Effects of Cancer Treatment on the Nervous System, Volume 1

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Edited by

Wolfgang Grisold, Riccardo Soffietti,
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PART 1

CHAPTER 1.1

WHAT IS CANCER: AN INTRODUCTION

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Abstract

Cancer names a large group of diseases caused by genetically aberrant cells that step out of line from behaving as a cell in a multicellular organism, but behave like an independent organism by sustaining uncontrolled cell division, regaining mobility, growing in other tissues, and exhausting the resources of their host organism. All multicellular organisms are potentially affected by cancer.

This paper presents a short overview of the historical development of understanding the mechanisms of cancer, the hallmarks of cancer, and the development of cancer-directed therapies.

Keywords: Cancer, unlimited cell division, avoiding apoptosis, immune escape, neovascularization, metastasis

Introduction

Huge progress has been achieved across all disciplines in the prevention, diagnosis, and treatment of patients with malignant tumors. On the basis of decades of clinical and basic research, the outcome of cancer patients may be changed from a deadly threat to a chronic illness, or even to a curable disease for an increasing number of patients. However, the perception of the cancer threat in the general population has barely changed: cancer is still perceived as the ultimate threat, closely linked to suffering and death—much more than cardiovascular diseases and degenerative metabolic diseases linked to sedentary lifestyles that are still the main cause of death worldwide.

There are many reasons that explain this discrepancy, not limited to the easier "mechanical" understanding of cardiovascular disease or to our coping styles that allow us to think that we will be able to change our lifestyle habits tomorrow, to the easier acceptance of sudden cardiac death compared to what is called "a long, severe illness" in obituary notices. Cancer remains scary, a betrayal of the body, as this is a noncommunicable disease, and arises from a malignant process taking place in the host him- or herself.

The definition of cancer

Cancers are a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. The progression from normal cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression. Cancers are caused by a series of mutations. Each mutation alters the behavior of the cell somewhat.[1]

Our understanding of cancer evolved with the development of diagnostic methods starting from the observation of the invasive growth of cancer, and its spread to lymph nodes and to distant organs, and of paraneoplastic phenomena, such as weight loss, sarcopenia, abnormal bleeding, and thrombosis, to the possibility of detecting cancer through liquid biopsies and by finding tumor-characteristic epigenetic changes in cell-free DNA or by refined imaging techniques that allow us to detect tumors of less than 3 mm diameter or even smaller.

Cancer appears in all multicellular organisms, including plants, fungi, and animals. Here, cancer is most certainly "the price to pay for multicellularity." We are all well aware that our individual life started from just one cell, a zygote, and that an adult human is composed of ten trillion cells in average. Each of these cells has the same genetic information, written down in our 46 chromosomes and this individual genetic information has to be reproduced at every mitosis and delivered to each daughter cell. One of the fundamental differences between unicellular and multicellular organisms is the organization of the genomes in chromosomes, which are no longer in circular DNA without a centromere. Moreover, the specialization of cells for different "duties" necessitates communication between them and their surroundings, the extracellular matrix (ECM), via specialized molecules, later called hormones, specialized structures evolving to ECM proteins with a scaffold function, or membrane-bound receptors for messenger molecules. This is an extremely shortened and simplified overview of tissue and organ formation. The

organization of differentiation of cells in multicellular organisms requires a complex interplay between the cells allowing development and growth, regeneration, and wound healing, and also senescence and the death of the organism after a variable lifespan. All these phases of life are regulated by specialized genes and the regulation of gene expression is also grounded in the genome, allowing differentiated and timely regulated gene expression for different tissues within an organism. All the fundamental pathways regulating key functions have been found highly conserved during evolution. The higher complexity of the genetic regulatory framework bears the potential for misuse, such as the evasion of cells from growth control and thus multiplication from cells that have acquired a different genetic constitution. When these genetically different cells survive and multiply within the original organism, using the resources of the host and evolve with further changes and spread in other tissues and exhaust the host organism, this is called cancer.

