Cox Model Survival Analysis to Evaluate Treatment of Electro-Capacitive Cancer Therapy (ECCT) For Cancer Patients

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Abstract. Cancer is a disease caused by uncontrolled growth of abnormal cells in the body. Lung cancer, brain cancer and breast cancer are a deadly threat to sufferers. Cancer treatment using a therapy called Electro-Capacitive Cancer Therapy (ECCT) has received a lot of medical attention. Since 2012, the C-Tech Labs Edwar Technology Cancer Research Tangerang has applied ECCT to the therapeutic treatment more than 11,000 cancer patients. In this study, the Cox Proportional Hazard model was used to assess factors that affect survival of cancer patients. Some prognostic factors are evaluated included age of patient and type treatments such as herbs therapy, chemotherapy, radiotherapy and monitoring frequency of ECCT. The all three survival models (breast cancer, brain cancer, and lung cancer) identified the same prognostic factors. The study showed that monitoring frequency of ECCT is significant factor that influenced in cancer survival for all three survival models. Based on the Cox survival model, the hazard ratio (HR) value ranges from are 0.8 – 0.9. It means that each additional one time the frequency of monitoring, the risk of experiencing death decreased by 0.8 – 0.9 times.

1. Introduction
Cancer is a disease caused by uncontrolled growth of abnormal cells in the body. The WHO (World Health Organization) stated that cancer is a very serious health problem because the number of sufferers increased by around 20% per year. Several types of cancer, including lung cancer, brain cancer, and breast cancer, etc [1]. The mortality rate of lung cancer in Indonesia reaches 19.3% compared to the total deaths from all other cancers. This disease is the leading cause of death cancer for men as much as 22.8% and is one of the main causes of death for women as much as 14.2% [1]. Meanwhile, brain cancer or glioma is a group of tumor that arise in the central nervous system. Brain cancer is still a global concern, because various advances in research and technology have not been able to maximize the results of brain cancer treatment [1]. Breast cancer is a malignant tumor originating from the skin glands, glandular ducts, and tissues outside the chest cavity. In Indonesia, an estimated 10 out of 100,000 residents are affected by breast cancer. The incidence of breast cancer has increased significantly every year and is the second killer after cervical cancer [2].

Most of the patients visit the doctor or hospital in an advanced stage. Cancer treatment varies, depending on the stage when it is found. Starting from surgery, radiotherapy, chemotherapy, or a combination of both. Some medical studies are to identify prognostic factors of patients' survival time.
Many researchers use survival analysis with a parametric approach if the distribution of survival times is known and semiparametric if the distribution is unknown. Cox regression as a semiparametric approach is well known for its application in the medical field [3]. The use of Cox regression aims to determine the effect of several variables on the survival data together [4]. In particular, Cox regression is widely used for the analysis of survival data for cancer patients such as cervical cancer [5,6], breast cancer [7,8], lung cancer [9], etc.

Cancer treatment using a therapy called Electro-Capacitive Cancer Therapy has received a lot of medical attention [10,11,12]. Since 2012, the C-Tech Labs Edwar Technology Cancer Research Tangerang has applied ECCT to the therapeutic treatment more than 11,000 cancer patients [13]. ECCT is a method for treating cancer using low intensity electro-static wave sources (<30Vpp) and low frequencies (<100KHz) that produce electrical polarization in nearby terrain areas limited by multiple capacitive electrodes mounted clothing worn daily by patients. The electro-capacitive approach generates relatively higher electrical field intensity in the area of tissue interfaces that leads to more effective treatment of peripheral and intra-tissue cancer development as compared to bulk cancer mass. This is especially the case of metastatic cancer cells to different organ in which small group of cancer cells are developed and spread throughout the organ. Therefore, the use of ECCT is suitable to small development of groups of cells regardless of the extension of the spread of the metastasis [11]. The highly specific effects of ECCT on dividing cells, together of the relative ease of applying this treatment, make it an attractive candidate to serve as a novel treatment modality in cancer [12]. Therefore, this study conducted a survival analysis using Cox regression with case studies of breast cancer, lung cancer and brain cancer to assess the use of ECCT in the survival of cancer patients.

