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ATHENS UNIVERSITY OF ECONOMICS AND BUSINESS

DEPARTMENT OF STATISTICS

POSTGRADUATE PROGRAM

ANALYSIS OF SURVIVAL DATA: ORAL SQUAMOUS CELL CARCINOMAS ON THE TONGUE

By

Eleni C. Costi

A THESIS

Submitted to the Department of Statistics
of the Athens University of Economics and Business
in partial fulfilment of the requirements for
the degree of Master of Science in Statistics

Athens, Greece
2005

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ΟΙΚΟΝΟΜΙΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΤΜΗΜΑ ΣΤΑΤΙΣΤΙΚΗΣ

Ανάλυση Δεδομένων Επιβίωσης: Στοματικά Ακανθοκυτταρικά Καρκινώματα στη Γλώσσα

Ελένη Κ. Κωστή

ΔΙΑΤΡΙΒΗ
Που υποβλήθηκε στο Τμήμα Στατιστικής
του Οικονομικού Πανεπιστημίου Αθηνών
ως μέρος των απαιτήσεων για την απόκτηση
Μεταπτυχιακού Διπλώματος Ειδίκευσης στη Στατιστική

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Eleni C. Costi

Approved by the Graduate Committee

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Athens, March 2005

Michael Zazanis, Professor
Director of the Graduate Program

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DEDICATION

I would like to dedicate the following study to my family, that is my parents and my older brother. I wish everybody had the chance to grow up in a home just like the one my parents created for my brother and myself.

A special dedication goes to those five friends of mine, with whom I shared the last two years, while completing this master, Antonia, Georgios, Lia, Nikos , and Tania.

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VITA

My name is Eleni C. Costi, and I was born in Nicocia, Cyprus, on the 21st of January in 1980. I graduated from the Pangryprio Lyceum of Larnaca in 1997, and during the same year I was accepted at the Mathematical Department of the University of Athens. I completed my mathematical studies in 2001, and I was accepted at the Department of Statistics, of the Athens University of Economics and Business, for postgraduated studies in Statistics.

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ABSTRACT

Eleni Costi

Analysis of Survival Data: Oral Squamous Cell Carcinomas on the tongue

November 2004

This work provides an analysis of biostatistical data, concerning 123 patients, treated for oral squamous cell carcinomas at the Maxillofacial Surgery Department of the St. Savvas Hospital in Athens. The aims of the research were to identify clinical variables that influence the survival time of patients with squamous cell carcinomas on the tongue, as well as to evaluate the existing classification and staging systems (TNM, STNMP) , and to investigate whether new prognostic factors should be added to the systems.

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ΠΕΡΙΛΗΨΗ

Ελένη Κωστή

Ανάλυση Δεδομένων Επιβίωσης: Στοματικά Ακανθοκυτταρικά Καρκινώματα στη Γλώσσα

Νοέμβριος 2004

Η παρούσα μελέτη παραθέτει την ανάλυση βιοστατιστικών δεδομένων, που αφορούν 123 ασθενείς, οι οποίοι νοσηλεύτηκαν με στοματικά ακανθοκυτταρικά καρκινώματα στο Γναθοπροσωπικό Χειρουργικό Τμήμα του Νοσοκομείου Αγ. Σάββας στην Αθήνα. Οι σκοποί της μελέτης ήταν ο προσδιορισμός κλινικών μεταβλητών που επηρεάζουν το χρόνο επιβίωσης των ασθενών με ακανθοκυτταρικά καρκινώματα στη γλώσσα, η αξιολόγηση των υπαρχόντων συστημάτων ταξινόμησης και σταδιοποίησης (TNM, STNMP), και η διερεύνηση του αν νέοι προγνωστικοί παράγοντες θα έπρεπε να προστεθούν στα συστήματα

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CHAPTER 1
Introduction

1.1. Introduction

The prevalence of oral cancer shows variable distribution in the different regions of the world, and it has been estimated that the squamous carcinoma of the area of the head and neck, overcomes the 800 000 new incidences annually in a universal scale. In the USA, 40 000 new incidences are being recorded annually with 11 000 annual deaths by the disease. In Brazil, the new incidences reach the 10 000 with 4 000 deaths, whereas in the UK, 5 000 new incidences are recorded with 1 200 deaths. These numbers are even higher in the developing countries, where the medical services are less reachable and developed (Chen et al, 2000). In Greece, unfortunately, there are no statistical evidence for the prevalence of the disease in the population, but it is calculated that in an annual basis the new incidences of head and neck cancer overcome the 1 500 with analogous number of deaths. About 80% of these patients develop the disease in the oral cavity (Αγγελόπουλος και συν, 2000).

In the oral cavity, the most frequent malignancy is the oral squamous cell carcinoma (scc), that corresponds to 95% of all oral malignant lesions, while the most affected sites are the tongue, the inferior lips and the floor of the mouth (Dantas et al, 2003). Males are affected twice as females and the vast of patients are more than 45 years old (Beltrao et al, 1999; Line et al, 1995; Gervasio et al, 2001).

The development of oral scc is associated with several mucosal conditions (Fitzpatrick et al, 1983). The most important ones are the chronic hyperplastic candidiasis, the lichen planus, the sideropenic dysphagia, which is particulary common in Swedish women, and the submucous fibrosis, which is virtually confined to the Indian subcontinent. On the other hand, tobacco and alcohol are held to be the two commonest causes of oral scc at the present time, and their effects are likely to be synergistic (Adewole, 2002). A poor dental state with sharp teeth, poor restorations, sepsis and ill fitting dentures have also often been found incriminated in the etiology of scc (Adewole, 2002).

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The aims of this research were to identify the clinical variables that influence the survival time of patients with squamous cell carcinomas on the tongue, and to evaluate whether new prognostic factors should be added to the existing classification and staging systems.

Utilized for this research, were the records of 123 patients, treated for oral scc at the Department of Maxillofacial Surgery, in St. Savvas Hospital of Athens, during the time period between 1992 and the 6^{th} of August 2004. Out of them, 76 were male (61,8%), and 47 were female (38,2%), thus giving a male:female ratio almost equal to 3:2. The variables considered for the formation of the database concerned demographic characteristics of the patients, initial symptoms, the time elapsed since treatment, predispositional factors, location of the lesions, histopathological characteristics, as well as the patients' classification and staging according to two systems. A descriptive study of the data was initially performed, followed by survival analysis using Kaplan-Meier (log rank test for the comparison among curves), and multivariate Cox's proportional-hazards model.

