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Roadmap

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Why do patients with cancer die?

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Abstract

Cancer is a major cause of global mortality, both in affluent countries and increasingly in developing nations. Many patients with cancer experience reduced life expectancy and have metastatic disease at the time of death. However, the more precise causes of mortality and patient deterioration before death remain poorly understood. This scarcity of information, particularly the lack of mechanistic insights, presents a challenge for the development of novel treatment strategies to improve the quality of, and potentially extend, life for patients with late-stage cancer. In addition, earlier deployment of existing strategies to prolong quality of life is highly desirable. In this Roadmap, we review the proximal causes of mortality in patients with cancer and discuss current knowledge about the interconnections between mechanisms that contribute to mortality, before finally proposing new and improved avenues for data collection, research and the development of treatment strategies that may improve quality of life for patients.

Sections

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Roadmap

Introduction

The phrase 'metastasis accounts for 90% of cancer deaths' is one of the most widely used in cancer research, yet it is overly simplistic, imprecise and it is difficult to find any primary analysis supporting the statement. Although patients with metastatic disease are overwhelmingly more likely to die than patients with non-metastatic cancer[1,2], the determinants of cancer mortality are multifaceted and frequently involve dysfunction of multiple interconnected systems within the body. Understanding the mechanisms underpinning the causes of mortality, and subsequently intervening, has the potential to make cancer a less destructive disease, improving both the quality and length of life for patients with cancer. However, systematic analyses of the acute and root causes of mortality in patients with cancer are scarce, in part because death certificates rarely record enough information to understand the exact reason why the patient died beyond them having a malignancy. Causes of death may be simply listed as 'metastatic carcinoma' or 'complications of cancer', which give little insights into why a patient actually died. Potentially concomitant comorbidities are also not fully recorded. Even in cases in which the cause of death may be attributed to a single event, for example, a thromboembolism, the underlying cause of that specific event may be complex. Indeed, metastatic cancer leads to perturbed function of multiple organ systems, and importantly, not just the organs to which disease has spread. This is probably due to the exuberant activation of local and systemic inflammatory, tissue repair and immune-suppressive programmes.

A simple view would be that death from metastatic disease correlates with the burden of disease. However, evidence suggests that the situation is more complex, with many factors influencing how metastases impact vital functions and ultimately lead to death. First, metastases to different organs will lead to different impacts on overall health. For example, brain metastases can lead to dysfunction of the central nervous system[3], whereas peritoneal metastases may cause obstruction of the bowel[4]. In addition, the size or extent of metastases may not necessarily correlate with dysfunction of the organ where it is located[5]. Second, the production of the molecular mediators of organ dysfunction can vary between metastases and cancers of different origins. Third, individual patient characteristics such as age, sex, overall health, pre-existing comorbidities, genetics and socio-economic status vary[6]. Together, these factors directly influence the course of and physiological response to metastatic disease and can have profound indirect effects by limiting available treatment options and/or the ability of patients to tolerate or complete all intended treatment[7,8]. To understand why patients with cancer die, a closer examination of the factors contributing to mortality in patients with cancer and a dissection of the intricate web of causes that shape the frequency and dynamics of death are required.

Death may be related to an acute event, but the underlying mechanisms which trigger it may be modifiable or even preventable. In addition, other deaths may be the end stage of a continuum of deterioration, allowing the possibility of targeted intervention to improve quality of life. Moreover, it has been noted that early palliative care improves survival[9]. Ultimately, increased understanding of the processes occurring in patients with advanced disease should lead to improved strategies to minimize ill-health and suffering at the end of life. Coupled to this, patients and those around them should be enabled to have essential discussions about their wishes and preferences, minimizing potentially inappropriate treatments and maximizing quality of life[10]. Therefore, in this Roadmap, we briefly review data considering the immediate causes of mortality, highlight the intricate interconnections between different aspects of patient deterioration and conclude with recommendations for future studies of late-stage cancer that may shed new light on this important aspect of cancer biology and medicine.

Acute events leading to mortality

Although some cancers can be considered a chronic condition, with many patients living with their disease for years, the immediate cause of mortality can often be an acute event. Here, we briefly summarize common acute events leading to death in patients with cancer (Fig. 1). Although it is not possible to precisely determine, it is likely that the acute causes discussed subsequently may account for up to half of cancer deaths[11,12]. Immediate causes of mortality in other patients are less clear, with a more gradual deterioration typically occurring in vital organ systems (Fig. 1).

Vascular coagulation and cardiac failure

Patients with cancer are at an elevated risk of thromboembolism, which may trigger respiratory failure, fatal strokes, heart failure or myocardial infarction[13]. In some cases, disseminated intravascular coagulation can lead to thrombotic obstruction of small and midsize vessels leading to organ failure[14]. Haemorrhagic complications from depletion of platelets, via either immune or non-immune mechanisms[15,16], and reduced levels of coagulation proteins can also be life-threatening[14]. Congestive heart failure can also be a proximal cause of mortality, although the underlying causes are complex and include loss of cardiac muscle (associated with cachexia), shifts in intravascular fluid status and thromboembolic events[17]. Interestingly, bone metastases are particularly associated with cardiovascular problems, although the underlying mechanism remains unclear[18]. Comorbidities affecting the cardiovascular system may also make patients more prone to such events. Spatial occlusion of or invasion into vessels by cancer metastases can also lead to failure in blood supply or catastrophic haemorrhage[19–22].

