabolism</td>
<td>Toxicity / Contraindications</td>
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<tr>
<td>Morphine</td>
<td>is a µ opioid agonist</td>
<td>Oral morphine is the drug of choice for the management of chronic cancer pain of a moderate to severe intensity because it provides effective pain relief, is widely tolerated, is simple to administer, and is comparatively inexpensive. Individual titration of dosages and the prevention of the adverse effects (e.g. nausea, vomiting, constipation) are recommended.</td>
<td>Morphine clearance decreases in patients over 50 years old, which helps to explain elderly patients’ higher sensitivity to the drug. Younger patients may need larger doses of morphine to achieve the same analgesic effect.</td>
<td>Morphine has three different metabolites: morphine-3-glucuronide (M-3-G), morphine-6-glucuronide (M-6-G), and normorphine. M-6-G is the active drug and binds to the µ receptor. M-3-G is not an opioid and may cause toxicity, such as myoclonus and agitation. Morphine is not safe in patients with impaired renal function.</td>
</tr>
<tr>
<td>Methadone</td>
<td>is a synthetic opioid and is a µ and δ opioid receptor agonist with NMDA receptor antagonist affinity</td>
<td>It has a long and unpredictable half-life, large interindividual variations in pharmacokinetics. Although it has been used mostly as the maintenance drug for opioid addicts, methadone has also proved to be a powerful analgesic and a suitable drug in treating cancer pain.</td>
<td>Considered one of the new analgesics based on impressive study results and clinical successes. It can be an interesting alternative 2° line option for patients with intolerable opioid side effects or pain difficult to manage. Methadone can prolong the QTc interval. Relative contraindication to its use is a QTc interval from 450 to 500 ms. Strong contraindication to its use is a QTc interval &gt;500 ms.</td>
<td>It is metabolised by the cytochrome P450 group of enzymes and does not produce active metabolites. The main enzyme mediating N-demethylation of methadone in the liver is CYP3A4, with lesser involvement of CYP1A2 and CYP2D6. Therefore, the most important interactions between methadone and other drugs are related to drugs that are able to induce or inhibit CYP3A4. In these circumstances, the methadone plasma concentrations will be reduced or increased, respectively. Methadone is safe in patients with impaired renal function.</td>
</tr>
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</table>
### Table 10 (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Pharmacology</th>
<th>Metabolism</th>
<th>Toxicity / Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>is a derivative of morphine with similar pharmacokinetic and pharmacodynamic properties</td>
<td>It is highly soluble and about 5–10 times more potent than morphine. The extended-release formulation “once a day” is suitable for patients with low compliance or taking many drugs per day</td>
<td>Hydromorphone administered subcutaneously has some advantages compared to morphine because of its high solubility, the availability of a high concentration preparation (10 mg/ml), and a bioavailability of about 78% and it is at least as effective as morphine when delivered by continuous subcutaneous infusion</td>
<td>It produces some metabolites, the principal one being hydromorphone-3-glucuronide and, like M-3-G, it is likely to be responsible for the neuroexcitatory adverse effects (myoclonus, seizure, hyperalgesia). High doses of the drug should be used with caution in patients with renal failure.</td>
</tr>
<tr>
<td>Oxycodone ± paracetamol</td>
<td>is a semisynthetic opioid that is a derivative of thebaine, with an agonist action at µ and κ receptors</td>
<td>has structural relationship to codeine but is nearly 10 times more potent. It is metabolised like codeine, that is demethylated and conjugated in the liver to form oxymorphone in a reaction catalysed by cytochrome P450 2D6 (CYP2D6), and is excreted in the urine</td>
<td>A meta-analysis of four randomised controlled trials attested that oxycodone was as safe and effective as morphine for cancer-related pain. Its potency is double with respect to morphine.</td>
<td>The antagonist effects of opioid receptors of naloxone administered orally at low dose should be limited to intestinal opioid receptors only. This explains the improvement of opioid-induced constipation when the association of oxycodone + naloxone is administered. The max daily dose is 40 mg twice a day for oxycodone and 20 mg twice a day for naloxone.</td>
</tr>
<tr>
<td>Drug</td>
<td>Class</td>
<td>Pharmacology</td>
<td>Metabolism</td>
<td>Toxicity / Contraindications</td>
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</tr>
<tr>
<td>Fentanyl</td>
<td>is a highly lipophilic semi-synthetic opioid</td>
<td>Fentanyl citrate has a very high potency (about 75 times more than morphine) and is skin compatible, having a low molecular weight with good solubility and thus suitable for transdermal (TD) administration. Moreover, fentanyl has a faster onset of analgesic properties when administered IV.</td>
<td>Intravenous fentanyl can be safely used for rapid titration in cancer patients with severe pain. The TD route of fentanyl administration is the most used in clinical practice. It is indicated in patients opioid-tolerant, with stable pain, with GI nausea and vomiting and difficulties in swallowing. The absorption increases and creates a risk in patients with fever or when the external temperature increases.</td>
<td>Intravenous, sublingual, buccal and intranasal, fentanyl drug delivery has a short onset of analgesic activity and is suitable in treating breakthrough pain. Fentanyl can be a valid alternative drug in patients with renal impairment. TD administration is not indicated in patients with generalised oedema.</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>is an semisynthetic analogue of morphine and a pro-drug</td>
<td>must be biotransformed to 6-acetylmorphine and morphine to produce the analgesic effect</td>
<td>It is about twice as potent as morphine when administered subcutaneously or intramuscularly</td>
<td>Is more soluble than morphine when administered parenterally; more rapid onset of analgesia and less vomiting but more sedation when administered intravenously.</td>
</tr>
<tr>
<td>Drug</td>
<td>Class</td>
<td>Pharmacology</td>
<td>Metabolism</td>
<td>Toxicity / Contraindications</td>
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<tr>
<td>Buprenorphine</td>
<td>is a semi-synthetic thebaine derivative&lt;br&gt;It is a potent partial agonist at the µ receptor. As a µ partial agonist, there is a ceiling to the morphine-like effects of the drug</td>
<td>Sublingual administration allows direct drug absorption into the systemic circulation, thus avoiding the hepatic first-pass metabolism</td>
<td>Like the mixed agonist-antagonists, buprenorphine may precipitate withdrawal in patients who have received repeated doses of a morphine-like agonist and develop physical dependence. Continuous administration of naloxone is necessary to reverse the respiratory effects of buprenorphine&lt;br&gt;Transdermal (TD) buprenorphine achieves good analgesia with adverse effects similar to those of other opioids</td>
<td>Buprenorphine can be administered at normal doses in patients with renal dysfunction because it is mainly excreted through the liver&lt;br&gt;It is prudent to limit treatment to patients who are opioid naive or are receiving a low-dose opioid regimen&lt;br&gt;Buprenorphine can also prolong the QTc interval; this effect is less than that produced by methadone&lt;br&gt;TD administration is not indicated in patients with generalised oedema</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>is a synthetic potent µ opioid agonist and also binds δ and κ receptors</td>
<td>is considered a useful alternative to morphine, hydromorphone, or fentanyl; however, it must be used cautiously to prevent accumulation. The κ receptor binding may explain its high prevalence of psychotomimetic effects (delirium, hallucinations) compared with other opioids</td>
<td>In a randomised trial levorphanol was administered in high-strength or low-strength capsules for neuropathic pain. Neuropathic pain was reduced by the higher dose but there were more side effects</td>
<td>It undergoes glucuronidation in the liver and is then excreted in the kidney. It can be delivered orally, intravenously and subcutaneously&lt;br&gt;It has a role in patients who are refractory to other opioids</td>
</tr>
</tbody>
</table>
Paracetamol and/or an NSAID are effective for treating mild pain and any intensity of pain at least in the short term and unless contraindicated. Opioids remain the mainstay of severe pain management in patients with cancer; however, intraindividual variability in response to different opioids is a common clinical phenomenon.

Although the role of “strong” opioids is universally recognised in the treatment of moderate to severe pain, there is no common agreement regarding the role and utility of the “weak” opioids for mild to moderate pain (Table 9). The first criticism concerns the absence of definitive proof of efficacy of weak opioids; moreover their use is limited by the “ceiling effect”, in which a dose increase does not correspond to an increase in their analgesic efficacy but only influences the appearance of side effects. As an alternative to weak opioids, low doses of strong opioids in combination with a non-opioid analgesic should be considered. Tapentadol is a new opioid with a ceiling effect that reduces the risk of addiction and has the potential to be effective in treating neuropathic pain. However, further studies on this new drug are necessary in cancer pain. Well-performed clinical trials are necessary to address the relevant issue of the role of weak opioids.

Table 10 shows the most used strong opioids available for treating moderate to severe cancer pain. Most of them are pure µ opioid agonists. However, there is no evidence from high-quality comparative studies that other opioids are superior to morphine in terms of efficacy and tolerability. Oral short-acting drugs such as morphine or hydromorphone, or a combination product containing an opioid plus paracetamol such as oxycodone or hydrocodone, are frequently the first-choice analgesics used in opioid-naive patients or patients with limited opioid exposure.

### Table 10: Strong Opioids for Cancer Pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Pharmacology</th>
<th>Metabolism</th>
<th>Toxicity / Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxymorphone</td>
<td>is a semisynthetic µ opioid agonist, considered more potent than morphine</td>
<td>is a metabolite of oxycodone with high lipidic solubility and rapid transfer across the blood-brain barrier</td>
<td>is an oral therapeutic option for acute and chronic/severe pain. Available as immediate-release and extended-release formulations</td>
<td>Safety and efficacy profiles were similar to commonly used pure opioids. It is metabolised by the liver</td>
</tr>
</tbody>
</table>
In patients with severe pain, where the relief of pain must be urgent, intravenous titration of parenteral opioid (usually morphine or fentanyl) is mandatory. New opioid analgesics are now available such as a oxycodone/naloxone combination, which has been shown to provoke less constipation in respect to other oral opioids. More research is necessary to better define the maximum daily dose and the cost/benefit of this new drug in cancer pain.

Hydromorphone or oxycodone, in both immediate-release and modified-release formulations for oral administration, and oral methadone are effective alternatives to oral morphine.

Oral opioid administration is the preferred route. However, in some clinical situations, such as vomiting, dysphagia, malabsorption, delirium, or in cases in which rapid dose escalation is necessary, oral administration may be impossible and alternative routes must be implemented.

Transdermal fentanyl and transdermal buprenorphine are best reserved for patients whose opioids requirements are stable. They are usually the treatment of choice for patients who are unable to swallow, or those with poor tolerance of morphine or poor compliance. In the presence of renal impairment, all opioids, but especially those with active metabolites, should be used with caution and at reduced doses and frequency. Fentanyl and buprenorphine via the transdermal route, or intravenously, are the safest opioids of choice in patients with chronic kidney disease.

Clinically, the adverse effects of opioids such as nausea, sedation, constipation, tolerance, and physical dependence need to be monitored regularly. It is also important to recognise the endocrine effects of opiates, because opioids reduce testosterone and produce hypogonadism and morphine has effects on prolactin and growth hormone.

**Adjuvant Drugs**

Adjuvant drugs are a class of co-analgesics to administer in combination with opioids in some pain syndromes. While a large number of adjuvant drugs have been suggested to have analgesic effects, unfortunately the evidence is largely anecdotal and few controlled trials of these drugs have been conducted in cancer patients.
Tricyclic antidepressants (amitriptyline, imipramine, desipramine) have shown analgesic efficacy in various neuropathic syndromes, particularly when pain has dysaesthetic and paraesthetic characteristics. In some controlled studies, both amitriptyline and desipramine showed efficacy in the treatment of post-herpetic neuralgia; chlorimipramine and nortriptyline showed their efficacy in the treatment of central pain; imipramine, clomipramine, desipramine, and fluoxetine proved efficient in the treatment of neuropathy-induced pain.

Corticosteroids are frequently administered to cancer patients, but their efficacy in inducing pain relief has been shown only in a limited number of studies. They are likely to exert their effect by decreasing peritumoural oedema and signs of inflammation, which, in turn, may reduce peripheral nerve stimulation. Dexamethasone has been shown to be effective in alleviating metastatic spinal cord compression and in treating headache related to endocranial hypertension.

Anticonvulsants (carbamazepine, phenytoin, valproic acid, clonazepam, gabapentin, pregabalin) are all drugs utilised in the treatment of neuropathic pain with a component referred to as “stabbing” or “lancinating”. Clinical experiences have been reported concerning the use of these drugs in the treatment of neuropathic pain caused by diabetes, radiotherapy-induced fibrosis or surgical lesions, herpes zoster, and deafferentation. Gabapentin appears effective in improving analgesia in patients with neuropathic cancer pain already treated with opioids.

Local anaesthetics: studies regarding the efficacy of intravenous and subcutaneous administration of local anaesthetics such as lidocaine in patients with neuropathic cancer pain have shown contradictory results.

**Particular Cases**

**Breakthrough Pain (BTP) or Episodic Pain (Table 1)**

Available pharmacological treatment options include oral transmucosal, buccal, or oral immediate-release morphine sulphate (IRMS) or nasal, subcutaneous, or intravenous opioids. Although these drugs are frequently used, only a few randomised controlled trials (RCTs) are available comparing fentanyl versus placebo or versus IRMS. Recently, a fen-
Taneryl nasal spray (FNS) was developed to optimise the absorption of the drug across the nasal mucosa. In RCTs FNS provided superior pain relief compared with placebo and with IRMS within 5 minutes but the difference was significant after 10 minutes. No patient reported significant nasal effects. Sublingual fentanyl orally disintegrating tablet (sublingual fentanyl ODT) produced a significant improvement of maximum BTP intensity within 5 minutes of administration in 68% of BTP episodes and a maximum effect within 30 minutes in 63% of episodes. BTP can be partially resolved by the above-mentioned short-acting and potent drugs. However, further studies are necessary to find the best solution for BTP episodes because their onset is rapid and the duration is generally of 5–15 minutes. IRMS is appropriate to treat predictable episodes of BTP pain.

Bone Pain
Bone pain must be treated with analgesic drugs according to the published guidelines. Moreover RT, radioisotopes, and TT given in association with analgesics have an important role in pain management. Bisphosphonates (BPs) are part of the standard therapy for hypercalcaemia and the prevention of skeletal-related events. Although BPs have an analgesic efficacy in patients with bone pain due to bone metastases, their use should not be considered as an alternative to analgesic treatment. In a randomised, double-blind study, denosumab demonstrated improved pain prevention and comparable pain palliation compared with zoledronic acid. In addition, fewer denosumab-treated patients shifted to strong opioid analgesics. Preventive dental measures are necessary before starting BP and denosumab administration.

Neuropathic Pain (NP)
Neuropathic pain has been associated with a less favourable response to opioid analgesics than other types of pain. However, opioids may also be effective in NP, even if high doses are often required. NP, either caused by tumour infiltration or due to paraneoplastic or treatment-induced polyneuropathy, may be adequately controlled by opioids with or without adjuvant drugs. There is evidence from systematic reviews that both
tricyclic antidepressants and anticonvulsant drugs are effective in the management of NP, even if the number needed to treat for these drugs is 3–5. Non-opioids ± strong opioids ± amitriptyline or gabapentin should be considered the treatments of choice. In patients with NP due to bone metastases, RT at the dose of 20 Gy in five fractions should be considered.

**Opioid Switching**

Opioid switching is a therapeutic approach to consider in clinical situations where: (1) pain is controlled but there are some intolerable adverse effects; (2) pain is not adequately controlled and it is impossible to increase the opioid dose because of adverse effects; or (3) pain is not adequately controlled, notwithstanding the continuous increase of opioid dose which does not produce adverse effects.

Different therapeutic strategies may prevent or treat adverse effects: (1) general measures (reduce the opioid dose, hydrate the patient, correct abnormal biochemistry if present, reduce the number of pharmacological associations); (2) administration of symptomatic drugs (adjuvant drugs); (3) administration by an alternative route; (4) administration of an alternative opioid; or (5) switching to both an alternative opioid and route. Data are not available to allow us to compare the advantages and disadvantages of the different therapeutic strategies such as the use of specific symptomatic drugs, the switching of opioid, and/or route of administration.

Patients who have poor analgesic efficacy or tolerability with one opioid will frequently tolerate another opioid well, although the mechanisms that underlie this variability in the response to different opioids are poorly known. The hypothesis is that the benefits of opioid switching are more likely to be related to subtle differences in pharmacology that emerge when a new opioid is substituted in a patient who has developed toxicity to another opioid, rather than to overt differences in pharmacological profile in patients in stable pain control. However, much more needs to be understood to answer these questions. For switching from one opioid to another, it is mandatory to know the dose ratios between the different opioids and to consider the incomplete cross-tolerance between them.
Refractory Pain

About 10% of cancer patients have pain which is difficult to manage with oral or parenteral analgesic drugs. Interventional techniques such as nerve blocks and intrathecal drug delivery (ITDD) (spinal or epidural) should be considered in cases of refractory pain. Peripheral nerve blocks or plexus blocks are indicated when pain occurs in the field of one or more peripheral nerves or if pain is caused by pathological fracture or vascular occlusion. The use of neurolytic agents on peripheral nerves produces a significant incidence of neuritis. Neurolytic blocks should be limited to those patients with short life expectancy because they are usually effective for 3–6 months.

Coeliac plexus block is useful in the presence of visceral pain due to the damage of organs in the upper abdomen. Figure 3 shows the algorithm for ITDD or epidural administration of opioids to be considered for patients with inadequate pain relief despite systemic opioid escalating doses or opioid switching.

Conclusions

The WHO 3-step analgesic ladder remains the clinical model for pain therapy. Its clinical application should be employed only after a complete and comprehensive assessment and evaluation, based on the needs of each patient. When applying the WHO guidelines, up to 90% of patients can find relief from their pain regardless of the settings of care and social and/or cultural environment.

Such a pharmacological approach is the standard treatment for patients with cancer pain. Only when such an approach is ineffective are interventions such as spinal administration of opioid analgesics or neuroinvasive procedures recommended.

Survivors need an adequate assessment of pain and its causes before opioids are prescribed to them, to avoid the possible risk of misuse or dependence.

Declaration of Interest:
Dr Ripamonti has reported no conflicts of interest.
Dr Bossi has reported no conflicts of interest.

Further Reading


Cancer-related Fatigue

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Introduction: Fatigue in Rehabilitation

Due to advances in modern oncology treatment, improved cure rates have been observed for some tumour sites such as lymphoma, breast or testicular cancer, and longer survival rates for most tumour types have been achieved. However, for many patients, this also means that they may suffer from short- and long-term sequelae subsequent to their illness and its treatment. Cancer-related fatigue (CrF) is the most common side effect or late effect of cancer and its treatment. CrF is commonly defined as: a self-recognised phenomenon that is subjective in nature and experienced as a feeling of tiredness or lack of energy that varies in degree, frequency, and duration which is not proportional to physical activities and not relieved by sleep or rest. Patients often describe CrF as an unusual feeling of exhaustion, weakness, or a loss of activity with sequelae to emotional and cognitive functions.