This presentation begins with a medical description of the oral cancer, and in specific of the oral squamous cell carcinoma. The classification of the intra-oral cancer is also shown, providing thus a more specific view of what we call "cancer of the tongue".

The next chapter in line, Chapter 3, provides a review of the literature on the topic, and a presentation of the evolution of the classification and staging systems used in the present research.

In Chapter 4, the statistical methodology is theoretically presented, and Chapter 5 includes the results of the statistical analysis of the data. In this analysis, a detailed statistical description is followed by the results of the applications of the Kaplan-Meier method and the Cox's proportional-hazard model. All significant relationships, revealed by the use of the chi-square test, are also presented in this chapter.

Finally, Chapter 6 provides all the main conclusions drawn from the research, as they were established by a combination of the results of all methods. The conclusions are compared with those of other, previous studies.

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CHAPTER 2
Medical description of the disease

2.1. Introduction

Nowadays it is known that what we call cancer is a big family of genetic diseases that are due to combinations of inherited and acquired changes of the cellular DNA. For the appearance of the phenotype of the cancer many genetic changes are needed both in the structure of the chromosomes and in the positions of the genes and the concatenation of the proteins that combine them (Ankathil et al(1996)).

2.2. Medical origin of the oral squamous cell carcinoma

The squamous cell carcinoma (scc) is a carcinoma created in the squamous cells. These cells are different from others, in that their membranes are full of small edges making them look like a star.

The oral scc in specific, may arise in a previously normal area of the oral mucosa or from an area of abnormal oral mucosa. The abnormal mucosa may contain a precancerous lesion or a premalignant condition. Leukoplakia is the most common malignant condition in the mouth. It is defined as a white patch attached to the mucosa that cannot be taken off and is a clinical diagnosis that does not understate dysplasia. The white patch might be uniformly white, wrinkled or have small red stigmas spread on it (erythroplakia). When it is combined with erythroplakia, it is considered to be precancerous lesion and its prognosis is not very good. When it does not manifest in the high risk sites of the squamous carcinoma (floor of the mouth, up and lateral surface of the tongue), it must be considered and investigated with great caution and suspicion (Fitzpatrick et al, 2001).

The cell carcinoma in situ of the oral mucosa corresponds to the Bowen's disease of the skin and is called "erythroplasia". It is a red patch on the surface of the mucosa that may or may not have a synthetic part of white color. It demonstrates reddish, velvet appearance, with different kinds of leukoplakia, or it might be a smoothed patch with minimum or no leukoplakia. It is usually manifested on the floor of the mouth in men, while in women the most usual manifestations appear on the tongue and the mucosa of the cheeks. The lesions might be relatively small (<2cm). This condition develops and becomes a squamous cell carcinoma (Fitzpatrick et al, 2001).

2.3. Classification of the intra-oral cancer

The oral squamous cell carcinoma is treated by using surgery, radiotherapy, chemotherapy or their combinations. The various surgical methods used nowadays are used according to the anatomical site of the lesion. For this reason it was necessary to classify the intra-oral cancer according to that, and to form the following four categories (Ραπίδης και συν, 2003): Cancer of the lip and cheek, Cancer of the tongue and floor of the mouth, Cancer of the mandible, Cancer of the maxilla and palate.

The cancer of the lip is the most common malignant neoplasm of the maxillofacial area. The inferior lip is the most commonly attacked part of the area (over 97%) with the patients being usually men of 55 years and more. There is a direct correlation between smoking and exposure to the solar radiation, and appearance of the disease. The lesions usually have to do with squamous carcinomata appearing to the red hem of the inferior lip and expanding towards the skin. In its early stages the disease appears like a rhagas or crust that bleeds easily and does not heal. The revolution of the disease causes ulceration with usually clear limits which present sclerosis. The lesions appear in equal numbers in the middle or one end of the lip and they are solitary. The diagnosis is given after the histological examination (Jovanovic et al, 1993).

The mucosa of the cheek, which spreads on side parts of the oral cavity, usually presents pachynsis and increase of the keratin's thickness in the area of the teeth's convergence. The appearance of white and red patches in the area of the cheeks is very common, while the appearance of squamous carcinomata is relatively uncommon (Vegers et al, 1979). The squamous carcinoma on the cheeks appears most commonly on parts where leukoplakia had appeared before. It appears like diabrotic ulcer or like exophytic mass. In very serious stages it inflates its neighboring tissues and reaches until the cheek's skin or the mandible's bone (Bloom et al, 1980).

The squamous carcinoma of the tongue's mucosa is the most commonly found malignant neoplasm of the intra-oral tissues with more than 30% of the cases appearing in this area. The tongue is divided in three parts: the anterior two thirds are the mobile part, whereas the posterior third, which includes and the base of the tongue, is described along with the stomatopharynx.

As cancer of the tongue we consider the neoplasmatic lesions which are found on its mobile part, whereas the lesions found on its base are described along with the stomatopharynx's cancer. The squamous carcinomata of the tongue's mucosa have to do with lesions of the tongue's anterior two thirds and in the majority of the cases, they appear on the lateral lip of its middle third. The appearance of the carcinomata situated on the apex of the tongue or on its dorsal surface is extremely rare. The tongue's cancer is clinically appeared mainly in two ways: as exophytic mass or more commonly, as ulcer. There is a probability that the cancer of the tongue might cause pain with reflection to the neck, cheek and the area of the ear. Causes problems to the tongue's mobility which consequently causes dysarthria and dysphagia.

We call floor of the mouth the area which is surrounded by the alveolar apophysis of the mandible and the tongue. The majority of the pure carcinomata of the mouth's floor are found on the anterior part, underneath the tongue, they usually occupy the one half of the mouth's floor and extend beyond the middle line. Clinically, the original forms appear like exophytic lesions or ulcers which quickly, extend towards all directions and occupy the tongue and the mandible's bone. The prognosis is the same as the one for the tongue's cancer. Because the distinction between the two is very difficult they are nowadays described together. It is a usual phenomenon for the tongue's cancer to extend towards the lateral part of the mouth's floor and the vice versa (Kondo et al, 1986; Larsson et al, 1982). The squamous carcinoma of the mouth's floor, along with the one of the cheek are the most common types of carcinomata that are developed on the ground of preexisted leukoplakia.