2. Literature Review

2.1 Survival Analysis

Survival analysis is a statistical technique used to analyse data with the aim of knowing variables that affect the response from the beginning of the event to the end of the event. Censored data is recorded when there is information about the time of individual survival, but do not know the exact time of survival. There are two basic quantities that are often used in survival analysis namely survival function symbolized by \( S(t) \) and hazard function symbolized by \( h(t) \). The survival function is defined as the probability that an individual can survive more than the t-time, expressed in the equation (5) following [14].

\[
S(t) = P(T > t) = 1 - P(T \leq t) = 1 - F(t)
\]  

(1)

The hazard function is defined as the rate at which an event occurs after the individual persists for the t-time, which is stated in the equation (6) following [14].

\[
h(t) = \lim_{\Delta t \to 0} \left\{ \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t} \right\}
\]  

(6)

The relationship between the survival function and the hazard function is stated in the equation (7) below.

\[
-\int_0^t h(t) dt = \ln S(t)
\]  

(7)

The Kaplan-Meier survival curve is used to calculate survival odds by describing the relationship between estimated survival function at t time and survival time. Kaplan-Meier's survival curve can be expressed in the equation (8) below.

\[
S(t_{f|j}) = S(t_{j-1}) \times Pr(T > t_{f|j} \mid T \geq t_{f|j})
\]  

(8)

\[
S(t_{(f-1)}) = \prod_{j=1}^{f-1} Pr(T > t_{f|j} \mid T \geq t_{f|j})
\]  

(9)
Meanwhile, the Log-rank test is a nonparametric statistical test used when the data is not symmetrical, used clinical trials to see the efficiency of a new treatment to compare with older treatments and can compare Kaplan-Meier in different groups. Here are the hypothesis and test statistics used in Log-rank testing:

$H_0$: there is no difference in the survival curve between different groups

$H_1$: there are differences in the survival curve between different groups

Test statistics,

$$X^2_{hitung} = \sum_{g=1}^{G} \frac{(O_g - E_g)^2}{E_g}$$  \hspace{1cm} (10)

Description,

$O_g$ : observation value

$E_g$ : expectation value

Reject $H_0$ when $X^2_{hitung} > \chi^2_{(a,G-1)}$ [14].

2.2 Cox Proportional Hazard Regression

Cox Proportional Hazard model (Cox PH) is called a semiparametric model that can be used when the existing data is not clearly known distribution. Although baseline hazard is not known functional form, Cox PH can still provide useful information in the form of hazard ratio [14]. The Cox proportional hazard regression model is shown in the equation (11) below.

$$\hat{h}(t, X) = \hat{h}_0(t) \exp \left( \sum_{j=1}^{p} \hat{\beta}_j x_j \right)$$  \hspace{1cm} (11)

$$\hat{h}(t, X) = \hat{h}_0(t) \exp \left( \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p \right)$$  \hspace{1cm} (12)

Description,

$\hat{h}_0(t)$ : baseline hazard at t-time

$\beta_j$ : j-regression parameters

$X$ : $(X_1, X_2, ..., X_p)$ / predictor variables

The best model is obtained by estimating the variable coefficient of predictor $X_1, X_2, X_3, ..., X_p$ i.e. $\beta_1, \beta_2, \beta_3, ..., \beta_p$. Parameters or $\beta$ regression coefficients $\beta$ in the Cox PH model can be estimated using the maximum partial likelihood estimation (MPLE) method. The survival time sequenced $r$ individuals experiencing events of $n$ individuals is symbolized $t(1) < t(2) < \ldots < t(i) < \ldots < t(r)$ and $t(i)$ are the time sequence of the $i$-th event. $R(t(i))$ is a set of individuals at risk of experiencing events at $t(i)$ time consisting of individuals who survive up to $t(i)$. $x(i)$ is a variable vector of an individual experiencing an event at $t(i)$ time. The partial likelihood function of the Cox PH model can be written equations (13) below.

