Competing risk: An illustration with aspiration pneumonia in head and neck cancer patients undergoing radical radiotherapy: A biostatistician’s perspective

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Abstract
Interest in survival analysis is to look and capture the information about the occurrence of events, i.e., death. In human life different types of events may happen at the same time. Sometimes, few events completely interrupt or make subtle changes on the occurrence of an event of interest. The method to capture information about the specific event of interest along with other events is known as competing risk modeling. This paper is dedicated to explore the application of competing risk model in oncology practice. It is aimed in near future that more and more survival analysis will be performed through application of competing risk modeling instead of traditional survival analysis to generate robust statistical inference.

Key Words: Competing risk, head and neck cancer, radiotherapy, survival analysis

Introduction
The time to death or event of interest during the study is the primary objective in survival analysis in cancer research.[1] For example, to estimate the overall survival (OS) in head and neck cancer (HNC) patients, every patient will be observed from the date of diagnosis until death. The study can be compiled through classification of all the patients into dead or censored. Patients alive at the time of study compilation are defined as censored observations. The death of patients may occur due to treatment failure or due to disease itself or other causes. The cause of death not due to disease or treatment is known as “competing risk event.” The objective of this paper is to illustrate the importance of competing risk in survival analysis for cancer research.

Survival Analysis and Concept of Competing Risk
Cancer studies often look on survival function estimation and do compare therapeutic outcomes by analyzing survival curves. The duration of being event-free and relapse-free are defined as OS and relapse-free survival (RFS), respectively. The OS and RFS are the follow-up durations measured in years, month, or days. It is quite obvious that the duration of the OS must be greater than the RFS. The Kaplan–Meier is the primary choice to estimate with basic data exploration and provide inference about survival analysis which provides the first line idea about the difference in therapeutic effect. It is a widely explored tool in cancer research.

Competing risks arise when an individual is exposed to several competing events but may eventually experience only one. Competing risk deals with the situation where more than one cause of failure is possible. If failures are various causes of death, only the first of these to occur is observed. In cancer, death due to disease may be of interest, and death due to other causes (iatrogenic mortality, old age, poor Karnofsky performance status, natural death) are competing risks. Alternatively, one could be more concerned time to relapse, where death due to any cause is a competing risk. Such an example can be the occurrence of aspiration pneumonia in patients who are receiving radiotherapy for HNCs. Though this adverse effect of radiotherapy is often ignored or unnoticed, but aspiration pneumonia-related death is a reasonable competing risk of an event of interest, i.e., death due to disease. Concurrent chemo-radiotherapy is currently the standard of care in locally advanced HNC. One of the predominant side effects of this treatment is dysphagia. Swallowing dysfunction may lead to malnutrition, diminished intake of food and reduced activity and frequent hospital admissions for treatment of pain, weight loss and infections or placement of a feeding tube. On top of dysphagia many HNC patients experience aspiration following treatment[3,4] but since aspiration in this patient group is often silent, i.e., without a cough or other symptoms, it may be under-noticed and under-reported. Aspiration and aspiration pneumonia have been described with an incidence rate of 65% for aspiration within the first 3 months after radiotherapy and 25% for aspiration pneumonia within the 1st year after radiotherapy[4] in HNC patients treated with concurrent chemo-radiotherapy. It is a potentially life-threatening complication with a reported mortality in the population studied of almost 10% in the first 12 months after chemo-radiotherapy treatment.[4] Aspiration during radiotherapy combined with neutropenia resulting from the chemotherapy may lead to aspiration pneumonia, sepsis, and respiratory failure.