The term cancer of the mandible includes the squamous carcinomata appearing on the mucosa of the gums, the alveolar apophysis and the posterior triangle of premolar teeth situated on the mandible. The carcinomata are also described by the same term. The lesions in this area of the oral cavity are less commonly found than the ones found on the tongue and the mouth's floor. In many cases of the alveolar apophysis's carcinomata the lesions are the result of metastases from other neighboring anatomical sites. The diagnosis of the lesions might delay, since the cancer usually is though to be traumatic ulcers from dentures or inflammative diseases of the region. So, a big part of the patients does not present in the early stages of the disease, but when the bone of the mandible is already attacked by the disease.

The malignant neoplasms of the maxilla and palate are nowadays referred as the "middle third of the face cancer" and they include squamous carcinomata, carcinomata of the glands and other tumors not coming from the epithelium. The malignant tumors coming from the epithelium constitute the 80% and more of the neoplasms (60% squamous carcinomata and 20% carcinomata of the glands) while the rest 20% is constituted by different kinds of sarcomas, lymphomas, melanomas and other more rare malignant neoplasms of the area (Harrison, 1971; Spiro et al, 1989). The cancer in the middle third of the face is less common than the one in the inferior third, whilst its discrimination from the maxilla's carcinoma is very difficult. The squamous carcinoma of the alveolar apophysis of the maxilla usually appears like exophytic mass and in its majority has a good discrimination. The most serious lesions inflate the bone of the maxilla or the palate and extend towards the Higmore's antrum.

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CHAPTER 3

Review of the literature

3.1. Introduction

Many researches have been contacted through out the years, for the identification of clinical variables that influence the survival time of patients with squamous cell carcinomas, and the estimation of whether new prognostic factors should be added to the existing classification and staging systems of the tumors. The present chapter provides a review of those researches.

3.2. Review of the variables that influence the survival of the patients with oral scc

One factor investigated by many was factor "sex". Some concluded that it did actually affected the survival of the patients (Waterhouse, 1974; Easson and Russel, 1968; Easson and Palmer, 1976; Berthelsen et al, 1977; Langdon et al, 1977; Ostman, 1995), whereas others concluded differently (Binnie et al, 1972).

Age was another variable that has concerned many researchers. Many of them concluded that patients younger than a certain age, had a different behavior than the rest, and thus age had an effect on the survival of the patients (Hyam et al, 2003; Veness et al, 2003; Ridge et al, 1998; Pitman et al, 2000; Friedlander et al, 1998).

Alcohol and smoking were also taken under suspicion. (Chen et al, 2000; Neville et al, 2002; Scussy et al, 2000; Shoaf, 2003; Adewole, 2002; Yeole et al, 2000) and so many others, have concluded that the above two did influence the survival time of patients with oral squamous cell carcinomas.

In 1982 Evans et al. contacted a research, and showed that the delay between the time of the beginning of the symptoms, and the time on which the patient appeared to the hospital for diagnosis and treatment, had an effect on the patients' survival, while others like Broders in 1920 and Esteban et al in 1998, showed that the histological characteristics of the intra-oral carcinoma played a significant role as well.

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Another factor that was researched is the "anatomical site of the lesion". Among the many researchers that worked on the subject, Zhang et al in 2001 pointed out the effect that the particular factor has on the patients' survival.

The size of the carcinoma, the presence and condition of the associated regional lymph nodes, and the presence or absence of distant metastases, are three other factors considered by the medical society (Ραπίδης και συν, 2003). This three were found to greatly affect the survival, and thus are used as the main prognostic factors for the classification and staging of the tumors.

3.3. Review of the classification and staging systems

The procedure of the discrimination of the tumors is consisted of two discrete parts. The first one is the classification of the tumor according to prognostic factors chosen by the researchers, and the other one is the staging of the tumor using the classification.

3.3.1 Classification

3.3.1.1. The TNM classification system

The first attempt for classification system was described by Steinthal in 1905 and it was applied on breast tumors. After that, various classification methods were proposed until 1954, when the Union Internationale Contre le Cancer (U.I.C.C.) proposed the TNM classification. TNM is a clinical classification and as such the information provided is entirely dependent upon the personal experience, opinions and skills of the examining clinician (Rapidis et al, 1976). The prognostic factors recorded for the TNM classification are the size of the primary tumor (T), the presence and condition of the associated regional lymph nodes (N) and the presence or absence of distant metastases (M). In the late 50's the American Joint Committee for Cancer Staging and End Result Reporting (A.J.C.C.) was created. A.J.C.C. adopted the TNM system, and since then the two organizations, together and separately, have created subcommittees for the continuing elaboration and modification of the systems according to the anatomical site of the primary tumor and its histological image (Ραπίδης και συν, 1978).

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3.3.1.1.a. Prognostic factor "size of the primary tumor" T

All three factors, when recorded, are divided in different categories. In Table 3.1, the categorization of the T factor is shown as it was proposed by Spiessl et al in 1973.

T_1 Up to 2 cms in the diameter, superficial exophytic

T_2 Up to 2 cms in the diameter, minimal depth infiltration, no radiological evidence of bone destruction

T_3 More than 2 cms in diameter with deep infiltration and/or radiological evidence of bone destruction

T_4 A tumor with extension to more than one neighboring region

Table 3.1: The categorization of the T factor, as it was proposed by Spiessl et al in 1973

In Table 3.2 the categorization proposed by the A.J.C.C. in 1967 is presented. It is noticeable that the American committee presented a more simple categorization, since there is no reference to the condition of the associated regional lymph nodes.