CrF has often been described as a multidimensional construct including physical, cognitive, and emotional dimensions. The physical domain describes fatigue as a loss of ability to perform activities due to somatic symptoms of tiredness and loss of energy. The mental or cognitive dimension includes loss of concentration, attention, reduced alertness, or impairment in short-term memory. The emotional dimension covers symptoms such as loss of motivation, reduced self-esteem, and depressive feelings.

The symptoms and signs of CrF may also be due to other diseases or functional impairments. CrF is primarily based on the patient’s subjective feeling of his or her symptoms and impairments. CrF has severe effects on functional levels and health-related quality of life (HRQoL).
The type and extent of CrF vary markedly from one patient to another and can change over time.

CrF does not affect only the individual patient and their spouse, but also has many consequences on health economy. Patients complaining about CrF show higher rates of requesting physician counselling, private practitioner support, or other health services and, also, higher rates of sick leave and loss of work capacity. Moreover, CrF has been proven to be a negative predictor for return to work after cancer.

Prevalence Rates

A huge number of studies have been published investigating the prevalence and the associating factors of CrF in cancer patients. Prevalence rates of CrF range from 59–100% in patients with cancer. The highest prevalence rates were found for CrF as a direct side effect of a combination of medical therapies such as surgery, chemotherapy, radiotherapy, and/or hormone therapy. CrF rates were higher in certain tumours (e.g. pancreatic, breast, lymphoma) and with the use of certain treatments, such as haematopoietic stem cell transplantation (HSCT) or high-dose chemotherapy. CrF during treatment is regarded as a risk factor for developing chronic CrF. Several studies reveal that fatigue commonly increases during treatment and decreases after the end of treatment.

CrF can persist or recur as long-term sequelae for many years after the cessation of anticancer and antineoplastic treatment. Long-term CrF may be present for a long period of time and may persist up to five years after completion of treatment. Although the label “chronic fatigue” may be accurate within this context, it should not be confused with the International Classification of Diseases (ICD) diagnosis of chronic fatigue syndrome (CFS). The prevalence rates of CrF in long-term survivors vary from 25–35%, depending on the criteria and method used for assessment.

For patients in palliative or end-of-life care, CrF can be associated with limiting, or even loss, of body functions and overall HRQoL.
Influencing Factors (Figure 1)

Despite a lot of research during the last decade, there is still no comprehensive theory explaining the pathogenesis or the aetiology of CrF. Numerous factors are discussed as influencing, or even causing, fatigue, including medical conditions, biochemical and psychological factors and, particularly, mood disturbances. Proposed mechanisms are pro-inflammatory cytokines, dysregulation of the hypothalamo-pituitary-adrenal axis, desynchronisation of circadian rhythm, skeletal muscle wasting, and also genetic dysregulation. Within the somatic perspective, factors include states of oxygen insufficiency, metabolic disorders, hormonal imbalance, as well as blood modifications (anaemia, hypokalaemia, hypocalcaemia). Extremely high fatigue levels are correlated with specific forms of cancer treatment such as interferon-α or interleukin therapy. There are also various psychosocial factors potentially explaining CrF. Studies on psychological factors focus on the correlation between CrF and psychiatric comorbidity, particularly depression and anxiety. This is described in the section on psychological assessment. A strong correlation of fatigue with sleeping disorders has been shown that may be either a result of distress or a potential secondary cause of fatigue.

Diagnosis and Assessment

Due to the complexity of CrF, a systematic assessment is a prerequisite for planning treatment strategies for the patient. Based on the overview of contributing factors, the assessment approach should include the following domains and data sources:

- **Clinical assessment**: pain, anaemia, insomnia, nutritional assessment, activity level, medication side effects, comorbidities;
- **Psychological assessment**: depression, anxiety, emotional distress, coping, non-cancer-related psychosocial distress; and
- **Self-rating**: questionnaires, screening.

Clinical Assessment

Clinical anamnesis of CrF takes a central role in the diagnostic process. The physician should ask specifically about the type, severity, and temporal course of the patient’s fatigue symptoms, focusing on vegetative functions (e.g. sleep pattern) and other factors such as types of medication, nutrition, use of alcohol, tobacco, recreational drugs, medical history before cancer, physical fitness, and other somatic comorbidities. Additionally, it is recommended to check the following laboratory parameters: electrolytes, glucose, transaminase, gamma-glutamyltransferase (GT), C-reactive protein levels, blood count (particularly red and white blood cell count, haemoglobin levels) and thyroid-stimulating hormone.

Psychological Assessment

There have been several studies focused on correlation and comorbidity in CrF and psychiatric conditions, especially depression and anxiety. As fatigue is a common symptom of depression, diagnostic efforts are required that reliably differentiate CrF. Symptoms such as a loss of drive, sleeping disorders, and cognitive disorders also show overlap with secondary symptoms of depression. With respect to the course of CrF, it may be that long-lasting CrF can trigger a depressive episode. For example, a continuing level of depression and anxiety may be exacerbated
by the perception of distress in knowing that cancer is a life-threatening illness, as well as the stress of the anticancer treatment itself, which may cause both physical and emotional exhaustion. CrF can be an expression of pre-existing depression and can also be a cause of depression. In clinical practice, a depressive disorder that may underlie CrF can be detected rapidly and sensitively using just two screening questions. If the patient answers both questions affirmatively, a depressive disorder is very likely to be present and, therefore, a further specialised psychiatric diagnostic evaluation is recommended. In one study, long-term fatigue, in particular, has been interpreted as a possible psychological “maladaptation” to remaining late effects of cancer or its treatment.

**Self-rating Measurement**

Assessment and clinical diagnosis of CrF is an important task for healthcare professionals in cancer care. There is a broad expert consensus that CrF as a complex and subjective phenomenon can only be measured by self-report assessment tools. Due to the increasing interest, numerous instruments to measure CrF have been developed. For screening of CrF, a global assessment based on linear analogue scale has been proven as a useful and valid tool. A review of the research literature shows that CrF may be assessed by either unidimensional or multidimensional instruments. Unidimensional instruments (e.g. FACIT Fa module or the Brief Fatigue Inventory) are focusing only on physical symptoms of fatigue. Most of the existing instruments are based on a multidimensional approach assessing physical, affective, and cognitive aspects of CrF (e.g. Multidimensional Fatigue Inventory [MFI] or EORTC FA13), which is in line with an understanding of CrF as a multifaceted syndrome. Most scales pertain to intensity, with only a few also addressing interferences with activities of daily living.

**Treatment Strategies**

Compared with other side effects such as pain or nausea, there is no clear evidence how to treat CrF. As there are multiple influencing factors on CrF, treatment is dependent on how easily the causes of CrF can be determined and treated, e.g. anaemia. If the causes are unknown or
unclear, treatment is focused on how to reduce the symptom itself or help the patient to improve coping or management strategies. Therefore, most of the treatment options consist of supportive strategies. Before planning any treatment, the diagnostic process must be completed, having excluded potential causes of CrF as discussed above (“Influencing Factors”). According to the NCCN guidelines for CrF, the treatment algorithm starts with the global screening of CrF followed by differentiated assessment procedures depending on the level of CrF (see Figure 2).

Figure 2  Algorithm for the assessment of cancer-related fatigue according to the NCCN guidelines. From NCCN 2013 Clinical Practice Guidelines in Oncology: Cancer Related Fatigue. Version 3.2013.
If the assessment process is completed and supportive strategies were chosen as the recommended treatment option, the subsequent treatment strategies are focused on alleviating the symptoms of CrF. They should be designed taking into account the clinical status of the patient (patients currently under treatment, patients after completion of treatment, or patients with progressive disease at the end of life). In addition, the decision should be made in accordance with the patient’s needs and individual desires.

The following treatment options for alleviating CrF have been proven to be effective in treating CrF:

- Physical exercise and training
- Psychosocial interventions
- Pharmacological treatment

Within the last decade, many studies have provided substantial evidence that individualised physical exercise and training help reduce subjective fatigue levels. The physical training is focused on improving muscle strength and endurance, sometimes in combination with relaxation techniques or exercises for body awareness. Physical exercise and training have been proven as effective strategies against fatigue and the continuing decline of physical functional status. A Cochrane Review (Cramp & Daniel 2008) shows moderate effects for physical training, especially for some subgroups of cancer patients, if applied early during ongoing adjuvant treatment. Various National Cancer Societies generally recommend physical activity to cancer patients. Frequency, as well as intensity, of exercise and training should be applied in an individualised fashion depending on the patient’s age, clinical status of cancer, and subjective level of fitness.

*Psychosocial interventions* for treating CrF cover a broad range of interventions such as psychosocial counselling, psychotherapy, or psychoeducation. Apart from communicating information about CrF, the main goals of these interventions are: to help the patients to restructure their cognitive appraisal of CrF; changing their coping strategies as well as their behaviour; and addressing self-help or self-care strategies to
alleviate the burden of CrF. Some of these interventions include elements such as relaxation techniques, recommendations for pacing, energy conservation, and stress management. Most psychosocial interventions can be carried out as either individual or group interventions. There is some evidence that such strategies can improve quality of life and reduce the subjective feeling of fatigue. A recently published Cochrane review (Goedentorp et al 2009) shows moderate effects of psychosocial interventions in decreasing CrF. Other reviews have pointed out that, among psychosocial treatment strategies, cognitive behavioural interventions have been proven as most effective against CrF. In addition, it has been demonstrated that the combination of exercise training and psychosocial interventions produces better effects than these interventions alone. A few studies have shown that mind–body interventions such as mindfulness-based stress reduction (MBSR) or yoga may be helpful to reduce CrF, but further research is needed for these types of intervention.

Among the different types of pharmacological treatment of CrF, psychostimulants are particularly discussed. There are some randomised controlled trials showing effects of methylphenidate, especially for patients with severe levels of long-lasting fatigue and in progressive disease without psychiatric comorbidity. Vertigo, increased blood pressure, and dryness of the mouth have been described as possible side effects. A systematic review has demonstrated heterogeneous results for the use of methylphenidate. Effects seem to depend on the dosage used, the stage of cancer, and the treatment setting. A randomised study showed significant effects of modafinil for patients with severe fatigue at an early stage of treatment. Modafinil is approved only for the treatment of narcolepsy but has been shown effective for treating CrF in some studies. However, a review of the literature analysing studies up to 2008 concluded that modafinil cannot be recommended as a medication for CrF due to shortcomings in most of the studies. Against this background, psychostimulants cannot be regarded as a standard medication for treating CrF. In some European countries, methylphenidate and modafinil are not approved for use in CrF and therefore prescription may be difficult.
Other therapeutic agents less well studied in relation to their use for reducing CrF include some substances in complementary and alternative medicine such as l-carnitine, ginseng, and guarana. There are also a few studies showing that bupropion or selective serotonin reuptake inhibitors (SSRIs) (e.g. paroxetine) may reduce CrF.

Conclusion

Among cancer-related symptoms, CrF has the highest prevalence rates over the whole trajectory of cancer. Although CrF is associated with cancer and its treatment, many somatic and psychosocial factors influence CrF. Nevertheless, a comprehensive model which includes somatic as well as psychosocial factors is still missing. For assessment, several instruments allow standardised uni- or multidimensional assessment of CrF. Although many assessment tools have been developed, there is no gold standard for assessing CrF. Among available non-pharmacological supportive care interventions for patients with CrF, exercise and physical training in particular, combined with psychoeducation, show the best results but with little magnitude of effect. These types of treatment strategies are delivered in inpatient or outpatient rehabilitation services. Among pharmacological treatments, psychostimulants are effective with even smaller magnitude of effect, and further research is necessary. In addition, some complementary drugs have been tested in only a few studies, but results are still unclear and depend on the individual clinical situation of the patient. Guidelines for assessment and treatment have been developed to improve recognition and assessment of CrF and to improve supportive care of patients suffering from CrF. CrF is still to be regarded as a major challenge for the future, especially in basic research, prevention and development of treatment strategies in aftercare, and rehabilitation programs for cancer patients.

Declaration of Interest:

Professor Weis has reported no conflicts of interest.
Further Reading


Psychological Deterioration

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Introduction

Once the diagnosis of cancer has been made, patients are often confronted with distressing thoughts concerning the meaning of life and death for the first time in their lives. Cancer patients, and their relatives, have many concerns that relate to all aspects of their lives and require a wide range of adaptations. In spite of improvements in treatment strategy and rehabilitation options, cancer patients still experience a variety of physical, psychological, and social problems. Fear, sadness, and the sense of losing control can disturb their emotional balance. Poor self-perception is one of many factors that can weaken a person’s identity or alter their life-orientation, while social, financial, and occupational consequences may threaten their sense of security. Studies around the world have shown that chronic illnesses in particular can lead to poverty, and that, conversely, poverty is a distressing factor in the course of illness and overall quality of life. Family, friends, community resources, and one’s individual attitudes and beliefs also influence the adjustment process in response to a cancer diagnosis.

Inefficient psychological, personal, and social resources increase a patient’s level of distress, as well as feelings of helplessness and hopelessness. Distress is described as an unpleasant experience on an emotional, psychological, social, or spiritual level. These emotional reactions and psychosocial consequences range from normal feelings of vulnerability, sadness, and fear to serious psychological disorders, such as adjustment disorders, anxiety disorders, post-traumatic stress disorders, depression, family conflicts, or existential crises (Figure 1).

Figure 2 shows a more extensive model depicting the pathways between stressors and the continuum of distress. One should realise that the different stressors could also affect caregivers. The medical team should aim at preventive measures, particularly if the coping resources available to the patient do not appear to be sufficient.

Mental Disorders

In recent scientific reports, the prevalence of mental disorders among cancer patients ranged from 9.8% to 38.2%. In one review, the prevalence of depression by Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria was 16.3% in oncological and haematological settings (95% CI 13.4–19.5). The prevalence of dysthymia was 2.7% (95% CI 1.7–4.0), the prevalence of adjustment disorders was 19.4% (95% CI 14.5–24.8), and the prevalence of anxiety disorders was 10.3% (95% CI 5.1–17.0). Including combination diagnoses, the total figure adds up to 38.2% (95% CI 28.4–48.6) of patients.

The prevalence percentages of depression, adjustment disorders, anxiety disorders, and combination diagnoses in palliative care settings (24 studies) were 16.5%, 15.4%, 9.8%, and 29.0%, respectively. The reported prevalence differs depending on the diagnostic procedure performed (e.g. clinical interviews, standardised questionnaires) and the stage of the disease, as shown in Figure 3.

**Epidemiology of mental disorders in cancer patients**

<table>
<thead>
<tr>
<th>Mental Disorder</th>
<th>Prevalence Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorders</td>
<td>Screening up to approx. 50%, clinical interview up to approx. 30%, in terminally ill patients up to 80%</td>
</tr>
<tr>
<td>Depression</td>
<td>Screening up to approx. 50%, clinical interview up to approx. 15%, in terminally ill patients up to 77%</td>
</tr>
<tr>
<td>Adjustment disorders</td>
<td>Screening or clinical interview up to approx. 50% (frequently mixed anxiety and depressed mood)</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>Screening or clinical interview up to approx. 30%</td>
</tr>
<tr>
<td>Cognitive disorders (delirium)</td>
<td>Screening or clinical interview up to approx. 85% in terminally ill patients</td>
</tr>
</tbody>
</table>

Adjustment disorders are one of the most frequent psychiatric diagnoses related to cancer and usually follow a stressful event, such as the diagnosis of cancer. They involve emotional and behavioural responses such as depressed mood, anxiety, or a combination of both. Prevalence rates range from 11–35%.

Anxiety disorders include generalised anxiety disorder, panic disorder, and post-traumatic stress disorder. In advanced stages of the disease, patients experience different fears concerning disease recurrence or progression: imminent death, being dependent on others, losing autonomy, and suffering associated with pain and toxic treatments.

Depressive disorders are defined by persistent depressed mood or loss of pleasure. Other symptoms include psychomotor changes and cognitive and somatic troubles. Depression is found more frequently in patients with advanced disease. Younger age, a family and/or individual history of depression, poor social support, low level of optimism, low self-esteem, poor communication skills, and a history of stressful or traumatic life events, are additional risk factors. Depression and sadness are understandable grief responses, particularly when patients are confronted with a terminal stage of illness, but clinical depression is a more severe, unfavourable condition that may further complicate cancer treatment and patient care.

Existential distress is defined as feelings of helplessness and hopelessness, delirium, loss of dignity, perception of being a burden to others, and the loss of a will to live or a desire for a hastened death. Whereas some cancer patients consider life more meaningful following a cancer diagnosis, others report a loss of meaning or a feeling of absence. The latter can trigger a search for meaning, but continued search for meaning without success is connected to maladaptive coping and severe anxiety and suffering. Suicidal thoughts are most common in patients with advanced disease, and can be seen as an attempt to recover a sense of control in a situation which is perceived as uncontrollable. Based on clinical reports, suicidal thoughts occur in approximately 15% of patients with advanced cancer.
Treatment Options

Psychological care should be provided for all patients with cancer. A broad spectrum of standardised methods are available for the psychosocial assessment of cancer patients, and include clinical interviews; questionnaires, both self-assessment and external-assessment instruments; criteria lists or checklists for the screening of diagnostic criteria; psychological tests, such as neuropsychological tests; and standardised behaviour observations.

Other procedures that can be used include psycho-physiological measures such as observations of behaviour, or psycho-physiological measures such as biofeedback, imaging procedures such as computed tomography or magnetic resonance imaging, psycho-neuro-immunological measures, and psycho-neuro-endocrinological measures.

In addition to standard treatment measures, the support of family and friends plays an essential role in both cancer treatment and long-term adaptation, as these individuals have a dual responsibility of caring for and caring about the patient. Family members may actively engage in emotive work with the patient while also attempting to manage their own inner feelings.

Psychotherapeutic Interventions

Psychotherapeutic interventions will vary depending on the patient, and also on the stage of the disease. For instance, cancer recurrence requires many adaptation strategies and techniques, e.g. to learn to live “in the here and now”. When facing the terminal stage of a disease, not only the patients but also their significant others will have specific wishes and needs. The quality of communication between the doctor and patient is a crucial variable, as good communication skills can reduce fear and anxiety through development of trust and confidence (rapport), as well as a clearer view of the situation.
Frequently performed psychotherapeutic interventions are detailed below.

*Psychoeducation* encompasses a broad range of activities that combine education and other activities such as counselling and supportive interventions. Psychoeducational interventions may be delivered individually or in groups, and may be tailored or standardised according to the needs of the patient. This type of intervention generally includes providing patients with information about treatments, symptoms, resources, and services, as well as suggestions for coping with cancer.