History of cancer

The eventful history of cancer and the development of modern cancer medicine have been summarized in *The Emperor of Diseases*, a recommendable book by Siddhartha Mukherjee.[2]

In the following, the present understanding of cancer will be described very briefly, with subjectively chosen highlights from the long evolution of the global search.

The name “cancer” dates back to ancient Greek times and was probably given due to the resemblance of multiple, enlarged, and distorted veins visible on the cut surface of a tumor or even at the surface of the body in the case of locally advanced breast cancer, which mimic the multiple limbs of a crab. Antique physicians already understood the difference between cancer and other diseases and its evolution from a localized disease to the invasion of other organs. The oldest preserved text describing cancer is found in the Egyptian Edwin Smith Papyrus, which is a copy of an older papyrus dating back to the twenty-seventh century BC. It relates the professional experience of Imhotep, who lived at the court of Pharaoh Djoser, and is structured in 48 case reports.[3] Case report 45 details physical findings of hard masses in a breast, which most probably was a case of advanced breast cancer. Contrasting with the other cases, Imhotep gives no treatment recommendation but states, “there is no therapy.” Asclepius, Galen, and other antique physicians have left pertinent descriptions of clinical pictures, as did later physicians as soon as post-mortem examinations became possible; however, no effective therapy

could be offered before the discovery of anesthesia and of aseptic surgical procedures. Nevertheless, some physicians contributed pertinent observations to the development of cancers, such as John Hill, who observed cancer in the noses of people who partook of tobacco snuff, and Percival Pott, who described scrotal skin carcinomas in chimney sweeps. Physicians of the sixteenth century understood breast cancer as coagulated milk clots, as poisoning of the organism, and even as a sort of infection. The microscopical examination of cancer tissues led to the definition of the common microscopical differences between normal cells and tumor cells: their often bigger cell nucleus, the variability of size from one tumor cell to the other, the higher mitotic rate of atypical cells as compared with normal cells, the formation of giant cells, the more frequent occurrence of apoptotic debris, the loss of typical features characterizing the differentiation of the specific tissue, the loss of orientation of the cells within the tissue, ignoring existing cell architecture, and finally the step to cell motility with the disruption of the basement membrane, the penetration into blood vessels, and, after exiting from the blood stream, ultimately the entry into other organs. All these features were observed in all tissues, indicating that cancero-genesis occurred similarly as a multi-step process in all different kinds of tissues. In fact, at least in humans, all cell types have a known malignant counterpart.

Among the 20,000 genes of the human genome, only around 100, later named “oncogenes” and “tumor suppressor genes,” have been found to be involved in the formation and evolution of malignant tumors. Those are mainly genes involved in regulating the cell cycle, responding to growth factors, and evading death signals.

Oncogenes are often present in normal cells in an inactive form as proto-oncogenes. In case of activation either by mutation or by evading negative regulation they gain their function and promote cell division. The second category of genes involved in tumorigenesis is the tumor suppressor genes, whose silencing prorogues the escape from cell-cycle control. The transformation from a normal cell to a cancer cell usually involves multiple steps.

Malignant transformation may happen at any level of differentiation for every known normal cell. Well-known examples are the different forms of leukemias and lymphomas with at least one malignant entity corresponding to each defined maturation step of hemopoietic cells. The rate of tumor formation may change, but there seems to be no exception. Even remnants of embryonic organs that are no longer maturated and built in humans bear the potential for the formation of

malignant tumors, such as yolk-sac tumors or tumors of the urachus or of the gill slits.

