

# Survivorship—Competing Mortalities, Morbidities, and Second Malignancies

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## KEYWORDS

• Head and neck cancer • Competing mortalities • Survival analysis • Comorbidities

## KEY POINTS

- The mortality from head and neck squamous cell cancer has declined over the past 30 years.
- There are many competing risk factors that contribute to death in cancer patients.
- Competing risk factors include the effects of age, gender, race, comorbidities, diet, quality of life (QOL), human papillomavirus (HPV) infection, and second primaries.
- The presence of these competing risk factors affect the survival outcome of patients with head and neck cancer.
- Traditional survival analysis using Kaplan-Meier statistics may not be appropriate in patients with multiple competing risk factors and may overestimate disease-specific survival (DSS) figures.
- Statistical models, which include competing risk factors in the survival analysis model, need to be developed.
- These statistical models should be incorporated into the design and analysis of future randomized controlled trials (RCTs) in head and neck cancer management.

Mortality of head and neck cancer has declined in the United States over the past 20 years.<sup>1,2</sup> This improvement has been linked to the use of multimodality treatment of advanced disease. Despite this improvement, DSS remains low.<sup>3–6</sup>

Patients who survive head and neck cancer are exposed to morbidity and mortality secondary to the same factors as the general population. It is also clear, however, that factors related to their cancer and cancer treatment predispose them to increased risk of mortality.<sup>7</sup>

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Improvements in head and neck cancer treatment, even among patients with advanced disease, have led to a scenario where an increasing proportion of patients die from causes other than the primary cancer. These other causes of death are called competing mortalities. The quantification of overall mortality (OM) may not be an adequate representation of the benefits of treatment. Instead, it may merely be a reflection of the baseline host factors (age, gender, comorbidity status, and so forth) of the patients receiving active treatment and/or the result of the emergence of treatment-related factors and new malignancies.

During the past 20 years, there have been important advances not only in head and neck cancer treatment but also in the way that survival and the factors that affect it are understood, especially the competing causes of death. Examples of such competing risks for mortality are listed in **Box 1**. The most important competing risks are death due to patient comorbidities, treatment-related complications, and death secondary to second malignancies. These conditions have been analyzed before in other types of cancers<sup>8–10</sup> and are receiving greater attention in head and neck cancer.

The existence of competing mortalities may preclude the observation of the event of interest, generating negative results instead of improvements in survival.<sup>11</sup> Competing mortalities are especially important in the context where survival is prolonged due to the use of better treatments; if they are present, getting positive will be more unlikely, generating bias toward the null hypothesis.<sup>12</sup> This review analyzes these factors, how they affect survival, and how they can be integrated into survival analysis.

## TRADITIONAL COMPETING MORTALITIES IN HEAD AND NECK CANCER

### *Effect of Age*

Long life expectancy has resulted in more elderly patients with cancer.<sup>13</sup> It has been reported that by 2030, 70% of all cancers will be diagnosed in older adults. This will result in a major public health problem in the future.<sup>14</sup> Elderly patients are likely to have serious comorbidities that can affect treatment decisions. Not all elderly patients will have serious coexistent disease, however, and some elders are healthy people. Unfortunately, older patients are often undertreated because of their age and not because of the presence of chronic diseases.<sup>15</sup> This has been reported before and seems especially true in head and neck cancer patients.<sup>16–18</sup>

In head and neck cancer patients, increasing age has been associated with poor survival.<sup>19,20</sup> When severe comorbidities are not present, however, age is not

<b>Box 1</b>
<b>Competing mortality factors</b>
Age
Gender
Race
Marital (partner) status
Comorbidities
Behavior lifestyles
BMI
QOL
Second primaries
HPV infection

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