Analysis of Hypothyroidism Development in Post-Radiotherapy Nasopharyngeal Cancer Patients using Survival Trees

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Abstract. Radiotherapy is one of the treatments for nasopharyngeal cancer (NPC). However, this treatment might produce an unfavorable effect on the thyroid gland, which eventually results in less production of thyroid hormone. This is condition is known as hypothyroidism. The development of hypothyroidism in each patient with post-radiative NPC differs according to several factors. This study aims to analyze the rate of development of hypothyroidism in post-radiated NPC patients. This aim is achieved by identifying subgroups of patients with different hazard rates of developing hypothyroidism, and further identify factors explaining hypothyroidism in each subgroup. Data on ninety-seven NPC post-radiation patients taken from one of the hospitals in Jakarta were analyzed. Survival tree with the relative risk tree algorithm was proposed to analyze the data. We identified three subgroups of patients with relatively slow, medium, and fast developing of hypothyroidism. For the slow subgroup, 26% of the patients developed hypothyroidism at 150+ weeks post-radiation, while it only took less than 30 weeks for those in fast-growing subgroup; and 70 until 130 weeks for the medium subgroup. We also found that sweat production and Zulewski’s total score were the important factors in explaining the development rate of hypothyroidism.

1. Introduction

Nasopharyngeal cancer is a head and neck cancer caused by abnormal growth of cells from the epithelial cells (cells that line the internal surface) in nasopharynx [1]. Nasopharynx is the upper part of the throat (pharynx) which is located behind the nose, to be precise at the top of the soft roof of the mouth, which is shaped like a box measuring 1.5 inches at each edge, serving as an outlet for the airways from the nose to the throat [2]. This cancer is an endemic disease that is often found in people in Southeast Asia and China, with an average number of cases of 39.84 per 100,000 in Guangdong Province, South China [3]. In Indonesia, the average recorded prevalence of nasopharyngeal cancer is 6.2 in 100,000, with 13,000 new cases of NPC every year [4].

Nasopharyngeal cancer is the fourth most common cancer in Indonesia after cervical, breast, and lung cancer [5]. Treatment given to patients with nasopharyngeal cancer includes radiation, chemotherapy, combination therapy, and symptomatic therapy according to the symptoms [6]. So far, radiotherapy is still the main option for treatment of NPC [7]. However, radiotherapy produces an
unfavourable side effects, that it might damage the thyroid gland. This eventually results in the lack of production of thyroid hormone, known as the hypothyroidism.

The thyroid gland produces hormones that control metabolism. When thyroid gland does not produce enough hormones, it would eventually result in a condition called hypothyroidism [8]. Symptoms that often occurred are easily tiredness, being sensitive to cold, weight gain, constipation, depression, slow movements and thoughts, muscle, aches and weakness, muscle cramps, dry and scaly skin, pain, numbness, and a tingling sensation in the hand and fingers (carpal tunnel syndrome) [9]. There are symptoms of hypothyroidism that developed slowly and required several treatments for the patient hypothyroidism.

Financially, hypothyroidism treatment requires a relatively high cost. In Ukraine, the total 12-month cost of illness of hypothyroidism per patient was $868.26 [10]. Due to the slow development of the disease, and considering the treatment cost it might incur, people with hypothyroidism might not seek for the treatment. While. When the underactive thyroid is not treated, the patient’s conditions could be worse than before, such as having goitre, change in body metabolism, nervous system problems, and heart problems [8].

Several studies have been conducted to analyze risk factors associated with hypothyroidism in post-radiation NPC patients. Wu et al. [11] implemented survival analysis, incorporating the Kaplan-Meier estimator, Cox regression, and the log-rank test to determine the long-term incidence and possible predictive factors for post-treatment hypothyroidism in nasopharyngeal carcinoma (NPC) patients after radiotherapy. It was found that significant risk factors related to hypothyroidism were young age and chemotherapy treatment. Moreover, Chao et al. [12] applied Cox regression to assess the incidence and risk of hypothyroidism among patients with nasopharyngeal cancer after radiation therapy. Age, gender, high urbanization rates, autoimmune diseases, and chemotherapy treatment were found to be significantly associated with hypothyroidism in post-radiation NPC patients.

