

**Prognostic Factors Associated with Survival in Laryngeal Squamous Cell Carcinoma**

**Patients Treated with Laryngectomy: A Retrospective Study**

Master of Public Health Integrating Experience Project

Research Grant Proposal Framework

By

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## List of Abbreviations

<b>AJCC</b>	American Joint Committee on Cancer
<b>AMD</b>	Armenian Dram
<b>ASCO</b>	American Society of Clinical Oncology
<b>BMI</b>	Body Mass Index
<b>CI</b>	confidence interval
<b>CIS</b>	carcinoma in situ
<b>EMC</b>	Erebuni Medical Center
<b>GERD</b>	gastroesophageal reflux disease
<b>HPV</b>	human papillomavirus
<b>HR</b>	hazard ratio
<b>IMB</b>	International Business Machines Corporation
<b>IRB</b>	Institutional Review Board
<b>KM</b>	Kaplan-Meier
<b>LSCC</b>	laryngeal squamous cell carcinoma
<b>NCO</b>	National Center of Oncology
<b>PH</b>	proportional hazards
<b>SEER</b>	Surveillance, Epidemiology, and End Results
<b>SPSS</b>	Statistical Package for the Social Sciences
<b>TORL</b>	transoral resection of the larynx
<b>US</b>	United States

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## **Executive Summary**

Laryngeal squamous cell carcinoma (LSCC) is a malignant tumor located in the throat - an essential organ for communication, breathing, and swallowing. Most commonly diagnosed at advanced stages, the most effective recommended treatment for this malignancy is a partial or total laryngectomy, which removes important structures of the throat. According to the National Institute of Health in Armenia, more than 2.3% of diagnosed malignancies in 2021 were cases of laryngeal cancer, 78% of which were diagnosed at late stages. According to available data, in 2020, 1.5% of cancer deaths in Armenia were due to laryngeal cancer.

Many studies have examined the prognostic factors and the 5-year survival for patients who underwent laryngectomy worldwide. However, the evidence is inconsistent in different countries. Therefore, it is important to identify the survival rate and prognostic factors for patients with such diagnosis and treatment in Armenia, as no such investigation has been conducted to date. The results of the study can identify the determinants of survival that can be used to develop interventions to improve patient outcomes. Therefore, this study aims to identify the 5-year survival rate and the host-, tumor-, and treatment-related prognostic factors for 5-year survival of LSCC patients after laryngectomy in Armenia. A retrospective study will be conducted with an estimated sample size of 317 patients who underwent laryngectomy before January 1, 2018. A formula for discrimination-based sample size calculation for time-to-event data for multivariable prognostic models was used to determine the sample size. Inclusion criteria are being a patient aged 18 and above with a biopsy-proven diagnosis of primary laryngeal squamous cell carcinoma who underwent laryngectomy in Erebuni Medical Center or National Center of Oncology named after V.A. Fanarjyan. Data will be collected from electronic

databases and patient information cards of both hospitals using a data extraction form. To identify the survival status of the patient and, in case of death, the date and cause of death, trained nurses (one from each hospital) will contact the relative of the patient and conduct an inquiry using a script. Survival function will be estimated to describe the five-year overall survival via Kaplan-Meier (KM) method. A predictive model of determinants of 5-year survival of patients with LSCC who underwent surgical removal of the tumor will be fitted using Cox Proportional Hazards regression analysis. Approximately 4 months and 1,101,540 AMD will be needed to conduct the study.

## 1. Introduction

### 1.1 Problem definition and magnitude

Despite the progress made in the diagnosis and treatment of cancer, it remains a significant worldwide public health issue. Laryngeal cancer is not an exception. It has been estimated that in 2020, the global incidence of laryngeal cancer was 2.7 cases per 100,000 people, the global prevalence was 14.3 cases per 100,000 people, and there were 1.6 cases of death per 100,000 people

.<sup>1</sup> According to the World Health Organization, the 5-year worldwide prevalence of laryngeal cancer is 6.7 per 100.000 population.<sup>2</sup> It is important to mention that about 95% of all laryngeal cancers diagnosed are a type called laryngeal squamous cell carcinoma (LSCC), and only 2%–5% of all laryngeal cancers are chondrosarcomas, leiomyosarcomas, and melanomas.<sup>1,3</sup> Following lung cancer, LSCC is the second most prevalent malignant tumor in the respiratory system.<sup>4</sup>