$$L(\beta) = \prod_{i=1}^{r} \frac{\exp \left( \sum_{j=1}^{p} \beta_j x_j \right)}{\sum_{i \in R(t(i))} \exp \left( \sum_{j=1}^{p} \beta_j x_j \right)}$$  \hspace{1cm} (13)

The ln-likelihood function of the equation (13) can be described as follows.

$$\ln L(\beta) = \sum_{j=1}^{p} \sum_{i \in R(t(i))} \beta_j x_j - \sum_{i=1}^{r} \ln \left( \sum_{i \in R(t(i))} \exp \left( \sum_{j=1}^{p} \beta_j x_j \right) \right)$$  \hspace{1cm} (14)

The next step is to maximise the first derivative of the likelihood equation using the Newton-Rhapson method.

Testing of parameter significance is carried out simultaneously and partially. The following are simultaneous and partial parameter significance tests.

Simultaneously the hypothesis used in the parameter significance test is as follows [4].

$H_0$: $\beta_1 = \beta_2 = \ldots = \beta_p = 0$
H₀: at least one, with k=1,2,...,p  βₖ ≠ 0

Test statistics

\[
G^2 = -2 \ln \left( \frac{\max_{\omega} \ln L(\omega)}{\ln L(\Omega)} \right) = -2 \ln \left( \frac{L(\bar{\omega})}{L(\bar{\Omega})} \right)
\]

L(ω): likelihood function for the initial model i.e. the likelihood function of the regression model before the predictor variable is entered

L(Ω): likelihood function for the final model i.e. the likelihood function of the regression model after the predictor variable is entered

H₀ reject decision when test statistical value \( G^2 > \chi_{(a,p)}^2 \)

To find out which predictor variables have a significant effect on the model, the next step is to perform a partial test of its parameters.

H₀: the kth predictor variable has  βₖ = 0

H₁: the kth predictor variable  βₖ ≠ 0

Test statistics

\[
W = \frac{(\hat{\beta}_k)^2}{(SE(\hat{\beta}_k))^2}
\]

Description

\( \hat{\beta}_k \) = estimated parameter βₖ

\( SE(\hat{\beta}_k) \) = standard error of βₖ

The decision rejects H₀ if \( W > \chi_{(a,1)}^2 \) or \( p-value < \alpha \) [4].

Modeling assumptions that must be met in Cox's regression Cox is that the hazard function must be proportional at all times because Cox regression does not accommodate variables that are Cox fickle all the time. Proportional hazard assumptions are variables of independent predictors of time and the relationship between cumulative constant hazards each time. Testing proportional hazard assumptions with the goodness of fit method using Schoenfeld residuals. Schoenfeld residuals are defined in each individual who experiences an event for each predictor variable in the model.

Hazard ratio is used to determine the increase or decrease in risk experienced by an individual subject to certain treatment or conditions. Comparison of the level of risk of failure experienced by the two individuals can be formulated as follows [4],

\[
\begin{align*}
\text{HR} & = \frac{\hat{h}(t,X)}{\hat{h}(t,X^*)} \\
& = \frac{\hat{h}_0(t) \exp \left( \sum_{j=1}^{p} \hat{\beta}_j X_j \right)}{\hat{h}_0(t) \exp \left( \sum_{j=1}^{p} \hat{\beta}_j X_j^* \right)} \\
& = \exp \left[ \sum_{j=1}^{p} \hat{\beta}_j (X_j - X_j^*) \right]
\end{align*}
\]

3. Methods

3.1 Data Source

The data used in this study is secondary data obtained from the C-Tech Labs Edwar Technology report. The data used was medical records cancer patients from January 2012 to May 2019. The data used in this study were cancer patients who used ECCT device for at least 6 months. Patients taking the ECCT device for less than 6 months were excluded from the analysis. Lung cancer consisting 259 patients but there were 162 patients treated in less than 6 months, so the data used in this analysis was 97 patients. Brain cancer consisting 372 patient data, but there were 203 patients who were treated for less than 6 months so that the analyzed data were 172 patients. While, Breast cancer consisting 1157 patients, 740 patients were excluded from the analysis.
The concept framework is used as a boundary of the area that becomes the research area. This research area includes all variables including Survival cancer patients who act as dependent variables, while the factors that affect them act as independent variables. Here is the concept framework used in this study.