Displacement, functional impairment or obstruction of vital organs

The volume of disease may impair the function of a vital organ. This can be the case with brain metastases and glioblastoma or other primary brain cancers, with extensive invasion, brain herniation or oedema resulting in midline shift or increased intracranial pressure irreversibly compromising brain function[22–24]. In addition, patients may develop seizures, which, if uncontrolled, can result in death[25,26]. However, this does not apply to all brain metastases, with leptomeningeal metastases having minimal impact on intracranial pressure and brain structure; instead, these commonly obstruct cerebrospinal fluid flow and/or affect nerve function resulting in hydrocephalus, deterioration of neurological function and death[26].

Large lung metastases may impair the essential function of gas exchange. However, patients with miliary-like disease – characterized by nodules too numerous to count – can live with extensive disease in an organ with surprisingly little impact on function until a hard-to-predict tipping point is reached, which is then followed by rapid deterioration[27]. As with brain metastases, the volume of disease is often not sufficient to account for organ failure, as even a relatively small volume (<100 ml lung metastases volume compared with 4–5 l total lung volume) can be fatal[28]. Lung oedema and pleural effusion are additional common contributors to death. Oedema may be caused by other pathologies such as infection or heart failure, whereas pleural effusion may be related to the presence of disease within the pleura as opposed to total tumour volume[28,29].

Bowel obstruction can be a cause of mortality, especially in patients with peritoneal disease as found in particular in ovarian, colorectal and gastrointestinal cancers[30]. Both liver and kidney failure will also cause death in patients with cancer. Reasons for the failure of these organs include obstruction of the bile duct or ureters by metastases, therapy-induced toxicity leading to compromised normal organ function (discussed subsequently) and reduced tissue perfusion owing to hypotension or dehydration[31–34]. In addition, sepsis can result from obstruction of the bile ducts or ureters, which occurs unpredictably and often progresses rapidly leading to multiple organ failure and ultimately death.

Infections

Bacterial infections are the most common infection in patients with cancer, owing to impaired immune systems resulting from both the cancer itself and certain cancer treatments (discussed in detail subsequently), which induce myelosuppression and leukopenia. Patients with cancer can have an elevated risk of opportunistic viral, fungal and protozoal infections, which would typically be considered mild in healthy individuals, but which can cause serious life-threatening complications in those with cancer. Pneumonia and other lung infections leading to respiratory failure are often listed as causes of mortality in patients with cancer[35,36]. One of the most striking recent examples of this is the increased mortality observed in patients with cancer, particularly those with haematological cancers, who succumbed to COVID-19 compared with the general population[36,37].

Paraneoplastic syndromes

Paraneoplastic syndromes are a group of rare disorders that can occasionally cause irreversible damage to critical organs and death. They are most associated with lung, breast, ovarian and lymphatic cancers, causing tissue or organ dysfunction at sites distinct from the location of the tumour[38]. Various mechanisms underpin paraneoplastic syndromes, including the inappropriate production of cytokines, hormones and antibodies. For example, excess parathyroid hormone-related protein (PTHRP) production by tumours can lead to hypercalcaemia[39,40]. Inappropriate anti-diuretic hormone production is commonly associated with small-cell lung cancer resulting in hyponatraemia[41]. Furthermore, some neuroendocrine pancreatic tumours (insulinomas) secrete large amounts of insulin[42]. Tumours can also trigger the aberrant production of autoantibodies leading to disorders such as Lambert–Eaton myasthenic syndrome (LEMS) or anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis and myasthenia gravis[43]. Although treatment can usually manage the symptoms, in a subset of cases the syndromes cannot be controlled and are fatal[38].

Therapy-induced toxicity

Although therapies are developed and administered with the intent of primarily targeting the tumour, almost all have some detrimental impact on normal tissue function. In some cases, the unintended consequences of therapy can be life-threatening. Autoimmune reactions resulting from targeting immune checkpoints can have fatal consequences, including myocarditis and encephalitis[44–46]. Chemotherapy can lead to death as a result of acute neutropenic sepsis[47]. Depletion of platelets because of therapy can lead to fatal bleeding[16]. Arrhythmias, cardiomyopathy and coronary vasospasm are also a cause of death related to some anticancer treatments such as 5-fluorouracil and capecitabine[48–50]. The long-term detrimental effects of some therapies are discussed in detail subsequently.

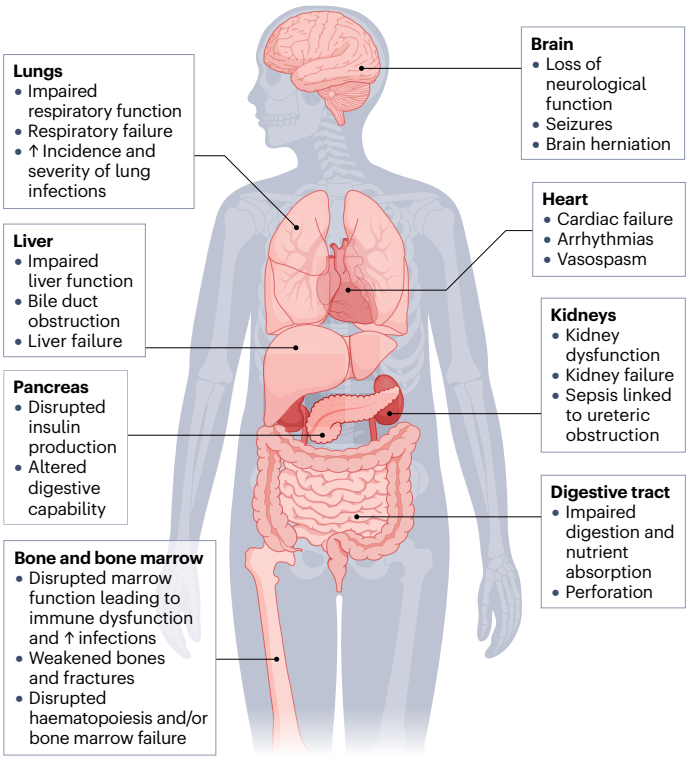

Fig. 1 | The proximal causes of mortality in patients with cancer. This schematic shows organs that frequently become dysfunctional in patients with late-stage cancer.