Laryngeal cancer is a type of malignancy that is located in the larynx or the throat, and there are four types of this tumor based on its site: glottic (at the level of true vocal cords), supraglottic (above the true vocal cords), subglottic (below the true vocal cords), and transglottic (involves both the vestibular and vocal folds).<sup>5,6</sup> The glottic area is where around two-thirds of



all laryngeal cancer cases originate, followed by the supraglottic area (30%), while subglottic and transglottic locations are rare.<sup>7,8</sup> There is also another classification based on the disease stage: Stage 0 (Carcinoma in Situ), Stage I, Stage II, Stage III, and Stage IV. In Stage 0 laryngeal cancer or Carcinoma in Situ (CIS), the abnormal cells are located in the lining of the laryngeal mucosa and can develop into cancer cells subsequently with the risk of spreading to other layers and parts of the larynx.<sup>9</sup> In the case of Stage I laryngeal cancer, the tumorous cells grow deeper into the layers of the larynx, but the process only involves one part of the larynx (supraglottis, glottis, or subglottis), and the function of the vocal cords is normal.<sup>10</sup> In Stage II laryngeal cancer, the process spread is even deeper than in Stage I, and the tumor grows into more than one part of the larynx; however, the vocal cords can still function normally.<sup>10</sup> When the tumor spreads to nearby tissues (e.g., postcricoid area, pre-epiglottic tissue) or to a single nearby lymph node, then the tumor is classified as Stage III laryngeal cancer. The last stage is Stage IV, where the tumor grows into nearby tissues and organs, the vocal cords can be affected, and it can spread to nearby lymph nodes and distant body parts.<sup>10</sup> It is unfortunate that the majority of laryngeal cancer cases are diagnosed in late III and IV stages (over 75%).<sup>11,12</sup> Data from the United Kingdom show that the 5-year-survival rate of LSCC is 60% for Stage III laryngeal cancer and 30% for Stage IV laryngeal cancer, and data provided by the American Society of Clinical Oncology (ASCO) shows that in the US, it is 46% and 34%, respectively.<sup>13,14</sup> The same sources show higher 5-year survival rates for Stage I and Stage II LSCC (75-90%).

The American Joint Committee on Cancer (AJCC) has come up with another classification for laryngeal cancer that is based on three important factors: the size of the tumor (T), the spread to regional lymph nodes (N), and the spread to distant parts of the body (metastases, M).<sup>15</sup>

### 1.2 Risk factors of laryngeal cancer

Etiologic studies have confirmed that the use of tobacco and alcohol is linked to the onset and future development of the disease, and patients who drink alcohol and smoke tobacco have a higher risk of developing laryngeal cancer.<sup>16,17</sup> A study shows that with an increase in tobacco and alcohol consumption, the prevalence of LSCC has increased by approximately 12% during the past three decades.<sup>18</sup> Another risk factor for laryngeal cancer is age. There is a higher risk for an old-aged patient (55 and older) to have laryngeal squamous cell carcinoma.<sup>18</sup> Gender is also a LSCC, with males having 4-6 times higher risk of laryngeal cancer than females, which might be related to their lifestyle.<sup>18</sup>

Studies have shown that patients with gastroesophageal reflux disease (GERD) have about 15 times higher risk of developing LSCC compared to patients with no GERD.<sup>19</sup> Also, patients who have a family history of LSCC are more likely to develop laryngeal cancer.<sup>8</sup> Finally, rare risk factors for developing LSCC include the human papillomavirus infection (HPV),<sup>20</sup> poor nutrition,<sup>21</sup> and workplace exposures (wood dust, asbestos).<sup>22,23</sup>

### 1.3 Treatment

Decisions about the treatment of laryngeal cancer should be made by using a multidisciplinary approach that will take into consideration the stage of cancer, its location, and existing comorbidities.<sup>24</sup> The main treatments for this type of cancer are surgery, chemotherapy, and radiotherapy. Radiotherapy uses the effect of high-energy radiation to destroy abnormal cells.<sup>25</sup> Radiation therapy or surgery alone is used for small, superficial tumors that do not involve lymph nodes. The radiation dose is determined by the size and the place of the cancer. For more advanced stages (Stage III and Stage IV), a combination of different treatment approaches, necessarily including surgery, is used.<sup>26</sup> Laryngectomy (removal of the larynx) is recommended with the combination of radiation and chemotherapy.<sup>24</sup> Surgeries performed to remove the cancer of the larynx include endoscopic resection, partial laryngectomy, and total laryngectomy.<sup>27</sup> In the case of endoscopic resection or transoral resection of the larynx (TORL), the removal of the tumor is done by using an endoscopic technique as opposed to an open surgical procedure. Through the use of an endoscope, tumors are identified and removed using lasers or other surgical techniques, leaving the wound bed exposed for subsequent healing.<sup>28</sup> All laryngeal structures and a portion of the upper trachea are removed during a total laryngectomy treatment, which results in the airway being disconnected and leaving a permanent breathing hole in the neck (tracheostoma). This method sacrifices the patient's voice in the name of curing