Being able to identify factors related to hypothyroidism is important. Yet, a more specific information on how fast is the disease development would be of an advantage. While eventually post radiation NPC patients would be likely to develop hypothyroidism, being able to predict the disease onset time would be helpful in anticipating the occurrence and thus a precaution or adjusted treatment could be prepared.

However, there are no studies related to the development of hypothyroidism in post-radiation NPC patients, to date. Therefore, in this study we propose to estimate the duration of hypothyroidism development, by means of the survival functions; and identify risk factors explaining the difference in the rate of hypothyroidism development.

In doing so, we propose to implement the survival tree method. The tree principle allows it to regroup observations into more homogeneous sub-groups, which represent patients with similar rate of disease development. The survival functions generated at the terminal nodes provide information on the rate of development, providing more insights than just identifying hypothyroidism occurrence or not as in a standard decision tree.

Moreover, there are several advantages offered by the survival tree. It can be viewed as an ensemble of decision tree and survival function methods. Decision tree offers the ease of interpretation. The visualization of tree structure is easy to interpret, it merely uses the if-then rule without the need of complex mathematical formulation, and thus can be easily understood. Several studies have shown the relatively high accuracy of classification by decision tree [13-16]. Although this method is often criticized for its tendency to overfit, yet implementing a proper pruning technique could remedy the overfitting problem [17]. On the other hand, survival function offers more insight on the waiting time until events are observed, or censored [18]. In this study, the event of interest is when a subject is diagnosed with hypothyroidism.

Thus, taking the advantages from the two constructing methods provides the flexibility of survival tree yet with the additional information on not only being able to predict whether a subject will likely to develop hypothyroidism, but also how long is the expected duration to develop the disease.

Moreover, survival tree can also handle a large number of covariates; thus, it is robust to small sample size. Moreover, survival tree can automatically detect certain types of interactions between covariates [19] and can classify patients based on each individual's survival behaviour pattern. This
property eases the researchers in the sense that they do not need to determine the type of interaction in advance.

A survival tree is an extension of a decision tree, where the survival tree allows for the analysis of the censored data that is usually found in the case of survival analysis. One of the well-known tree method algorithms is CART (Classification and Regression Tree) [20]. CART is a nonparametric model that works by building recursive predictive risk models. In this study, we use the relative risk algorithm proposed [21] to grow the survival tree. This algorithm will be discussed further in Section 3.

2. Method
2.1. Data Set
Data on 97 post-radiotherapy nasopharyngeal cancer patients from one hospital in Jakarta were used in the study. Among these 97 patients, 63 of them already developed hypothyroidism and the remaining 34 were right-censored. Data consists of 81 covariates in 7 section measurements, as 11 measurements in identity subject, 2 measurements in thyroid hormone, 12 measurements in signs and symptoms of hypothyroid Zulewski’s questionnaire, 30 measurements in quality life of NPC patients (questionnaire of EORTC QLQ C-30 version 1.0), 7 measurements in physical examination, 4 measurements in laboratory examination, and 16 measurements in other medical records. In this research, there are two other measurements, the hypothyroid status of patients and survival time.

We designed two schemes for data analysis, namely Scheme 1 dan Scheme 2. The schemes are differentiated based on the covariates (and/or their transformation) to be included in the model. This approach is proposed due to the nature of the data and the representativeness of the information contained in the data. Scheme one consists of more detailed information, that is taking into account all measurements (in the form of each single item question in the corresponding instruments, e.g. Zulewski questionnaire) in 81 covariates. Scheme two, however, uses the summary information in the form of total scores of items (in 3 sections, e.g. from 12 measurements of the Zulewski questionnaire in scheme 1 into 2 items the total score of Zulewski) of the questionnaire. By doing this, the number of covariates included is 42. In both schemes, the target variables are whether patients experienced hypothyroidism or not, and the length of time (in weeks) from the last radiotherapy until hypothyroidism is diagnosed, or until censored for those who did not develop hypothyroidism. Scheme 2 not only reduces the number of covariates that simplify the model but also expected to provide a more robust result.