Underlying causes

Determination of the proximal cause of mortality prompts further questions around the underlying factors giving rise to lethal pathology and ultimately how metastatic cancer triggers or accelerates those factors. In this section, we consider how chronic disruption of three major physiological organ systems is perturbed in patients with cancer and how these might contribute to mortality.

The immune and haematopoietic systems

In patients with cancer, the immune system becomes progressively less able to mount effective responses to infectious challenge, a phenomenon often generically termed 'immune exhaustion' (this usage is distinct from the more specific usage of immune exhaustion as a failure of tumour-reactive T cells to function). As a result, patients with metastatic disease have increased susceptibility to a wide range of infections and typically suffer more severe consequences than would otherwise be observed in healthy individuals[51]. Multiple mechanisms contribute to the reduced capability of the immune system to respond to infection. The presence of cancer cells in diverse organs triggers similar cellular and molecular events to wound responses[52]. The production of cytokines including interleukin 6 (IL-6), granulocyte colony-stimulating factor (GCSF) and granulocyte–macrophage colony-stimulating factor (GM–CSF), both by tumour cells and by other cells of the tumour microenvironment (TME), perturbs haematopoiesis leading to altered subsets of leukocytes[53]. Although, in the short term, this may have limited consequences on the ability of

the body to respond to other challenges, prolonged disruption to haematopoiesis can strain the ability of haematopoietic stem cells (HSCs) to generate sufficient cells of the right type to cope with infections, with increased myeloid-to-lymphoid cell ratios. Clonal haematopoiesis can be increased in patients with cancer, with myeloid skewing of immune cells and overall myeloid-mediated immune suppression and diminished naive T cell reservoirs[53]. Reduced production of platelets and altered iron metabolism leading to compromised oxygen carrying by red blood cells is also observed in many patients[54]. Other problems such as immunoparesis can arise, with a high frequency observed in patients with multiple myeloma[55].

T cell responses to infection are impaired in the presence of cancer with decreased proliferation and expression of granzyme B typically observed[56]. The chronic stimulation of T cells with neoantigens arising from ongoing mutational processes may also contribute to their weakened functionality. Moreover, immune surveillance of tumours inevitably selects for the production of immune suppressive factors by cancer cells, which further compound the issue[57]. Once again, comorbidities leading to either immune suppression or autoimmunity can intersect with the detrimental effects of cancer on the immune system.

Other consequences of cancer can indirectly result in an increased likelihood of infection. For example, vessel obstruction from cancer results in decreased flow of fluids such as bile, urine and lymph, creating environments in which bacteria can thrive[58]. Blockage of the bronchial tree can lead to pneumonia[59]. The invasive phenotype of cancer can result in fistula formation (for example, rectovaginal in colorectal cancer), which enables bacteria to invade[60]. Furthermore, patients are often rendered bedbound or have limited mobility as cancer progresses, resulting in an increased chance of infections through decreased respiratory ventilation and atelectasis, as well as pressure sores and oedema[61].

Disruption to haematopoiesis can also contribute to defects in coagulation and haemostasis. Elevated platelet numbers, termed thrombocytosis, are found in patients with cancer and are correlated with higher mortality[62]. The altered inflammatory cytokine milieu caused by the tumour may promote megakaryopoiesis, potentially through increasing thrombopoietin (TPO) production by the liver, and leading to higher platelet numbers. The risk of clotting can be further increased by the production of tissue factor, which is responsible for initiating the clotting cascade, by tumour cells[63]. These mechanisms increase the likelihood of fatal thromboembolisms[63].

Iatrogenic effects also have a role in the reduced immune function in patients with cancer. Cytotoxic therapies interfere with the proliferation and division of haematopoietic stem cells and can leave the immune system unable to mount effective responses to pathogens, leading to mortality[64]. In severe cases, pancytopenia results, marked by a substantial decrease in all three major blood cell lineages (red cells, white cells and platelets)[65]. This can lead to severe anaemia, increased infection susceptibility and increased likelihood of bleeding[47,66,67]. In other cases, more limited subsets of haematopoietic cells are affected. Thrombocytopenia — low platelet levels — leads to hypocoagulation and elevates the likelihood of haemorrhage[66]. Therefore, during cancer development and treatment, haemostasis mechanisms may be either augmented or attenuated; in both cases, the result is less predictable and less well-controlled coagulation. Neutropenia — low neutrophil levels — renders patients less able to fight infection and contributes to cancer mortality from infections that in many cases are thought to arise from resident mucosal flora[68]. Treatments, including chemotherapy and radiotherapy, often result in the breakdown of mucosal barriers (for example, oral mucositis) resulting in higher numbers of infections from pathogens, which normally reside on these surfaces[69]. In addition, corticosteroids, which are often given to alleviate symptoms or manage toxicity, can also contribute to the suppression of immune responses and compound the risk of infections in patients[70]. Clonal haematopoiesis, which as mentioned earlier is already more frequent in patients with cancer, can be further increased by chemotherapy[71]. More generally, cancer therapies can increase ageing-associated processes and reduce organ function[72]. Opioid pain relief administered to those with late-stage disease can also suppress the function of various bodily systems[73]. Finally, infections can arise owing to the insertion of drains and stents, or central venous catheters (CVCs; also known as lines) for the delivery of therapies. Infections from such lines are estimated to be around 0.5–10 per 1,000 CVC-days[74,75].