cancer.<sup>29</sup> However, there are cases when due to the location of the cancer, it can be removed without having to remove the entire larynx. This surgery is called partial laryngectomy.<sup>26</sup> Depending on the part of the larynx that gets removed during the surgery, there are various types of partial laryngectomy, some of which are cordectomy (vocal cords are removed) and hemilaryngectomy (removal of the vocal cords, the arytenoid cartilage, and the thyroid wing).<sup>24</sup>

#### 1.4 Prognostic factors of LSCC

The outcome of the disease depends on different prognostic factors, which can be grouped into three categories – host, tumor, and treatment factors.

##### 1. Host Factors

- a. Age – Data on the survival of patients with LSCC depending on age is ambiguous. A study conducted in the US in 2000 shows that the probability of a good prognosis among patients who are younger than 40 is higher than among those who are older.<sup>30</sup> Better survival with younger age was also found in a population-based analysis.<sup>31</sup> However, a study conducted at the Oslo University Hospital shows that younger people have a higher chance of cancer recurrence.<sup>32</sup>
- b. Gender – Survival rates differ among males and females. When compared to females, males had inferior survival rates.<sup>33</sup>

- c. Smoking status – Smoking at diagnosis is an independent prognostic factor for laryngeal cancer survival, and it is associated with poor survival. A population-based study showed that current smokers (patients who smoked at least once a month during a year prior to diagnoses) had a 36% increased cancer death rate compared to those who never smoked. Ex-smokers had a nonsignificant, modest increase in the cancer-related death rate. The study also mentioned that a possible reason for these results might be the impact of smoking on treatment effectiveness.<sup>34</sup>
- d. Alcohol use – Pre-diagnostic alcohol use is associated with poor survival among LSCC patients. A pooled analysis showed that the status and intensity of alcohol consumption were prognostic factors for both overall survival and disease-specific survival.<sup>35</sup>
- e. Nutritional status – Malnutrition is another factor that has been identified to influence the prognosis of the disease. Good nutritional status was shown to be favorable for better prognosis: low Body Mass Index (BMI) before treatment was an independent prognostic factor for LSCC and was significantly associated with poor survival.<sup>36</sup>
- f. General health status of the patient – Comorbidities of the patient can alter the outcome of the disease. A Danish study showed that poor health condition and

comorbidities decreased the chances of survival for patients with cancers of the head and neck.<sup>37</sup>

## 2. Tumor-related Factors

- a. Site – According to the Surveillance, Epidemiology, and End Results (SEER) database, patients with glottic carcinoma have a higher 5-year survival rate, about 77%, whereas patients with supraglottic cancer have the lowest 5-year survival rate – about 46%.<sup>38</sup>
- b. Class – Higher T, N, and M classes of the cancer were noted as risk factors for the recurrence of glottic squamous cell carcinoma and for lower survival rates.<sup>33,39</sup>
- c. Histological grading of malignancy – Patients who have laryngeal squamous cell carcinoma with poor differentiation have a worse prognosis of survival compared to patients with carcinomas that are well or moderately differentiated.<sup>40</sup>

## 3. Treatment-related Factors

- a. Combination of laryngectomy with chemotherapy produces better results than surgery alone. In a study conducted in 1991 among patients with Stage III and IV LSCC, the results showed that 20% of patients in the chemotherapy group had a recurrence, compared with 7% in the group where patients underwent chemotherapy and laryngectomy.<sup>41</sup>

- b. The same is true for combination of surgery with radiotherapy. A study conducted in China showed that the overall 5-year survival rate of patients with glottic carcinoma who received radiotherapy combined with surgery was 72.2% for total and 92.3% for partial laryngectomy.<sup>42</sup> For comparison, a study conducted in Denmark showed that the disease-specific survival for patients with total laryngectomy alone was about 54%.<sup>43</sup> A similar study conducted in China in 2006 showed that the 5-year survival rate among patients with advanced (Stage III and Stage IV) LSCC was 18.3% for patients who underwent radiotherapy alone and 51.0% for patients who received laryngectomy after the radiation therapy.<sup>44</sup>