T_1	A tumor of 2 cms or less in greatest diameter
T_2	A tumor greater of 2 cms but less than 4 cms
T_3	Any tumor greater than 4 cms

Table 3.2: The categorization of the T factor, as it was proposed by A.J.C.C in 1967

Of course, other investigators have proposed different kinds of categorization for the T. The German Study Group of the oral cancer D.O.S.A.K., has proposed the modification of factor T with the addition of the clinical parameter "tumor thickness". Even though, the authors reported statistical improvements concerning the prognosis of the patients, the findings are based on retrospective and not preoptic studies (Ραπίδης και συν, 2003). Another modification, called TANIS, was proposed by Jones et al. This system used the size (T), and the condition of the associated regional lymph nodes (N) and combined the clinical findings, classifying them into 7

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categories. This system has been found to provide a more accurate classification of the patients than TNM.(Jones et al, 1993).

3.3.1.1.b. Prognostic factor "presence and condition of the associated regional lymph nodes" N

In the next table, Table 3.3, the N categorization proposed by the U.I.C.C. is presented.

N_0	No palpable lymph nodes
N_1	Mobile homolateral lymph nodes,
N_2	Mobile contralateral or bilateral lymph nodes
N_3	Fixed nodes

Table 3.3:The N categorization proposed by the U.I.C.C.

Naturally, just like for the T characteristic, there were proposed modifications. Many authors, mostly working in the U.S.A., (Moss et al, 1973; Ditroia, 1972; Wang, 1972; Landa and Zarem, 1973; Fries et al, 1973), described lymph nodes that contain tumor as metastases and they subdivided N into 4 categories.

N_0	No metastasis suspected
N_1	Clinically palpable homolateral lymph nodes that are not fixed, metastasis suspected
N_2	Clinically palpable contralateral or bilateral cervical lymph nodes that are not fixed, metastasis suspected
N_3	Clinically palpable lymph nodes that are fixed, metastasis suspected

Table 3.4: The N categorization proposed by different American authors.

Apart from these authors, others managed to relate the size of the involved lymph nodes to prognosis (Fazekas et al, 1972; Westbrook, 1974) and others found that regional lymph node involvement varied considerably according to the site of the

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primary tumor (Fayos, 1972; Fayos and Lampe, 1972). It should also be noted that there are many studies indicating that factor N has a greater prognostic value than factor T (Synderman et al, 1995).

3.3.1.1.c. Prognostic factor "presence or absence of distant metastases" M

The last characteristic, M, was the "lucky" one, since in all TNM classification systems it remains the same.

M_0	No evidence of distant metastases is present
M_1	Distant metastases are present

Table 3.5: The M categorization

3.3.1.2. Other prognostic factors used for the classification of the tumors

The TNM system was based on three prognostic factors. Since its appearance many authors have challenged this number and proposed the addition of new factors. Nowadays there are six clinical prognostic factors being used for the classification and staging of the carcinomata. Apart from the three used by TNM, the anatomical site of the lesion, the parameters from the histological examination of the lesion and the velocity of tumor growth play a key role (Rapidis et al, 1977; Evans et al, 1982).

3.3.1.2.a. Prognostic factor "anatomical site of the lesion" S

The addition of the prognostic factor site (S), is very essential, especially for oral cancer, since the area of the head and neck is the most complicated area of the human body. For example, a lesion arising in the posterior third of the tongue will have a graver prognosis than a lesion of the same dimensions arising in the lower lip. Langdon et al in 1977-78 have pointed out that, even though the classifications of the TNM system for the head and neck have been modified according to the anatomical sites of the lesions, as far as the intra-oral carcinomata are concerned, there has been no discrimination between carcinomata from different sites.

3.3.1.2.b. Prognostic factor "histological characteristics of the lesion"

The histological characteristics of the intra-oral carcinoma are certainly affecting its biological attitude. Broders was the first one in 1920 (Broders, 1920), that identified the differentiation of the tumors' histological parameters and classified the tumors according to their degree of differentiation. The degree of the differentiation is determined by recognition of the squamous carcinoma's parameters, such as the degree of cornification, the intercellular pons, the nucleus' polymorphism and the number of mitoses (Broders, 1922,1925,1927)). Broders's example was followed by the World Health Organization (W.H.O.), that in 1972 introduced the "histological typing of oral and oropharyngeal tumors", proposing the subdivision of squamous cell carcinoma into three differentiation grades (Wahi, 1972). During the same year another system was proposed by Jakobsson et al. They developed a system for the multifactorial grading of histological malignancy, with the purpose of securing a more precise evaluation of the growth potential of squamous cell carcinomata of the head and neck (Jakobsson et al, 1973). Almost after a decade, Glanz proposed a more easily applied in practice system that can be used in serried sections of non-irradiated tumors (Glanz, 1984). An extensive review of the pathological malignancy grading and prognosis of head and neck can be found in the Esteban et al, 1998 article.

3.3.1.2.c. Prognostic factor "velocity of tumor growth"

The suggestion for the addition of the factor of the delay between the time of the beginning of the symptoms and the time on which the patient appeared to the hospital for diagnosis and treatment, was done by Evans et al in 1982 after studying the prognostic factors of the squamous carcinoma. Before that, in 1977, Evans and his associates had noticed that a long delay was advantageous, and that a likely explanation for this observation was that a long delay was only possible when the velocity of growth was low, and that a slowly growing tumor carried a better prognosis (Evans, 1978).

3.3.2 Staging

3.3.2.1. The TNM staging system

All TNM classifications lead to staging systems that were formed by combinations of the prognostic factors' categories. Two main systems are in use and these do not differ very much. The first one is the one proposed by the American

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Cancer Society in 1969 and is shown in Table 3.6. The other one is the one proposed by Shwab in 1968 and is shown in Table 3.7.

STAGE I: $T_1N_0M_0$
STAGE II: $T_2N_0M_0$
STAGE III: $T_3N_0M_0$, $T_{1\text{-}3}N_1M_0$
STAGE IV: $T_{1\text{-}3}N_2M_0$, $T_{1\text{-}3}N_3M_0$ and any T or N category with M_1

Table 3.6: The staging system that was proposed by the American Cancer Society, 1969

STAGE I: $T_1N_0M_0$
STAGE II: $T_2N_0M_0$
STAGE III: $T_3N_0M_0$ or $T_{1\text{-}3}N_{1\text{-}3}M_0$
STAGE IV: $T_4N_{0\text{-}2}M_0$ or $T_{1\text{-}4}N_3M_0$ or $T_{1\text{-}4}N_{0\text{-}3}M_1$

Table 3.7: The staging system that was proposed by Shwab, 1968

3.3.2.2. The STNMP staging system

The STNMP classification and staging system was proposed in 1977 by Rapidis et al. This system differed from all previous ones in that both the site and the pathology had been taken into consideration in addition to the conventional ones.