Immunotherapies present a different set of immune complications from conventional therapies. These primarily relate to overactivation of the immune system leading to autoimmunity and, in some cases, cytokine storms that are treated with anti-cytokine therapies such as tocilizumab, anakinra and ruxilitinib, all of which can further suppress the immune response[76]. However, deaths attributable to autoimmune side effects of immune checkpoint inhibitors are rare (<1% in an analysis of more than 8,000 patients) especially if toxicity is managed promptly[77,78]. Colitis is a frequent problem, with disruption to colonic barrier function leading to increased susceptibility to perforation, which can be life-threatening. Guillain–Barré syndrome, hepatitis and myocarditis are also causes of immune checkpoint inhibitor-related deaths[79–81]. Once again, high-dose corticosteroids are the main first-line treatment to manage autoimmune side effects in patients receiving immunotherapy and can lead to suppression of the immune system. Hyperprogressive disease is observed in some patients following immunotherapy, the reasons for which are still being delineated, but there is probably a role for innate lymphoid cells releasing pro-growth cytokines[82]. Cell-based immunotherapies can also lead to disrupted bone marrow function and subsequent myelosuppression[83].

The nervous system

The brain serves as a central nexus, orchestrating all vital functions. It is the hub of thought processes, emotions and sensory perception and regulates, directly or indirectly, everything from heartbeat and breathing to appetite. In addition to physical disruption of brain structure and intracranial pressure (discussed earlier)[84], brain metastases impact the nervous system in multiple ways. Tumours in the brain or its surrounding tissues can substantially impair neural connections, leading to cognitive deficits, motor and sensory dysfunction, and even personality changes[84–86]. Interactions between brain metastases and neurons lead to changes in cortical function[87–89]. Even in regions of the brain without overt metastases, neuro-excitability can be increased, leading to changes in cognition, alertness and mood[90]. Tumours can slow the posterior dominant rhythm, leading to reduced alertness, loss of working memory and deterioration of quality of life[91]. Circadian rhythms are also impacted, leading to problems in memory and sleep, which is vital for the repair processes of the body that are essential for overall health and functioning[92]. Ultimately, many of these changes are not sustainable long-term. How these changes may lead to death is unclear, but they may follow similar trajectories to those in patients with dementia.

Brain function can also be disrupted in patients without brain metastases, with autonomic nervous system dysfunction often

reported[93]. Intriguingly, anhedonia — a lack of ability to experience pleasure — occurs in many patients[94]. The mechanistic causes of this are unclear, but it is not restricted to patients with brain metastasis suggesting that circulating systemic factors may play a role. The wider effects of metastatic cancer on the mental well-being of a patient are discussed in Box 1. However, beyond an effect on well-being, the disruption of brain function can contribute to anorexia, and reduced nutrition can influence many other physiological and pathophysiological processes[95,96].

The role of the peripheral nervous system in cancer-related death is not well described. Although the burgeoning field of cancer neuroscience provides evidence that the efferent system can support local and metastatic tumour growth[97–99], at this time, it is unclear whether the reverse is also true. As mentioned earlier, there is clear evidence of autonomic nervous system dysfunction in patients with cancer[93], raising the possibility that cancer-mediated interruption of afferent impulses might impact overall survival. Further studies are needed to explore this possibility.

Metabolism and cachexia — catabolic effects of cancer

The presence of metastases presents altered energetic and anabolic demands on the body, leading to detrimental imbalances in metabolism[100]. Progressive and involuntary loss of body weight — termed cachexia — is a widespread multiorgan phenomenon commonly seen in patients with metastatic cancer[100,101]. This complex syndrome is characterized by a net negative energy balance, driven by the combination of increased energy expenditure and catabolism, with reduced appetite and caloric intake. A persistent decrease in nutrient intake is a key component across patients with many different cancer types, leading to breakdown of host tissues, with the degree of loss of adipose tissue and muscle mass varying between patients and among different cancer types[102]. However, the contribution of increased energy expenditure (as a result of tumour burden) is less clear. Sarcopenia may be particularly prominent in some patients, possibly representing an independent pathology from other more global tissue wasting phenotypes, and in extreme cases, loss of cardiac or intercostal muscle mass can be fatal owing to insufficient cardiac or respiratory function, respectively[103,104]. These events have also been observed in the context of extreme starvation in patients with non-cancer conditions; for example, anorexia nervosa, in which cardiac dysfunction, in particular bradycardia and sinus pauses, can cause pulseless electrical activity and death[105,106]. Electrolyte disturbances and hypoglycaemia that are often observed in cases of severe malnutrition may exacerbate the risk of such arrhythmias[105]. Cachexia also has effects on other organs and tissues, including the brain and immune system[107]. Compromised immune function is a major consequence of starvation-induced tissue wasting[108] and suggests that altered systemic metabolism leading to, or associated with cachexia, may be a contributor to the immune dysfunction present in some patients with cancer[108]. Conversely, several studies have shown that both the brain and immune system can contribute to cachexia[100,101].