*Coping skills training* includes interventions such as instruction in relaxation and stress management, assertive communication, cognitive restructuring and problem solving, counselling, and the planning of pleasant activities.

*Cognitive-behavioural therapy* is a type of psychotherapeutic treatment that helps patients understand the thoughts and feelings that influence behaviours. It can be employed in the treatment of cancer patients to eliminate nausea and to control anxiety, pain, and depression.

**Declaration of Interest:**

Dr Andritsch has reported no conflicts of interest.

**Further Reading**


Mucocutaneous Changes

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Introduction

The mucosal tissues and the skin are commonly affected by cancer treatment including conventional chemotherapy and targeted therapy, as well as radiation therapy. Antineoplastic therapies have, to a greater or lesser extent, mucocutaneous adverse events in common. They are defined as side effects affecting the skin, hair, nail, nail bed, eyes, nostrils, mouth, throat, alimentary tract, and external genitals. This chapter will discuss some of the more prominent mucocutaneous toxicities in oncology patients. We discuss the presentation and management of mucositis associated with chemotherapy and radiation therapy, preventive measures to keep the skin in a healthy condition while on targeted therapy, and paronychia. Management options for other skin complaints can be assessed at ESMO’s OncologyPRO portal (http://oncologypro.esmo.org/).

Mucositis

*Epidemiology*

Mucosal damage due to cancer therapy can affect the entire gastrointestinal (GI) tract. Oral mucositis was reported in 10–40% of patients receiving conventional chemotherapy for solid tumours, 80% of patients receiving head and neck radiotherapy, and 89% of patients undergoing high-dose chemotherapy prior to haematopoietic stem cell transplantation. Of 599 patients receiving chemotherapy for solid tumours or lymphoma,
51% developed oral and/or GI mucositis. Oral mucositis developed in 22% of 1236 cycles of chemotherapy, GI mucositis in 7% of cycles, and both oral and GI mucositis in 8% of cycles.

**Clinical signs and symptoms**

Oral mucositis may present as erythema, erosion, or ulceration of the oral mucosa. Lesions are typically limited to non-keratinised areas of the mouth such as the ventral and lateral tongue, buccal mucosa, and soft palate. The severity of mucositis lesions is directly proportional to the dose of chemotherapy or radiotherapy. The most common symptom of oral mucositis is mouth pain. GI mucositis can present as abdominal pain, bloating, or diarrhoea. In patients receiving conventional chemotherapy, mucositis may resolve between 10 to 14 days after cessation of chemotherapy, while in patients who have received high-dose radiation, several weeks may be needed for healing.

**Morbidity**

Mucositis can be very painful and can significantly affect nutritional intake, mouth care, and quality of life (QoL). Secondary infection of mucositis lesions can cause systemic sepsis, especially during immunosuppression. Severe mucositis has been correlated with systemic infection and transplant-related mortality. During chemotherapy for solid tumours or lymphoma, the rate of infection was doubled during cycles with mucositis and was directly proportional to mucositis severity. A dose reduction of chemotherapy was twice as likely after cycles with mucositis. In patients receiving head and neck radiation therapy, mucositis can lead to severe pain, weight loss, hospitalisation, and unplanned breaks in radiation therapy. Thus, severe mucositis can be a dose-limiting toxicity of cancer therapy.

**Economic impact**

Supportive care measures for mucositis include analgesics, liquid diet supplements, feeding through gastrostomy tubes or total parenteral nutrition (TPN), fluid replacement, and management of infections. In a study of chemotherapy patients, the cost of hospitalisation was US$3893 per cycle.
without mucositis, $6277 per cycle with oral mucositis, and $9132 per cycle with both oral and GI mucositis. In head and neck cancer patients receiving radiation therapy, oral mucositis was related to an increase in costs of US$1700 to $6000 per patient, depending on mucositis severity.

**Management**

The management of mucositis has traditionally been focused on alleviating mucositis symptoms to ensure patient comfort and allow the continued delivery of cancer therapy. This includes management of pain, as well as management of other symptoms such as diarrhoea. While such symptomatic care continues to be very important, there are also some targeted interventions that can be used to prevent or reduce the severity of mucositis. The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has recently updated evidence-based clinical practice guidelines for oral and GI mucositis. These guidelines include recommendations (based on higher level evidence), and suggestions (based on lower level evidence). In cases of inadequate or conflicting evidence, a determination of “no guideline possible” was made. The MASCC/ISOO Mucositis Guidelines are presented in Tables 1 and 2. The MASCC/ISOO Mucositis Guidelines have also been included in mucositis guidelines published by other organisations including the European Society for Medical Oncology (ESMO), the Oncology Nursing Society (ONS), and the US National Comprehensive Cancer Network (NCCN).

**Skin Complaints**

At present, evidence for the effectiveness of the management options for skin complaints is lacking, and the effect of the skin complaints on health-related QoL and adherence remains poorly understood. Because of the paucity of adverse event studies from which evidence-based advice for these complaints can be formulated, we have to base our recommendations on other sources. There are many reports about successful management and expert opinion consensus available that can be applied until more evidence is available. Since preventive measures are key in the management of targeted therapy-associated skin complaints,

(Level of Evidence for each guideline is in brackets following the guideline statement)

<table>
<thead>
<tr>
<th>RECOMMENDATIONS IN FAVOUR OF AN INTERVENTION (i.e. strong evidence supports effectiveness in the treatment setting listed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The panel recommends that 30 minutes of oral cryotherapy be used to prevent oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy (II).</td>
</tr>
<tr>
<td>2. The panel recommends that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to prevent oral mucositis (at a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a haematological malignancy (II).</td>
</tr>
<tr>
<td>3. The panel recommends that low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimetre treated with the required time to a tissue energy dose of 2 J/cm²), be used to prevent oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy, with or without total body irradiation (II).</td>
</tr>
<tr>
<td>4. The panel recommends that patient-controlled analgesia with morphine be used to treat pain due to oral mucositis in patients undergoing HSCT (II).</td>
</tr>
<tr>
<td>5. The panel recommends that benzydamine mouthwash be used to prevent oral mucositis in patients with H&amp;N cancer receiving moderate-dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUGGESTIONS IN FAVOUR OF AN INTERVENTION (i.e. weaker evidence supports effectiveness in the treatment setting listed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The panel suggests that oral care protocols be used to prevent oral mucositis in all age groups and across all cancer treatment modalities (III).</td>
</tr>
<tr>
<td>2. The panel suggests that oral cryotherapy be used to prevent oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT (III).</td>
</tr>
<tr>
<td>3. The panel suggests that low-level laser therapy (wavelength around 632.8 nm) be used to prevent oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for H&amp;N cancer (III).</td>
</tr>
<tr>
<td>4. The panel suggests that transdermal fentanyl may be effective to treat pain due to oral mucositis in patients receiving conventional and high-dose chemotherapy, with or without total body irradiation (III).</td>
</tr>
<tr>
<td>5. The panel suggests that 0.2% morphine mouthwash may be effective to treat pain due to oral mucositis in patients receiving radiation therapy for H&amp;N cancer (III).</td>
</tr>
<tr>
<td>6. The panel suggests that 0.5% doxepin mouthwash may be effective to treat pain due to oral mucositis (IV).</td>
</tr>
<tr>
<td>7. The panel suggests that systemic zinc supplements administered orally may be of benefit to prevent oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (III).</td>
</tr>
</tbody>
</table>
**Table 1 (Continued)**

### RECOMMENDATIONS AGAINST AN INTERVENTION (i.e. strong evidence indicates lack of effectiveness in the treatment setting listed)

<table>
<thead>
<tr>
<th></th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The panel recommends that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste not be used to prevent oral mucositis in patients receiving radiation therapy for H&amp;N cancer (II).</td>
</tr>
<tr>
<td>2.</td>
<td>The panel recommends that iseganan antimicrobial mouthwash not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II), or in patients receiving radiation therapy or concomitant chemoradiation for H&amp;N cancer (II).</td>
</tr>
<tr>
<td>3.</td>
<td>The panel recommends that sucralfate mouthwash not be used to prevent oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for H&amp;N cancer.</td>
</tr>
<tr>
<td>4.</td>
<td>The panel recommends that sucralfate mouthwash not be used to treat oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (II) for H&amp;N cancer.</td>
</tr>
<tr>
<td>5.</td>
<td>The panel recommends that intravenous glutamine not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).</td>
</tr>
</tbody>
</table>

### SUGGESTIONS AGAINST AN INTERVENTION (i.e. weaker evidence indicates lack of effectiveness in the treatment setting listed)

<table>
<thead>
<tr>
<th></th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The panel suggests that chlorhexidine mouthwash not be used to prevent oral mucositis in patients receiving radiation therapy for H&amp;N cancer (III).</td>
</tr>
<tr>
<td>2.</td>
<td>The panel suggests that granulocyte–macrophage colony-stimulating factor (GM-CSF) mouthwash not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (II).</td>
</tr>
<tr>
<td>3.</td>
<td>The panel suggests that misoprostol mouthwash not be used to prevent oral mucositis in patients receiving radiation therapy for H&amp;N cancer (III).</td>
</tr>
<tr>
<td>4.</td>
<td>The panel suggests that systemic pentoxifylline, administered orally, not be used to prevent oral mucositis in patients undergoing bone marrow transplantation (III).</td>
</tr>
<tr>
<td>5.</td>
<td>The panel suggests that systemic pilocarpine, administered orally, not be used to prevent oral mucositis in patients receiving radiation therapy for H&amp;N cancer (III), or in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).</td>
</tr>
</tbody>
</table>

Abbreviations: HSCT = haematopoietic stem cell transplant; H&N = head and neck.
**Table 2** MASCC/ISOO Clinical Practice Guidelines for Gastrointestinal Mucositis (not including the oral cavity). From Lalla RV, et al and The Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014; 120:1453–1461, with permission

(Level of Evidence for each guideline is in brackets following the guideline statement)

<table>
<thead>
<tr>
<th>RECOMMENDATIONS IN FAVOUR OF AN INTERVENTION (i.e. strong evidence supports effectiveness in the treatment setting listed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The panel recommends that intravenous amifostine be used, at a dose of ≥340 mg/m², to prevent radiation proctitis in patients receiving radiation therapy (II).</td>
</tr>
<tr>
<td>2. The panel recommends that octreotide, at a dose of ≥100 μg subcutaneously twice daily, be used to treat diarrhoea induced by standard- or high-dose chemotherapy associated with HSCT, if loperamide is ineffective (II).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUGGESTIONS IN FAVOUR OF AN INTERVENTION (i.e. weaker evidence supports effectiveness in the treatment setting listed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The panel suggests that intravenous amifostine be used to prevent oesophagitis induced by concomitant chemotherapy and radiation therapy in patients with non-small cell lung carcinoma (III).</td>
</tr>
<tr>
<td>2. The panel suggests that sucralfate enemas be used to treat chronic radiation-induced proctitis in patients with rectal bleeding (III).</td>
</tr>
<tr>
<td>3. The panel suggests that systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to prevent radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (II).</td>
</tr>
<tr>
<td>4. The panel suggests that probiotics containing Lactobacillus species be used to prevent diarrhoea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (III).</td>
</tr>
<tr>
<td>5. The panel suggests that hyperbaric oxygen be used to treat radiation-induced proctitis in patients receiving radiation therapy for a solid tumour (IV).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RECOMMENDATIONS AGAINST AN INTERVENTION (i.e. strong evidence indicates lack of effectiveness in the treatment setting listed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The panel recommends that systemic sucralfate, administered orally, not be used to treat gastrointestinal mucositis in patients receiving radiation therapy for a solid tumour (I).</td>
</tr>
<tr>
<td>2. The panel recommends that 5-acetyl salicylic acid (ASA), and the related compounds mesalazine and olsalazine, administered orally, not be used to prevent acute radiation-induced diarrhoea in patients receiving radiation therapy for a pelvic malignancy (I).</td>
</tr>
<tr>
<td>3. The panel recommends that misoprostol suppositories not be used to prevent acute radiation-induced proctitis in patients receiving radiation therapy for prostate cancer (I).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUGGESTIONS AGAINST AN INTERVENTION (i.e. weaker evidence indicates lack of effectiveness in the treatment setting listed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None.</td>
</tr>
</tbody>
</table>
these are discussed, as well as one example of a skin reaction, paronychia. Recommendations for other skin complaints can be assessed at the ESMO OncologyPRO portal, including the medical education programmes Management of Skin Toxicities from EGFR Inhibitor Therapies and Dermatological Side Effects of Multikinase Inhibitors.

**Preventive measures**

Prophylactic measures, early detection, and early intervention are of the utmost importance for skin complaints of targeted therapy. The primary objectives of adverse event management strategies are: to avoid interference in the patient’s daily living activities; to maintain or restore patient comfort and QoL; and to maintain therapy for as long as possible. Patients should be educated on the most widely accepted best practices for managing adverse events.

Ideally, all patients should be informed at initiation of their therapy about the measures they should take to keep their skin in a healthy condition. Targeted agents dry the skin, therefore use of a fatty cream is recommended to provide oil and maintain hydration of the skin. However, petrolatum (petroleum jelly) is too fatty and can clog the sebaceous glands. A cream consisting of the correct ratio of water and oil should be used. The different topical products for the skin, depending on their composition, are divided into petrolatum, ointment, body butter, balm, cream, lotion, and gel; petrolatum is the most oily, and gel the most watery, of these products. In general, products with a higher water content are easier to spread and better penetrate the skin. Petrolatum should be applied only to areas with few sebaceous glands, such as fissures on the hands/fingers and feet/heels.

In addition, patients should also be instructed about moisturising recommendations. A liberal amount of moisturising cream to at least the face, chest, hands, and feet should be applied regularly throughout the day and generously at bedtime. Thick emollient creams should be applied gently and immediately after washing.

Furthermore, infections may develop at a later stage due to skin or mucosal injury, and special attention is required to avoid or decrease
the risk of infection. In case of an infection, sterile swabs with cotton or rayon tips are most commonly used for obtaining a culture. If the wound is moist, a dry swab may be used straight from the packaging. If the wound is dry, then the swab tip should be moistened with sterile saline to increase the chance of disinfecting the site.

Patients should be monitored in treatment cycles 1 and 2 actively every week. From cycle 3 onwards, actively monitor every cycle or every 4 weeks, depending on the treatment schedule. Treating symptoms early may prevent them from becoming worse. Consider dose modifications for non-life-threatening adverse events only after management failure and after consulting with the patient. Avoid two dose modifications for one non-life-threatening adverse event! In many cases, a single dose reduction or a dose delay will be sufficient; therefore, it is essential that the adverse event is treated.

**Paronychia**

Paronychia, an infectious process in the tissues adjacent to a nail on a finger or toe, has been reported with EGFR (epidermal growth factor receptor) and mTOR (mammalian target of rapamycin) inhibitors. Paronychia affects the area around the fingernail or toenail, and occurs in the toes more often than in the fingers. It is unknown why some fingers are affected by targeted therapy and others are not. Paronychia presents as erythema and oedema of the nail bed and folds, sometimes accompanied by a warm feeling of the skin. The infected nail fold may be swollen, inflamed, and tender. As paronychia can be painful, even simple manual work may be difficult. Pain can also impede the wearing of shoes and normal ambulation. In some cases, only sandals can be worn. The lesions may also bleed easily upon exposure to trauma or ill-fitting shoes. In addition, paronychia can worsen in colder seasons.

The onset of paronychia is generally after one to two months of treatment with the targeted agent. In addition, patients who have had previous nail toxicity due to cytotoxic chemotherapy may be at increased risk. Paronychia may also progress to painful, lateral nail fold pyogenic granuloma-like lesions. Pyogenic granuloma is a vascular lesion that may occur on both mucosa and skin, and appears as an overgrowth of tissue.
Clinical signs and symptoms

Assessment of nail beds of the hands and feet should be part of the full body skin exam at baseline, and at every visit. Crusted lesions with inflammation of the nail fold usually appear as a first sign of paronychia. Paronychia, including pyogenic granuloma, is associated with both subjective and objective components: burning sensation, skin pain, skin tenderness, crust formation, cuticle disruption, nail fold oedema, nail plate separation or discharge (onycholysis), periungual abscesses, pyogenic granuloma, erythema, and elevated skin temperature.

Management

If paronychia occurs, treatment is started with the goal of decreasing inflammation, reducing the extent of granulation tissue, and preventing superinfection. With mild paronychia, topical treatment of the affected fingers or toes will be sufficient. In more severe cases, treatment involves a combined approach, with topical management and systemic antimicrobials.

The patient should continue the use of antiseptic soaks 2–3 times a day for 15–20 minutes each time (1:1 vinegar in warm water, diluted bleach [0.005%], povidone-iodine 1:10, potassium permanganate 1:10 000). In addition, povidone-iodine-based ointments and oral antibiotics (tetracyclines if not superinfected, otherwise consider oral quinolones) for 7 to 14 days may be prescribed. In resistant infections, a specimen for culture of the infected area should be taken to determine antibiotic sensitivity and resistance. The antibiotic may be adjusted according to the result of the culture (antibiogram). In case of an infection caused by yeast or fungus (Candida), antifungals may be prescribed. Ultrapotent topical corticosteroids may be applied to reduce inflammation.

Painful paronychia may be treated with topical anaesthetics such as lidocaine HCl gel 4%. If topical anaesthetics are insufficient, oral analgesics such as acetaminophen/paracetamol or a non-steroidal anti-inflammatory drug (NSAID) may be prescribed.

Pyogenic granuloma can be treated by electro- or chemical cauterity with liquid nitrogen, silver nitrate, or trichloroacetic acid. Silver nitrate applicators should be used once or twice a week. Surgical nail removal is
generally contraindicated, since the skin overgrowth can be managed with cauterisation. Although the level of evidence is weak for partial or full nail avulsion, it may be recommended in extreme cases, if other treatments fail.

Declaration of Interest:

Dr Lalla has received research funding from BioAlliance Pharma and has served as a Consultant for Sucampo AG, iNova Pharmaceuticals, Fera Pharmaceuticals, and Phillips Gilmore Oncology Communications. Ms Boers-Doets has received honoraria from or been a consultant or speaker with Amgen, AstraZeneca, Bayer Pharmaceuticals, Boehringer Ingelheim, Eusa Pharma, GlaxoSmithKline, Merck Serono, Merck Sharp & Dohme, Nordic Pharma, Takeda, Novartis, Pfizer, and Roche.

Further Reading

Mucositis


McGuire DB, Fulton JS, Park J, et al; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of


Skin complaints


Dermatological Side Effects of Multikinase Inhibitors – Medical Education Programme. European Society for Medical Oncology, 2014. Available at: http://
oncologypro.esmo.org/Guidelines-Practice.