#### 1.5 Prognostic factors related to the specifics/outcomes of laryngectomy

- **Lymph node dissection during laryngectomy** – During laryngectomy, if the cancerous cells are spread into lymph nodes, dissection is performed. Lymph node dissection during laryngectomy is associated with poor prognosis of survival after laryngectomy.<sup>43</sup>
- **Histopathology of the resection margins (negative margins, positive margins)** – According to the National Cancer Institute of America,<sup>45</sup> resection margin is the edge of the tissue removed during cancer surgery. It can be negative, meaning that the edges are clean and during pathologic examination, no cancer cells were found, and positive when

pathological examination finds cancerous cells in the tissue. Negative surgical margins are a significant independent predictor for better survival for patients with laryngectomy.<sup>46</sup>

- **Postoperative complications within one year after laryngectomy** – Laryngectomy can be followed by complications such as wound infection, hematoma, and fistula.<sup>47</sup> A study conducted in Denmark found that the presence of postoperative complications within one year after laryngectomy is a prognostic factor for shorter disease-specific survival after laryngectomy.<sup>43</sup>

## 1.6 Situation in Armenia

According to the National Institute of Health in Armenia, more than 2.3% of malignant neoplasm cases in 2021 were patients with laryngeal cancer; moreover, 78% of them were diagnosed in the late stages of the disease.<sup>48</sup> According to the World Health Organization, the 5-year prevalence of laryngeal cancer in Armenia is 13.3 per 100,000 inhabitants (twice higher of the global rate of 6.7 per 100.000 inhabitants).<sup>49</sup> The same source mentions that in 2020, about 1.5% of cancer deaths in Armenia were due to laryngeal cancer.



There were two main hospitals providing surgical care to patients with laryngeal cancer in Armenia before 2018. One of them was the Erebuni Medical Center (EMC)<sup>50</sup>, and the other one was the National Center of Oncology, named after V.A. Fanarjyan (NCO).<sup>51</sup> These hospitals are still the main sites for laryngeal cancer treatment. Both hospitals are equipped to perform TORL, partial and total laryngectomy.

### 1.7 Rationale of the study

International literature provides inconsistent evidence on the length of survival of LSCC patients and the factors having prognostic value for LSCC outcome in different countries. Therefore, it is important to conduct a study to identify the survival rate of these patients and to find out prognostic factors for LSCC treatment outcome in Armenia, where no such investigations have been conducted to date.

**The aim** of this study is to identify the 5-year survival rate and possible prognostic factors associated with survival in laryngeal squamous cell carcinoma patients treated with laryngectomy in Armenia.

**The objectives** of this study are:

- To assess the 5-year survival rate of patients with LSCC who underwent laryngectomy in Armenia before January 1, 2018.

- To identify the prognostic value of the available host-, tumor-, and treatment-related factors for 5-year survival of LSCC patients after laryngectomy.
- To develop a predictive model of determinants of 5-year survival for patients with LSCC who underwent laryngectomy.

## **2. Methods**

### 2.1 Study design and setting

The study will utilize a retrospective design enrolling patients who have undergone laryngectomy (partial or total) in two hospitals, Erebuni Medical Center (EMC) and the National Center of Oncology (NCO). Taking into consideration that EMC and NCO are the main hospitals conducting this surgery, and no hospitals in rural areas of Armenia perform it, this study will account for almost all the surgeries for LSCC conducted in Armenia.

### 2.2 Study population

The target population of the study includes all patients with total or partial laryngectomy for laryngeal squamous cell carcinoma. The study population includes all patients from EMC and NCO who were 18 years old or older at the time of the diagnosis, who were diagnosed with laryngeal squamous cell carcinoma, and underwent laryngectomy surgery before January 1, 2018. Patients with recurrent laryngeal cancer will be excluded.