The radiation therapy (RT) fields usually encompass a large area of head and neck to ensure that primary tumor and regional lymph nodes receive an adequate dose. Critical structures necessary for normal deglutition, such as tongue, larynx and pharyngeal muscles during radiations, may get a high radiation dose. The increased radiation dose results in hyperactivation of transforming growth factor β-1, a peptide involved in collagen deposition and degradation.[3] Excessive fibrosis may be responsible for abnormal motility of the constrictors and may lead to the aspiration, dysphagia, and stenosis observed following head and neck chemoradiation.[9] The post-RT swallowing studies in different trials showed changes in the swallowing mechanism that promote aspiration. These changes included diminished coordination between the various phases of the deglutition process, reduced laryngeal elevation, and closure, and reduced inversion of the epiglottis, all of which may lead to aspiration during the swallow. In addition, reduced

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movement of the base of tongue and pooling of residue in the valleculae and pyriform sinuses promote aspiration of the residue after the swallow. Loss of laryngeal sensation often accompany these abnormalities, resulting in silent aspirations.[7,8]

Data Methodology

A total of 126 patients of locally advanced HNC were included to identify the incidence and patient- and treatment-related events responsible for pneumonia acquired during radiotherapy. The patients were treated with radical radiotherapy alone with a follow-up period of 36 months in Department of Radiation Oncology, Indira Gandhi Medical College, Shimla between September 2009 to August 2010. Prescribed doses were 66 Gy to gross tumor/involved nodal metastases, 60 Gy to high-risk subclinical disease, and 56 Gy to low risk disease. The treatment was delivered in 33 fractions over a period of 61/2 weeks using shrinking field technique in cobalt 60 teletherapy machine. Acute and late toxicities were recorded according to RT oncology group toxicity criteria. At a median follow-up period of 941 days overall 13 patients suffered from aspiration pneumonia after conservative management. For illustration purpose data of only 10 patients are provided as

Table 1: Illustration of data structure on HNC patients through consideration of competing risk

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Follow-up duration in days</th>
<th>Status</th>
<th>Status-decided</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>10</td>
<td>Dead</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>73</td>
<td>PA</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>75</td>
<td>Alive</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>77</td>
<td>Alive</td>
<td>0</td>
</tr>
<tr>
<td>65</td>
<td>79</td>
<td>Alive</td>
<td>2</td>
</tr>
<tr>
<td>62</td>
<td>89</td>
<td>PA</td>
<td>0</td>
</tr>
<tr>
<td>77</td>
<td>113</td>
<td>PA</td>
<td>1</td>
</tr>
<tr>
<td>81</td>
<td>119</td>
<td>Dead</td>
<td>2</td>
</tr>
<tr>
<td>92</td>
<td>101</td>
<td>Alive</td>
<td>2</td>
</tr>
<tr>
<td>107</td>
<td>1036</td>
<td>Alive</td>
<td>1</td>
</tr>
</tbody>
</table>

*PA=Pneumonia aspiration; HNC=Head and neck cancer

Table 2: Kaplan–Meier estimates about probability of survival of HNC patients

<table>
<thead>
<tr>
<th>Duration (t_{i+1}−t_i) interval</th>
<th>Patients at risk at time t (n_i)</th>
<th>Number of events (d_i)</th>
<th>Probability of survival n_i−d_i/n_i</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–150</td>
<td>126</td>
<td>11</td>
<td>91.26</td>
</tr>
<tr>
<td>151–300</td>
<td>115</td>
<td>20</td>
<td>82.6</td>
</tr>
<tr>
<td>301–450</td>
<td>95</td>
<td>17</td>
<td>82.40</td>
</tr>
<tr>
<td>451–600</td>
<td>78</td>
<td>22</td>
<td>71.79</td>
</tr>
<tr>
<td>601–750</td>
<td>56</td>
<td>1</td>
<td>58.92</td>
</tr>
<tr>
<td>751+</td>
<td>33</td>
<td>33</td>
<td>0</td>
</tr>
</tbody>
</table>

HNC=Head and neck cancer

Analysis

Initially, the nonparametric approach is adopted in this HNC patient’s data. The Kaplan–Meier method is one of the widely used nonparametric approaches where the patients died due to other reasons are considered as “death due to treatment failure.”