Mucocutaneous Changes
Gastrointestinal Sequelae

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Department of Gastroenterology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

L. Smith
Macmillan Cancer Support, London, UK

J. Maher
Macmillan Cancer Support, London, UK

Introduction

Gastrointestinal (GI) problems such as nausea, vomiting, diarrhoea, and constipation are very common during and immediately after systemic cancer treatments. The (often prophylactic) management of these is usually the responsibility of the medical oncology team. Sometimes, patients present as emergencies and may be initially managed by hospital Emergency Departments or an acute/emergency oncology service. Guidelines and protocols for acute GI problems have been produced by organisations such as ESMO and the National Comprehensive Cancer Network. Oncologists are therefore familiar with managing these acute issues, and so we have not covered them in depth in this chapter. However, cancer care and primary care professionals tend to be much less familiar with long-term or late-onset GI effects of treatments, especially where systemic therapies have been used in conjunction with surgery and/or radiotherapy for cancers of the upper and lower GI tract and the pelvic area. Despite the potential for very serious adverse effects on patients’ quality of life, this continues to be an under-recognised area of cancer rehabilitation and follow-up. This chapter therefore focuses on the key management strategies for chronic problems.
## Potential GI Side Effects

Table 1 shows the range of potential GI side effects that may arise acutely, subacutely, or chronically after cancer treatment.

**Table 1** Presentation of Gastrointestinal Side Effects: Acute, Subacute Or Chronic. Republished with permission of BMJ Publishing Group Ltd, from Andreyev HJN, et al. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. Gut 2012; 61:179–192; permission conveyed through Copyright Clearance Center, Inc.

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Acute</th>
<th>Subacute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Bacterial</td>
<td>Small intestinal bacterial overgrowth (SIBO)</td>
<td>SIBO</td>
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<tr>
<td></td>
<td>Viral</td>
<td></td>
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<tr>
<td></td>
<td>Fungal</td>
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<td></td>
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<tr>
<td></td>
<td>Opportunistic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation (acute)</td>
<td>Neutropenic enterocolitis</td>
<td>Graft versus host disease</td>
<td>Graft versus host disease</td>
</tr>
<tr>
<td></td>
<td>Perforation</td>
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<tr>
<td></td>
<td>Haemorrhage</td>
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<tr>
<td></td>
<td>Graft versus host disease</td>
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<td></td>
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<tr>
<td></td>
<td>Pancreatic insufficiency</td>
<td></td>
<td></td>
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<tr>
<td>Ischaemic/fibrotic</td>
<td>Gastric outflow obstruction</td>
<td>Graft versus host disease</td>
<td>Biliary strictures</td>
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<td></td>
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<td></td>
<td>Bowel obstruction</td>
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<td></td>
<td></td>
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<td>Enteropathy and loss of</td>
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<td></td>
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<td>Graft versus host disease</td>
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<td>Pancreatic insufficiency</td>
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<td>Metabolic</td>
<td>Malabsorption</td>
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<td>Malabsorption</td>
</tr>
<tr>
<td></td>
<td>Hepatic insufficiency</td>
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<tr>
<td>Vascular (ischaemia)</td>
<td>Mesenteric vascular insufficiency</td>
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<td>Enteropathy and loss of</td>
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<tr>
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<td>physiological function</td>
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<td>Mesenteric thrombosis</td>
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<td></td>
<td>Veno-occlusive disease</td>
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<tr>
<td>Vascular (proliferative)</td>
<td>Telangiectasia causing bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Effect on Patients

The many side effects listed in Table 1 produce unpleasant and disabling symptoms that can be highly disruptive to a person’s daily life. Dealing with the physical effects of GI dysfunction causes many difficulties, such as problems with eating/nutrition, requiring use of faecal incontinence products, coping with severe pain, washing of soiled clothing and bedding, or needing frequent or lengthy visits to the toilet. The psychological and social impact of having to cope with very unpredictable
and embarrassing symptoms can be severe, to the extent that people become “prisoners in their own homes” and feel unable to work, go on holiday, or enjoy a normal social life. The effect on partners, family, and friends should not be under-estimated, as they too may have to share in the restrictions to daily life and any financial hardship, while trying to support the patient when professional help is unavailable.

Testimonies from people affected by chronic GI problems reveal the extent of issues that may occur; however, research indicates that many people are unwilling to tell their oncology team about issues that they find embarrassing to talk about, think nothing can be done about them, or think that the doctor is interested only in their cancer cure. The onus is, therefore, on cancer care professionals to ensure that patients and carers are aware and informed about the potential GI side effects of treatments, and that they know who to contact should these problems arise. More importantly, patients should be questioned regularly about GI problems, so that early interventions can be initiated. Simple questions such as: “Do you have any gastrointestinal symptoms that prevent you from living a full life?” can help to overcome patients’ embarrassment and reluctance to mention distressing symptoms.

Pathophysiology

Systemic therapies such as cytotoxic chemotherapy, hormonal therapy, and biological agents directly affect the GI tract. Inflammation, oedema, atrophy, and ulceration are common acute side effects of treatment which can cause considerable pain and discomfort for patients. Immunosuppression plus increased bowel permeability increases the risk of septicaemia. Alterations to the bacterial flora in the gut may result in small intestinal bacterial overgrowth (SIBO). Some agents may cause the reactivation of hepatitis B infection. Bile acid malabsorption, pancreatic insufficiency, steatosis, and severe sinusoidal obstruction syndrome are also potential acute side effects of treatment.

Increasingly, cancer treatment involves the combination of one or more systemic therapies with surgery and/or radiotherapy. Both surgery and radiotherapy are also well-known causes of immediate and long-term effects
on GI function, and treatment combinations are constantly evolving. The stem cell transplant treatment regimen may result in graft versus host disease (GVHD), which can also adversely affect the GI tract. Pre-existing non-malignant GI diseases may also be exacerbated by cancer treatment, or revealed during the cancer diagnostic testing process. In these circumstances, it is difficult to ascribe a patient’s GI problems to one form of treatment or another. Therefore, every member of the cancer multidisciplinary team should have responsibility for recognising and managing treatment-induced GI problems that are probably multifactorial. A key element is having access to expert advice from a gastroenterology team.

**Prevention and Self-management of GI Problems**

GI problems during and after cancer treatment may be minimised by ensuring that patients and their carers fully understand the effect on the GI function, how to manage minor symptoms themselves, and when and where to seek help. A personalised approach to information provision is recommended, so that patients and carers are offered and are able to repeatedly access high-quality advice and support in a format that they find useful and relevant. This should be offered at several time points before, during, and after treatment.

The importance of taking appropriate precautions against GI infections when immunosuppressed and of seeking urgent medical help for red flag symptoms should be stressed clearly for patients. At the end of treatment and during follow-up, the risk of long-term effects must be highlighted, to allow appropriate referral for patients who develop late-onset symptoms even after discharge from oncology services. For some, patient support groups are highly beneficial, especially for those with chronic problems, where tips for coping with problems can be shared.

With the right advice and support, patients can often self-manage certain long-term problems with techniques such as:

- Dietary changes, such as low-fat diet, low-fibre diet, lactose-free diet
- Pelvic floor exercises
- Biofeedback methods
However, a chronic symptom (such as diarrhoea) may be the result of several different diagnoses, and it is important that all causes are investigated (see the section on Chronic GI Side Effects).

**Clinician-led Management of Acute GI Side Effects**

Acute GI side effects can rapidly lead to life-threatening situations. The urgent management of neutropenic sepsis, enterocolitis, haemorrhage, perforation, ischaemia, infarction, thrombosis, sinusoidal obstruction syndrome, vomiting, and bowel obstruction are covered in a number of publications (see Further Reading).

Where gastroenterologists (i.e. non-cancer specialists) are involved in the management of urgent cases, it is important that they are aware of the cancer treatment regimen, as the bioavailability of targeted cancer therapies may be altered by GI treatments.

Key facts for gastroenterological management of acute GI syndromes during and after cancer treatments are:

- Urgent cross-sectional imaging may help assessment and management
- Perform early upper GI endoscopy and duodenal biopsies and duodenal aspirate and lower GI endoscopy with biopsies for diarrhoea
- Flexible sigmoidoscopy rather than colonoscopy is usually adequate initially
- Always consider taking biopsies and asking for histological evidence of viral infection, especially if multiple ulcers are seen, even if there has been bleeding
- Ensure platelet support is available before endoscopic intervention when the platelet count is below $80 \times 10^9$
- Avoid biopsies from an area of obvious radiation-induced change unless absolutely necessary
- Colonoscopy is contraindicated in neutropenic enterocolitis
- Infections in the neutropenic patient can kill quickly; early empirical treatment may be required
- Seek specialist help early
Clinician-led Management of Chronic GI Side Effects

Cytotoxic chemotherapy, biological agents, and hormonal therapy used alone may affect the GI tract long term, but this has not been well studied. Some of these patients may have problems which continue long after systemic treatment, or are late-onset or are as a result of hormonal therapy – constipation, diarrhoea, pain, flatulence, and bloating have been reported. It is likely that SIBO is the primary cause, which can be treated with antibiotics (see below).

If radiotherapy (to the pelvic area or upper GI area) and/or surgery (to the upper/lower GI tract) is used in conjunction with chemotherapy, then the complex interactions of these interventions on the GI tract can often be very disruptive to normal physiology. While most patients will not experience long-term problems, a significant number have their quality of life affected by chronic symptoms (Table 2), and close monitoring will be needed.

There has been a commonly held but erroneous view that nothing can be done for patients with chronic GI problems, and, as a result, oncologists rarely make referrals to gastroenterology. Evidence is now available that patient outcomes can be improved by having a referral route from oncology to a gastroenterologist who uses a systematic approach to diagnosing and treating post-cancer bowel dysfunction.

Each symptom has a number of potential diagnoses. For example, chronic diarrhoea may have several different causes (see Table 3). Chronic dysphagia, retching, and nausea can also have multiple causes, including stricture, inflammation, infection, or abnormalities in the motility of the upper GI tract.

A systematic approach to identifying each symptom and then conducting the appropriate battery of tests in order to make accurate GI diagnoses has proved to be clinically effective in the ORBIT trial. This approach has several advantages – firstly, it highlights that significant GI problems can be adequately treated; secondly, it is a reminder that several different conditions may need to be treated before symptoms resolve themselves; and thirdly, it supports the premise that most patients can be managed by a suitably trained and supported nurse.
The first step is to take an accurate history of cancer treatments and to understand the full range of symptoms (not just GI) that the patient is experiencing through the use of standardised, holistic needs assessment. The patient’s diet and bowel habits should also be fully elucidated by using bowel and food diaries for at least a week. This may help to identify any food triggers for certain symptoms, or whether there is excessive intake of nutritional supplements, fibre, fat, or alcohol.
For each symptom, a range of investigations will be required. Space does not permit the full description of the National Cancer Survivorship Initiative (NCSI) algorithm, which is currently under review. The current version is available at www.ncsi.org.uk (see Further Reading).

Basic investigations such as haematological and biochemical profiles and inflammatory and tumour markers should be carried out. Vitamin B12 levels, thyroid function test, coeliac screen, selenium homocholic acid taurine (SeHCAT) scan, and upper/lower endoscopy (as appropriate) are useful.

Treatments will vary according to the abnormalities found, which may be multiple. These may include:

- Loperamide for rapid transit
- Cholestyramine or colesevelam for bile salt malabsorption
- Antibiotics for SIBO (such as metronidazole, tetracyclines, quinolones, and rifaximin), although most data supporting these are from small, open-label trials
Specialist dietetic support is an important component of managing patients who may have poor or imbalanced nutritional intake, as well as providing support for weight loss or weight gain, both of which are common after cancer treatment. They will also advise on time-limited trials of specific diets, such as those low in carbohydrates (for carbohydrate malabsorption), low in lactose (if lactose intolerance), or low FODMAP (fermentable oligonucleotides, disaccharides, monosaccharides, and polyols, for irritable bowel syndrome).

A helpful series of cases studies are described by Muls et al (2013).

Psychological counselling may be needed; for example, where severe GI problems have been the cause of breakdown of relationships, loss of confidence, anxiety, or depression.

Specialist care of people with GI problems due to GVHD should follow appropriate guidance, such as the British Committee for Standards in Haematology guidelines.

**Conclusion**

There is a growing body of evidence that a significant number of people experience poor quality of life for years after cancer treatment, due to unresolved GI problems such as diarrhoea, faecal incontinence, bleeding, and pain. Oncology teams and primary care physicians have a responsibility to ensure that potential side effects are regularly discussed with patients, and that diagnosis and treatment of symptoms are a routine part of the post-treatment follow-up of all cancer patients. Patients can be encouraged to self-manage certain symptoms with dietary changes and exercises. However, a clear referral route to gastroenterology is essential to ensure that chronic problems are accurately diagnosed with a systematic, algorithmic method. Patients who are successfully treated often report that they have “got their life back”.

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Further Reading
Introduction

To put the risk, incidence, diagnosis, and treatment of urological sequelae of oncological and urological oncological treatment in one frame is not easy. There are differences in tumour grade and type, differences in patient age and general condition, and differences in treatment modalities and application techniques to be considered. Finally, the clinical history of the individual patient will determine which complications exist and how they should preferably be managed.

Radiotherapy

Radiation Cystitis

A number of patients treated with radiotherapy in the pelvic region develop lower urinary tract (LUT) symptoms. Radiotherapy is more likely to cause radiation cystitis in patients being treated for prostate cancer than for bladder cancer. After external beam therapy (70–78 Gy), up to 9% develop radiation-induced cystitis with recurrent haematuria. Zelefsky et al (1999) described acute grade 2 problems in 28% and grade 3 in 1/772. In terms of late complications, 9% grade 2 and 0.5% grade
3 problems were found using the Radiation Therapy Oncology Group (RTOG) criteria (Table 1).

**Table 1**  
**Acute and Chronic Toxicity Grading of Radiation Therapy on the Lower Urinary Tract of the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Frequency of urination or nocturia twice pre-treatment habit / dysuria, urgency not requiring medication</td>
<td>Slight epithelial atrophy; minor telangiectasia (microscopic haematuria)</td>
</tr>
<tr>
<td>2</td>
<td>Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic (e.g. Pyridium)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Frequency with urgency and nocturia hourly or more frequently / dysuria, pelvis pain or bladder spasm requiring regular; frequent narcotic / gross haematuria with/without clot passage</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Haematuria requiring transfusion / acute bladder obstruction not secondary to clot passage, ulceration or necrosis</td>
<td></td>
</tr>
</tbody>
</table>

The acute reaction is an inflammatory response, with tissue oedema and hyperaemia occurring within 4–6 weeks. In the second phase, necrosis of the vascular endothelium and perivascular fibrosis may appear. The obliterating endarteritis increases bleeding tendency and makes the bladder wall more sensitive to infection, which could result in fistula formation.

With recurrent and progressive ischaemia, the bladder wall develops fibrosis and shrinks. This process may develop 10 or more years after the radiation therapy.

**Signs and symptoms**

Radiation cystitis can cause symptoms of dysuria, urgency, urinary frequency, nocturia, haematuria/haemorrhage, recurrent infections, and pain. In the case of fistula formation, urinary leakage and pneumaturia can appear. Urethral stricture has been described and can worsen the symptoms.

Diagnosis is based on history, cystoscopy, and imaging. Quality of life...
can be measured with the Expanded Prostate Cancer Index Composite (EPIC) questionnaire.

**Treatment**

Haematuria can be treated with increased diuresis and/or bladder irrigation. The first step in treatment should be clot evacuation, which can be carried out by placing a two- or three-way wide-lumen bladder catheter and irrigating with water or sodium chloride solution.

*Cystoscopy* with eventual coagulation of the bladder wall is indicated in persistent haematuria, with bladder tamponade, or to confirm the cause of bleeding.

*Oral antifibrinolytic therapy* should be continued for several weeks, especially with persistent bleeding after endoscopic haemostasis.

**Intravesical therapy:**

- Aminocaproic acid 0.02% solution as a continuous bladder irrigation over a number of days
- Instillation with guanylhydrazone (GAG) products such as chondroitin sulphate or hyaluronic acid to restore the GAG protection layer on the bladder wall gives results comparable with those of hyperbaric oxygen
- Potassium aluminium sulphate (ALUM) 1% solution irrigation at 100–600 ml/h. Be prepared for toxic reactions
- Formalin 1% solution under anaesthesia for 10 min. Note: there are many side effects and vesicoureteral reflux must be ruled out before application
- Silver nitrate 0.25–1% solution as an alternative to formalin

*Hyperbaric oxygen therapy.* There is no generally accepted treatment regimen (examples from the literature: 10–74 treatments, 1.4–3 atm of oxygen, 75–130 min duration). There are few side effects, but long-term response rates differ in the literature: 30–74%, 80%, and 96%.
Salvage cystectomy. This is to be performed in very resistant cases only. The complication rate is high.

Sexual Problems

Erection

Erectile problems and other sexual dysfunctions can be a complication of radiation therapy. The onset is usually slow. In recent studies sexual dysfunction was reported by 35.9% and 43% at presentation. Radiotherapy adversely affected all aspects of sexual function. This is caused by interference with the blood supply and the nerves of the penis.

Treatment starts with phosphodiesterase-5 (PDE5) inhibitors, first as monotherapy, followed, if needed, by combination therapy with intra-corporeal injection of vasoactive drugs. Eventually, vacuum devices and surgery can be used. Comorbidities, such as cardiovascular disease and diabetes, should be taken into consideration. Positive results have been described in 66–77% of cases.

Fertility problems

These are discussed separately in the chemotherapy section.

Urinary Incontinence

At 15 years follow-up, urinary leakage rates appear comparable for radiotherapy and radical prostatectomy. Urinary frequency with episodes of leakage is most often seen. Decreased capacity of the bladder and bladder over-activity (OAB) can be present. Stress incontinence can be the consequence of radiotherapy after surgery in up to 12% of cases. Transurethral resection of the prostate (TURP) after radiotherapy is also a risk factor for incontinence. Urodynamic investigation can help refine the causal diagnosis.

Initial therapy encompasses pelvic floor exercises, biofeedback, and electrical stimulation. Behavioural modification with adaptation of drinking habits, voiding frequency, optimal weight, and medication changes related to incontinence are important. Bladder-relaxing drugs can be prescribed to treat OAB and urinary urgency/leakage. Surgery (artificial sphincter,
bladder augmentation, bulbourethral sling) or injection of bulking agents can be used, but carry a higher risk for complications after radiotherapy. Condom catheter drainage or diaper use can limit the negative social effects of incontinence.