### 2.3 Sample size calculation

To calculate the sample size, a formula for discrimination-based sample size calculation for time-to-event data for multivariable prognostic models was used. <sup>52</sup>

$$e_2 = \lambda_m \frac{(\delta)^{-2}}{(zz)}, \text{ where}$$

$e_2$  = the number of events

$\lambda_m$  = a structural constant

$$\lambda_m = c_0 + c_1 D^{1.9} + c_2 (D * cens)^{1.3}, \text{ where}$$

$$c_0 = 2.66; c_1 = 1.26; c_2 = (-1.65)$$

$D$  = the prognostic ability of the model (the value of 1.4 is suggested to use)

$cens$  = the expected percentage of the censored (taken from a previous study as 30%)<sup>13</sup>

$$\lambda_m = c_0 + c_1 D^{1.9} + c_2 (D * cens)^{1.3} = 2.66 + 1.26(1.4)^{1.9} + (-1.65)(1.4 * 0.3)^{1.3} = 4.526$$

$\delta$  = the desired difference in  $D$  (recommended to be within the interval of 0.2-0.4, taken as 0.4

for feasibility reasons)

$$zz = z_{1-\alpha/2} + z_{1-\beta}, \text{ and for } \alpha = 0.05 \text{ and power} = 80\%$$

$$zz = 1.96 + 0.84 = 2.8$$

$$e_2 = \lambda_m \frac{(\delta)^{-2}}{(zz)} = 4.526 \frac{(0.4)^{-2}}{(2.8)} = 4.526 * 49 = 221.8$$

$$n = (221.8 * 100) / 70 = 317$$

#### 2.4 Study instruments

The form for the data extraction from electronic databases and patient information cards is developed by the student-investigator after conducting a literature review about the topic. Information on patients' demographic data, comorbidities, cancer specifics, and treatment details will be extracted using this medical record data abstraction form (Appendix 1). The student-investigator also developed a script for a telephone inquiry, aimed at identifying the survival status and, in case of death, the time and the cause of death of the participant (Appendix 5). Both the data extraction form and the telephone script will be pre-tested to identify and apply any necessary changes.

#### 2.5 Data collection

After receiving permission from EMC and NCO administrations, complete lists of patients who underwent laryngectomy for LSCC will be obtained from the otorhinolaryngology departments of both hospitals. The eligible participants will be recruited starting from January 1, 2018, and going back until the needed sample size is reached. Data will be collected by the

student-investigator with the use of the data extraction form to retrace data from the electronic databases and patient information cards (Appendix 1).

To identify the survival status and, in case of death, the time of death, and the cause of death of the patients, the relatives of the participants will be contacted by nurses (one in EMC, one in NCO), using the contact number of the relative provided in the electronic databases. The student-investigator will apply the eligibility criteria, generate the list of the study participants, and pass the corresponding patient lists to the nurses for contacting the patients' relatives and identifying their survival status. The list will include the ID numbers of the participants, which will be assigned by the student-investigator. The nurses will contact the relative using the script for the telephone inquiry (Appendix 4). The nurses will be trained by the student-investigator to conduct the telephone inquiries. The reason for contacting the relative instead of the participant is that patients who undergo laryngectomy have difficulties speaking or cannot talk at all.

## 2.6 Study variables

### Dependent variable

The dependent (outcome) variables of the study are the 5-year survival status (event(death)/censored (alive)) and the time-to-death of the participant who was diagnosed with LSCC and treated with laryngectomy. The time variable will be measured from the date of the surgery until the last day of the five-year follow-up period or death from any cause (in months).

## Independent variables

Independent variables include host factors – the date of birth; gender of the participant (male, female); current smoking status (defined as smoked at least once a month during a year prior to the diagnosis), ever smoking status, alcohol consumption (never, less than one drink a week, more than one drink a week), comorbidities such as diabetes, hypertension, gastrointestinal diseases, respiratory diseases; tumor factors – site of the tumor (supraglottic, glottic, subglottic), clinical stage of the tumor (I, II, III, IV), its pathological differentiation (high, low); treatment factors – type of the surgery (total laryngectomy, partial laryngectomy), preoperative chemotherapy, postoperative chemotherapy, preoperative radiotherapy, postoperative radiotherapy, etc. Appendix 2 provides the full list of variables with the type of each.

## 2.7 Data management and analysis

Data entry and analysis will be conducted using the IBM SPSS 25 software. The data will be checked for any missing or erroneous values, and data cleaning will be performed.

Descriptive statistics will be run to summarize continuous variables by their median, mean, and standard deviations and categorical variables by frequencies and percentages. For comparing continuous variables between the groups of those who died and those who were alive at the end of the 5-year follow-up, t-test and for categorical variables, Chi-square tests will be

used. Survival function will be estimated to describe the five-year overall survival via Kaplan-Meier (KM) method. To assess the predictors of overall survival, a time-to-event analysis will be conducted using Cox proportional hazards (PH) regression analysis. To show the significance of the association between the predictor and the outcome, a univariate Cox PH analysis will be carried out, in which the hazard ratios (HR), 95% confidence intervals (CI), and p values for each prognostic factor will be produced. After examining the univariate associations for PH assumptions, variables will be chosen using the stepwise forward selection procedure to fit the multivariable Cox PH model. The thresholds for the variable inclusion and exclusion will be  $p < 0.25$  and  $p > 0.05$ , respectively. Kaplan-Meier survival curves will be used to estimate the overall survival rate in relation to predictor variables.