Cachexia is multifactorial and has many potential causes. In some limited cases, tumour metabolism leads to systemic changes that increase energy usage. For example, high levels of lactate secretion by tumours can trigger the liver to convert lactate back to glucose, which requires energy input — termed the Cori cycle[109]. Such cycles can increase metabolic demand on the liver leading to further perturbation of liver function. However, cachexia does not correlate with disease volume in many cancer types[110]. Therefore, it is hard to reconcile a model in which the energetic and anabolic demands of the volume of disease are the main trigger for cachexia. Numerous studies have begun to reveal the possible molecular underpinnings of cachexia in some cancer types. Disruption of signalling by transforming growth factor-β (TGFβ) and related ligands is a recurring theme[111–113]. For example, circulating growth/differentiation factor 15 (GDF15; also known as MIC1), a highly conserved member of the TGFβ superfamily, is a known mediator of anorexia and weight loss, and increased circulating levels of this molecule in patients with lung cancer have been shown to correlate with cachexia development[114]. Clinical trials are currently underway to determine whether blockade of GDF15 ameliorates cachexia[115]. TGFβ itself can also promote muscle loss via the induction of myostatin[116], and the induction of signalling by activin — another TGFβ superfamily ligand — can also have similar effects on muscle mass[117,118]. Furthermore, modulation of ryanodine receptor 1 (RYR1) downstream of TGFβ can perturb sarcomere organization and thereby lead to muscle weakness[111]. As such, preclinical studies have demonstrated the potential utility of TGFβ blockade in preventing cachexia[112].

Box 1 | Psychosocial and societal factors contributing to the deterioration of patients with late-stage cancer

Psychological and social factors can have major and wide-ranging impacts on patients with incurable cancer. This manifests in more than threefold higher suicide rates[145–147]. Of note, these rates were further exacerbated in less advantaged sociodemographic groups[148], arguing that financial issues and possibly health-care access are linked to suicide in patients with cancer. However, psychological symptoms are far more extensive than those captured in studies of suicide. Anhedonia and depression are frequent in patients with cancer, impacting their overall well-being, treatment adherence and outcomes including mortality[149]. These psychological challenges often intertwine with physical symptoms, compounding the burden of each[150]. Several studies have linked stress-related psychosocial factors to cancer mortality[151], with recent work beginning to uncover the cellular and molecular mechanisms at play[152].

Research on the psychosocial aspects of cancer care, including emotional and cognitive well-being, remains under-emphasized. Barriers to the integration of psychosocial care into cancer care include stigma, difficulty identifying substantial distress, limited access to evidence-based psychosocial treatments and concerns about cost[153]. Yet, an integrated system of psychosocial care including population-based screening and targeted treatment and access to good-quality palliative care improves emotional wellbeing[154] and physical symptoms[155] and is likely to be cost-saving[156]. A deeper understanding of the mechanisms underlying neuropsychological systems and insights into how metastatic disease impacts the physiological and chemical axes of the brain will be crucial. Such insights could inform tailored interventions, therapies and support structures that address the emotional toll of cancer, enhancing the holistic care approach and improving quality of life. Expanding psychosocial research can help bridge gaps in addressing mental health in patients with cancer, ultimately improving quality of life of patients during and after treatment[146,147].

Elevated levels of cytokines, including tumour necrosis factor (TNF), IL-1 and IL-6, can also have roles in cachexia[119–121]. TNF induces multiple aspects of cachexia[122]. Muscle wasting is promoted through increased TNF and downstream nuclear factor-κB (NF-κB)-dependent ubiquitin-mediated proteolysis of muscle protein[123,124]. IL-6 triggers muscle loss through both NF-κB-dependent and JAK/STAT-dependent mechanisms[120]. Lipid metabolism is impacted by TNF reducing the expression of lipoprotein lipase and free fatty acid transporters, thereby reducing the accumulation of fat[125]. TNF can also reduce appetite through the production of corticotropin-releasing hormone (CRH). IL-1, which triggers similar proximal changes in cell signalling to TNF, can activate many of the same processes[125]. It is also interesting to note that TGFβ, IL-1 and IL-6 are associated with programmes in cancer cells that drive metastasis, which could potentially explain why metastatic disease is linked to cachexia more strongly than the presence of primary disease alone.

Whole body dysfunction

Although consideration of different organ systems is useful for highlighting some of the key events contributing to cancer mortality, the interconnected nature of body systems and the pleiotropic characteristics of the molecular mediators at play mean that it is essential to consider whole body dysfunction when thinking about causes of cancer mortality. Furthermore, such analyses may explain cancer deaths without an acute proximal cause. As discussed earlier, cytokines with potent effects on the immune system, as well as effects on appetite, can be contributors to cachexia. Therefore, it is unsurprising that tumours impact both immune and metabolic function. The immune and nervous systems are highly sensitive to metabolite availability; for example, the brain has a high demand for glucose[108,126]. Several factors, including lactic acid production and kidney dysfunction, can lead to life-threatening systemic acidosis in patients with cancer, particularly haematological malignancies with high cell turnover[127]. These can be further exacerbated upon initiation of cytotoxic therapy resulting in tumour lysis syndrome which can be fatal[128]. Consequently, metabolic perturbations and cachexia impact these systems. Over time, the cumulative stress of metabolic alterations caused by metastases, chronic changes in the level of cytokines, constant generation of tumour (neo)-antigens, aggressive therapies and incidental infections lead to exhaustion of the adaptive immune system and hamper the regenerative capacity of many organ systems with debilitating effects[18]. This multifaceted burden can ultimately trigger a body-wide shutdown leading to death.

