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Toward Restored Bowel Health in Rectal Cancer Survivors

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As technology gets better and better, and as clinical research provides more and more knowledge, we can extend our ambition to cure patients from cancer with restored physical health among the survivors. This increased ambition requires attention to grade 1 toxicity that decreases quality of life. It forces us to document the details of grade 1 toxicity and improve our understanding of the mechanisms. Long-term toxicity scores, or adverse events as documented during clinical trials, may be regarded as symptoms or signs of underlying survivorship diseases. However, we lack a survivorship nosology for rectal cancer survivors. Primarily focusing on radiation-induced side effects, we highlight some important observations concerning late toxicity among rectal cancer survivors. With that and other data, we searched for a preliminary survivorship-disease nosology for rectal cancer survivors. We disentangled the following survivorship diseases among rectal cancer survivors: low anterior resection syndrome, radiation-induced anal sphincter dysfunction, gut wall inflammation and fibrosis, blood discharge, excessive gas discharge, excessive mucus discharge, constipation, bacterial overgrowth, and aberrant anatomical structures. The suggested survivorship nosology may form the basis for new instruments capturing long-term symptoms (patient-reported outcomes) and professional-reported signs. For some of the diseases, we can search for animal models. As an end result, the suggested survivorship nosology may accelerate our understanding on how to prevent, ameliorate, or eliminate manifestations of treatment-induced diseases among rectal cancer survivors.

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Introduction

The Paradox For Rectal Cancer Survivors

A cancer survivor lives with a paradox. The same cancer treatment that saved her or his life becomes a threat to her or his health after the cancer has been eliminated. Surgery, irradiation, cytotoxic chemotherapy, biological anticancer substances or other drugs in the treatment that provide the cure from cancer also influence normal tissue. When the cancer treatment damages nerves, vessels, or other parts of the normal tissue, this tissue may not heal with restored normal function. Not least before today's technology had been developed, the normal tissue may heal with aberrant anatomical structures such as fistulae. The surgeon also may need to remove an entire organ with the associated functional loss. Moreover, pathophysiological changes may start processes that continue as long as the cancer survivor lives.

Tissue that has not been restored, ongoing pathophysiological processes, aberrant anatomical structures, and the removed organs may decrease the rectal cancer survivor's health in many different ways. The aftermaths of treatment for cancer in the small pelvis include long-lasting and long-term symptoms that decrease bowel, urinary, and sexual health among the survivors. The technological developments in surgery, together with the growth of knowledge regarding

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anatomy and physiology, has resulted in less normal-tissue damage as well as preservation of important nerves and vessels. Modern radiotherapy techniques may reduce long-term toxicity in rectal cancer, but the need to treat some functionally important anatomical structures with curative doses remains in all radiotherapy concepts. We can raise the level of our ambition to cure by radiotherapy while restoring physical and psychological health in the cancer survivor. We also have a growing palette of remedies other than improved surgery and radiotherapy that may increase the ratio between tumor-cell elimination and normal-tissue damage.

Toxicity, Long-Term Side Effects or Survivorship Diseases

We are not used to considering the conditions that afflict survivors in the long term as being manifestations of survivorship diseases. Instead, we use terms such as toxicity or side effects. Philosophically, one may discuss what a disease is. What is the real phenomenon, Das Ding an Sich? Many of the diagnoses enumerated in the World Health Organization's International Classification of Diseases (ICD)-list do not have a natural cause (eg, a virus or bacteria); they are a product of our culture and medical practice (side effects). Many of the "diseases" given a diagnosis in the ICD-list are syndromes in the sense that they may reflect 1 or several different pathophysiological processes and are defined as a combination of 1 or several symptoms. Some diagnoses, for example fractures, may be the consequence of an accident. Nevertheless, when the concept of a "disease" was introduced, and health care professionals developed more and more targeted and evidence-based treatment strategies for each disease, health care professionals could increase the rate of survival and make the quality of life of their patients better. A symptom such as thirst was seen under certain conditions as a manifestation of a disease, diabetes mellitus. With time, diabetes mellitus type 1 was recognized as a separate disease—a pathophysiological process was identified (autoimmunity against beta cells) and a mechanism was understood (lack of insulin). So, in the 1920s, with this biological and medical knowledge as a background, a remedy was presented for this previously deadly disease, administration of insulin extracted from animals. We suggest a similar knowledge process for cancer survivors. What we today cite as toxicity or long-term side effects after cancer therapy we now suggest might better be regarded as manifestations of certain survivorship diseases.

Survivorship Diseases

As soon as we take the position that the problems after treatment, particularly in the long term, are to be regarded as survivorship diseases, we encounter a large number of new challenges. How many of these are survivorship diseases? What would a nosology look like that defined these survivorship diseases and, in the end, would give them an ICD-code? Obviously, there were no survivorship diseases before we had cancer survivors. To what extent do we need to invent a new and a distinct survivorship pathophysiology and to what extent can we use insights from other more historical diseases? Which symptoms in the short and long term are manifestations of a specific survivorship disease? These questions cannot be answered based on available information. In the following, we look first at the literature concerning manifestations of survivorship diseases associated with the treatment of rectal cancer and then present an outline of a future nosology for survivorship diseases. We use current terminology, that is, we refer to the manifestations of the survivorship diseases as toxicity, or in the trial context, as adverse events.

Current Toxicity Scores

Professional-Reported Scoring

Documentation of adverse events related to cancer treatment can be achieved in 2 ways. The classic approach is the objective scoring of symptoms by health care professionals, for example, physicians or nurses. Whereas in the past, different objective scoring systems have been used to classify acute and late toxicities as well as toxicities (presumably) induced by different treatment modalities (separate classifications, eg, for radiotherapy-related and chemotherapy-related events); the Common Terminology Criteria for Adverse Events (CTCAE) classification is now available as a universal approach used to systematically describe adverse events in trials investigating cancer treatment. The document is currently available from the National Cancer Institute in the version CTCAE v. 4.0, published in 2009.[1] In the so-called system-organ class "gastrointestinal disorders," a total of 117 types of adverse events are listed, each graded on a scale from 1 (with the general definition of "mild; asymptomatic or mild symptomatic; clinical or diagnostic observations only; intervention not indicated") to 4 ("life-threatening consequences; urgent intervention indicated") and 5 ("death related to adverse events"). It should be noted that additional adverse events related to radiotherapy of rectal cancer are found in other system-organ classes (eg, for renal and urinary disorders), but are not the subject of this article. The large number of different adverse gastrointestinal events results in part from the separate designation of toxicities for each anatomical location. An ulcer may occur in the anal canal, in the rectum, and in the small intestine. An example of CTCAE v. 4.0 toxicity grades relevant in radiotherapy of rectal cancer is shown in Table 1 (extensive list in Supplementary material).

It is challenging for clinical trials to select a core set of the most relevant CTCAE v. 4.0 toxicities for which patients are routinely evaluated or to summarize the adverse event data appropriately if all 117 gastrointestinal events are to be recorded as they occur. Definitions of individual adverse events may overlap as well as fail to make a distinction between objective signs and subjective experience of symptoms. A typical example is the following 3 events: enterocolitis, colitis, and diarrhea. Consequently, the use of all 117 gastrointestinal events in a clinical setting may lead to a dilution effect because of the confusion caused by the overlap. Another problem is the differentiation between tumor-related symptoms and treatment-related symptoms. A patient with rectal

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