### **3. Budget**

The proposed study is estimated to cost around 1,101,540 Armenian Drams (AMD). This amount includes the salaries of the personnel and operational costs. Two nurses (one from EMC and one from NCO) will receive a monthly salary to conduct telephone inquiries. Data extraction from patient information cards and electronic databases, data entry, and data analysis will be conducted by the primary researcher. Operational costs include printing of data extraction forms,

journal forms, and scripts, obtaining stationary, and expenses for telephone calls. The full list of expenses is presented in Table 1.

#### **4. Ethical Considerations**

A preliminary approval from the Institutional Review Board of the American University of Armenia was granted. Permission from the administration of both hospitals (EMC, NCO) will be received to have access to patient information. A telephone inquiry script will be used by the nurses to explain to the relatives of the study participants the aim of the study, why they were contacted, and how their phone number was accessed. All the electronic documents will be kept in an encrypted computer, and the papers will be kept in a locked drawer, and the student-investigator will be the only one who has access to it. All the paper journal forms that include the identifiable information of the participant will be kept separate from the scripts and medical record review forms to avoid disclosure and will be destroyed after finishing the data checking and cleaning.



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## Tables

**Table 1: Budget**

	<b>Unit type</b>	<b>Cost per unit in AMD</b>	<b>Number of units</b>	<b>Total in AMD</b>
<b>Personnel</b>				
<b>Primary researcher</b>	Months	150,000	4	600,000
<b>Interviewer 1</b>	Months	80,000	2	160,000
<b>Interviewer 2</b>	Months	80,000	2	160,000
<b>Operational Costs</b>				
<b>Printing</b>	Pack for 1 participant *	8 * 25 (price of one page) = 200	317	63,400
<b>Stationary</b>	Pack	6,000	1	6,000
<b>Telephone expenses</b>	Monthly	6,000	2	12,000
<b>Taxes/unforeseen expenses</b>				100,140
<b>Total in AMD</b>				1,101,540

\*Pack for 1 participant includes the journal form (1 page), the medical record data abstraction form (6 pages), and the telephone interview script (1 page), = 8 pages.



## Appendices

### Appendix 1: Medical Record Data Abstraction Form

<b>Administrative Data</b>		
1. Patient ID _____		
2. Date of first visit __/__/__	3. Date of surgery __/__/__	4. Date of discharge __/__/__
<b>Demographic data</b>		
5. Date of birth                      __/__/__		
6. Gender	1.Male__ 2.Female__	
7. Weight	____ kg	
8. Height	____ cm	
9. Marital status	1.Single    __ 2.Married    __ 3.Divorced    __ 4.Widowed    __ 99.Missing    __	
10. Place of residence	1.Yerevan    __ 2.Lori        __ 3.Shirak     __ 4.Tavush     __ 5.Gegharkunik    __ 6.Ararat     __ 7.Armavir    __ 8.Vayots Dzor    __ 9.Syunik     __ 10.Kotayk    __ 11.Aragatsotn    __ 12.Artsakh    __ 99.Missing    __	

<b>Health Behavior Data</b>	
11. Current smoker	1.Yes ___ 2.No ___ 99.Missing ___
12. If Yes → how many cigarettes/day?	_____
13. Ex-smoker	1.Yes ___ 2.No ___ 99.Missing ___
14. If Yes → how many cigarettes/day?	_____
15. Alcohol consumption	1.Never 2.Less than 1 drink a week___ 3.More than 1 drink a week___ 99.Missing ___
<b>Comorbidities</b>	
16. Diabetes	1.Yes ___ 2.No ___ 99.Missing ___
17. Hypertension	1.Yes ___ 2.No ___ 99.Missing ___
18. Gastrointestinal diseases	1.Yes ___ 2.No ___ 99.Missing ___
19. Respiratory diseases	1.Yes ___ 2.No ___ 99.Missing ___
20. Distant metastasis	1.Yes ___ 2.No ___ 99.Missing ___