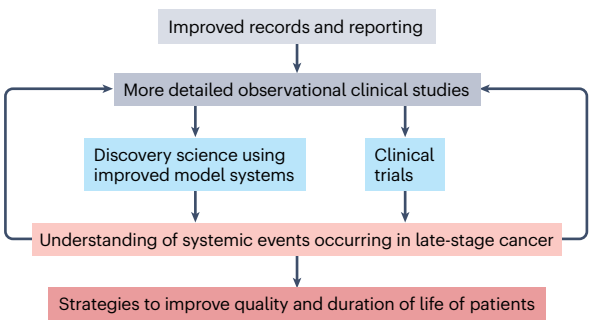

Fig. 2 | Recommendations for improving understanding of causes of cancer mortality. This scheme shows how recommendations can interlink to provide both an improved understanding of the underlying biology behind late-stage cancer and strategies to improve quality of life of patients.

Are mortality causes cancer-specific?

Although a subset of mortality causes are cancer-specific, such as metastatic invasion compromising specific organ function, the progressive and interconnected deterioration of multiple organ systems probably underlies many cancer-related deaths. This may be further influenced by interaction with other comorbidities. Of note, similar progressive deterioration is sometimes observed in the context of chronic infection and inflammation, with both cachexia and immune exhaustion associated with diseases such as tuberculosis (TB) and human immunodeficiency virus (HIV) infection[129–131]. This raises the question of whether the causes of death in patients with cancer are specific to cancer, or whether cancer (or any other chronic disease) is simply an accelerant of ageing processes occurring in healthy individuals. This hypothesis has practical implications because, if proven, it would suggest that lessons and approaches from other disease contexts could be readily transferable to patients with metastatic cancer. For example, the targeting or modulation of senescent cells is an active area of anti-ageing research, and numerous preclinical studies have indicated that similar strategies can attenuate the systemic effects of cancer[132–134].

Recommendations

One goal of this Roadmap is to propose ways to improve our understanding of why patients with cancer die and thereby develop better strategies to ameliorate symptoms and prolong life with good quality. To this end, we propose that the following steps would be useful (Fig. 2).

Improved records and reporting

It is notable that systematic reviews of the precise causes of cancer mortality are infrequent. This gap in knowledge, and recognition that this is often simply not known, is a major hindrance to learning and progress. Although improved accuracy of reporting on death certificates would be desirable, it would require a shift in longstanding clinical habits and may not be easily achievable in health-care systems under strain. Nonetheless, we advocate for locally enacting more consistency in death certificates, with specific acute causes included in addition to the underlying cause of cancer where known. Palliative care primarily focuses on symptom control for patients while balancing the potential benefits and burdens of additional diagnoses. Nevertheless, to address the gaps in our knowledge, it would be desirable to fund and establish prospective studies that continue active monitoring of patients as they transition from active disease treatment to palliative care. If possible, monitoring should be non-invasive as to not compromise patient comfort at the end of life. The great advances being made in patient monitoring with wearable technologies might facilitate this and could be used for earlier detection of infections enabling quicker intervention. Caregiver involvement in reporting of symptoms may also play a role. Furthermore, consent to obtain more detailed information from the community and palliative care teams on the contributing factors to death would provide further insight. Patient and public engagement in this type of research will be critical, with studies indicating patient desire to participate in the right context[135,136]. In addition to information gathered before death, research autopsies have the potential to shed further light on the aetiology of death, such as thromboembolic events that may not have been detected in the absence of symptoms or diagnostic testing — discussed in Box 2. Moreover, the availability of post-mortem samples can aid research into the biological underpinnings of metastases and processes leading to death. The greatest amount of information would be gained from cohorts additionally enrolled into warm autopsy programmes (Box 2).

More detailed observational clinical studies

Disease burden is not well correlated with survival; however, we propose that the accurate identification of prognostic factors correlating with survival should provide important insights into what ultimately precipitates mortality. As the cost of both targeted and non-targeted analyses of proteins and metabolites decreases, it should also become more feasible to explore molecular predictors of survival. Once identified, such factors could then be monitored in a targeted way prospectively with the potential to intervene where possible. In this setting, both the tumour and patient trajectory would receive precision-tailored treatments, the impact of which would need to be studied in randomized controlled trials. Even in the context of early phase trials, additional data could be obtained about patient symptoms in addition to safety considerations and tumour burden. Clinical imaging could also be exploited. Many patients receive computed tomography (CT) and positron-emission tomography (PET) scans, which contain abundant information about the burden and location of metastases and offer the opportunity to study changes in extent of adipose and muscle tissue and therefore body composition in relation to cachexia. Machine learning and artificial intelligence can be capitalized on to accurately measure these parameters, meaning that what would have previously been prohibitive owing to hours of radiologist time being required is now feasible[137,138]. In addition to the analysis of scans, the application of machine-learning approaches to metabolite, cytokine, immune cell and wearable technology-derived multimodal and multidimensional data may also uncover previously unknown parameters that correlate with mortality[139]. As outlined in Box 1, incorporating psychosocial metrics into the study of late-stage cancer could also enable improvements in mental well-being of patients.