2.2. The Sampling Model
Let the data consists of measurements on \( N \) patients. Let \( t_i \) denote the survival times for patient \( i \) and \( t_i = \min(U, V) \) where \( U \) denote the observed times, that is time until diagnosed with hypothyroidism since the last radiotherapy, and \( V \) denote the censored times, \( \delta_i \) is the indicator of failure (\( \delta_i = 1 \) if the observed time of diagnosed with hypothyroidism, \( \delta_i = 0 \) if \( i \) is censored). Then, \( X = \{X_1, ..., X_p \} \) is a vector for \( p \) covariates. Assume that the \( U \) and \( V \) are independent given \( X \). So, the sample data that is used to build survival tree consists \( N \) independent and identically observations \( \{t_i, \delta_i, X\} \).

Leblanc and Crowley [21] proposed a relative risk tree by adopting the proportional hazard model. So, for an individual with covariate vector \( X \),

\[
\lambda(t | X) = \lambda_0(t) s(X)
\]

where \( \lambda_0(t) \) is baseline hazard function and \( s(X) \) is log-linear function of a vector of parameters. They were proposed full likelihood for the sample for a tree \( T \) can be expressed as

\[
L_F = \prod_{(h \in T^*) \times \delta_i \in S_h} f_h(t_i)
\]

where \( T^* \) is the set of terminal nodes for a tree \( T \), \( S_h \) is the set of observation labels, \( \{i: X_i \in S_h\} \), for the observation in region \( S_h \) corresponding to node \( h \), and \( F_h(t_i) = \lambda(t_i) S(t_i) \) where \( \lambda(t_i) \) is the hazard function and \( S(t_i) \) is the survival function. Therefore, formulation in (2) can be rewritten as,
\[ L_F = \prod_{h \in T} \prod_{i \in S_h} (\lambda_h(t_i))^{\delta_i} S_h(t_i). \]  

It can be shown that \( S(t_i) = \exp[-\Delta(t_i)] \) with \( \Delta(t_i) \) is the cumulative hazard function, and so the full likelihood function can be written as,
\[ L_F = \prod_{h \in T} \prod_{i \in S_h} (\lambda_h(t_i))^{\delta_i} \exp(-\Delta_h(t_i)). \]

Assume that the proportional hazards model \( \lambda_h(t) = \lambda_0(t) \exp(\beta_h) \) is true, where \( \lambda_0(t) \) is baseline hazard function and \( \beta_h \) is the constant of relative risk values [22] of node \( h \). It follows that the likelihood for the data given tree \( T \) is
\[ L_R = \prod_{h \in T} \prod_{i \in S_h} (\lambda_0(t_i) \theta_h)^{\delta_i} \exp(-\Delta_0(t_i) \theta_h) \]

where \( \theta_h = \exp(\beta_h) \) and \( \Delta_0(t_i) \) is baseline cumulative hazard.

2.3. Splitting Criteria

The process of growing a survival tree is the same as that of a decision tree. First, all observations converge on a single node, which is called the root node. At the root node, the data is still heterogeneous. Then, it splits into two nodes by a covariate using a measurement. The nodes that resulted were called internal nodes. The measurement as a splitting criterion called impurity measurement. Splitting criterion aims to create the data to be more homogeneous. The tree grows by splitting criterion until the tree reaches a stopping criterion, which is called a leaf node.