* Variables not used in research

**Figure 1.** Research Concept Framework

**Source:** Dimyati & Sri (2014), Kemenkes (2016), and Rasyid et al (2001)

### 3.2 Research Variables

The variables used in this study are described in Table 1.

**Table 1.** Research Variables

| Variable | Description | Operational Definitions | Scale |
|----------|-------------|-------------------------|-------|
| $T$ | Survival Time | Length of cancer patients when first using ECCT until declared died (in days) | Ratio |
| $d$ | Censored Status | Cancer patients have an event or not | Nominal |
| $X_1$ | Age | Age of cancer patients when first using ECCT | Ratio |
| $X_2$ | Monitoring Frequency of ECCT | Number of visits of cancer patients at C-Tech Labs Edwar Technology | Ratio |
| $X_3$ | Herbs | Patients consume herbs or not during cancer treatment | Nominal |
| $X_4$ | Chemotherapy | Patients treated with chemotherapy or not during cancer treatment | Nominal |
| $X_5$ | Radiotherapy | Patients treated with radiotherapy or not during cancer treatment | Nominal |
| $X_6$ | Alternative Medicine | Patients treated with alternative treatment or not during cancer treatment | Nominal |
4. Results

4.1 Descriptions of cancer patients

The cross-tabulation results of cancer patients data at C-Tech Labs Edwar Technology are as follows.

| Variable               | Lung Cancer | Brain Cancer | Breast Cancer |
|------------------------|-------------|--------------|---------------|
|                        | Censored (n=24) | Died (n=73) | Censored (n=111) | Died (n=61) | Censored (n=590) | Died (n=567) |
| Herbs (X₃)             |              |              |                |              |                |              |
| No                     | 21           | 52           | 103           | 54           | 485             | 448          |
| Yes                    | 3            | 21           | 8             | 7            | 105             | 119          |
| Chemotherapy (X₄)      |              |              |                |              |                |              |
| No                     | 19           | 54           | 109           | 57           | 549             | 514          |
| Yes                    | 5            | 19           | 2             | 4            | 41              | 53           |
| Radiotherapy (X₅)      |              |              |                |              |                |              |
| No                     | 24           | 62           | 107           | 52           | 574             | 547          |
| Yes                    | 0            | 11           | 4             | 9            | 16              | 20           |
| Alternative Medicine (X₆) |          |              |                |              |                |              |
| No                     | 12           | 60           | 87            | 43           | 415             | 427          |
| Yes                    | 12           | 13           | 24            | 18           | 175             | 140          |

Based on Table 2 it can be known that as many as 75% of patients experience died for lung cancer, 65% for brain cancer and 49% for breast cancer. The majority of patients undergo treatment, be it herbs, chemotherapy, radiotherapy and alternative treatments.

Table 3 states descriptive statistical results covering survival time, age factors and monitoring frequency of ECCT.

| Variable               | Mean | Standard deviation | Minimum | Maximum |
|------------------------|------|--------------------|---------|---------|
| Survival time (days)   |      |                    |         |         |
| Lung cancer            | 517.6| 441.2              | 181     | 2414    |
| Brain cancer           | 805.4| 617.2              | 187     | 2840    |
| Breast cancer          | 769.2| 649.4              | 181     | 2850    |
| Age (years)            |      |                    |         |         |
| Lung cancer            | 57.9 | 12.8               | 24      | 83      |
| Brain cancer           | 39.2 | 17.8               | 24      | 82      |
| Breast cancer          | 48.4 | 11.8               | 12      | 86      |
| Monitoring Frequency ECCT |   |                    |         |         |
| Lung cancer            | 5.8  | 4.2                | 1       | 25      |
| Brain cancer           | 7.1  | 4.9                | 1       | 27      |
| Breast cancer          | 9.1  | 6.8                | 1       | 62      |

Based on Table 3, it can be explained that the survival time of breast cancer patients is longer than lung cancer and brain cancer patients. The average age of lung cancer patients was the oldest, while brain cancer patients had the youngest average age. The monitoring frequency of ECCT has an average of 5-9 times. Monitoring at C-Tech Labs Edwar Technology is a patient consultation activity to check whether the ECCT device conforms to the established standards. A consultation is recommended once a month, but there are still patients who only consult once during treatment.