The STNMP staging system differs from all previous ones, in that it does not use the conventional way of combinations in staging. In this system an arithmetic value for each of the categories of the five variables is computed, and by summing the values for a particular tumor, a figure is arrived which falls on a scale 0-155, (Stage I: 0-30, Stage II: 31-50, Stage III: 51-70 and Stage IV: 71-155) (Langdon et al, 1977-78; Rapidis et al, 1977).

Nowadays, there is no universal acceptable classification, even though it is generally agreed that it would be essential in clinical research and prognosis determination. The first aim of such a classification would be to obtain homogenous statistically equivalent groups of the patients for the purpose of assessing , evaluating

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and comparing various therapeutic approaches, while the second aim would be to determine the efficacy of different methods of treatment in patients attending various hospitals, through an interchange of information concerning the clinico-theurapeutic response of these patients to the various methods of treatment (Rapidis et al, 1976).

This need of a universally acceptable classification is more apparent to the special case of oral cancer, since the area of the head and neck is the most complicated and sensitive area of the human body.

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CHAPTER 4
Statistical methodology

4.1. Introduction

There were two main methods used for the statistical analysis of the data, the Kaplan-Meier method and the Cox's proportional-hazards model. The results of the first one were always confirmed by the use of three significance tests, while the relationships between the variables of the protocol were revealed by using the chi-square test. The present chapter provides a theoretical presentation for each of the statistical "tools" used in the research.

4.2. Kaplan-Meier method and significance tests

4.2.1. The Kaplan-Meier method

Survival analysis is concerned with studying the length of time elapsing before some event occurs (such as death), that is, the survival time of the patients. There are two kinds of methods being used in survival analysis, the parametric and the non-parametric. The Kaplan and Meier method is a non-parametric one, since it does not assume a specific distribution for the given data, and has nothing to do with procedures that try to select from an admissible class of distributions, one which best fits the observations.

When all survival times in the sample chosen are known and exact, the group of patients used, is considered to be a random sample from a much larger population of similar patients (Lee, 1992). So, if $t_1, t_2, \ldots, t_n$ are the n survival times of the patients, $t_{(1)}, t_{(2)}, \ldots, t_{(n)}$ is their ascending order. The survival function at each $t_{(i)}$ survival time is estimated by

$$\hat{S}(t_{(i)}) = \frac{n-i}{n} \qquad (4.1)$$

where $n-i$ is the number of patients that managed to survive longer than $t_{(i)}$. If there are any tied, observed survival times, the largest i is used, and a conservative estimate of the tied observations is given (Lee, 1992).

It is obvious that, since all patients are alive at the beginning of the study, and none of them survives longer than $t_{(n)}$, $\hat{S}(t_{(0)}) = 1$ and $\hat{S}(t_{(n)}) = 0$.

When the survival function, $\hat{S}(t)$ is plotted versus time, t, a step function appears, starting at 1 and decreasing in steps of $1/n$ (if there are no ties) to zero (Lee, 1992).

The above estimate of the survival function is applicable only when there are no censored observations for the patients' survival times. Censored observations occur when the event of interest does not occur for the patient during the study period, or when the patient is lost during the study period, because of an independent to the event of interest cause. In the case of censored survival times, methods, such as the Product Limit (PL) estimate of Kaplan and Meier (1958), must be used.

According to the method, time is effectively grouped into a large number of short time intervals. Each of these intervals is constructed to be such that one observed event of interest is contained in the interval, and the time of this event is taken to occur at the start of the interval. Sometimes there are censored survival times which occur at the same time as the events of interest. In this case the censored survival time is taken to occur immediately after the event time.

To produce the PL estimate, the observed survival times of the individuals, censored and non-censored, are put in order of increasing magnitude. So, if $t_1, t_2, \ldots, t_n$ are all the survival times, $t_{(1)} \le t_{(2)} \le \ldots \le t_{(n)}$ is their ascending order. Further more, if it is supposed that at time $t_{(j)}$ there are d_j events (such as death), and that just before the events occurred there were n_j patients surviving, then the estimated survival probability at time $t_{(j)}$ is given by

$$p_{t_{(j)}} = \frac{n_j - d_j}{n_j} \qquad (4.2)$$

If in any time interval there are no events, but there are only censored survival times, $p_{t_{(j)}} = 1$ (4.3)

This is easily understood , if one considers the estimated probability of the event $q_{t_{(j)}} = \frac{d_j}{n_j}$. In the case of lack of events in an interval, $q_{t_{(j)}} = 0$ and $p_{t_{(j)}} = 1 - q_{t_{(j)}} = 1 - 0 = 1$.

When there are censored survival times occurring at the same time as the events of interest, the censored are considered second in order and again,

$$p_{t_{(j)}} = \frac{n_j - d_j}{n_j} \qquad (4.4)$$

The Product Limit estimator (PL), which estimates the survival function at time t , is given by

$$\hat{S}(t) = \prod_{t(j)\le t} p_{t_{(j)}} = \prod_{t(j)\le t} \frac{n_j - d_j}{n_j} \qquad (4.5)$$

The estimator is also the maximum likelihood estimator.

An equivalent form of the PL estimator at time t is

$$\hat{S}(t) = \prod_{t(j)\le t} \frac{n-j}{n-j+1} \qquad (4.6)$$

where j runs through those positive integers for which $t(j) \le t$ and $t(j)$ is uncensored . The values of j are consecutive integers $1,2,\dots,n$, if there are no censored observations (Lee, 1992). The last form of the PL estimator is equivalent to the estimator of $\hat{S}(t)$, when there are no censored observations.

Again, when the survival function, $\hat{S}(t)$ is plotted versus time, t, a step function appears, starting at 1 and decreasing in steps to zero (Lee,1992). The censored times are noted on the survival curve, usually by small crosses.

Along with the PL estimator, which is also a maximum likelihood estimator, the estimated median survival time can be calculated. This estimated value is the 50th percentile of the estimated survival function, that is, the value of t at $\hat{S}(t) = 0,50$ (Lee, 1992).