**Brachytherapy**

Brachytherapy is used as a stand-alone treatment or in combination with external beam radiotherapy. Urological complications occur in approximately 2% of patients.

Acute complications include urinary retention, necessitating in-dwelling catheterisation and sometimes transurethral resection. The latter increases the risk of developing urinary incontinence. Acute irritative urinary symptoms disappear during follow-up in most patients. In high-dose rate (HDR) brachytherapy as monotherapy, acute grade 3 morbidity has been low. Late toxicity has been described: dysuria in 10.3%, haematuria in 1.3%, and urinary retention in 9%, but no urinary incontinence. Potency problems have been described in 14–66% of patients. Erectile dysfunction was found in 31% of cases.

Long-term health-related quality of life (HRQoL) was not different after brachytherapy, when compared with radical prostatectomy or external beam radiation. The addition of external beam radiotherapy to HDR brachytherapy does not seem to increase the risk for early and late grade 3 and 4 urological complications. Eight years after such treatment, erectile dysfunction was seen in 42% of cases.

**General Chemotherapy**

**Haemorrhagic Cystitis**

This is caused by acrolein, a metabolite of the oxazaphosphorine-alkylating agents cyclophosphamide and ifosfamide, which is excreted by the kidneys and concentrated in the bladder. After a single application, oedema and hyperaemia of the bladder urothelium can occur within hours of administration, progressing to ulceration and rupture of blood
vessels. Haemorrhage can be very severe. With repeated treatments, the bladder wall changes become irreversible and the bladder wall becomes less elastic, less compliant, and with a small bladder capacity. Induction of transitional cell carcinoma has been reported.

To prevent haemorrhagic cystitis, *aggressive hydration* and *mesna*, which neutralises the toxicity of the cyclophosphamide metabolite acrolein, may reduce the risk. However, mesna is ineffective once haemorrhagic cystitis has developed.

**Intravesical Chemotherapy**

Intravesical thiotepa has resulted in leukopenia in 8% to 54%, thrombocytopenia in 3% to 31%, and irritative voiding symptoms in 12% to 69% of cases. Close monitoring of blood counts prior to weekly instillations remains vital in preventing myelosuppressive complications. The complications associated with mitomycin C are mainly chemical cystitis and contact dermatitis. Additionally, allergic reactions have been documented. Most of these complications respond to cessation of therapy with application of topical steroids as needed. Toxicities associated with the use of doxorubicin, epirubicin, and ethoglucid are almost exclusively local and usually described as mild to moderate dysuria, urinary frequency, or urgency. Case reports of systemic reactions to doxorubicin are notable in that patients responded well to diphenhydramine and, in one severe case, epinephrine. Newer agents such as mitoxantrone are undergoing evaluation studies. The ideal agent, which would be highly effective and minimally toxic, is still to be developed.

Intravesical administration of Bacillus Calmette-Guerin (BCG), which is used as adjunctive therapy for superficial bladder cancer, can result in local and/or systemic infections, which require systemic therapy.

**Chemotherapy-induced Renal Dysfunction**

Nephrotoxicity is a known complication of several chemotherapeutic agents. Well-known side effects are cisplatinum-induced renal insufficiency, haemolytic–uraemic syndrome, antidiuretic hormone secretion problems, and more. Several treatments and trials for prevention have been described.
Fertility

Alkylating drugs and radiotherapy can have cytotoxic effects on the testicular germ tissue, and can cause erectile dysfunction or disruption of the hypothalamic–pituitary–gonadal axis. A recently updated guideline published by the American Society of Clinical Oncology (ASCO) stated that, as part of the process of education and informed consent that takes place before cancer therapy, healthcare providers should address the possibility of infertility with patients treated during their reproductive years (or with parents or guardians of children), and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. Sperm banking and cryopreservation are helpful tools to assist fertility later on. In most cases, two semen samples, produced through masturbation, are adequate. When infertility becomes an issue, intracytoplasmic sperm injection (ICSI) can be combined with in-vitro fertilisation (IVF) so that an individual sperm cell can be directly injected into an oocyte.

Sperm banking should be performed before or in the early phase of treatment to obtain the best results. A recent study has shown that, although the initial chemotherapy was considered to be low risk for infertility, prior to bone marrow transplantation, 39% of adolescent patients were azoospermic and another 15% were oligospermic. With an increasing percentage of paediatric oncology patients surviving their disease, the impact of cancer and cancer therapies on future reproductive health has become a major issue. For adolescents the issue of future reproduction is complicated by the fact that parents are required to give consent to treatments associated with fertility. For personal or cultural reasons, some parents prefer not to discuss masturbation with their son or are more concerned with the survival of their child than about their child’s future fertility. These situations create ethical dilemmas.

In prepubescent boys before spermache, some new, promising therapies are being developed. Testicular biopsies can be taken before the start of therapy, and spermatogonial stem cells, the cells responsible for lifelong production of sperm cells, can be used for cryopreservation. It is expected that for restoration of later fertility, these cells can be injected or grafted back into the patient, although more studies are necessary to
validate this concept. However, all of these techniques are quite costly. In addition, a recent survey showed that only 7% of cryopreserved sperm is actually used for assisted reproduction. Associated with this superfluous sperm is the ethical dilemma of sperm disposal. Fertility is an issue that is increasingly being recognised as a concern in boys and sexually active adults treated for cancer. However, there are solutions that warrant discussion between doctor, patient, and parent.

Urological Sequelae of Oncological Surgery

The risk of developing genitourinary dysfunction is highest after pelvic surgery. The autonomic plexus runs along the lateral sides of the rectum, branching off in the endopelvic fascia, and innervating the detrusor muscle and the bladder neck, alongside colon, rectum, prostate, vagina, and uterus. The pudendal nerves, except for some intrapelvic branches, run beneath the levator ani fascia. The location of these nerves in the operative area makes them susceptible to surgical damage and/or peripheral neuropathies, which may lead to urinary retention, incontinence, erectile and sexual dysfunction, and pelvic pain. Possible improvement during the postoperative period will depend on the type of lesion: neuropraxia from traction during surgery, or partial or complete denervation. Pelvic nerve damage may result in decreased detrusor activity with incomplete bladder emptying, need for Valsalva voiding, and even urinary retention. Injury of the hypogastric sympathetic fibres may cause decreased bladder compliance, bladder hyperactivity (beta-adrenergic denervation), or bladder neck incompetence (alpha-adrenergic denervation). In male patients, ejaculatory and erectile dysfunction may occur. The incidence of LUT dysfunction varies in the literature: from 8–70% after abdominoperineal rectum resection, 16–80% post-hysterectomy, and 20–25% after low anterior resection. Sexual dysfunction after rectal cancer surgery occurs in 76% of males and 59% of females. Following radical hysterectomy, decreased sexual satisfaction is reported due to decreased sexual interest, decreased lubrication, and dyspareunia, whereas other sexual and vaginal problems disappear over time.

A detailed preoperative urological history is mandatory, as pre-existing voiding difficulties, incontinence, or pain may predispose the patient
to increased urinary problems postoperatively. Postsurgical monitoring should address both current and pre-existing voiding complaints such as poor stream, hesitancy, interrupted voiding, sensation of incomplete bladder emptying, and signs of recurrent urinary tract infections, as well as storage symptoms such as urinary frequency, urgency incontinence, and pain. Cystometric evaluation allows for objective identification of underlying functional pathology. Uroflowmetry is often not accurate enough. More specialised tests such as pelvic floor needle electromyography (EMG) and sacral latency testing can assist with evaluation of the urethral sphincter and sacral reflex integrity, whereas electrical perception threshold determination in the bladder and urethra can help to identify peripheral neuropathy in the LUT. Although no clear guidelines exist on the specific time points of evaluation, urodynamic evaluation of symptomatic patients seems feasible after 4–6 weeks.

In case of incomplete bladder emptying or urinary retention, clean intermittent catheterisation is the preferred treatment method, indefinitely or until bladder contractility has improved. For storage symptoms due to decreased bladder compliance or insufficiency of bladder neck and/or urethral sphincter, medication (antimuscarinics, beta 3-adrenergic agonists, alpha-blocking agents) should be considered first. Since the extent of nerve damage during surgery is unknown and variable for different patients, the timecourse and extent of recovery is often unpredictable. This can make repeated evaluations useful over time. Treatment should be conservative, waiting at least 6 months before any surgical procedure is considered.

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**Further Reading**


Sexuality/Reproductive Issues

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Sexual Function

The potential changes in sexual function are increasingly seen as a relevant issue in oncology and as an object of clinical trials. Sexuality is a delicate topic and, in cancer patients, discussion of sexual function may seem inappropriate, when questions of survival are more important. However, sexual function is not a “lifestyle” problem, but a serious topic that requires attention. Sexual difficulties have a profound effect on one’s wellbeing and quality of life; they affect relationships and are associated with high levels of patient distress. Several factors must be taken into account when evaluating possible problems for sexual well-being: marital status, gender, age, ethnicity, and education. Older age and treatment with radiation have been consistently associated with impaired sexual function.

Sexuality issues potentially play a role in patients of all ages. Impairment of sexual function is found in adult oncological patients, but also in those who experienced cancer in childhood. This stresses the fact that patients need counselling at all ages.

Regarding sexuality and cancer, two differentiations must be made: (a) between male and female patients, and (b) between sexual organ-related and non-sexual organ-related cancers. In the past, research has been focused on sexual organ-related cancers, meaning prostate or testicular cancer in men and breast or gynaecological cancer in women. Among non-sexual organ-related cancers, most research has been performed on colorectal cancer. Sexual changes have also been observed in patients with lymphatic, head and neck, or lung cancer.
The quality of a relationship is important as a couple’s quality of life and marital satisfaction are linked. Glantz et al (2009) described the risk of being abandoned by a partner after surviving a severe disease to be significantly higher for women (20.8%) than for men (2.9%). When counselling a patient with cancer, the partner should not be neglected. This may lead to misunderstandings and a vicious cycle. Most women would also have appreciated their partner being informed about the possible treatment side effects on sexuality and relationships. Raising the topic of psychological, relational, and sexual functioning by healthcare providers, could help pave the way for an easier discussion on this topic, giving patients the opportunity to improve their coping strategies and reduce anxiety.

What can the physician do?

Cancer and cancer treatment can exacerbate former sexual function problems or may create new ones. As sexual dysfunction may be present in healthy individuals, these issues can often be overlooked initially. Awareness of these potential problems will help the patient to adapt to post-treatment difficulties. A pretreatment discussion of sexuality and intimacy provides a baseline for comparison with the subsequent re-evaluation during and after treatment.

People have different opinions on what is normal, so the doctor has to find out whether the patient has been content with his/her sexual life in the past. Questions like “Has anything changed in your sexuality after the diagnosis?” are very helpful to ascertain if there is any need to go deeper into this topic. Asking “How were your sexual desires recently? How was it on your partner’s side?” help to start the conversation. For some patients, the cancer diagnosis can be used as an excuse to refrain from being sexually active.

According to the Pfizer Global Study, 80% of cancer patients would like to have more information about the impact of their illness and subsequent therapy on their sexuality. Ninety-one percent of cancer patients were afraid to ask their treating physician about sexual problems, and 97% of doctors did not inform their patients about possible sexual dysfunction. This emphasises the need for intensive training in communication skills.
Physicians need to be aware that the way they approach, counsel and address sexual problems may be influenced by their own sexual experiences. When talking about sexuality issues, the doctor should try to use similar language to that of the patient and avoid, as best as they can, technical medical terminology. Somatic and psychological problems of sexual dysfunction are difficult to differentiate and are interdependent.

**Physical limitations**

Treatment of cancer is often multimodal, which makes it necessary to differentiate between the side effects of the various therapeutic interventions. Stigma may be obvious, such as alopecia, scars, a colostomy, or a urostomy. These can greatly alter the patient’s body image and self-esteem. Cancer of sexual organs, in particular, can lead to mutilating changes, including negative body image, decreased body function, or weight gain or loss. Women tend to agree to coitus, even when having pain, in order not to disappoint their partners. Some side effects of cancer treatment may be transient, but changes in sexual functioning, sense of self, and relationship interferences may be ongoing. Furthermore, the patient’s situation before the disease – for example, whether the integrity of the body has been an important aspect for the patient – has an impact on the coping process.

**Psychological issues**

It might be difficult to differentiate between problems related to the sequelae of the disease, fatigue, or depressive symptoms. Patients suffering from depression should be offered antidepressant therapy. Some of these agents can induce a lack of desire, but a severe depression can also impair sexual function. Specific pharmacotherapy may be necessary, often for only a few weeks, to improve the mental situation as well as the patient’s sexual desire. If overall well-being increases, sexual life and the patient’s relationship with their partner may benefit. In a randomised trial, breast cancer patients who received group intervention had a higher rate of symptom resolution regarding sexual problems.
Fertility Issues in Cancer Patients

One in 46 women and one in 69 men will develop cancer before reaching 40 years of age. Survival rates are higher in the population aged 15–44 years at diagnosis. The 5-year survival rate of 81% in this population group is linked with increased detection at an early stage and optimised treatment.

Highly toxic, multidrug chemotherapy and radiotherapy improve the outcome of young patients but lead to more severe side effects and long-term physical and psychological sequelae. Chemotherapy and radiotherapy are known to be gonadotoxic by damaging ovarian follicles in females and spermatogonia in males.

The risk of impaired fertility or permanent infertility after oncological treatment depends on a range of factors such as radiotherapy, chemotherapy agents (Table 1), and cumulative dosage of the medication. Age is another important factor: due to socioeconomic and lifestyle changes, especially in the Western world, parenthood is increasingly postponed to a later moment in reproductive life. Consequently, many cancer patients have not fulfilled their family planning at the time of diagnosis. Fertility concerns are, therefore, common in young patients.

Partridge et al (2004) showed that, in breast cancer patients, about 60% of women specify concerns of becoming infertile after treatment. Up to 29% reported that infertility concerns influence their decision-making process. As reported by Ruddy et al (2014), approximately 10% of breast cancer patients will discontinue endocrine therapy before the specified time and up to 1% will refuse to receive chemotherapy. There are still gender differences in providing fertility-related information. New data by Armuand et al (2012) show that about 80% of males received information about the impact of treatment on fertility and nearly 70% on fertility preservation methods. Twenty-five percent to 50% decided to store frozen sperm. In contrast, only 48% of females were counselled about the impact of treatment on fertility, 14% received information about fertility preservation, and only 2% to 10% underwent fertility preservation.

Directly after diagnosis, all young patients should be referred to a specialist because fertility preservation should be started before onset of oncological therapy to obtain optimal results.

<table>
<thead>
<tr>
<th>Gonadotoxicity</th>
<th>Chemotherapy in males and females</th>
<th>Radiotherapy in females</th>
<th>Radiotherapy in males</th>
</tr>
</thead>
</table>
| Low risk       | • Treatment protocols for Hodgkin’s lymphoma without alkylating agents  
• Bleomycin  
• Actinomycin D  
• Vincristine  
• Methotrexate  
• 5-Fluorouracil | • Pelvic or whole abdominal radiation dose 5–10 Gy in postpubertal girls  
• Pelvic or whole abdominal radiation dose 10–15 Gy in prepubertal girls  
• Craniospinal radiotherapy dose ≥25 Gy | • Testicular radiation dose 1–6 Gy from scattered pelvic or abdominal radiation  
• Craniospinal radiotherapy dose ≥25 Gy |
| Intermediate risk | • Cisplatin with low cumulative dose  
• Carboplatin with low cumulative dose  
• Doxorubicin | | |
| High risk       | • Cyclophosphamide  
• Ifosfamide  
• Melphalan  
• Busulfan  
• Nitrogen mustard  
• Procarbazine  
• Chlorambucil | • Total body irradiation for bone marrow transplant/ stem cell transplant  
• Pelvic or whole abdominal radiation dose ≥6 Gy in adult women  
• Pelvic or whole abdominal radiation dose ≥10 Gy in postpubertal girls  
• Pelvic or whole abdominal radiation dose ≥15 Gy in prepubertal girls | • Total body irradiation for bone marrow transplant/ stem cell transplant  
• Testicular radiation dose >2.5 Gy in adult men  
• Testicular radiation dose ≥6 Gy in prepubertal boys |
| Unknown risk    | • Taxanes  
• Oxaliplatin  
• Irinotecan  
• Monoclonal antibodies  
• Tyrosine kinase inhibitors | | |
Fertility preservation in women

In women, the oocyte pool is generated during foetal life, continuously declining as a result of intrinsic factors such as the initial pool and genetically determined oocyte apoptosis. This process is non-reversible. Extrinsic factors like chemotherapy and radiotherapy can accelerate the decline of the oocyte pool, leading to premature ovarian failure (POF) or infertility.

Fertility preservation methods help oncological patients to maintain the possibility of giving birth and the gonadal function. Several fertility preservation methods are well established, while others are still experimental.

Ovarian stimulation with gonadotrophins is a standard method and leads to multiple follicular growths. The obtained oocytes can be cryopreserved, either fertilised or unfertilised. The live birth rate per transfer using thawed frozen fertilised oocytes is \(~30–40\%\) in women under 35 years of age. The ovarian stimulation can be started at any time in the menstrual cycle, due to random-start antagonist protocols. More than one stimulation cycle can be performed if the delay of oncological therapy is reasonable. For women with hormone-positive tumours, letrozole administration during ovarian stimulation impedes high serum oestrogen levels, which are undesirable in this situation.

Due to new technologies like vitrification of unfertilised oocytes, the live birth rates per embryo transfer achieved with this method are almost 34%. This is an optional method for single women or young patients.

A second method of fertility preservation in young female cancer patients is suppression of ovulation function by administration of a gonadotrophin releasing hormone agonist (GnRHa). The published data are still controversial. A recently published meta-analysis shows promising results. The data prove a highly significant reduction in the risk of POF. In patients treated with GnRHa, only 22% developed POF, versus 37% in controls. Karimi-Zarchi et al (2014) reported a significant improvement in ovarian function after leuprorelin administration in hormone-negative breast cancer survivors, whereas the German ZORO study found no differences (Gerber et al 2011). Unfortunately, data are scarce regarding long-term fertility outcomes, such as pregnancy and successful birth rates.
Another option for fertility preservation is the freezing of ovarian tissue and retransplantation after cancer treatment. Retransplantation can be performed in an orthotopic or heterotopic site. After retransplantation, a temporary restoration of ovarian function has been observed in almost all cases. Thereafter, pregnancies can be achieved either by natural conception or by assisted reproduction methods. The expected pregnancy rate per transplantation is approximately 20%. To date, 24 live births have been reported in the literature. This is the only method of fertility preservation that can be offered to prepubertal girls. However, patients who have been diagnosed with systemic haematological malignancies are not eligible for this method, because of the risk of cancer retransmission.