Splitting criteria of relative risk tree is the deviance for node \( h \) (node in a tree \( T \)) is given by
\[ D(h) = \frac{1}{N} \sum_{i \in S_h} \left[ \delta_i \ln \left( \frac{\delta_i}{\Delta_0(t_i) \theta_h^\Delta_i} \right) - \left( \delta_i - \Delta_0(t_i) \theta_h^\Delta_i \right) \right] \]  

where \( N \) is the number of the observation in node \( h \). We compute equation 6, every time when we split a node into two, that is required to maximize the likelihood in equation (5). When we computed it that would be ambitious computation [23] (too many iterations until it converges), and commonly the \( \Delta_0(t) \) is unknown. As a solution, Leblanc and Crowley [21] suggested a one-step estimator for \( \Delta_0(t) \).

It only requires one iteration on computation. So, \( \Delta_0^\theta(t_i) \) indicates estimation of cumulative baseline hazard (without covariates \( X_i \)) for the first iteration,
\[ \Delta_0^\theta(t_i) = \sum_{i : t_i \in t} \frac{\delta_i}{\sum_{h \in T} \sum_{i : t_i \in h} \theta_h^\Delta_i} \]  

where \( \theta_h^\Delta_i = 1 \), for \( h \in T \). For the first iteration and \( \theta_h^\Delta_i \) indicates the maximum likelihood estimation of \( \{\theta_h : h \in T \} \) for node \( h \) in terminal nodes, that computed by iterative,
\[ \theta_h^\Delta = \frac{\sum_{i \in S_h} \delta_i}{\sum_{i \in S_h} \Delta_0^\theta(t_i)}. \]

Equation 7 can be interpreted as the observed number of deaths divided by the expected number of deaths in node \( h \) under the assumption of no structure in survival times. By no structure that means it does not require a distribution assumption in survival times.

The measurement of goodness of split for the survival tree is
\[ \Delta D(X, h) = D(h) - [D(h_l) + D(h_r)] \]

where \( \Delta D(X, h) \) indicates difference of the deviance for split \( X \) for node \( h \), \( D(h_l) \) and \( D(h_r) \) indicates deviance for left node and right node. The tree is split by the variable at \( X \) whose split \( X \) leads to smallest value \( \Delta D(X, h) \)[24]. In conclusion, equation 6 is the most important equation for splitting the nodes in survival tree.
2.4. Stopping Criteria

There are several methods that commonly used to stop growing the tree. Stopping criteria is required to limit the growth of trees or prune the trees after it grows [25]. So that the tree is not too complex yet still informative. One of the stopping criteria is to set a minimum size of observation in the terminal node or stop growing when node $h$ has reached a specified threshold [26]. In this study, we use node deviance as the stopping criterion.

To summarize, the method to grow a relative risk tree is as follows:

1. Calculate $\hat{\Delta}_0^1(t_i)$ where assume the value of $\hat{\theta}_h^1 = 1$, for each node $h \in T^*$. 
2. Update $\hat{\theta}_h^1$ using $\hat{\Delta}_0^1(t_i)$ that was obtained from Step 1.
3. Calculate $D(h)$ in equation (6) for root node, left node, and right node. After that, calculate $\Delta D(X, h)$ in equation (9). 
4. Repeat steps 1 to 3 until the tree reaches the stopping criteria.

Data analysis were conducted using R 3.6.1 [27], implementing rpart package[26].

3. Result and Discussion

3.1. Survival Tree for Scheme 1

Figure 1 shows that there are 3 sub-groups of patients were identified: namely fast (node 4), medium (node 5), and slow (node 3) developing hypothyroidism. Majority of the patients (16 out of 97) were in fast developing sub-group, with 11 of them experienced hypothyroidism. While in slow developing sub-group, 30 out of 97 patients with 4 of them experienced hypothyroidism. For the medium developing sub-group, 51 out of 97 patients with 48 of them experienced hypothyroidism.