Among the first basic science researchers, Theodor Boveri, a German biologist working on sea urchins, stated that organisms need intact chromosomes for correct embryonic development. He postulated as early as 1902 that all causes able to disrupt the integrity of chromosomes, such as radiation, chemicals, or other physical threats, are able to cause cancer. The American geneticist Alfred G. Knudson observed in 1971 that children with familial retinoblastoma developed their tumors earlier in life than children without such a family history, who mostly developed retinoblastoma in one eye and at an older age. His theory of the "two-hit hypothesis" of the development of retinoblastoma stated that the familial predisposition was caused by an inherited genetic aberration and that the formation of a retinoblastoma in such individuals occurred earlier in life because fewer additional mutations were needed than in sporadic cases. This hypothesis led to the discovery of cancer genes. To start malignant growth, at least two different genetic changes have to be introduced in a cell of an experimental animal. For human cells, even more hits appear to be necessary. Vogelstein et al. described the multi-step evolution from the normal epithelium of the colon to mucosal hyperplasia, to the formation of mucosal polyps, and finally to their further transformation to polyps with atypical mucosa growing into an invasive colonic cancer.[4] Understanding this process and identifying colonic polyps as precursors of the lesions of cancer provided the rationale for preventive colonoscopy with polypectomy to prevent the formation of invasive cancer of the colon. Cancer of the colon is still a major cause of death, even in developed countries; nevertheless, it should be fully preventable through lifestyle changes and adherence to preventive colonoscopy. Similar stepwise evolution of malignancy was observed for other tumors as well.

Until the mid-twentieth century, cancer therapy relied mainly on two therapeutic modalities: surgery and radiation therapy. Systemic treatment mainly concentrated on supportive care, as no direct medications for cancer cell therapy were yet available. The first clinical studies with anti-cancer drugs were made shortly after World War II. Meanwhile, much progress has been made in the development of other cytotoxic drugs, and because of the increased understanding of the molecular changes caused by cancer, the development of small molecules inhibiting cancer signaling, and the development of cancer-directed immunotherapy. However, although the number of cancer survivors is increasing, so are the number of patients developing several primary cancers. There is still room for improvement in cancer diagnosis.

Understanding the mechanisms of cancer growth

In 2000, Hanahan and Weinberg compiled the accumulated knowledge in cancer research and formulated their hypothesis of the six hallmarks of cancer: the acquired genetic traits that are necessary and sufficient to transform normal cells into tumor cells.[5]

First hallmark: sustained growth of cells

To maintain tissue homeostasis, the rhythm of cell divisions of normal cells is tightly regulated; nevertheless, the control mechanisms of normal tissue homeostasis are not fully understood. Normal tissues and organs seem to sense how much cell division is needed to obtain or maintain the dimension of the specific organ. No cell undergoes cell division without getting a growth signal. These signals are usually growth factors produced by other cells and sensed by a transmembrane growth-factor receptor—mostly a tyrosine kinase. The signal is transmitted into the cell and further downstream into the cytoplasm involving a signaling cascade of other enzymes, finally reaching the cell nucleus. In the case of growth signaling, actions to prepare cell growth and mitosis are undertaken. However, to grow in a Petri dish, normal cells need to be stimulated by their growth factor. Further supply is needed from their tissue-specific integrins for them to become attached to their used-matrix proteins; and even with all requirements fulfilled, they will not grow further once a monolayer of cells is reached. Only tumor cells are able to grow in serum-free media, producing their own growth factors and producing several cell layers.

To obtain the sustained growth of tumor cells, the normal pathway of growth stimulation has been modified at each step. Tumor cells have been found to be able to produce their own growth factors in an autocrine loop, whereas in normal tissue no autocrine stimulation takes place; there, the growth factors are produced by another type of cell.[6]

Moreover, tumor cells present much higher growth factor receptors on their cell surface than normal cells do, rending them more able to react to growth-factor stimulation. Mutations in the growth factor receptors make them fire constantly, even without external stimulation, such as the truncated epithelial growth factor variant III (EGFRvIII) in glioblastomas. Moreover, during malignant transformation, mutations alter the transfer of signals into the nucleus, favoring entrance into the cell cycle.

Tumor cells are able to influence their neighboring cells in the tissue, for example, fibroblasts, endothelial cells, and bone-marrow-derived blood cells to promote their incessant growth.