21. If Yes → where is it located?	_____
22. Other cancers	1.Yes ___ 2.No ___ 99.Missing ___
23. If Yes → specify the location of other cancers	_____
<b>LSCC specifics</b>	
24. Site of the cancer	1.Supraglottic ___ 2.Glottic ___ 3.Subglottic ___
25. Clinical stage of the cancer	1.I ___ 2.II ___ 3.III ___ 4.IV ___
26. Pathological differentiation	1.High ___ 2.Low ___
<b>Treatment</b>	
27. Preoperative chemotherapy	1.Yes ___ 2.No ___ 99.Missing ___
28. Preoperative radiotherapy	1.Yes ___ 2.No ___ 99.Missing ___
29. Preoperative concurrent radiochemotherapy	1.Yes ___ 2.No ___ 99.Missing ___
30. Type of the surgery	1.Total laryngectomy ___ 2.Partial laryngectomy ___ 3.TORL ___
31. Lymph node resection	1.Yes ___ 2.No ___ 99.Missing ___

32. Postoperative complications	1.Yes ___ 2.No ___ 3.Other ___ 99.Missing ___
33. If Yes → date of the complication	___/___/___
34. If Yes →What type of complication?	1.Wound infection ___ 2.Hematoma ___ 3.Fistula ___ 99.Missing ___
35. Resection margins	1.Negative ___ 2.Positive ___ 99.Missing ___

## Appendix 2: Codebook of Variables

Variable	Type	Measure	Description
<b>Demographic</b>			
Date of Birth	Ordinal	Dd/mm/yy	
Gender	Nominal	1 = Male 2 = Female	
Weight	Continuous	Kg	
Height	Continuous	Cm	
Marital Status	Nominal	1 = Single 2 = Married 3 = Divorced 4 = Widowed	
Place of residence	Nominal	1 = Yerevan 2 = Lori 3 = Shirak 4 = Tavush 5 = Gegharkunik 6 = Ararat 7 = Armavir 8 = Vayots Dzor 9 = Syunik 10 = Kotayk 11 = Aragatsotn 12 = Artsakh	
Current smoker	Binary	0 = No 1 = Yes	Smoked at least one cigarette once a month during a year prior to diagnosis
If yes, number of cigarettes per day	Continuous		
Ex-smoker	Binary	0 = No 1 = Yes	Ever smoked
If yes, number of cigarettes per day	Continuous		
Alcohol consumption	Nominal	1 = Never 2 = Less than one drink a week 3 = More than one drink a week	one drink is described as a glass of wine, one bottle of beer, or one small glass of vodka)

<b>Variable</b>	<b>Type</b>	<b>Measure</b>	<b>Description</b>
<b>Comorbidities</b>			
Diabetes	Binary	0 = No 1 = Yes	
Hypertension	Binary	0 = No 1 = Yes	
Gastrointestinal diseases	Binary	0 = No 1 = Yes	
Respiratory diseases	Binary	0 = No 1 = Yes	
Distant metastasis	Binary	0 = No 1 = Yes	
Other cancers	Binary	0 = No 1 = Yes	Cancers other than laryngeal cancer.
<b>Cancer: LSCC</b>			
Site of the cancer	Nominal	1 = Supraglottic 2 = Glottic 3 = Subglottic	
Clinical stage of the cancer	Ordinal	1 = I 2 = II 3 = III 4 = IV	
Pathological differentiation		1 = High 2 = Low	
<b>Treatment</b>			
Preoperative chemotherapy	Binary	0 = No 1 = Yes	
Preoperative radiotherapy	Binary	0 = No 1 = Yes	
Preoperative concurrent radiochemotherapy	Binary	0 = No 1 = Yes	Combined radiotherapy and chemotherapy before surgery
Type of the surgery	Nominal	1 = Total laryngectomy 2 = Partial laryngectomy 3 = TORL	
Lymph node resection	Binary	0 = No 1 = Yes	

<b>Variable</b>	<b>Type</b>	<b>Measure</b>	<b>Description</b>
Postoperative complications	Binary	0 = No 1 = Yes	
Type of the complication	Nominal	1 = Wound infection 2 = Hematoma 3 = Fistula 4 = Other	
Resection margins	Binary	1 = Negative 2 = Positive	

**Appendix 3: Journal Form**

Date \_\_\_/\_\_\_/\_\_\_\_\_

ID #	Name of the participant who underwent laryngectomy	Relative's phone number	Date of the surgery (dd/mm/yy)	Birth date of the participant (dd/mm/yy)	Result code*

\* Result codes:

- |                         |                |
|-------------------------|----------------|
| 1. Completed inquiry    | 5. No response |
| 2. Incomplete inquiry   | 6. Other _____ |
| 3. Refusal              |                |
| 4. Wrong name or number |                |



#### **Appendix 4: Script for Telephone Inquiry**

Hello. My name is (the name of the nurse) from Erebuni Medical Center/ National Center of Oncology otorhinolaryngology department.