The probability of survival for lung cancer patients is relatively low compared to patients with brain cancer and breast cancer (Figure 3(a)). The probability of survival decreased sharply, even up to the 1000th day the probability was only around 0.3. Meanwhile, the probability of survival in brain cancer patients is relatively higher. The decrease in the probability of survival was not so sharp, until stable
conditions were reached on day 1500 with a survival probability of about 0.5. For breast cancer patients, the survival probability steadily decreased until day 1500 reaching a probability of only 0.4.

![Survival Curve of Kaplan-Meier of Lung Cancer, Brain Cancer, and Breast Cancer](image)

**Figure 3.** Survival Curve of Kaplan-Meier of (a)Lung Cancer (b)Brain Cancer (c)Breast Cancer

First of all, here is the Kaplan-Meier Survival Curve of lung cancer on each variable then followed by a Log-rank test to find out the difference in survival curve between groups of each of these factors. From Figure 4 (a) it can be seen that there are differences in the survival curves of monitoring frequency in each category, this is reinforced by a *p*-value <0.05. Likewise, for alternative medicine factors (Figure 4 (e)), patients who underwent alternative medicine had a significantly higher probability of survival than those who did not undergo alternative medicine (*p*-value =0.02).

![Kaplan-Meier Survival Curve of Lung Cancer](image)

**Figure 4** Kaplan-Meier Survival Curve of Lung Cancer (a)Monitoring Frequency of ECCT (b)Herbs (c)Chemotherapy (d)Radiotherapy and (e)Alternative Medicine

From Figure 5.a, the Kaplan-Meier curve of Brain Cancer for the frequency of monitoring also shows a significant difference in the curve between categories (*p*-value <0.05). The radiotherapy variable also showed a significant difference in the survival curve with a *p*-value = 0.01 (Figure 5.d).
The last figure is survival curve of breast cancer. The frequency of monitoring ECCT and chemotherapy are variables that there are significantly differences between categories. From all analysis of KM curve and log rank test on lung cancer, brain cancer and breast cancer, it can be concluded that the survival probability of ECCT monitoring frequency differs significantly in each category. Therefore, we will further study the effect of ECCT monitoring frequency on survival time by adjusting other variables, namely age and treatment of cancer patients (herbs, chemotherapy, radiotherapy and alternative medicine) using Cox regression.

4.2 Cox Regression Analysis for cancer patients
In this survival modeling will be used Cox regression on all cancer data. The first step is to perform parameter estimation, parameter significance test, proportional hazard assumption test, and model selection using backward method.
Table 4. Goodness of fit test of Proportional Hazard Assumption of Cancer data

| Variable                | Lung cancer | Brain cancer | Breast cancer |
|-------------------------|-------------|--------------|---------------|
| Age                     | 0.708       | 0.654        | 0.734         |
| Monitoring Frequency    | 0.233       | 0.117        | 0.219         |
| Herbs                   | 0.537       | 0.282        | 0.352         |
| Chemotherapy            | 0.327       | 0.964        | 0.763         |
| Radiotherapy            | 0.909       | 0.886        | 0.656         |
| Alternative Medicine    | 0.241       | 0.531        | 0.311         |

The first model, the dependent variables used are the survival time of lung cancer patients, while the independent variables are all factors that are suspected to affect the survival of lung cancer patients including factors to alternative treatments that are as many as 6 independent variables. Based on the goodness of fit test (Table 4), the results show that all variables meet the proportional hazard assumptions. After that, the best model is selected using the backward method. Backward elimination is done by excluding one by one the least significant variables. The least significant variable is the variable that has the largest p-value in a partial test. The variable of chemotherapy has the largest partial test value, which is 0.865 so that further regression modelling of Cox proportional hazard without including those variables. Furthermore, partial testing was carried out again and the least significant variables sequentially were herbs, ages, radiotherapy, and alternative treatments removed from the model. The elimination process will stop until the partial test results are found all variables have been significant less than 0.05. The following are the results of estimating the parameters of the best Cox proportional hazard (PH) model.