Second hallmark: disruption of negative feedback mechanisms that attenuate proliferative signaling

As tissue homeostasis is so tightly monitored in normal cells, there are a number of negative feedback loops to provide growth inhibitory signals. When normal cells enter the cell cycle, their progress through this cycle is very carefully controlled by a multitude of tumor-suppressor genes whose loss or inactivation promotes escape from negative feedback mechanisms such as the retinoblastoma gene, transforming growth factor beta, PTEN phosphatase, and mTOR signaling. Compromised negative feedback loops are widespread in cancers. Moreover, some of these mechanisms "convince" cells to enter irreversibly into postmitotic differentiated states[7] as a module of negative feedback. Tumor cells avoid this terminal differentiation—and thus also the building of functional tissue.

Third hallmark: resisting cell death

Apoptosis or programmed cell death was first described in 1842 by the German zoologist Karl Vogt. In multicellular organisms, apoptosis is the most important way of destroying old or ineffectual cells and saving their constituent parts. Each day in an average adult person more than 50 billion cells undergo apoptosis. The pathway is highly regulated and takes 30 to 120 minutes.[8] Intracellular and extracellular sensors report either damage to a cell's DNA or the receiving of pro-apoptotic signals from the cell's environment by the Fas receptor and Fas ligand system. Once a point of no return is reached, the process goes on and cannot be stopped. The different phases of apoptosis run down one after the other, leading to small apoptotic bodies that are engulfed by macrophages or other immune cells.

Cancer cells however have developed many mechanisms of evading apoptosis, ensuring their survival even with substantial genetic changes. The most common change is the loss of the TP53 function, which is the most prominent DNA-damage sensor and activates pro-apoptotic circuitry. Another important mechanism is increasing the levels of anti-apoptotic signals like Bcl-2 or survival signals like insulin growth factor 1. There are multiple ways by which cancer cells have managed to survive apoptotic signals, showing how important these traits are for tumorigenesis.[9]

Autophagy is a way to survive under challenging conditions. In such highly stressful conditions, cells manage to break down even their own organelles like ribosomes and mitochondria in order to use their constituents for energy expenditure. The cells generate intracellular vesicles, fusing with the organelles and then with lysosomes that degrade the organelles. Furthermore, autophagy pathways are highly regulated and there are links between autophagy and apoptosis. However, cells that undergo autophagy may fall into states of cell dormancy and thus this mechanism may allow them to survive radiation therapy or exposure to cytotoxic drugs and to re-enter the cell cycle when environmental conditions have improved. Thus, autophagy is not only a form of cell death, but also a potential survival strategy for tumor cells.

Such a Janus-faced outcome is even more related to the third form of cell death, cell necrosis, where the involved cell swells until it bursts. The cell constituents are scattered around in the micro-environment provoking the recruitment of inflammatory immune cells. This might lead to the presentation of tumor antigens to the immune system and enhance the activity of the immune system against the tumor; however, more often the pro-inflammatory environment directly stimulates tumor cell growth and tumor angiogenesis.

Fourth hallmark: enabling replicative immortality

In normal tissues the replicative capacity of cells is tightly regulated and after a variable amount of cell divisions—related to the specific differentiation status—cells stop dividing and survive in senescence or enter a crisis phase resulting in cell death. Normal cells might be maintained in culture even under optimal conditions only until they reach the end of their replicative potential and enter senescence or crisis. This is monitored by the shortening of the telomeres at the end of the chromosomes at each cell division. Telomeres are hexanucleotid repeats situated at the end of chromosomes protecting the end of the coding sequences of the chromosome. At each DNA duplication, telomeres are truncated—shown by the fact that the telomeres of humans at birth are about 11 KB long and only 4 KB long at old age. However, in most cancer cells the enzyme telomerase is reactivated, which elongates the telomeres and thus provides unlimited replicative capacity. The reactivation of telomerase—which is silenced in nearly all cells after the end of the embryonic phase with only a few exceptions, such as cells with high replicative potential, for example, male sperm, epithelial cells, or immune effector cells, or the much rarer

activation of an alternate pathway to maintain telomere length—enables tumor cells to escape the barriers of unlimited replication.[10]