At terminal nodes, it can be seen that by the time of 50 weeks post-radiotherapy, only around 5 percent of those in fast-developing subgroup have not developed hypothyroidism yet. While, for the slow-developing group, only around 27 percent of those have not developed hypothyroidism at 150+ weeks; and for the medium group, only around 3 percent of those have not developed hypothyroidism at 120-130 weeks.

Moreover, the fast-growing subgroup characteristics could be identified: there was no decrease in sweat production, and experience increase relative body weight. While in the slow-growing subgroup, there was no decrease in the patients' sweat production, and no weight gain. For the medium-developing subgroup, patients experienced decrease in sweat production.

3.2. Survival Tree for Scheme 2

Figure 2 shows that there are 4 sub-groups of patients were identified, namely fast (node 6 and node 7), medium (node 5), and slow (node 2) developing hypothyroidism. Majority of the patients (49 out of 97) were in fast developing sub-group, with 46 of them experienced hypothyroidism. While in slow developing sub-group, there were 29 out of 97 patients with 1 of them experienced hypothyroidism. For the medium developing sub-group, 1 out of 19 patients with 48 of them experienced hypothyroidism.

At terminal nodes, it can be seen that by the time of 60 weeks post-radiotherapy, only around 3 percent of those in fast-developing subgroup have not developed hypothyroidism yet. While, for the slow-developing group, almost of patients have not developed hypothyroidism at 150+ weeks; and for the medium group, only around 3 percent of those have not developed hypothyroidism at 120-130 weeks.

Characteristics in the fast-growing subgroup were identified: Zulewski's total score hypothyroid symptom $\geq 1.5$, a pulse rate with cut-off 79, and they experienced no or very infrequent pain. While in the slow-growing subgroup, the patients have Zulewski's total score hypothyroid symptom $< 1.5$. For the medium-developing subgroup, the patients have Zulewski's total score hypothyroid symptom $\geq 1.5$, a pulse rate $\geq 79$, and they experienced pain frequently.
3.3. Discussion

In this study, we showed that there are sub-groups of post-radiative NPC patients with regards to the rate of developing hypothyroidism (i.e. fast, medium, and slow). The results extend the study conducted by Rahman [27] that provides clinical features related to hypothyroidism in post-radiation NPC patients. In addition to the risk factors identification, we also provided the rule of assigning a patient into fast, medium, or slow sub-group. Moreover, we could estimate the likelihood of a patient to suffer from hypothyroidism in a certain time period, by taking into account the survival function in the appointed sub-group.

We proposed 2 schemes for analyzing the data. While Scheme 1 is using all information as it is, Scheme 2 used the compound covariates, that is, the covariates that were derived from raw covariates (used in Scheme 1) by taking the total of the individual items in (3 section of) the instrument. We might identify some items that are statistically significant (important). However, when considering something specific as in the Zulewski questionnaire, EORTC QLQ-30 questionnaire, and a section of other medical records, there are still possibilities that this result is limited to the data at hand; and might too risky to over-generalize it; due to the limitation that we only have data from one hospital. Thus, some possible variability in the possible symptoms were not fully represented by this data. Therefore, we provide an alternative way of elaborating the data, which is by Scheme 2. By this scheme, since the total score summarizes the symptoms, regardless of which symptoms occur, it is expected to provide a more robust result, and thus allows for generalization.

We restrict not to recommend which scheme provides the best result. Both schemes have different concern and thus it is up to the readers which scheme seems fit for their purpose of analysis, and use the result from that scheme. Besides, based on the result, it can be seen that the characteristics of the group of patients who have the fastest rate of development of hypothyroidism compared to other patient groups. Therefore, it is hoped that this patient group can be given the best treatment.
4. Conclusion

Based on the result, there are three sub-groups of patients were identified, namely fast, medium, and slow-developing hypothyroidism. The factors associated with the rate of hypothyroidism in schemes 1 were reduced sweat production and increased body weight. While the factors associated with the rate of hypothyroidism in schemes 2 were Zulewski’s total score hypothyroid symptom, pulse rate with cut-off is 79, and frequency of pain.

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