In both sexes, germ cells are very sensitive to irradiation (Table 1). The extent of the damage is dependent on the number of treatments, the cumulative dose, and the radiation field. The gonadotoxic effect of radiotherapy is well known; a dose of 2 Gy applied to the gonadal area will reduce the oocyte pool by up to 50%, a dose of 6 Gy in adult women or 10 Gy in postpubertal girls leads to a high percentage of permanent gonadal damage.

In women receiving radiation therapy, transposition of ovaries or gonadal shielding are appropriate methods to reduce ovarian damage. The success rate of this method is approximately 50%.

In malignancies of the lower genital tract of low risk, conservative gynaecological surgery should be taken into consideration. Approximately 50% of women diagnosed with cervical cancer under the age of 40 years can be adequately treated by this method. Patients with borderline tumours of the ovaries or low-risk ovarian cancer can be offered a unilateral oophorectomy. Young (obese) females with well-differentiated endometrioid uterine cancer may be treated with progestins over possibly several years instead of hysterectomy. They need regular histological biopsies of the uterine cavity during this treatment. When the biopsy is proven benign, starting a pregnancy may be safe. In the future, uterine transplantation may become possible in young patients who have undergone hysterectomy.
**Fertility preservation in men**

In boys, spermatogonial stem cells located on the basement membrane of seminiferous tubules start to develop with the beginning of puberty. By age 13 to 14 years, effective spermatogenesis is usually established.

Chemotherapy and radiotherapy impair spermatogenesis (Table 1). The degree of damage is dependent on the agent applied, the dosage, and the fractionation schedule of radiation. If a population of germ stem cells survives therapy, regeneration of spermatozoa may continue for years. Sperm banking is an inexpensive and well-established method for fertility preservation prior to chemo- or radiotherapy, without delay of the subsequent treatment. Sperm can be obtained after ejaculation or, in cases of azoospermia, by biopsy of the testicle. In case of radiation, shielding of the testicles should be offered, as even a small dosage will lead to irreversible azoospermia.

Fertility-sparing surgery in testicular cancer may be offered to patients with low-risk cancer in the form of partial or unilateral orchidectomy, in cases where the contralateral testicle is not involved. Prepubertal boys may benefit from freezing testicular tissue. If diagnosed with azoospermia later in life, retransplantation of germ stem cells may lead to resumption of spermatogonia generation. Preclinical trials in this field are very promising; nonetheless, this method is still highly experimental.

**Evaluation of fertility after cancer treatment**

After successful treatment of the malignancy, many young survivors are interested in their reproductive potential. In women, regular menstrual cycles do not rule out reproductive dysfunction. The fertile lifespan is shortened, even if menstruation is restored after therapy. Ovarian function can be assessed by measurement of the antral follicle count, anti-Müllerian hormone, and follicular stimulating hormone (FSH) concentration during the early follicular phase. In men, reproductive function can be evaluated by semen analysis, FSH level, and testosterone level.

**Parenthood after cancer**

Approximately 80% of long-term cancer survivors of reproductive age see themselves as potential parents. Unfortunately, both men and women
have an increased risk of infertility as shown in the Childhood Cancer Survivor Study.

Patients infertile due to oncological therapy can be advised to adopt a child or to use third-party reproduction such as heterologic insemination or embryo donation, depending on the particular national guidelines and individual ethical aspects. Nevertheless, most long-term survivors prefer to have biological children. A high percentage of those who remain childless will suffer from psychological alterations such as distress (up to 30%) and depression (up to 40%).

However, patients who maintained their reproductive function may have concerns regarding the health of the future offspring. Women who conceived after cancer therapy showed a live birth rate of 63–73%. A higher miscarriage rate was noted after pelvic irradiation. An exposure of the genital organs of >10 Gy in women or more than 2.5 Gy in prepubertal girls led to increased risk for stillbirth and neonatal death. The risk of preterm birth and low birth weight are increased as well. No association was found in men after irradiation of the testicles.

Fortunately, there is no increased risk of congenital malformations, single-gene defects, or cytogenetic abnormalities among children of childhood cancer survivors, irrespective of the applied therapy.

Conclusion
It is of major importance to sensitise physicians working with cancer patients on the issues of quality of life, fertility, and sexuality. The potential long-term consequences of oncological therapy must be considered and discussed with the patient and his/her partner, and the doctor should address these issues frankly. By understanding that sexuality is an important and normal aspect of life and not a “luxury issue” even in a palliative situation, physicians can support their patients and help them to maintain a good, or at least acceptable, quality of life. Special training in sexual medicine may be helpful but is not mandatory.

Fertility preservation counselling should be an integral part of treatment in young cancer patients. A close collaboration between oncologists and
fertility preservation specialists is essential. There is also an important psychological aspect of fertility preservation counselling: perhaps for the first time since diagnosis, patients may envision life after cancer. As new techniques in the field of onco-fertility have made great advances, these patients have a good chance to maintain their reproductive potential in the face of a potentially life-threatening circumstance, and in spite of highly toxic therapy. Thus, with these successes, they have a good chance of leading a normal, fulfilled family life.

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Dr Schwab has reported no conflicts of interest.
Professor Hasenburg has reported no conflicts of interest.

Further Reading


Prevalence
In recent years there has been growing awareness that cancer is not only a medical problem but a social one too. Social support, social functioning, relationships, and impact on family have been identified as major issues across all age groups, genders, and diagnoses of cancer. Social issues account for at least a third of the problems mentioned by patients. The main ones are social life, relationship with spouse or partner, coping with children, communication, and getting on with family.

Social problems were reported by patients also before the recent surge in cancer survival. An early study showed that more than 50% of patients rated interactions with family and friends, communication with spouse, care provided by spouse, dating, and sexuality as problems. Social issues figure prominently as problems revealed in social media such as Facebook and Twitter.

Social Problems as a Source of Distress
Social problems constitute a serious source of distress for cancer patients. The level of psychological distress in cancer patients is higher than in other patients despite a similar level of physical distress, and it reflects mainly worry over future prospects or social issues. Patients better able to solve social problems have less anxiety and depression, and suffer less from cancer-related problems. In brain cancer patients, the main reasons for hospitalisation included social issues. Social issues strongly affect the patients’ quality of life. Thus, dealing with the social issues is likely
to have a greater impact on the well-being of cancer survivors than other factors.

Despite their prevalence, social issues are discussed in clinical consultations to a lesser extent than other psychological problems. A study of general practitioners found that the doctors waited until close to death before discussing end-of-life issues and then dealt more with physical symptoms than with the involved social problems. A study of the contents of communications in clinical consultations showed that 44% of the patients and 39% of clinicians reported that they would discuss social activities. Social issues were actually discussed in 46% of the consultations, but patients felt they were discussed less often than the physicians reported.

Social Relations and Contacts

The patient and the family

Social issues in the relations with and communication within the family are mentioned by most patients. Cancer has long been identified as a family disease as much as an individual’s disease. Cancer of a family member may cause an anxiety-laden crisis situation for the family, which undergoes changes in its sense of stability, its regular allotment of roles, and its routine behaviours and interactions. In addition, family members may be overburdened, and the patient may react to this situation with increased stress and suffering.

Relations with the spouse

A major social problem in the family involves gaining support from the spouse. For this to occur, the patient must be ready and able to share his or her experiences and suffering with the spouse, whereas the spouse needs to be able to provide understanding, empathy, emotional support, and acceptance. Adequate communication seems to be a basic requirement. Communication is, however, often less than perfect. Common reasons are that the patient may be unable or reluctant to share all of his or her suffering, while the spouse may be unable or unwilling emotionally to shoulder the burden, may be distressed, may be too busy with
helping in daily tasks, or may lack the skills in order to provide adequate support. The result would be increased tension in the patient–spouse dyad. Studies show that spouses may behave toward the patient in a way that seems unsupportive or insensitive because they do not always accept the patient’s views about what is happening and do not behave in accordance with the patient’s expectations. A patient who feels that he or she does not have sufficient support from the spouse is frustrated and disillusioned, and suffers from heightened levels of distress, anxiety, and depression.

Tension is particularly high when the patient and spouse hold different views about the treatment that should be given or have different styles of communicating about cancer – whether open discussion or denial.

The level of social and other problems in the family is of such great importance for the well-being of the patient that a recent meta-analytic review concluded that, in terms of distress, the major factor is the state of the couple considered as an emotional system rather than the state of each individual separately.

**Relations with other close family members**

Children may also contribute to the patient’s social problems. Minors may feel anxious and confused and may require attention and support from the patient. Tension may be evoked by the difficulty or reluctance of the patient (and sometimes the spouse too) to disclose the medical situation to the children. Children may harbour different misconceptions about cancer that may intensify their fear and suffering. Their resulting emotional reactions may enhance the social burden on the patient. Vulnerable children may manifest symptoms (e.g. anorexia, phobias) that require care and attention, which may be withdrawn from the support focused on the patient.

Grown-up children are often expected to provide emotional and instrumental support to the sick parent. However, this may not always be forthcoming for several reasons: faulty communication on the part of the parents, who expect help without asking for it, or who may not explain to the children the seriousness of the situation, as well as the inability or
reluctance of the children to stop their other obligations and occupations and free themselves for helping the sick parent. This may drive a wedge in the relations between the parent-patient and the grown-up children.

Sometimes the patient still has elderly parents. One’s parents may provide the patient with support in many ways, emotional and otherwise. However, relations with one’s parents may also contribute to the load of the patient’s social problems. One problem relates to the issue of communication. Patients may hesitate to disclose their diagnosis to the parents for reasons such as the desire to protect them if their health is frail or shame because of having violated the expected order of things, according to which children die after their parents. In addition, patients may feel guilty for being unable to help their parents while they are sick. Sometimes elderly parents (mainly the mother) may become overly involved in supporting the patient, who may be a grown-up married son or daughter. The situation may become complicated when the parent tries to replace the patient’s spouse. In such circumstances, the patient may be torn in the conflict between the spouse and the parent.

Thus, it is evident that families may potentially create social difficulties for patients. Not surprisingly, among women with a high social burden, those with a higher number of first-degree relatives had higher all-cause and breast cancer mortality.

*Relations with other close individuals*

Family relatives, lovers, friends, and acquaintances may constitute a source of support in different respects. A precondition for their help is that they receive adequate information about the cancer diagnosis and treatment. Patients may be reluctant to provide information to individuals who are not close family members because they would like to preserve their image as “healthy” and avoid pity from others. Further, these “close individuals” have needs of their own that are not always easy to meet. Some may need detailed communication about the medical issues, while others may want to know as little as possible. In return for the support they provide, some may desire appreciation on the part of the patient, or even help from others, including the patient, with problems
they themselves may have. Often the close individuals do not know how to help the patient. They may also overlook the fact that the patient is weak and sick, so that it may be difficult for him or her to spend a lot of time with the many different supporters. These difficulties may explain findings, such as that patients with sexual partners had more problems in social and domestic environments and lower scores on psychological well-being. A study with prostate cancer patients found that 3 out of 10 patients living in a relationship could not confide in their spouse.

A serious source of social problems concerns maintaining former relationships. A person who becomes a cancer patient naturally expects one’s friends to provide the needed support. Often they do, but sometimes they do not, or they reduce their support or even disappear from the person’s life over time. The reasons may be discomfort with the cancer diagnosis, the wish to dissociate from suffering, fear that they may be called upon to provide more help than they are ready to give, or because they no longer enjoy the relationship with the patient. Disappointment from friends is a difficult social issue for cancer patients, who may anyway regard their life during the disease as a series of losses.

Studies show that individuals tend to distance themselves from cancer patients because they regard cancer as a stigma. Also, cancer patients tend to distance themselves from others because they do not want to overburden them with their suffering or are ashamed of their external appearance. These factors render it difficult to maintain former relationships or form new ones.

Relationships with therapeutic carers and internet groups

Patients tend to look for support from others, notably those involved in cancer. This includes the doctors and clinicians who are expected by many patients to manifest understanding for their plight, as well as other patients, mainly survivors and the internet-based organised or non-organised groups that provide information, support, understanding, advice, and the sense of belonging to a community.
Special Aspects of Social Issues in Cancer

Loneliness and isolation

Due to difficulties in maintaining former relationships and forming new ones, many cancer patients find themselves isolated from social contacts. However, even when this is not the case, many patients feel loneliness. The complaint of loneliness is very common and has been documented extensively. It is shared by patients of all ages, diagnoses, or disease stages. It reflects the helplessness and hopelessness patients experience in view of their existential plight in losing contact with life and approaching death, a plight they feel no one can understand or alleviate. Loneliness may persist even when it is discussed with others. It leads to despair, depression, and demoralisation and may intensify suffering from the disease and the treatments. Loneliness affects not only a patient’s emotional state and quality of life but also his or her health and pain by intensifying stress reactivity, weakening physiological repair processes, and increasing immune dysregulation.

Communication

Communication is the pivotal point which can make the difference between more or fewer social problems for the patient. The major barriers to communication on the patient’s side are: reluctance to share and thus reveal one’s weaknesses, low trust in others, desire to experience one’s strength through coping by oneself, a wish to maintain one’s independence and avoid indebtedness to others, feeling different from healthy people, desire to guard one’s secrets and privacy, fear of being rejected and ridiculed, and shame and guilt about the disease. The major barriers on the part of the targeted listeners are: desire to dissociate from suffering, fear of getting over-involved, fear of cancer, and not knowing how to respond. On both sides, there may be beliefs in certain taboo topics that may not be discussed, prohibitions against emotional expression, and lack of communication skills. To improve communication, it is important to consider that contents, styles, and degree of communication vary with culture.

Social support

Social support is probably the most widely researched theme in psycho-oncology. The majority of studies show positive effects of social support
in improving quality of life, lowering depression and anxiety, enhancing benefit finding, increasing compliance with treatment, and even improving medical outcomes. The positive effects may be attributed to emotional factors, such as the patients’ increased confidence in themselves, enhanced feeling of being guarded and loved, and the sense that one’s well-being is important to others. However, social support also enables cognitive elaboration of the difficulties and hence better adjustment.

Notably, too much social support may overburden an exhausted patient. Furthermore, not every kind of social support is equally beneficial. The best type is “positive social interaction”, without conflict. Additionally, not every patient is able to use social support. There is a set of beliefs referring to themes such as emotional expression, readiness to limit one’s independence and privacy, trusting others, and feeling similar to others that renders an individual receptive to social support. When this motivational disposition is weak, the individual may be reluctant to seek social support or unable to benefit from it.

Conclusions

Many studies and observations prove the importance of social issues for the patient’s quality of life, emotional state, and health. Social factors may contribute to the patient’s well-being as well as disrupt the patient’s peace of mind and undermine efforts for recovery. They are operative in the different stages of the disease, in both genders, and in all age groups and cultures. They become evident in the relations with one’s spouse, children, parents, family members, friends, acquaintances, other patients, and members of common internet groups.

All people need contact with others. Cancer patients are even more in need of contact with others, especially with those with whom they can share their anxieties and pain. Many cancer patients complain of loneliness, which reflects their unfilled need for contact with others who can listen and provide support. Some patients complain also of solitude. Many patients report social problems which probably reflect the feeling that they do not gain enough support and understanding from others. When support is available, it instils hope and strength in the patient, but, when missing, it
fuels despair and demoralisation. Inadequate communication is one major cause for lack of support. Barriers to optimal communication characterise both the patient and those expected to provide support.

It is recommended that assessment of social issues should become part of routine clinical practice. When problems are detected, it is advisable to initiate interventions for improving the situation, including the teaching of communication skills and of social problem-solving methods.

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Dr Kreitler has reported no conflicts of interest.

**Further Reading**


Introduction

The financial burden of cancer and its treatment can be substantial. In addition, work disability and job loss after treatment may also lead to financial problems. Extra cost during treatment may be related to lost income, increased insurance premiums, deductibles, co-payments, transportation costs, and child care expenses.

Cost concerns are common among patients with cancer who have health insurance. A relatively high prevalence of present and future cost concerns is present among patients treated at both academic and community hospitals. Patients may have a wide range of cost concerns and additional expenses. Healthcare providers may be accustomed to identifying vulnerable populations for whom cost-related concerns may be a significant barrier to care, such as the poor or underinsured. However, cost concerns may extend beyond the groups that are traditionally considered vulnerable. For example, a quarter of patients who were treated at an academic centre reported travel costs as an additional expense. Many patients receiving care at a tertiary care centre travel farther from home than those cared for in a community site. Given both the economic uncertainty many patients face and the increasing costs of cancer treatment, it may be helpful for healthcare providers to discuss concerns with all patients, rather than relying on demographic characteristics to determine with whom costs should be discussed.

What is the impact of financial problems? Nearly one-third of adult cancer survivors reported cancer-related financial problems. Survivors
reporting financial problems were more likely to report forgoing or delaying recent medical care, prescription medications, dental care, eyeglasses, or mental health care within the past year, specifically because of concerns about cost. The development of interventions to aid cancer survivors and their families as they confront financial stress is challenging, in part because it entails expansion of existing models of survivorship care as well as multilevel intervention efforts.

A recently proposed model of cancer rehabilitation recognises the need for comprehensive care. It is suggested to give attention to social and vocational needs, as well as expanding survivorship care to include services that promote self-management, and encourage survivors to remain in, or return to, the workforce. This has the potential to reduce overall and individual cancer costs and should be considered as a way to reduce financial burden.

Despite the potential benefits of outpatient cancer rehabilitation services, accessing this care entails navigating multiple barriers. The diversity of health insurance coverage with its broad mix of payers and numerous plan types has complicated authorisation and reimbursement. Most rehabilitation services are fully or partially covered through the majority of insurance plans. However, the limited coverage schedule, funding caps, and strict guidelines for continuation of therapy may mean that some survivors of cancer cannot receive their recommended therapy. Private health insurers are mandated to cover physical and occupational therapy services in some countries and regions, but coverage for these services can vary widely and have substantial co-payments that discourage the financially stressed survivor of cancer.

Finally, accessing rehabilitation services is dependent on referral, and the ability of providers and administrative staff to understand health insurance plans, so that the appropriate services can be obtained. Providers must be able to ensure timely pre-authorisations and prescriptions for continuation of services, locate high-quality in-network providers, understand referral processes, and assist patients in making sense of complex benefits schedules. At present, the existing patchwork of national or regional mandates, complex benefits schedules, and variable patient cost sharing among health insurance plans may be contributing to the underuse of cancer rehabilitation services.
Job Loss

The most widely used method to make money and decrease financial burdens is by having paid work. However, cancer survivors are hit harder with job losses. A recent meta-analysis showed that cancer survivors were 1.37 times more likely to be unemployed than healthy people (33.8% compared with 15.2%). Increased risks for unemployment were identified for survivors of breast cancer, gastrointestinal cancers, and cancer of the female reproductive organs. Survivors of blood cancer, prostate cancers, and testicular cancer did not have a higher unemployment risk. Cancer survivors who live in countries or time periods — such as the current economic climate we have today — with high unemployment rates may especially be at risk. These data were collected before the deterioration of the world economy; experts now wonder if this gap could be widening.