Fifth hallmark: inducing angiogenesis

During embryogenesis, normal vessels form through the multiplication of endothelial cells and elongation within tubes and sprouting from existing vessels. In adults, angiogenesis is limited mainly to wound healing and to sustaining the menstrual cycle in females. Yet a growing tumor requires a growing supply with oxygen and nutrients and evacuation of carbon dioxide and metabolic wastes for sustaining its formerly non-existing tissue. Thus, an "angiogenic switch" activating the formation of tumor vessels is needed as a tumor reaches 2–3 mm in diameter for further growth, induced by hypoxia and by oncogenic signaling. Typically, blood vessels produced by excessive tumor angiogenesis are different from normal vasculature, showing multiple, tortuous branches, variable diameters, premature capillary sprouting, erratic blood flow and leakiness, and lacking the lean and order-oriented design of normal vasculature.[11]

Neo-angiogenesis involves a multitude of cells, not only the tumor cells themselves, but of course endothelial cells, pericytes, fibroblasts, and a lot of bone-marrow-derived cells, such as neutrophils, macrophages, mast cells, and other myeloid-derived cells infiltrating the tumor mass, whose participation in the process of tumorigenesis, immune surveillance, and immune tolerance is as yet incompletely but increasingly understood.

Sixth hallmark: invasion and metastasis

The ability to overcome normal growth barriers, such as the basal lamina in endothelial cells, to invade other tissues, or even to survive cell detachment, enter into the vasculature, exit from it, and survive within a different microenvironment from the inherent one was the most obvious characteristic of cancer cells, demonstrating how much their genetic traits have evolved from their original setting. One of the characteristics enabling the tumor cells to exhibit these features are called "epithelial-mesenchymal transition" (EMT), a process reminiscent of embryonic potentials or processes activated by wound healing that also enables invasion and metastasis. As in other hallmarks too, this multi-step process is enabled by the reactivation of functions active during embryogenesis, such as the increased mobility of cells.[12] Moreover, the role of the neoplastic stroma in stimulating invasive behavior is increasingly

understood. Macrophages at the invasive borders of tumor nodules can facilitate invasion by breaking down matrix proteins. It could be shown that macrophages stimulate breast cancer cells by producing EGF and the breast cancer cells vice versa stimulate the macrophages by colony stimulating factor 1 (CSF-1).

The changes that invasive cancer cells undergo during the metastatic process might be at least partly reversible, as the microenvironment in the new organ no longer provides stimulatory conditions as before. Thus, they may undergo a "mesenchymal to epithelial transition" in return, regaining an aspect of epithelial cells, as in the primary tumor before EMT. To become macroscopic metastatic lesions, the invading cells must resolve the problem of thriving in this new environment and the angiogenic switch. The primary tumor may send out signals maintaining the micro metastases in a state of dormancy that reverts when the primary tumor is resected. Or metastases might grow rapidly, decades after the elimination of the primary tumor, as they have solved their local growth problems.

Recently, an updated version of the "Hallmarks of Cancer" was released, taking into account the new insights made in the decade between the first and the second hallmark review. The following new hallmark was added: enabling characteristic: genome instability.

The analysis of tumor genomes, as compared with the original genome, highlights evidence of a loss of control of genome integrity in cancer genomes and of recurrent genetic amplifications and losses that might be associated with tumor growth. Genetic instability seems to favor tumor growth.

Enabling condition: tumor promoting inflammation

Another emerging enabling characteristic of tumor growth might be tumors that promote inflammation. The presence of immune cells within nearly every tumor has long been known and mostly interpreted as an attempt by the immune system to reject the tumor. But increasing evidence has accumulated that tumor inflammation is enhancing tumorigenesis and progression.

