Commentary

Historical and Current Advances That Incorporate Competing Risk for Benefit and Mortality in Older Patients With Cancer

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ABSTRACT

Competing risk occurs when patients have >1 disease or condition that can affect an important outcome, such as mortality. In older adults who develop cancer, the presence of comorbid chronic diseases or functional impairments can change the likelihood that the cancer will lead to an adverse outcome. The recognition and incorporation of competing risk into oncology research started during the experimental development of chemotherapy. A related concept of considering performance status in clinical trials of cancer therapies also occurred in the context of treatment interventions using chemotherapy. Statistical methodologies for competing risk have advanced substantially over time, and a patient's performance measurements remain common in deciding how best to care for older patients with cancer. The historical development of these 2 uses of competing risk, statistical adjustment in research and patient performance measurement, is explained. Furthermore, this article discusses more recent advances in merging these 2 approaches. Particular attention is given to advances in calculating life expectancy that are specific to a patient's condition, status, or setting, and to describing how these estimates might be used to inform decisions about cancer care in older patients. Frameworks for moving beyond mortality as the only considered competing outcome to describe other outcomes, such as functional loss or the need for institutionalization, are also described. Finally, approaches that could more fully leverage the advanced methods for incorporating competing risks into clinical decision making are presented. (*Clin Ther*. 2018;40:504–511) Published by Elsevier HS Journals, Inc.

Key words: cancer, competing risk, decision support, life expectancy, older adults.

INTRODUCTION

The concept of competing risk is deeply imbedded in both the evidence for oncology treatments and the clinical decision making that governs the decisions made by cancer care providers. This concept is especially important in the growing population of older patients with cancer, who frequently have multiple chronic diseases and functional comorbidities.[1] The connection of competing risks to trial methodology is an important historical legacy of cancer research. However, the potential value of methodologies that incorporate competing risk as a statistical tool for clinical trials has not been as rigorously leveraged for clinical decision making. In an era of personalized cancer care, improved clinical decision-informing tools that include quantified information about individual risk are emerging. This article reviews the history and development of competing risk as a methodology within oncology research, the initial steps that seek to connect the statistical methodologies to clinical decision making, and the emerging models that are likely to improve the decisions made by clinicians who care for older patients with cancer.

DISCUSSION

In its simplest construction, *competing risk* describes the concept that the natural history of one disease may be interrupted or superseded by the outcome of another disease or condition.[2] In most studies, the "interruption" is a death from one disease that occurs

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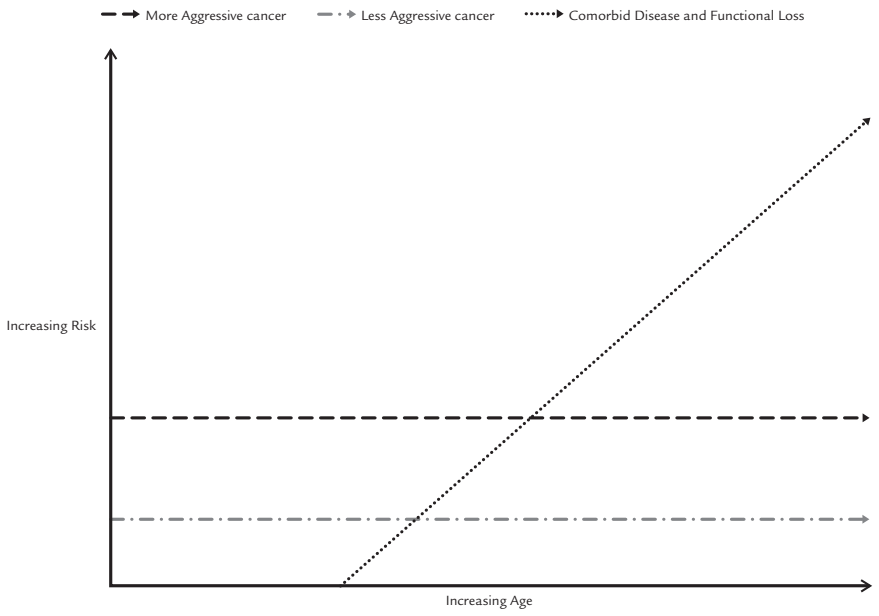

Figure. Conceptual illustration of competing risk for cancer specific mortality from comorbidities and functional decline associated with aging.

before another disease can lead to mortality (Figure). At a lay level, this idea is often expressed for slow-growing cancers by the adage that a person is more likely to die with that cancer than from that cancer. While more data is available to define competing mortality risk, there is no inherent reason for death to be the only studied competing outcome. For instance, older patients may also be concerned about the competing risk for some functional outcome, such as cognitive impairment, or the competing risk for a life event, such as institutionalization.[3]

In the clinical care of older patients with cancer, competing risk is frequently framed in terms of potential for benefit. In this construction, clinicians may decide to withhold a treatment from a patient who has poor function or other conditions because the patient is "unlikely to benefit from treatment."[4] This decision framework is often related to consideration of which older patients are unlikely to tolerate a given cancer treatment.[5] Clinicians often use simple tools or scales to inform these decisions about treatment for cancer care.

Historical Development of Competing Mortality Risk Methodologies

Competing risks have been studied as a methodologic issue across many disciplines,[6] but many of the initial examples from medicine are derived from cancer research. In 1956, Goldberg[7] studied increasing lifetime cancer risks in the state of New York, and attributed much of the increase in cancer prevalence to the gains in life expectancy over the period of study. These life-expectancy gains occurred because of a reduction in other, non–cancer-related competing risks for death. Around this time, competing risks were also noted to be important for studying carcinogenesis. In 1957, Cornfield[8] noted this as a methodologic issue and pointed out that because of competing risks, "older animals will appear to have a lower risk of developing the disease of interest" (p.602) when exposed to carcinogens and followed longitudinally. He described methods for adjusting experimental data that reached back to the 1930s.[9,10] Focusing on human studies, in 1960 Berkson and Elveback[11] used data relating smoking to lung cancer to point out that "a special problem arises when more than one risk must be measured at the same time," (p.415) raising concern that the strong causal association between smoking and lung cancer might obscure the competing risk for dying from coronary artery disease.

By the 1960s, techniques for statistically adjusting for competing risks based on life expectancy were becoming more widespread, and were being applied to the cancer treatment. Axtell[12] described adjustment