Increasing the relevance of model systems

Preclinical models will also have a place in determining the linkage between events found to precede death and cause of death; however, there should be an emphasis on reverse translation of questions from human studies to preclinical models. By way of example, this could involve modelling how metastases impinge on the ability of the body to respond to infection by challenging metastatic mouse models with a pathogen. Animal ethics and husbandry considerations mean that mice are housed in controlled environments in which exposure to pathogens is rare and the types of pathogen exposure are very narrow, so this type of information is currently lacking. To be optimally informative, practical and ethical complications around studying end-of-life physiology seen in patients need to be considered. Most models are chosen for their rapid progression, often with less than a month between primary or metastatic tumour seeding and death. These are not optimal for studying longer timescale chronic changes in patients. The development of slower progressing models, implementation of multiple lines of treatment and mimicking presence of other comorbidities should enable models to more accurately recapitulate observations made in patients. Furthermore, most preclinical cancer research currently uses young mice that fail to accurately mirror the interplay between ageing and cancer seen in humans[140], with differences between chronological and immunological age providing a further confounding factor[141]. Researchers need to recognize the importance of and adopt more age-appropriate mouse models to better understand cancer mortality. In addition, most studies focus solely on tumour burden (which may only be possible at the point of death rather than longitudinally) or tumour size as a marker of disease, owing to the technical challenges of accurately quantifying organ impairment. Furthermore, tumour volume response and progression are poor surrogates of mortality in patients[142]; therefore, better modelling of other metrics of tumour activity and impact on the body system may lead to better drug development. Minimizing and alleviating suffering in experimental animals is critical; hence ethical considerations limit the ability to study mortality in mice. Therefore, an expanded repertoire of analysis would help to understand how metastases impact specific systems and events, including the haematopoietic and nervous systems, as well as whole-body physiology and metabolism. Analysis of small volumes of blood can provide data on metabolites and cytokines, as well as complete blood counts (red blood cells, white blood cells and platelets), whereas increasingly sophisticated and automated technology is available to monitor mouse behaviour[143]. It is worth noting that weight loss is frequently used as a humane end point, which indicates that many cancer models trigger cachexia and that with appropriate measurements there is an opportunity to learn more about this phenomenon in existing models. We advocate more detailed reporting of why mice were culled in experimental studies — for example, tumour volume, weight loss, laboured breathing, complete blood cell counts and blood chemistry.

Clinical trials

The types of analyses detailed earlier will provide correlation between different factors and mortality, but not causative linkage. Ultimately,

Box 2 | Research Autopsy Programmes and their optimization

Research autopsies are initiatives that involve the prompt collection of tissues from deceased individuals shortly after death, whereas tissue morphology is intact, and cells and tissues have not undergone substantial post-mortem changes. Research autopsy studies can be labour-intensive, and care is required in their logistical planning. The post-mortem interval (PMI) to autopsy can vary depending on the infrastructure available and can have implications for the utility of samples collected after death. For example, shorter PMIs achieved in rapid warm autopsy studies can more effectively facilitate in vitro (for example, cell line) and in vivo (for example, organoid and xenograft) models and can derive better quality RNA[157,158]. However, such studies are not easily established in the absence of out-of-hours facilities and expert input. Autopsies performed with longer PMIs, for example, up to several days after death, have been shown to have maintained tissue morphology and adequate DNA and RNA to facilitate cellular imaging techniques and genomic sequencing approaches[159,160]. Therefore, there is merit and general scientific value with autopsies regardless of the PMI, provided that consideration is given to the question being addressed, and the experimental approach.

The most powerful data are obtained from patients already involved in clinical studies before death. Information about disease course, longitudinal scans and tissue and blood analysis (cell counts, electrolytes, cytokines, metabolites and possibly circulating tumour DNA (ctDNA)) greatly enhances what can be learnt from post-mortem tissues. However, sensitivity is required to align the desire to acquire data with the wishes of the patients and their families, such that ultimately each autopsy has the potential to be meaningful and shed light on the biological processes leading to death.

Glossary

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis
An autoimmune encephalitis characterized by complex neuropsychiatric features and the presence of immunoglobulin G (IgG) antibodies against the NR1 subunit of the NMDA receptors in the central nervous system.

Atelectasis
Partial collapse or incomplete inflation of the lung.

Brain herniation
Pressure-induced movement of brain tissue.

Clonal haematopoiesis
An ageing-associated process in which haematopoiesis becomes dominated by one or a small number of genetically distinct stem or progenitor cells. Clonal haematopoiesis is linked to an increased risk of haematological malignancies.

Congestive heart failure
Inability of the heart to pump blood properly.

Coronary vasospasm
Constriction of the arteries that supply blood to the heart.

Corticotropin-releasing hormone
(CRH). One of the major factors that drives the response of the body to stress.

Disseminated intravascular coagulation
(DIC). A rare but serious condition in which abnormal blood clotting occurs throughout the blood vessels of the body.

Encephalitis
Inflammation of the brain.

Fistula
An abnormal connection that forms between two body parts, such as an organ or blood vessel and another often unrelated structure in close proximity.

Guillain–Barré syndrome
A rare disorder in which the immune system of a body attacks the nerves, which can lead to paralysis.

Haemostasis
The stopping of flow of blood, typically associated with the bodies response to prevent and stop bleeding.

Hydrocephalus
A build-up of fluid within the cavities of the brain.

Hypercalcaemia
Elevated calcium levels in the blood, often caused by overactive parathyroid glands. Hypercalcaemia is linked to kidney stones, weakened bones, altered digestion and potentially altered cardiac and brain function.

Hyperprogressive disease
(HPD). Rapid tumour progression sometimes observed during immune checkpoint inhibitor treatment.