Seventh hallmark: reprogramming cell metabolism

Cancer cells definitely pursue other goals beyond differentiated tissue cells; and given their focus on cell growth and division, they are in constant need of building new cell components. It has long been known

that cancer cells depend on aerobic glycolysis as observed by Otto Warburg as early as 1930. The importance of glucose to tumors is used for diagnostic purposes, with radiolabeled F18 glucose as the reporter in the FDG-PET. Despite the low efficiency of glycolysis to produce ATP, its advantage for tumor cells lies in the potential of the synthesis of nucleosides and amino acids that are needed to assemble the constituents of new cells.[13] As the altered metabolism of tumor cells is better understood, potential therapeutic targets emerge that could be exploited therapeutically, thus opening new forms of cancer therapy.

Eighth hallmark: evading immune destruction

The role of the immune system in recognizing and eliminating malignant tumors was challenged as the tumor-promoting effects were increasingly understood. However, the immune system has undeniable tumor-protecting effects, as demonstrated by epidemiologic data showing a higher tumor frequency in persons with compromised immune systems such as transplant recipients—for example, transplant-related lymphoma, where often a remission can be obtained as soon as the "immuno-rejection prophylaxis" is reduced, as well as in animal models, which show that transplanted tumors grow much more efficiently in immunodeficient mice than in immunocompetent animals.[14] Further proof of the activity of the immune system against malignant tumors is demonstrated by the better outcomes of patients with colon cancer or ovarian cancer with a high density of infiltrating killer lymphocytes in the tumor. On the other side, tumors were shown to secrete high levels of TGF-ß and other immune-suppressive factors or to recruit regulatory T-cells or myeloid-derived suppressor cells to evade the immune response.[15] This is an actively moving research field where hopefully the next few years will bring new insights and effective therapeutic applications.

Cancer stem cells

In recent decades, it became more and more evident that not all tumor cells are able to generate a complex neoplasm and that few cancer stem cells are able to initiate and maintain the evolution of a malignant tumor. The origin of these cancer stem cells has not yet been clarified for all tumors and may vary between tumor types. Normal tissue stem cells may undergo malignant transformation to tumor stem cells, or this role may be assumed by fairer differentiated progenitor cells undergoing malignant transformation and becoming tumor stem cells. However, cancer stem

cells show common properties as unlimited self-renewal potential and resistance to radiation and to most chemotherapeutic agents. Recently, it was demonstrated that cancer stem cells have undergone an EMT transformation and are thus mobile and able to recruit a proinflammatory microenvironment to sustain their survival and to build up tumor-stroma-facilitating replication and infiltrative behavior.[16]

Tumor stroma

Most, if not all, the previously presented hallmarks involve the tumor stroma in one way or the other, showing the profound transformations and interactions of tumor cells with adjacent "stromal" cells as fibroblasts, endothelial cells, or myeloid-derived cells such as macrophages, bone-marrow-derived pericytes, or immune cells with either tumor-promoting or tumor-suppressing properties. This emerging concept shows that the formation of a malignant tumor requires more than "the tumor cell" itself, but always involves the whole organism and can no longer be understood as a locally arising problem. The potential early dissemination of EMT-transformed cancer stem cells explains clinical findings as metastases become evident years or decades after the eradication of a malignant tumor. There is still much research needed to unravel all the mechanisms exploited by malignant tumors in order to find more effective cures.

A major advance in recent years was gaining insights into the role of commensal micro-organisms in the development of the immune system and into the development of diverse pathologies and among cancers as well as in the modulation of treatment responses by the microbiota.

Microbiota

Only in the last few decades have our commensal prokaryotes come to attention; they are increasingly being investigated and their essential contributions to health and disease are being unraveled. In fact, like all multicellular organisms, we live in close contact with many micro-organisms that constitute our commensal flora, as archae, fungi, bacteria, and viruses. They colonize all barrier surfaces, for example, the skin, the oral cavity, the airways and the lungs, the gut, and in women the vagina. The gut microbiome alone outnumbers our body cells by a factor of 10:1. The microbiome interacts with its host in many essential functions, like the development of the innate and adaptive immune system.[17] During evolution, the microbiota and the host evolved together to build a symbiotic relationship, avoiding immune reactions against the symbiotic

flora as well as infections with pathogenic organisms. It is also essential for the development of a functional systemic immune system.[18]