To obtain confidence intervals for the estimated survival function at any time t, the variance and standard error of the PL estimate of $\hat{S}(t)$ are required. Thus, the variance is approximated by

$$Var\left[\hat{S}(t)\right] \cong \left(\hat{S}(t)\right)^2 \sum_j \frac{1}{(n-j)(n-j+1)} \qquad (4.7)$$

The mean survival time μ can be shown to be equal to the area under the survival curve, and thus, it can be estimated by $\hat{\mu}$, which is equal to the area under the estimated survival function. So, if there are m uncensored observations, and their corresponding survival times are ordered as $t^{(1)} \le t^{(2)} \le \ldots \le t^{(m)}$, then μ is estimated as

$$\hat{\mu} = t^{(1)} + \hat{S}(t^{(1)})(t^{(2)} - t^{(1)}) + \hat{S}(t^{(2)})(t^{(3)} - t^{(2)}) + \ldots + \hat{S}(t^{(m-1)})(t^{(m)} - t^{(m-1)}) \qquad (4,8)$$

which is the sum of the rectangles under the survival curve formed by the uncensored observations (Lee, 1992).

In the above form, $t^{(m)}$ is supposed to be the largest observation, $t_{(n)}$. But if $t_{(n)}$ is a censored observation, the estimation of the mean with the use of this form, might be a low estimate. In such a case, Irwin (1949) suggested the use of a time limit in the place of $t^{(m)}$.

Every estimator is accompanied by its corresponding variance, and $\hat{\mu}$'s variance is given by

$$Var(\hat{\mu}) = \sum_j \frac{A_j^2}{(n-j)(n-j+1)} \qquad (4.9)$$

where j takes the values of all those integers that correspond to t_j uncensored survival times. A_j is the area under the estimated survival curve to the right of t$t_{(j)}$ and is equal to

$$A_j = \hat{S}(t^{(j)})(t^{(j+1)} - t^{(j)}) + \hat{S}(t^{(j+1)})(t^{(j+2)} - t^{(j+1)}) + \ldots + \hat{S}(t^{(m-1)})(t^{(m)} - t^{(m-1)}) \qquad (4.10)$$

where $t^{(1)} \le t^{(2)} \le \ldots \le t^{(m)}$ are the uncensored survival times.

4.2.2. Significance tests

Three significance tests are being used in the present study, along with the Kaplan-Meier method, the logrank test, the Breslow test, and the Tarone-Ware test.

The logrank test is a non-parametric test used in censored-data survival analysis applications. Even though, the test can be used for the comparison of more than two samples, it is more commonly used in two-sample data. On such applications Peto & Peto's (1972) had focused the original development of the test, although their derivations were quite general.

Logrank is used in formally testing differences in the survival between two, or more than two, groups. So, when using the test, the hypothesis used is the following:

H_0: There is no statistically important difference in the risk of death of the groups

vs

H_1: There is statistically important difference in the risk of death of the groups

The null hypothesis is rejected when the p-value of the test is less than the percentage chosen by the researcher (usually 0.05).

To illustrate the procedure being used in the test, it is assumed that there are two groups at hand, group A and group B. The first step is to arrange in rank order the survival times, both censored and non-censored. So, if $t_1, t_2, ..., t_{N_A}$ are the survival times for group A and $t_1, t_2, ..., t_{N_B}$ the ones for group B, $t_{(1)}, t_{(2)}, ..., t_{(N_{A+B})}$ are the survival times in order. The second step is to calculate the proportion of survivors of one, chosen group, at any time t. So, if at time $t_{(j)}$ there are $d_{(j)}$ events observed ($d_{(j)A}$ for group A and $d_{(j)B}$ for group B), and there were $n_{(j)A}$ and $n_{(j)B}$ patients at risk just before time $t_{(j)}$, then the proportion of the survivors, let's say, of group A at time $t_{(j)}$, is given by

$$p_{(j)A} = \frac{n_{(j)A}}{n_{(j)}} \qquad (4.11)$$

where $n_{(j)} = n_{(j)A} + n_{(j)B}$. This proportion can also be thought as the 'expected' number of events in group A and be noted as $E(d_{(j)A})$. Thus, the difference between $d_{(j)A}$ and $E(d_{(j)A})$ is evidence against the null hypothesis. The logrank test is the combination of these differences over all the times at each event occurred (Armitage et al, 1994).

So, the third step is to calculate $O_A = \sum_j d_{(j)A}$, $E_A = \sum_j E(d_{(j)A})$ and $V_A = \sum_j \text{var}(d_{(j)A}) = \sum_j p_{(j)A}(1 - p_{(j)A})$. Using these numbers one moves on to the fourth step, the calculation of the test statistic

$$X_1^2 = \frac{(O_A - E_A)^2}{V_A} \qquad (4.12)$$

which is approximately a χ_1^2. An alternative test statistic, which does not require the calculation of the variance, V_A, is

$$X_2^2 = \frac{(O_A - E_A)^2}{E_A} + \frac{(O_B - E_B)^2}{E_B} \qquad (4.13)$$

This also is approximately a χ_1^2 and it can be expanded to more than two-dimensioned data (Armitage et al, 1994).

The above illustration of the logrank test is only a version of the test, and is a chi-square test that compares the observed and expected numbers, in order to conclude about any difference in the risk of death between two groups of patients. Another version of the test, takes into account the estimates of the log survival function at all $t_{(j)}$, by using

$$-e(t_{(j)}) = -\sum_{k \le t_{(j)}} \frac{m_{(k)}}{r_{(k)}} \qquad (4.14)$$

where $m_{(k)}$ is the multiplicity of $t_{(k)}$, and $r_{(k)}$ is the number of patients who are alive and at risk at time $t_{(k)}$.

For each observation a score, w_j, is taken. Thus, $w_j = 1 - e(t_{(j)})$ for an uncensored observation $t_{(j)}$, and $w_j = -e(t_{(j)})$ for a censored one. The logrank test is based on the sum, S, of the scores in one of the two groups.

It can be shown that,

$$Var(S) = \frac{n_A n_B \sum_{j=1}^{n_A+n_B} w_j^2}{(n_A + n_B)(n_A + n_B - 1)} \qquad (4.15)$$

and that the test statistic for this version of the logrank test is

$$L = \frac{S}{\sqrt{Var(S)}} \qquad (4.16)$$

which has an asymptotically normal distribution under the null hypothesis of the test (Lee, 1992).