One of our physicians, who is also a graduate student in the Master of Public Health program at the American University of Armenia, in the scope of her thesis project, is conducting a study, which aims to identify the survival rate and assess the factors associated with survival in patients with a laryngectomy. For that purpose, we would greatly appreciate any information you can share regarding the patient's current health condition. Your telephone number was taken from the patient's medical record provided by Erebuni Medical Center/ National Center of Oncology.

- Do you know \_\_\_\_\_(name), who underwent laryngectomy in the Erebuni Medical Center/ National Center of Oncology.

- If NO – *apologize and finish*
- If YES – *continue.*

- If it is possible, could you please provide an update on the patient's current health status?

- He/she has passed away
  - If he/she has passed away, ask – When? \_\_\_/\_\_\_/\_\_\_\_\_
  - What was the reason for death? \_\_\_\_\_

*Thank and finish.*

- He/she has health complaints
  - offer to book a doctor's appointment for a consultation
  - *thank and finish.*
  
- He/she has no health complaints, is feeling well
  - *thank and finish.*

**Հեն ախոս այ ի ն հարցման սցենար**

Բարև Ձեզ : Ես Էրեբունի ԲԺՀ կական կենտրոնի /

Ուսուցիչ քարտուսանության ազգային կենտրոնի քիթ-կոկորդ-

ական ջարտանության քաժանմունքի բուժքույր եմ, անունս \_\_\_\_\_ է :

Մեր ԲԺՀ կենտրոնից մեկը, ով ուսուցիչն է Հայաստանի ամերիկյան

համալսարանի Հանրային առողջապահության ֆակուլտետում, իր

ավարտական թեզի շրջանակներում իրականացնում է

հետազոտություններ, որի նպատակն է հասկանալ կոկորդի

վիրահատություններից հետո հիվանդներին ապրելիություն

ցուցանելու գնահատել ապրելիություն հետևյալով

գործունեությունը : Այդ նպատակով, մենք շատ շնորհակալ կլինենք ,

եթե կարողանաք մեզ տրամադրել հիվանդի ներկայիս առողջական

վիճակի վերաբերյալ ցանկացած տեղեկություն : Ձեր

հեն ախոսահամարը վերցրել ենք հիվանդի ԲԺՀ կական քարտից ,

որը տրամադրել է Էրեբունի ԲԺՀ կական

կենտրոնը /Ուսուցիչ քարտուսանության ազգային կենտրոնը :

Դուք ճանաչում եք (հիվանդի անուն, ազգանուն) ով Էրեբունի

ԲԺՀ կական կենտրոնում /Ուսուցիչ քարտուսանության ազգային

կենտրոնում տարել է կոկորդի վիրահատություն :

• Եթե ՈԶ – ներողություն չի կարողանա ավարտել :

• Եթե ԱՅՈ – շարունակել :

- Եթե հնարավոր է, կարող եք հիվանդի ներկայիս վիճակի մասին

տեղեկություն տրամադրել :

- Մահացել է

- Եթե մահացել է, հարցրեք՝ Ե՞րբ \_\_\_\_\_

-Ո՞րն էր մահվան պատճառը □ \_\_\_\_\_

*Շնորհակալ նւթյ նւն հայ տնէք և ավարտէք:*

- Ունի գանգատներ

- առաջարկեք խորհրդատվություն համար այց գրանցել

բժշկի մոտ

- Շնորհակալ նւթյ նւն հայ տնէք և ավարտէք:

- Գանգատներ չունի, և ավելի զգուս

- Շնորհակալ նւթյ նւն հայ տնէք և ավարտէք:

### Appendix 5: Timeline of Activities

<b>Task</b>	<b>1<sup>st</sup> month</b>	<b>2<sup>nd</sup> month</b>	<b>3<sup>rd</sup> month</b>	<b>4<sup>th</sup> month</b>
<b>Obtaining list of participants</b>	X			
<b>Pretesting the instruments</b>	X			
<b>Training the nurses</b>	X			
<b>Data extraction</b>	X	X		
<b>Telephone inquiry</b>	X	X		
<b>Data entry and cleaning</b>	X	X	X	
<b>Analysis</b>			X	X
<b>Preparing final report</b>			X	X