The essential prognostic role of the microbiota in modulating immune cell infiltration of tumors and more generally, an inflammatory stroma was first recognized in colorectal cancer,[19] reflecting as well potential cancer prevention and promoting the effects of the microbiota. Dysregulation of the microbiota or damage to the barrier function, like after antibiotic therapy, can cause chronic inflammation, which is one of the main causes for the development of cancer,[20–21] as it is also on distant sites, such as in breast cancer. By regulating the function of myeloid-derived cells in the tumor stroma, the gut microbiota may also influence the response to cancer treatment. In murine experiments, the efficacy of chemotherapy with platinum compounds was dramatically reduced in antibiotic pretreated mice.[22] Moreover, the side-effects of chemotherapy and radiotherapy to the composition of microbiota and the disturbance of the intestinal barrier function modulate the systemic inflammation and the activities of the immune system. Such interactions and their potential modulation have not yet been fully elucidated. More research is needed to understand and to optimize the influence of microbiota, tumor development, tumor prevention, and therapy.

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CHAPTER 1.2

EPIDEMIOLOGY OF NERVOUS SYSTEM INVOLVEMENT IN PATIENTS WITH CANCER

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Abstract

The involvement of the nervous system occurs in up to a quarter of patients with cancer, either as metastatic disease or as an adverse event of cancer treatment. Metastatic disease may manifest as a circumscribed lesion in the brain or spinal cord, or be a more widely disseminated spread of tumor cells to leptomeningeal spaces, peripheral nerves, roots, or plexuses. While solid metastases may occur as the first sign in a patient with previously unrecognized cancer or years after the primary diagnosis, leptomeningeal or neural metastasis is typically a late complication of cancer with poor prognosis and limited treatment options. While lung, breast, and colorectal cancer account for the majority of solid metastases, hematologic malignancies, lung cancer, breast cancer, and melanoma are frequently involved in leptomeningeal and neural metastasis. The incidence increases with advancing age, with variation according to the primary cancer. Of note, CNS metastases account for a large fraction of tumors in the nervous system, readily outnumbering primary brain tumors by a factor of 10. Thus, with ageing societies and the prolonged survival of cancer patients (due to improved diagnostic assessments, therapy, and long-term patient management), their incidence is expected to further increase and pose a rising challenge to health care systems. In contrast to primary brain tumors, however, epidemiological data of patients with CNS metastases are not systematically monitored through cancer registries, which grossly limits our knowledge of their societal impact and the resources needed, as well as hampering the development of strategies for primary or secondary disease prevention.

Keywords: Epidemiology, brain metastases, incidence, outcome, population ageing

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Introduction

In 2018, 18.1 million individuals were diagnosed with cancer, and this number will further increase to 29.5 million by 2040 (see https://gco.iarc.fr/tomorrow/home). In up to 35% of these patients, the nervous system is involved either through metastatic disease or due to neurotoxicity caused by cancer treatment.[1]

Metastatic disease may manifest not only as solid CNS metastasis but also as the disseminated spread of tumor cells to the leptomeningeal spaces—a process that is known as neoplastic meningitis or leptomeningeal metastasis (LM). Likewise, in the peripheral nervous system, cranial and peripheral nerves, nerve roots, and plexuses may be infiltrated by solid or hematological malignancies. Common cancer-treatment-related complications include chemotherapy induced peripheral neuropathy as well as radiation-induced leukoencephalopathy and secondary tumors, which add to considerable patient morbidity and mortality.

The purpose of this chapter is to summarize the current evidence on the incidence and outcome of the various manifestations of metastatic cancer and cancer-treatment-related involvement of the nervous system.

Metastatic disease involvement of the central nervous system

Solid metastases

The first estimates of the *incidence* of brain metastases were typically based on single center *post-mortem series*. While those varied considerably in sample size (ranging from as few as 50 to 2,300 cases), they estimated that brain metastases occur in approximately 25% of patients who had died from cancer, with significant variation according to