A recent meta-analysis with a focus on predictors of return to work and employment in cancer survivors showed that job demands, such as heavy work, create a barrier for cancer survivors to return to work. Heavy work and chemotherapy were negatively associated with return to work. Less invasive surgery was positively associated with return to work. Breast cancer survivors had the greatest chance of return to work. Old age, low education, and low income were negatively associated with employment. Moderate evidence was found for extensive disease being negatively associated with both return to work and employment. For female gender a negative association with return to work was found. Based on these findings a limited number of prognostic factors of return to work and employment can be identified at the time of cancer diagnosis. Clinicians should be aware of these prognostic factors (Table 1) and should consider early rehabilitation or even prehabilitation of cancer patients. Consequently, development of interventions involving clinicians and other professionals to enhance work participation of cancer survivors is needed. The need to improve efforts of oncology specialists, primary care providers, and occupational health professionals in the return to work process is essential to success.
### Table 1 Prognostic Factors for Return to Work and Employment

<table>
<thead>
<tr>
<th>Factor</th>
<th>Return to work</th>
<th>Employment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect</td>
<td>Level of evidence</td>
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<tr>
<td><strong>Socio-demographics</strong></td>
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<td></td>
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<tr>
<td>Age (old)</td>
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<td>weak</td>
</tr>
<tr>
<td>Gender (female)</td>
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<td>moderate</td>
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<tr>
<td>Education (low)</td>
<td>↓</td>
<td>weak</td>
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<tr>
<td>Income (low)</td>
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<td>insufficient</td>
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<tr>
<td>Marital status (single)</td>
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</tr>
<tr>
<td>Ethnicity (minority)</td>
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<td>inconsistent</td>
</tr>
<tr>
<td>Urbanicity (high)</td>
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<td>↑ weak</td>
</tr>
<tr>
<td><strong>Job characteristics</strong></td>
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<td></td>
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<tr>
<td>Physical exertion (high)</td>
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<td>strong</td>
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<tr>
<td>Working hours (high)</td>
<td>↑</td>
<td>insufficient</td>
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<tr>
<td>Self-employment</td>
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<td>weak</td>
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<tr>
<td>Occupational class (low)</td>
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<td>weak</td>
</tr>
<tr>
<td>Job tenure (long)</td>
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<td>weak</td>
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<tr>
<td>Paid sick leave</td>
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<tr>
<td>Employee accommodation</td>
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<tr>
<td>Occupational healthcare</td>
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</tr>
<tr>
<td>Social support</td>
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<tr>
<td><strong>Disease</strong></td>
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<tr>
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<td>Less invasive surgery</td>
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<tr>
<td>Chemotherapy</td>
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<td>Extensive disease</td>
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</tr>
<tr>
<td>Cancer site</td>
<td>↑</td>
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</tr>
</tbody>
</table>
Interventions

Interventions aimed at work participation and securing income can be divided into three groups: ‘stay at work’ interventions (prehabilitation), ‘return to work’ interventions (rehabilitation), and interventions aimed at patients in a palliative phase.

Stay at Work

The principle behind ‘stay at work’ or prehabilitation is prevention. In the case of cancer and work, it is tertiary prevention. Where primary and secondary prevention aim at preventing the disease – cancer – tertiary prevention aims at minimising the impact of cancer. Tertiary prevention is often conceptualised as care-related prevention. It has three goals: preventing complications, curing or stabilising the disease, and reducing the effects of loss of, for example, mobility or sensory functions.

In 2009, a large-scale cancer rehabilitation research programme – the A-CaRe programme – was launched in The Netherlands. The aim of the programme was to strengthen the evidence for the contribution of direct and early physical rehabilitation on physical fitness and mental health. The intervention did not require extra skills and knowledge beyond the normal daily practice of doctors, physiotherapists, and other healthcare providers. However, the timing of the interventions was innovative. It is uncommon for rehabilitation to start in anticipation of future complications. Consequently in The Netherlands and most of the other European countries, prehabilitation is not covered by basic healthcare insurance.

In The Netherlands, basic healthcare insurance is prescribed by the Healthcare Insurance Law. Although this legislation states that the treatment for a high risk of a disease cannot and should not be distinguished from the treatment of the disease, this is not implemented in Dutch healthcare. Dutch healthcare providers are therefore challenged to search for alternative ways to finance prehabilitation. The possibility for patients to stay at work during their treatment makes it interesting for employers or employment insurance companies to finance prehabilitation.
Return to Work

Return to work interventions are often considered as the default – vanilla – flavour of rehabilitation in relation to work resumption. There is some evidence that rehabilitation or vocational therapy speeds up partial return to work. Evidence regarding full and, more importantly, stable return to work is lacking.

Different approaches to rehabilitation are currently investigated in the Dutch A-CaRe programme. In the clinical part of the programme, the effectiveness of state-of-the-art exercise interventions with respect to physical fitness and fatigue are evaluated. In addition, interventions aimed at restoring psychosocial functioning and quality of life in specific cancer patient and survivor groups are evaluated. Determining the cost-effectiveness of these interventions is also part of this programme. The second part of the programme focuses on web-based interventions to increase patient empowerment, return to work interventions to strengthen the societal position of the patient, cancer rehabilitation at home, and implementation of the clinical care programmes focusing on physical exercise.

Similar studies and programmes exist in other European countries. Hopefully, new data regarding return to work interventions will be made available in the coming years.

Palliative Support

Evidence on the effectiveness of stay at work and return to work interventions for patients in a palliative phase is lacking. However, from the patients’ perspective there is certainly a great need for evidence-based interventions. Patients in a stable palliative phase may live for many years and may have increased healthcare expenses. Not working is, from a financial perspective, not an option. A large number of these patients may lose their jobs because they cannot work as productively as co-workers without cancer.

In addition, patients in a terminal palliative phase may want to end their working career in dignity. They often want to finish their last project or want to instruct a colleague how to take over their work. In these cases,
cancer rehabilitation may help to set and achieve individual goals during those few months that a patient may have to live.

Compensation for Occupational Disease

Sometimes cancers are work related. However, clinicians are often unaware of the relation between disease and work. In 1981, in their report to the US Congress, Doll and Peto estimated that 4% of cancer deaths in the USA were attributable to occupation. For over 25 years since the report, this occupational proportion had been used as the basis to estimate the burden of occupational cancer in many European countries. In 2005 a similar research study was undertaken to estimate the burden of occupational cancer in Great Britain. This found that 5.3% (8.2% for men and 2.3% for women) of all cancer deaths recorded in 2005 in Great Britain could be attributed to past occupational exposure. In addition 4.0% (5.7% for men and 2.1% for women) of all newly diagnosed cancers in 2004 in Great Britain were also attributed to past occupational exposure.

![Figure 1](http://www.nationalarchives.gov.uk/doc/open-government-licence/version/2/)

In many European countries, financial compensation schemes are available for occupational disease. Clinicians should always consider occupational disease when diagnosing cancer. This is not only applicable to working patients, but also to formerly employed patients and pensioners, as occupational cancer often takes many years to become detectable after exposure to occupational carcinogens. In many European countries, institutions are available where clinicians can send patients to have their claim of an occupational disease assessed. Compensation schemes may help to alleviate the financial burdens of patients and may be used to pay for additional expenses that are not covered by health insurance.

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Dr Schuurman has reported no conflicts of interest.

Further Reading


Lifestyle Changes

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Introduction

Unhealthy lifestyles are thought to be the cause of approximately 50–75% of cancer cases worldwide. These lifestyle behaviours include smoking, physical inactivity, alcohol consumption, poor dietary choices, and unsafe sexual conduct. It is estimated that if such unhealthy behaviours could be avoided or minimised, up to 2.8 million cancer cases would be prevented each year.

Once cancers are diagnosed, lifestyle plays a significant role in achieving the best outcome possible. Thus, with the increasing number of cancer survivors (associated with improvements in prevention, early detection and treatment, as well as increased population longevity), lifestyle-related interventions should continue to be included in rehabilitation programmes. These programmes include an array of diversified activities: information and counselling on possible changes of lifestyle and behaviour, psychological support, social support, strategies for coping with side effects of anticarcinogenic treatment, and additional treatment of numerous clinical conditions.

Additionally, cancer survivors are at risk for recurrence, second malignant neoplasm (SMN), and other psychological or physical conditions, including cardiovascular disease and diabetes. These problems may result from cancer treatments, genetics, or lifestyle behaviours. Adopting healthier lifestyles reduces the risk of recurrence, and at the same time improves the patients’ health-related quality of life (HRQoL) (e.g. patients experience less fatigue).
In this chapter, we describe the benefits of lifestyle change for cancer survivors. To achieve this general objective, lifestyle changes will be framed in the global perspective of rehabilitation programmes.

**Lifestyles and the Four Most Common Cancers**

In the following sections, we review some of the evidence on the role of lifestyle interventions for breast, lung, colorectal, and prostate cancer – the four most common cancers worldwide. However, this does not imply a less important role for lifestyle in the development and progression of other types of cancer, as well as the development of chronic diseases.

**Breast Cancer**

For breast cancer survivors, maintaining regular physical activity, adopting a healthy diet, and quitting smoking are important steps to enhance health and well-being over the long-term, as well as attaining relapse-free survival. However, post-intervention assessment of the maintenance of physical activity and dietary outcomes in breast cancer survivors is rare.

Excess body weight is correlated with an increased risk of postmenopausal breast cancer, and obesity is associated with poor prognosis in early-stage breast cancer. Weight gain after breast cancer diagnosis also represents an increased risk for poor outcome.

Breast cancer survivors have increased fruit and vegetable consumption, higher physical activity, and decreased fat and meat intake. However, evidence also shows that breast cancer survivors do not present with changes in alcohol consumption, body mass index, or smoking when compared with cancer-free women.

Physical activity has a key role in survival after breast cancer treatment: it is safe, feasible, and promotes physical and psychological health benefits. Post-treatment physical activity interventions result in small to moderate effects on aerobic fitness, overall HRQoL, fatigue, and insulin-like growth factor-1, and a reduction of treatment side effects. Compared with inactive women, those who showed increased physical activity after diagnosis had a 45% lower risk of death, whereas women who decreased physical activity after diagnosis had a four-fold increase in risk of death. In breast cancer
survivors, physical activity and dietary interventions have been demonstrated as effective in producing short-term behavioural change. There are, however, fewer data for maintenance of these behavioural changes.

There is also a link between breast cancer survival and history of smoking. However, smoking appears to be more likely to increase all-cause mortality as opposed to cancer-specific mortality.

Data on the contribution of socio-demographic factors to successful changes in lifestyle behaviour are still inconsistent. Nevertheless, younger women are more likely to implement changes, and associations between low levels of education with lower levels of physical activity have also been made.

Breast cancer diagnosis has been suggested as a “teachable moment” when a woman is more receptive to make healthier lifestyle choices. Thus, lifestyle recommendations must be provided, particularly: to achieve and maintain a healthy weight; exercise at a moderate intensity for at least 150 min/week; consume a balanced diet, high in vegetables, fruits, and whole grains; and limit alcohol consumption. Additionally, this is also an opportunity to provide smoking cessation services.

Lung Cancer
Smoking has a key role in lung cancer. The prevalence of current smoking among lung cancer survivors is relatively low (20.9%), but remains higher among survivors of other smoking-related cancers (38.8%). In early-stage small-cell lung cancer there is an association between continued smoking and recurrence, as well as an increase in the incidence of a second primary tumour. Additionally, it is estimated that patients with early-stage lung cancer who quit smoking have a 70% chance of survival, compared to a 33% chance if they continue to smoke.

Lung cancer survivors generally report lower HRQoL than other cancer survivors. However, for those patients who increase exercise after diagnosis, improvements are seen both in HRQoL and symptoms. In fact, physical activity in lung cancer patients improves pulmonary function and perfusion and decreases the risk of pneumonia and thrombotic events, and thereby improves overall survival and HRQoL.
Many survivors of lung cancer have smoked cigarettes in the past, so they also have a high risk of heart disease, stroke, emphysema, and chronic bronchitis. Quitting can help improve lung function and has other health benefits as well. Thus, people recovering from lung cancer must be encouraged to follow established guidelines for successful recovery.

Colorectal Cancer

For colorectal cancer survivors, healthy lifestyles (diet, physical activity, low alcohol intake, smoking cessation, and obesity management) have positive outcomes in terms of HRQoL and physical functioning, as well as reduced morbidity and mortality.

Nevertheless, a high proportion of colorectal cancer survivors have suboptimal health behaviours, and this is associated with a poorer HRQoL. While the proportion of smokers and those who had consumed alcohol is lower compared with the general population, excess weight is more prevalent among colorectal survivors. Overweight colorectal cancer survivors are more likely to suffer from comorbid cardiovascular disease. In addition, having received chemotherapy is significantly associated with being overweight. Thus, reducing excess weight should be one of the most important targets for intervention, particularly for males, those who received chemotherapy, and those who are of lower socioeconomic status.

Despite these findings and recommendations, when comparing behaviours from before and after diagnosis, few lifestyle changes are observed. Some small changes are, however, observed in terms of fruit and vegetable intake and physical activity. Lifestyle interventions in colorectal cancer patients, implemented 6 to 24 months after primary treatment for colon cancer, were found to produce significant impacts on dietary behaviour, fatigue, aerobic exercise tolerance, functional capacity, and waist-to-hip ratio.

Initially, colorectal cancer patients can be sceptical about the role of diet and physical activity as causes of cancer, in part because they believe their lifestyles have been healthy. Thus, they cannot see how reinstating healthy behaviours would reduce future disease risk. But ultimately, patients who make and maintain dietary changes highlight the importance of these changes in contributing to well-being and a sense of control in their life.
Therefore, personalised, evidence-informed guidance on lifestyle choices must be part of care planning and should be built into survivorship programmes for colorectal cancer patients. Interventions focusing on weight management are particularly crucial, since they may reduce functional decline and improve survival.

**Prostate Cancer**

In men with early-stage prostate cancer for whom “watchful waiting” was the medical decision, undertaking major lifestyle changes for one year was shown to improve prognosis (including reduced prostate-specific antigen [PSA] levels). However, the intervention intensity required to achieve these results might not be easily translatable into practice.

Engaging in more than three metabolic equivalent (MET) hours of weekly physical activity post-diagnosis may reduce the risk of death by 35% in prostate cancer patients. According to current evidence, smoking has not been established as a critical factor in prostate cancer survival.

**Lifestyle and Cancer In General**

Surviving and recovering from a cancer diagnosis represents an exceptional opportunity to change or improve lifestyle. Nonetheless, many patients still maintain unhealthy habits in the post-cancer period. United States (US) estimates (from 2009) show that these habits are still highly prevalent among cancer survivors: 15.1% were current cigarette smokers, 27.5% were obese, and 31.5% had not exercised during the previous 30 days.

In fact, a cancer diagnosis has been shown to have somewhat contradictory effects on lifestyle changes. Most studies found modest or no differences between adult cancer survivors and individuals with no history of cancer. However, others also identified positive influences on smoking and diet and a negative influence on exercise. Even surviving childhood cancer does not seem to influence lifestyle choices in adult age. The same pattern is seen in young adult cancer survivors. Yet, data from 9105 cancer survivors revealed a positive association between the number of lifestyle recommendations being met and HRQoL.
Nutrition, Obesity, and Exercise

Obesity and energy imbalance (i.e. excessive energy intake and suboptimal levels of physical activity) are important factors after cancer diagnosis. They influence the course of disease, as well as overall health, well-being, and survival.

Healthy eating plans usually comprise the following goals: (1) meet nutritional needs through diet alone, not diet supplements; (2) reduce saturated fats; (3) increase fish intake; (3) reduce red meat intake and avoid processed meat; (4) consume a varied diet to ensure adequate intake of vitamins and essential minerals; (5) limit salt; and (6) increase consumption of green and cruciferous vegetables, as well as brightly coloured fruits and vegetables that contain carotenoids. For cancer patients, there are even guidelines for “Informed Choices on Nutrition and Physical Activity During and After Cancer Treatment”. However, a survey investigating clinicians’ knowledge of the risks and benefits of weight management to cancer survivors indicated a lack of awareness of these guidelines. In addition, it was found clinicians tend to be overly cautious when promoting lifestyle changes to cancer survivors. This perception is corroborated by estimates of the diet in survivors of six major cancers, which indicated that less than 20% of cancer survivors were meeting adequate fruit and vegetable intake.

Therefore, despite these recommendations, obesity and sedentary lifestyles remain highly prevalent among cancer survivors. This is particularly serious when evidence shows an association between low levels of physical activity as well as obesity and cancer recurrence and death in several malignancies (including breast, colon, endometrium, and prostate cancers). Several biological mechanisms have been proposed to explain this relationship: changes in insulin-like growth factor levels, immune regulation, sex and metabolic hormone levels, and prostaglandin ratio.

Of course, the adoption and maintenance of adequate levels of physical activity is a significant challenge for most healthy adults, and is likely to be even more challenging after a cancer diagnosis. Frequently, cancer diagnosis and treatment results in decreased physical activity. Even survivors who were not exercising before diagnosis may experience declines.
Nevertheless, physical activity is usually well tolerated during and after cancer treatment. Even in older patients, physical activity was found to be beneficial; additionally, older patients also presented favourable responses to dietary interventions, and were found to maintain these lifestyle changes, ultimately leading to sustained weight loss.

Cancer survivors are recommended to do at least 30 minutes of moderate-intensity physical activity on five or more days per week. There is a dose-related response (more physical activity produces greater benefits), and even a modest amount of exercise is beneficial versus doing nothing at all. Physical activity programmes should, of course, be tailored to the clinical situation and accompanied by a healthcare professional. Involving family or friends in the exercise programme may also be beneficial, since it gives the patient an extra motivation to keep going. However, despite these benefits of physical activity, less than 50% of all cancer survivors report meeting physical activity recommendations. Studies also show that cancer survivors are actually more likely to be physically active than those without cancer, but in any case most survivors remain insufficiently active.

Good nutritional and exercise habits in cancer patients are linked with reduced risks of treatment side effects and increased HRQoL during therapy. Benefits are seen with respect to fatigue, constipation, thromboembolism, body composition, and psychological well-being. Adoption of healthy lifestyles is linked to a reduction in the risk of recurrence and improvement in survival.

Elderly long-term survivors of breast, prostate, and colorectal cancer present a particularly high prevalence of suboptimal health behaviours. Here, diet and exercise intervention reduces the rate of self-reported functional decline. This intervention has been successfully undertaken using telephone counselling and mailed print materials.