In the equation $U = \sum_{j=1}^{n_A+n_B} u_{(j)}(d_{(j)} - E(d_{(j)}))$, the logrank test weighs equally all cases. This its difference from the other two tests used in the study, Breslow test, and the Tarone-Ware test. The least conservative of the three, the Breslow test, weighs earlier events more heavily, since $u_{(j)}$ is the number of cases at risk at event time $t_{(j)}$, while the most conservative one, the Tarone-Ware test, weighs earlier events less heavily, since $u_{(j)}$ is the square root of the number of cases at risk at event time $t_{(j)}$. The Breslow test, also known as the generalized Wilcoxon test, is more likely to detect early differences in two survival distributions, than logrank, whereas Tarone-Ware test, is found to be more effective in detecting differences between survival distributions, which are restricted in a certain time interval.

4.3. The Cox's proportional hazards model

When the relationship between the survival time of patients and k possible prognostic variables is under investigation, multiple techniques are more efficient than univariate ones, since they take into consideration simultaneous effects of the variables. The multiple-regression is one of these methods, and its objective is to identify that relationship between the survival time and the prognostic variables, that can be expressed in a regression function. So, if t_i is the survival time of the i_{th}, and $x_{1i}, x_{2i}, \ldots, x_{ki}$ the observed values for each of the k possible prognostic variables, the regression function that is looked for is

$$t_i = f(x_{1i}, x_{2i}, \ldots, x_{ki}) \qquad (4.17)$$

The regression models proposed for survival distributions generally involve the assumption of proportional hazard functions. The hazard function is the death rate in mortality studies whose variable of interest is the survival time, and usually varies with time since entry to study, t. The hazard function is given by the formula $h(t) = \dfrac{f(t)}{1-F(t)} = \dfrac{f(t)}{S(t)}$, where $f(t)$ is the probability density of survival time, $F(t)$ the corresponding distribution function, and $S(t) = 1 - F(t)$ the survivor function. This formula is derived from the fact that death rate is the rate at which deaths occur divided by the proportion of the population surviving (Armitage et al, 1994). In realistic situations the death rate does not depend only on time, but is also affected by other prognostic variables. So, the hazard function should be written as a function of both time and the covariates $x = (x_1, x_2, \ldots, x_k)$.

Since regression models involve the previously mentioned assumption, a proportional hazards model is the one that possesses the property, that the ratio $h(t \mid x_i) / h(t \mid x_j)$ of the hazard functions of any two patients with covariates $x_i = (x_{1i}, x_{2i}, \ldots, x_{ki})$ and $x_j = (x_{1j}, x_{2j}, \ldots, x_{kj})$, is invariable to time t. This property

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implies that the hazard function, given a set of covariates $x=(x_1,x_2,\ldots,x_k)$, can be written as

$$h(t \mid x)=h_0(t)g(x) \qquad (4.18)$$

where $g(x)$ is a function of x and $h_0(t)$ can be reconsidered as a baseline hazard function of the patient for whom $g(x)=1$ (Lee, 1992).

A special form of the proportional hazards model, when survival times of the patients are continuously distributed, is

$$\begin{aligned} h(t \mid x) &= h_0(t)\exp(\beta x) \\ &= h_0(t)\exp\left(\sum_{i=1}^{k}\beta_i x_i\right) \qquad (4.19) \end{aligned}$$

where βx represents the regression function $\beta_1 x_1+\beta_2 x_2+\ldots+\beta_k x_k$ and $h_0(t)$ is the time dependent part. The parameters of $h_0(t)$ and the regression coefficients $\beta_1,\beta_2,\ldots,\beta_k$ have to be estimated so as to achieve inference. For this purpose the assumption of some particular form of $h_0(t)$ is needed, but that is often impossible since the form is unknown. So, it would be more convenient if this assumption was unnecessary. This was the approach used by Cox in 1972 when he proposed the Cox's proportional hazards model, which is non-parametric with respect to time, but parametric in terms of the covariates (Armitage et al, 1994).

Cox's proportional hazards model is appropriate for the analysis of survival data with and without censoring, and it is clear, that the model assumes that the hazard of the study group is proportional to that of the underlying survival distribution $h_0(t)$, when all the x variables are ignored, or equivalently, when all the x variables are equal to zero (Lee, 1992).

Between the Cox's proportional hazards model and the standard multiple-regression model there is an analogy, that becomes obvious when both sides of Cox's model are divided by $h_0(t)$ and logarithm is afterwards applied. The obtained form for every i patient is

$$\log\frac{h_i(t)}{h_0(t)}=\beta_1 x_{1i}+\beta_2 x_{2i}+\ldots+\beta_{ki}x_{ki}=\sum_{j=1}^{k}\beta_k x_{ji}\,. \qquad (4.20)$$

From the form, it becomes apparent that if $y_i = \log\frac{h_i(t)}{h_0(t)}$, then the possible prognostic variables are analogous to the independent variables of the standard multiple regression model, and a function of the hazard is analogous to the dependent variable. For each patient, $y_i = \log\frac{h_i(t)}{h_0(t)}$ is a prognostic index or ratio, that can be used to compare prognosis between patients, that is, to compare the relative risk for patients with different values of the independent variables (Lee, 1992).

Cox's model has as its main objective, to identify from the k independent variables a subset of variables that relate significally to the hazard. For this purpose, the estimation of the coefficients $\beta_1, \beta_2, ..., \beta_k$, along with significance tests for each one of them, are needed, since, if any β_j is equal to zero, the corresponding prognostic variable will have no relationship to survival, when adjustment is made for the other variables.