Hyponatraemia
The condition that occurs when the level of sodium in the blood is low.

Iatrogenic effects
Harm, which is often unavoidable, caused by cancer treatments.

Immunoparesis
The marked suppression of polyclonal immunoglobulins in the body.

Lambert–Eaton myasthenic syndrome
(LEMS). A neuromuscular junction disorder affecting communication between nerves and muscles, which manifests as a result of a paraneoplastic syndrome or a primary autoimmune disorder. Many cases are associated with small-cell lung cancer.

Leptomeningeal metastases
When cancer cells spread to the tissue layers covering the brain and spinal cord (the leptomeninges).

Lung oedema
Also known as pulmonary oedema is a condition caused by excess fluid in the lungs. This fluid collects in the alveoli compromising function and making it difficult to breathe.

Midline shift
The observation of displacement of brain tissue across the centre line of the brain, suggestive of uneven intracranial pressure.

Myocardial infarction
Decreased blood flow to the myocardium, commonly called a heart attack.

Myocarditis
Inflammation specifically of the middle layer of the heart wall.

Paraneoplastic syndromes
A group of rare disorders that occur when the immune system reacts to changes in the body triggered by the presence of a neoplasm.

Peripheral nervous system
A dense network of nerves that transmit information from the brain (efferent neurons) to the periphery and conversely transmit information from the periphery to the brain (afferent neurons). A component of the peripheral nervous system is the autonomic nervous system.

Pleural effusion
A build-up of fluid between the tissues that line the lungs and the chest wall.

Sarcopenia
A condition characterized by loss of skeletal muscle mass and function.

Thromboembolism
The lodging of a circulating blood clot within a vessel leading to obstruction. Thromboembolisms may occur in veins (venous thromboembolism) and arteries (arterial thromboembolism).

Tissue factor
A key component of the pathway regulating blood clotting, specifically the receptor and cofactor for factor VII/VIIa.

Tumour lysis syndrome
A syndrome occurs when tumour cells release their contents into the bloodstream, either spontaneously or more typically, in response to therapeutic intervention.

Wearable technologies
Devices worn on the body, typically in the form of accessories or clothing, that incorporate advanced electronics and technology to monitor, track or enhance various aspects of human life. Examples include smartwatches and fitness trackers.

this information depends on testing in the context of clinical trials. Many of the mediators of immune dysfunction and cachexia can now be targeted with function blocking antibodies or forms of receptor traps and are being actively explored in clinical trials[115,144]. Several of these interventions were originally developed for chronic inflammatory conditions, which further highlights links between cancer and inflammation. The use of appropriately chosen secondary end points would provide an opportunity for testing whether correlative associations have a causal basis. In addition, many cancer drug trials stop providing an intervention at the point where a cancer progresses. The mechanisms behind cancer cachexia suggest that trials should be adapted to additionally consider clinical benefit in terms of weight, muscle loss and other specific determinants of efficacy, rather than solely monitor cancer progression.

Concluding remarks

Although efforts at cancer prevention and the development of curative treatment rightly receive considerable attention, we argue that understanding the precise events leading to cancer mortality should not be overlooked by funding bodies. Understanding the causes of dysfunction across multiple organ systems may provide novel strategies to manage symptoms of advanced cancer. Furthermore, better knowledge of the processes leading to death could enable patients and those around them to have essential discussions about their wishes and preferences, minimizing potentially inappropriate treatments and maximizing quality and enjoyment of life. In addition, more precise biomarkers of the likely timing of death may enable patients and their families to better utilize the time that is left. In the longer term, strategies to prevent organ dysfunction should offer considerable benefits to both patients with high tumour burden and those who have low disease burden but die from factors produced by cancer.

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Author contributions

All authors researched data for the article. A.B., K.B., T.R.C., T.G., T.J., C.S., M.G.V.H, R.K., M.J.-H. and E.S. contributed substantially to discussion of the content. T.C., R.L. and E.S. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

A.B. is an inventor on pending patents 63/449,817, 63/052,139 as well as awarded patents 11,305,014 and 10,413,522; all issued to the Sloan Kettering Institute. She has received personal fees from Apelis Pharmaceuticals and serves as an unpaid member of the Evren Technologies SAB. K.B., T.R.C., T.G., T.J. and R.K. declare no competing interests. M.J.-H. reports support from Achilles Therapeutics Scientific Advisory Board and Steering Committee, Pfizer, Astex Pharmaceuticals, Oslo Cancer Cluster and Bristol Myers Squibb outside the submitted work. R.L. reports personal fees from Pierre Fabre and has research funding from BMS, Astra Zeneca and Pierre Fabre outside the submitted work. E.S. reports grants from Novartis, Merck Sharp Dohme, AstraZeneca and personal fees from Phenomic outside the submitted work. C.S. reports grants and personal fees from Bristol Myers Squibb, AstraZeneca, Boehringer-Ingelheim, Roche-Ventana, personal fees from Pfizer, grants from Ono Pharmaceutical, Personalis, grants, personal fees and other support from GRAIL, other support from AstraZeneca and GRAIL, personal fees and other support from Achilles Therapeutics, Bicycle Therapeutics, personal fees from Genentech, Medixci, China Innovation Centre of Roche (CiCoR) formerly Roche Innovation Centre, Metabomed, Relay Therapeutics, Saga Diagnostics, Sarah Canon Research Institute, Amgen, GlaxoSmithKline, Illumina, MSD, Novartis, other

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Additional information

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