Lifestyle advice in the cancer context has been demonstrated as an acceptable means of intervention. A population survey in the United Kingdom verified that most individuals with a history of cancer (or involved in social networks of people with cancer) think that lifestyle advice would be beneficial. Therefore, it is important that healthcare professionals provide patients with lifestyle recommendations, and, if necessary, make referrals in this regard.
On a general basis, cancer patients (and then survivors) should be advised to embrace a healthy diet and exercise programme. This will allow them to maintain a stable healthy weight, which can ultimately offer health benefits in terms of general health condition, and may influence cancer recurrence and death.

**Smoking**

Smoking is estimated to cause about 30% of all deaths from cancer. Thus, avoiding all tobacco use is the most important single step individuals can take to reduce the cancer burden.

Continued smoking after cancer diagnosis can: (1) reduce the effectiveness of cancer therapies as well as increase their toxicity, (2) delay healing after surgery, (3) impede patient recovery, (4) and decrease the patient’s chances for survival.

Despite the evidence, many cancer survivors continue to smoke. Estimates show a similar prevalence of smoking for US middle-aged or older adults with or without a cancer history. However, for young adult cancer survivors (18–44 years), smoking prevalence is 70% higher than for the remaining population (40.4% vs 24.6%). In a survey of 9105 cancer survivors from six major cancer areas, more than 80% of lung cancer survivors were meeting the smoking recommendations. Nonetheless, tobacco use among other tobacco-related cancer survivors remains higher than among other cancer survivors and people without a history of cancer.

Quitting smoking is extremely difficult. Therefore, smoking cessation services must be proposed to all cancer survivors, with programmes that promote effective tobacco cessation. Cancer diagnosis and treatment have been identified as a “teachable moment” for smoking cessation interventions. Here, interventions should be as close to treatment as possible to attain higher success rates. Higher quit rates are seen among patients with smoking-related cancers, but one should be attentive to relapses, which can occur after long periods of abstinence.
Summary

Surviving cancer is now an established reality for millions of people worldwide, who need an adequate rehabilitation programme.

Cancer survivors are a vulnerable population, who are likely to benefit from the choice of healthy lifestyle behaviours. However, most cancer survivors are not currently adopting healthy behaviours, which ultimately results in greater disease risk and healthcare costs.

While cancer survivors should have the same diet, weight, and physical activity recommendations as the general population, there is also a need for individual assessment and risk stratification. Particular attention should be paid to high-risk patient groups: patients who have comorbidities, are overweight, or are sedentary, as well as those who smoke.

Healthcare providers must understand and recognise the needs of cancer survivors which are unique and different from other patients. These needs are related to both the cancer disease and the cancer treatment, and require surveillance and follow-up care frequently unknown to the healthcare community. Healthcare systems must take this into consideration.

The increasing importance of nutrition and physical activity for cancer survivors has been recognised in diverse guidelines. There are recommendations for cancer survivors to have a treatment summary and survivorship care plan to serve as a roadmap and a communication tool to optimise co-ordination of care. Several models have been presented; however, the “shared-care model” is proposed as the optimal approach to co-ordinate activities between specialised cancer care and primary health care. These models should, of course, be adapted to local health resources and personalised in accordance with the patient’s needs.

Due to the large and increasing number of cancer survivors, more research is needed to evaluate the impact of lifestyle changes on health-related outcomes in this population. Concurrent research also needs to address the relative benefit in various subpopulations as defined by phenotype, genotype, exposure to treatment, and other lifestyle and environmental factors.
In conclusion, cancer survivors must be enrolled in rehabilitation programmes that include strategies to promote healthy lifestyles. Patients, family, healthcare professionals, and even health systems must be engaged in these efforts.

Declaration of Interest:
Dr Pimentel has reported no conflicts of interest.

Further Reading
Introduction

Over 12 million new cases of cancer are diagnosed worldwide every year. Encouragingly, due to improvements in early detection combined with more effective treatments, mortality rates have dropped significantly over the past three decades for some of the most prevalent cancers. As a result, there are now over 28 million individuals worldwide living with a personal history of cancer (“cancer survivors”). With continued projected increases in the incidence of cancer and improvements in overall survival rates, this number is expected to double by 2050.

While the increasing number of cancer survivors is a positive trend, patients transitioning from primary cancer treatment to follow-up care, termed the “re-entry phase”, face multiple adaptive physical, functional, psychosocial, and spiritual tasks. The evidence suggests that the majority of cancer survivors adjust well over the long term; however, a number of unmet needs have been identified and very few cancer survivors receive any comprehensive post-treatment survivorship care. It is therefore not surprising that patients commonly report that they do not know what to expect once treatment is over; some feel that they are not being cared for and others describe feeling “abandoned”. Over the last two decades, patient advocacy groups, expert consensus panels, and a number of governmental reports have recommended improvement in the quality of post-treatment survivorship care. These improvements will ensure continuity of care and help to address the unmet needs of
cancer survivors, particularly their need for support as they transition from acute cancer treatment to the follow-up phase of the trajectory.

In 2006, the Institute of Medicine (IOM) released a pivotal report “From Cancer Patient to Cancer Survivor: Lost in Transition”, which identified cancer survivorship as a distinct yet relatively neglected phase of the cancer trajectory. The recommendations included in this report defined components for clinical care, research, training, and education and catapulted the “cancer survivorship” movement and related initiatives in the United States, Canada, Australia, and countries across Europe. Since that time, there has been agreement on the essential elements of survivorship care delivery, which include: surveillance for recurrence of the primary cancer and screening for new cancers; assessment of medical and psychosocial late effects; development of interventions for addressing the consequences of cancer and its treatment; health promotion; and better co-ordination of care between oncology specialists and primary care practitioners.

The definition of rehabilitation in cancer care closely aligns with the philosophy of survivorship care with its focus on rebuilding the lives of people with cancer and maximising functioning as well as quality of life. In fact, some suggest rehabilitation could be considered “a surrogate” for survivorship care due to their overlapping objectives. Rehabilitation for late effects is identified as an essential high-need element of survivorship care delivery and further integration of a rehabilitation approach and/or specific cancer-focused rehabilitation services in survivorship care planning and service delivery requires further development.

Survivorship Care Plans

One of the key recommendations of the IOM report is the need for follow-up “survivorship care plans” (SCPs) to prepare survivors for transition from the active treatment to the post-treatment survivorship phase of the cancer trajectory (Figure 1). These plans of care are essential tools to empower and inform both survivors and primary care practitioners of the follow-up care, screening and surveillance monitoring required. It is recommended that all patients completing primary cancer treatment should receive a written SCP delivered in a designated clinic visit to facilitate the
transition to the lifelong surveillance and follow-up phase of cancer care. SCPs are a communication tool for patients and defined as a dynamic, comprehensive care summary and follow-up plan written by the principal provider(s) of oncology treatment.

<table>
<thead>
<tr>
<th>Post-treatment care plan</th>
<th>Survivorship care plan components</th>
<th>Survivorship programmes</th>
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</thead>
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<tr>
<td>• Post-treatment summary</td>
<td>1. Information about timing and content of follow-up</td>
<td>Multidisciplinary care: focused on the specialist rather than the primary care provider; the key provider in these survivorship models has been the cancer specialty team</td>
</tr>
<tr>
<td>• Advice on screening for new cancers</td>
<td>2. Identification and management of late and long-term effects</td>
<td>Integrated care: emphasis on establishing primary care-based support for the survivor with the expectation that communication between the oncology team and primary care provider will continue</td>
</tr>
<tr>
<td>• Surveillance for recurrence</td>
<td>3. Recommendations for healthy living, diet, exercise, and smoking cessation</td>
<td>Rehabilitation: enhances recovery after acute illnesses through vocational rehabilitation that promotes return to functional capacity and well-being</td>
</tr>
<tr>
<td>• Care co-ordination strategy with primary care practitioners</td>
<td>4. Information about financial benefits and return to work</td>
<td>Self-management: promote skills for chronic illness management including problem solving, decision-making, making the best use of professionals, and taking action</td>
</tr>
<tr>
<td>• Ongoing symptom management</td>
<td>5. Referral to specialists including psychological and social support</td>
<td></td>
</tr>
<tr>
<td>• Health promotion</td>
<td>6. Family and caregiver support</td>
<td></td>
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</tbody>
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Figure 1 Critical elements of survivorship care planning. Republished with permission of John Wiley & Sons, Inc., from McCabe M, et al. Survivorship programs and care planning. Cancer 2013; 119(11 Suppl):2179–2186; permission conveyed through Copyright Clearance Center, Inc.

The basic components recommended for inclusion in a SCP are as follows:

- Cancer type, treatments received, and their potential consequences
- Specific information about the timing and content of recommended follow-up
- Recommendations regarding preventive practices and how to maintain health and well-being
- Information on legal protections regarding employment and access to health insurance, and
- Information about available psychosocial services in the community
More recently, the American Society of Clinical Oncology (ASCO) has also recommended a number of additional care components to consider in the development of SCPs and survivorship care delivery, including: (1) account for the increased risk for other chronic diseases and outline methods to address this risk; (2) assess and address psychosocial needs; (3) information about fertility planning for patients at reproductive age; (4) known side effects (persistent and late effects) of cancer and treatment; (5) screening guidelines and symptoms of recurrence including secondary primaries; (6) discuss and incorporate survivors’ values and preferences regarding their care; (7) use discussions about cancer-related concerns as teachable moments to educate survivors about behaviour change: tobacco cessation, obesity control, reduction in alcohol use, and other health promotion issues, i.e. exercise. These elements are synonymous with preferences for SCP components identified by cancer patients and a need for education about late and long-term effects of treatment and access to resources/referrals for clinical management.

As a clinical tool, the SCP can be used to prepare patients for the transition to post-treatment care. In addition, the SCP has the potential to foster patient use of self-care strategies that manage the ongoing effects of treatment, while facilitating the uptake of health behaviours that have the potential to reduce the risk of future complications. The inclusion of standardised information in the SCP may also help to reduce variation in clinical practice and help to foster improvement in the quality of transition care processes.

Globally, over the past decade there has been growing momentum in the implementation of SCPs, and various types of care plans and SCP templates have now emerged in response to the IOM recommendations. Regardless of differing adaptations of the SCP, there is consensus that the essential IOM elements should be addressed and that SCPs are a core element of survivorship care delivery and a standard of quality care for cancer programmes.

Ultimately, SCPs must be tailored to the individual and consideration given to differences in risk for late and long-term effects based on factors such as patients’ age, their type and stage of cancer, treatments received, degree and intensity of follow-up care required, and the needs for clinical and rehabilitation interventions. Active engagement of patients in
the development of care plans that emphasise their role in their recovery is important. An explanation should be given, detailing the various health sector professionals who are available to offer guidance and support in the surveillance and clinical management of late and long-term effects of treatment. SCPs are considered an essential tool to facilitate communication among healthcare sectors and could help the transition of patients to primary care and leverage changes in healthcare integration.

Progress in Survivorship Care Delivery

The development of cancer survivorship initiatives in North America, including the development and implementation of SCPs, has been influenced by organisations such as the IOM, National Cancer Institute (NCI), ASCO, the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), and the Canadian Partnership Against Cancer (CPAC). In both the USA and Canada, a growing number of institutions have developed SCPs for their patients. In addition, a handful of internet-based SCPs are also available including the LIVESTRONG Care Plan (www.livestrongcareplan.org), which provides a tailored SCP that may be printed or stored electronically in portable document format. Data from the first three years since the launch of the LIVESTRONG Care Plan demonstrated increasing use by survivors from nearly every continent, with international users accounting for 16% of total users. Other examples of web-based SCPs include the Journey Forward, which integrates current follow-up care guidelines and tailored links to educational materials (www.journeyforward.org), and SCP templates developed by ASCO based on current follow-up guidelines (http://www.cancer.net/survivorship/asco-cancer-treatment-summaries). Despite these initiatives, the reality is that most cancer survivors in North America still do not receive SCPs and, when they do, most SCPs fail to include all of the IOM-recommended elements.

In Europe, recognition of the need for the development of survivorship programmes and SCPs is variable across countries. The majority of countries have yet to include survivorship in national cancer plans. In spite of this variation, European initiatives in cancer survivorship do exist in a number of countries, with dedication of some resources to post-treatment
care and rehabilitation. The National Cancer Survivorship Initiative (NCSI) in the UK has emerged as a leader of survivorship care in Europe. It has put into practice an approach to care that includes the main features of SCPs (www.ncsi.org.uk). In this programme, a clinical nurse specialist is assigned to each patient and is the main contact for the entire course of treatment and follow-up care. The nurse conducts regular holistic assessments to provide targeted and personalised care and support to each person. At the end of treatment a SCP is provided to the primary care physician and the patient’s follow-up care is based on a risk-stratified pathway. Pan-European organisations such as the European Cancer League (ECL) and the European Oncology Nursing Society (EONS) are also advocating collaboration regarding cancer survivorship among medical organisations such as the European Society for Medical Oncology (ESMO) with education on survivorship at annual meetings. With the exception of NCSI, SCP initiatives have yet to emerge, though there have been published descriptions of rehabilitation discharge papers provided by oncologists to family physicians that outline plans for follow-up care.

Despite consensus on the need for SCPs as an essential element of survivorship care delivery, to date there has been limited formal evaluation of these plans and their implementation among cancer survivors. Consequently, the impact of SCPs on reducing cancer-related morbidity and mortality is one of the major issues still to be addressed. A handful of studies have provided preliminary evaluation data on SCPs. These studies have included both qualitative and quantitative approaches. In general SCPs are highly rated by patients and health professionals and are perceived as useful tools to facilitate co-ordination of care post-treatment. In a study by Shalom and colleagues (2011), healthcare providers reported that SCPs increased their feelings of confidence and care for patients post-treatment. Benefits for patients have included increased knowledge and understanding of post-treatment care and enhanced feelings of well-being. Evaluations of the online LIVESTRONG and Journey Forward plans have demonstrated high satisfaction among users. Evaluation of the UK NCSI programme reported improvements in patient satisfaction and confidence, and reductions in healthcare utilisation and costs. The largest randomised controlled study of SCPs to date was conducted by Grunfeld and
colleagues (2011) and included 408 breast cancer survivors, at a median 35 months post-treatment, whose care was being transferred back to primary care. Participants randomised to the intervention group received a SCP with a 30-minute educational session with a nurse. The study results did not find that the intervention improved distress (primary outcome) or quality of life, patient satisfaction, or continuity of care (secondary outcomes). Since its publication, a number of authors have provided alternative explanations of the results, highlighting the urgent need to identify relevant outcomes and populations that would derive the most benefit from SCPs. Further high-quality research on SCPs is needed.

While further efficacy studies are clearly warranted, the provision of SCPs is now viewed as an essential element of cancer care and their delivery is now being required as part of accreditation in order to standardise current practice in the USA. For example, by 2015 the American College of Surgeons (ACS) Commission on Cancer will require that ACS-accredited facilities, which treat approximately 70% of newly diagnosed cancer patients in the United States, provide SCPs to all patients. Thus, there is also a need to evaluate the viability of SCPs and the care processes necessary for their effective delivery in the context of overloaded clinical oncology care delivery. Numerous challenges to implementation have been identified including workforce and reimbursement issues, absence of guidelines to inform care plans, and lack of training for both those who deliver SCPs and primary care providers. Given the volume of patients in ambulatory cancer treatment centres, a feasible SCP will need to be efficient. In a recent US survey of healthcare providers, the majority of oncologists reported that SCPs should take no more than 20 minutes. In reality, Stricker and colleagues (2011), who recently reviewed SCPs delivered within the LIVESTRONG Network of Cancer Survivorship Centers in the USA, found that one-third of sites providing SCPs spend more than 60 minutes just to create the SCP, with the majority reporting an additional 15–60 minutes delivering the SCP to the patient. Studies are underway to determine the feasibility of implementing SCPs as part of standard practice that will generate knowledge for application by others. In addition, an electronic solution for care plan development is recommended as a key priority in future research. Engaging key stakeholders throughout the
implementation process and using effective knowledge translation strategies inclusive of training programmes for SCP providers that include person-centred communication are fundamental to uptake as part of routine care.

It must be recognised that a SCP is only one of the essential elements of survivorship care delivery for which there is now consensus. Other elements must also be considered to ensure the development of quality survivorship care delivery models and processes of care and to meet the multidimensional needs of cancer survivors. These elements also include health promotion education, care co-ordination strategies, late effects education and programmes to reduce risk (i.e. weight management), comprehensive medical and psychosocial assessment, rehabilitation programmes, and patient navigation. In addition, strive elements such as self-advocacy training, medical education, counselling, clear pathways for access to specialist care, and population-based quality improvement are equally important.

Summary/Future Directions

The burgeoning population of cancer survivors can no longer be ignored and healthcare sectors must work collaboratively to address the multidimensional needs of this population. A number of landmark reports provide clear direction on the essential elements of survivorship care delivery to address these needs. Significant variation in the application of these essential elements is reported, but their application may improve further with elements such as SCPs, endorsed as part of accreditation standards. Consensus on the integration of SCPs in routine care delivery to facilitate the transition of patients from active treatment to follow-up care suggests this is a high priority that is actionable and supported by a clear evidence base. However, further research on the best approaches for facilitating uptake in real-world settings and their effectiveness for improving outcomes is warranted. The integration of a rehabilitation approach and specific cancer-focused rehabilitation services is an essential high-need element of survivorship care delivery. It requires further development and integration within survivorship care programmes and may be essential to realise health outcomes. Efforts are under way to prioritise the most essential elements of survivorship care delivery that may provide the lessons learned for uptake by other healthcare organisations and the investments
needed. As noted by Earle (2012), just starting the adoption of essential elements is a beginning, as trying to achieve perfection may be the enemy of the good. The IOM suggests some elements of care simply make sense to improve survivors’ experience of living with cancer.

Declaration of Interest:
Dr Jones has reported no conflicts of interest.
Dr Howell has reported no conflicts of interest.

Further Reading


LIVESTRONG. The LIVESTRONG Essential Elements of Survivorship Care: A LIVESTRONG Brief; 2011; Available at: https://assets-livestrong-org.s3.amazonaws.com/media/site_proxy/data/6f57b05726c2db3f56a85a5bd8f5dad166b80b92.pdf.


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REHABILITATION ISSUES DURING CANCER TREATMENT AND FOLLOW-UP

Edited by Henk van Halteren

The ESMO Handbook of Rehabilitation Issues During Cancer Treatment and Follow-Up is intended primarily to be read by physicians working in the field of medical oncology. The aim of this publication is to provide key information in the form of a comprehensive and well-arranged handbook that will help physicians gain better understanding of the issues surrounding patient rehabilitation.

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