Table 5. The best Cox PH Model of Lung Cancer

| Variable                | Parameter Estimation | Standard Error | Wald (W) | P-value | Hazard ratio |
|-------------------------|----------------------|----------------|----------|---------|--------------|
| Frequency Monitoring of ECCT | -0.17317            | 0.03904        | -4.436   | 9x10^{-6} | 0.84         |

Based on Table 5, the Cox proportional hazard model of Lung Cancer as follows.

\[ h(t) = h_0(t) \exp \left[ -0.17317 \text{ Monitoring Frequency} \right] \]

The value of hazard ratio = 0.841, it means that once time addition of the frequency monitoring, the risk having an event (die) will decrease by 0.84 times.

The second model is the Cox model for brain cancer data. The goodness of fit test results show that all variables also meet the proportional hazard assumptions, so the model used is Cox PH. Furthermore, using the Backward method, the best model is obtained as presented in Table 6. The Cox PH model of Brain cancer can be written as follows:

\[ h(t) = h_0(t) \exp \left[ -0.15016 \text{ Monitoring Frequency} + 0.83918 \text{ Radiotherapy} \right] \]

Table 6. The best Cox PH Model of Brain Cancer

| Variable                | Parameter Estimation | Standard Error | P-value | Hazard ratio |
|-------------------------|----------------------|----------------|---------|--------------|
| Frequency Monitoring of ECCT | -0.15016            | 0.03631        | 3.54e-05 | 0.86         |
| Radiotherapy            | 0.83918              | 0.36426        | 0.0212  | 2.31         |

The hazard ratio of frequency monitoring of ECCT is 0.86, it means that once time addition of the frequency monitoring, the risk having an event (die) will decrease by 0.84 times. Meanwhile, the hazard
ratio for radiotherapy variable is 2.31, which means that the patient risk of undergoing radiotherapy is 2.31 times compared to patient who do not undergo radiotherapy.

The last model is Cox model of Breast cancer data. The model used is Cox PH because all variables meet the PH assumption (Table 4). The best Cox model resulting from the backward elimination can be seen in Table 7 below.

| Variable                        | Parameter Estimation | Standard Error | P-value   | Hazard ratio |
|---------------------------------|----------------------|----------------|-----------|--------------|
| Age                             | 0.008927             | 0.003629       | 0.01389   | 1.01         |
| Frequency Monitoring of ECCT    | -0.089600            | 0.007723       | 2x10^{-16}| 0.91         |
| Alternative Medicine            | -0.296831            | 0.098291       | 0.00253   | 0.74         |

Finally, the best model of Breast Cancer as follows.

\[ h(t) = h_0(t) \exp \left[ 0.008927 \text{Age} - 0.0896 \text{Monitoring Frequency} - 0.296831 \text{Alternative Medicine} \right] \]

From Table 7 it can be seen that age, monitoring frequency of ECCT and alternative medicine are variables that have a significant effect on survival time. The hazard ratio of age is 1.01, which means that each increase in age will increase the risk of dying by 1.01. Meanwhile, the hazard ratio for variable ECCT monitoring frequency and alternative treatments were 0.91 and 0.74, respectively. This means that when patients monitor ECCT and undergo alternative medicine, the risk of dying is decreased by that value.

5. Conclusions and recommendation

Based on the results of descriptive statistical analysis, 75% of lung cancer patients experienced an event (died), while for brain cancer patients as much as 65%, and breast cancer patients by 49%. The study showed that monitoring frequency of ECCT is significant factor that influenced in cancer survival for all three survival models. Based on the Cox survival model, the hazard ratio (HR) value ranges from are 0.8 – 0.9. It means that each additional one time the frequency of monitoring, the risk of experiencing death decreased by 0.8 – 0.9 times.

From the results of this study, it can be recommended to the Edwar Lab that monitoring the ECCT device on patients is very important and this must be done by patients according to the standards given by the Edwar Lab.

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