In next step, competing risk events are considered separately in the same data set. Let the duration of follow-up (i.e., time) is denoted as t. The study sample size is n and number of death of patients is d. The probability survival at any time point t is:

\[ \hat{S}(t) = \frac{n_i - d_i}{n_i} \]

Suppose the two consecutive event times are t_{i+1} and t_i. The probability of survival till time, t_{i+1} and t_i are denoted as \( \hat{S}(t_{i+1}) \) and \( \hat{S}(t_i) \) respectively. The relation between \( \hat{S}(t_{i+1}) \) and \( \hat{S}(t_i) \) provides the Kaplan–Meier estimates for different time points as:

\[ \hat{S}(t_{i+1}) = \hat{S}(t_i) \times \frac{n_i - d_i}{n_{i+1}} \]

In the above data set, our interest is to estimate the cumulative incidence of death among HNC patients. The above stated Kaplan–Meier estimate (Equation 2) is adopted to show the progression of death among the patients. The estimate of \( \hat{S} \) provides the probability of survival during the follow-up period, i.e. 36 months. The illustrated plot in Figure 1 shows the survival curve without considering the aspiration pneumonia as competing risk. Figure 2 reveals the progression of survival with consideration of competing risk (i.e., aspiration pneumonia). It can be stated that the contribution towards death due to aspiration pneumonia has not been observed in Figure 1. Figure 2 provides the impact of aspiration pneumonia on survival. Further, Figure 3 gives the incidence of death due to aspiration pneumonia. The cumulative incidences of death due to aspiration pneumonia with 95% confidence intervals are shown in Figure 4.

Discussion

In this paper, we have illustrated an example of competing risk as aspiration pneumonia in patients undergoing radiotherapy for HNC. Our results revealed the importance of considering competing risk on survival analysis. It is important to emphasize on the event of competing risk from study initiation to study compilation. Figures are provided to compare the presence/absence of competing risk in HNC patient’s data separately. Pneumonia after accelerated
radiation or radiation concurrent with chemotherapy is well-reported in the literature. Delaney et al. noted that pharyngeal fibrosis after an accelerated radiotherapy regimen predisposed patients to overt aspiration.\(^6\) Abitbol et al. reported the outcome of a regimen of hyper-fractionated RT concurrent with 5-fluorouracil, cisplatin, and mitomycin C, causing a high rate of mucositis and a putative association between severe acute mucositis and aspiration pneumonia in 4 patients.\(^7\) Kies et al. reported that three patients who were progression free after induction chemotherapy and concomitant radiation and chemotherapy died from infectious respiratory complications.\(^8\) Robbins et al. reported three cases of death from pneumonia during or shortly after radiation concurrent with intra-arterial high-dose cisplatin; two of these cases were likely related to aspiration.\(^9\) Aspiration pneumonia has also been reported after standard radiation without chemotherapy: In a report of 31 patients with complaints of dysphagia after irradiation for nasopharyngeal cancer, it was noted that 11 were clinically compromised by either significant weight loss or due to aspiration pneumonia.\(^1\) Aspiration pneumonia is an underreported sequela of intensive chemo-radiation or altered fractionation radiotherapy that cannot be considered as a cause of death due to disease, rather it is competing the event of interest. Recently, the application of competing risk and cumulative incidence rate has been emphasized by several authors. The theoretical extension of cumulative incidence rate is well-established.\(^2\) The application of competing risk through consideration of covariates of interest has also been discussed.\(^3\) The extension of Cox proportional hazard has also been elaborated to estimate the cumulative incidence of a specific event of interest.\(^4\) Currently, several software are existing to deal with competing risk. Especially, the “crmpsk” package in open Source Software-R is useful for competing risk analysis. It is also possible to consider competing risk event for data analysis in commercial software such as SPSS (Statistical Package for Social Science) and SAS (Statistical Analysis System). The failure to consider the competing risk may raise issues regarding overestimation of the cumulative incidences. This could be considerable when the competing risk event is in linked with disease of interest. It is to be noted that the decision about therapeutic effect may be biased due nonavailability of potential competing risk data for study analysis. The intention of this study is to introduce the importance of competing risk to the oncology community that may help them to plan their future research accordingly.

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**References**

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