To estimate the coefficients, Cox suggested a maximum likelihood procedure, where the likelihood function is based on a conditional probability of failure. So, the n exact failure times of the patients are ordered so as $t_{(1)} < t_{(2)} < ... < t_{(n)}$, and $R(t_{(i)})$ is assumed to be the set of patients whose survival times are at least $t_{(i)}$. For the particular failure at time $t_{(i)}$, conditionally on the risk set $R(t_{(i)})$, the probability that the failure is on the patient as observed is

$$\frac{\exp\left(\sum_{j=1}^{k}\beta_j x_{ji}\right)}{\sum_{l\in R(t_{(i)})}\exp\left(\sum_{j=1}^{k}\beta_j x_{ji}\right)} \qquad (4.21)$$

Each failure contributes a factor and thus, the required conditional log-likelihood is

$$LL(\beta) = \sum_{i=1}^{n}\sum_{j=1}^{k}\beta_j x_{ji} - \sum_{l=1}^{n}\log\left[\sum_{l\in R(t_{(i)})}\exp\left(\sum_{j=1}^{k}\beta_j x_{jl}\right)\right] \qquad (4.22)$$

Maximum likelihood estimates of the coefficients are obtained by solving simultaneously the k equations that derive from $LL(\beta)$, with respect to $\beta_1, \beta_2, ..., \beta_k$, respectively, equating to zero. The k equations are

$$U(\beta_1,\beta_2,...,\beta_\kappa)=\sum_{i=1}^{k}\left[x_{ui}-A_{ui}(\beta_1,\beta_2,...,\beta_\kappa)\right]=0,\quad u=1,...,k \tag{4.23}$$

where

$$A_{ui}(\beta_1,\beta_2,...,\beta_k)=\frac{\sum_{l\in R(t_{(i)})} x_{ui}\exp\left(\sum_{j=1}^{k}\beta_j x_{jl}\right)}{\sum_{l\in R(t_{(i)})}\exp\left(\sum_{j=1}^{k}\beta_j x_{jl}\right)} \tag{4.24}$$

The k equations can be solved numerically by the Newton-Rapshon method of iteration. In the method, the estimates of the coefficients are obtained by iterative use of $U(\beta_1,\beta_2,...,\beta_\kappa)$ and the second derivative of $LL(\beta)$ (Lee, 1992):

$$I_{uh}(\beta_1,\beta_2,...,\beta_k)=-\sum_{i=1}^{n}C_{(uh)}(\beta_1,\beta_2,...,\beta_k) \tag{4.25}$$

where

$$C_{(uh)}=-A_{ui}(\beta_1,\beta_2,...,\beta_k)A_{hi}(\beta_1,\beta_2,...,\beta_k) \tag{4.26}$$

The estimated regression coefficients $\beta_1,\beta_2,...,\beta_k$ give the proportional change that can be expected in the hazard , related to changes in the covariates, and thus, a positive regression coefficient means that hazard is higher, and thus the prognosis is worse for subjects with higher values of that covariate, whereas a negative regression coefficient implies a better prognosis for subjects with higher values of that covariate.

If a continuous survival time can be achieved in practice, in the case of ties, a more general model in discrete time, is proposed by Cox. The model uses a logistic transformation and reduces to the model of the continuous case.

The corresponding standard errors for the coefficients derive from the $I_{uh}(\beta_1,\beta_2,...,\beta_k)$ solutions, and with the use of the normal distribution, 100(1-α) percent confidence intervals for each coefficient can be constructed.

$$\hat{\beta}_i \pm z_{\alpha/2}(estimated\ s.e.\ of\ \hat{\beta}_i) \tag{4.27}$$

When using the Cox's model for dichotomous variables, 100(1-α) percent confidence intervals for the relative risk can be obtained by using the corresponding confidence intervals for the coefficients. So, if (β_{iL},β_{iU}) is the confidence interval for coefficient β_i, then ($\exp(\beta_{iL}),\exp(\beta_{iU})$) is the corresponding one for the relative risk.

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4.4. The chi-square test

The Pearson's chi-square test of statistical significance is a hypothesis test introduced by Karl Pearson in 1900 and it is one of a variety of chi-square tests-statistical procedures, whose results are evaluated by reference to the chi-square distribution . The test is included in Pearson's Mathematical Contribution to the Theory of Evolution, a group of 18 papers that Pearson wrote from 1893 to 1912 and is most commonly used to test for the significance of relationships between variables cross-classified in a bivariate table, but it can also be applied in tables of higher dimensions.

The hypotheses made in the test for a bivariate table are the following:

H_0: There is no relationship between the variables in our table (i.e., they are statistically independent) and any difference between them is actually just due to random sampling error

Vs

H_1: There is a real relationship between the variables in the population from which the sample is drawn

The chi-square statistic is computed as

$$X^2 = \sum_j \frac{(O_j - E_j)^2}{E_j} \qquad (4.28)$$

, where O_j are the observed frequencies in the table and E_j the expected frequencies, asserted by the null hypothesis. The statistic is compared with the chi-square distribution with one degree of freedom, and the null hypothesis is rejected when the value of the obtained Pearson chi-square statistic is higher than the critical value of the chi-square distribution . Of course, one can also reach a conclusion by comparing the reported p-value to the chosen alpha level. In cases when any of the expected values, E_j, is found to be below 5, it is suggested that the likelihood ratio-test is used.

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CHAPTER 5

Statistical analysis of the data

5.1. Introduction-Data set

This study was based on a database produced at the Maxillofacial Surgery Department of St Savvas Hospital. For each of the 123 patients, that took part in this study, a protocol was filled in. This protocol contained various variables, such as age, initial symptoms, the time elapsed since treatment, predispositional factors, location of the lesions, histopathological characteristics, along with two classification and staging systems. The patient's survival time since treatment was also noted in the protocol, as well as the treatment followed by the doctors. The protocol's form, and the medical terminology of the variables, as well as the coding, are presented at the Appendix.

5.2. Statistical analysis

The statistical analysis of the data included descriptive statistics, and analysis with the non parametric method of Kaplan-Meier and the Cox's proportional-hazards model.

5.2.1. Descriptive statistics of the data

There were 123 patients taking part in this research, 76 (61,8%) of them being men and 47 (38,2%) being women. The youngest patient in the research was 20 years old, while the oldest was 92. As it can be seen in the Table 5.1, most patients were between 50 and 70 years old. The mean of the age of the patients was 61.

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Age	Frequency	Percent	Cumulative Percent
<50	30	24,4	24,4
51-70	62	50,4	74,8
71-96	31	25,2	100,0
Total	123	100,0	

Table 5.1: Frequencies of the patients' age

Figure 5.1 provides a better view of the distribution of the patients' age. It is apparent that most patients were people in their seventies.

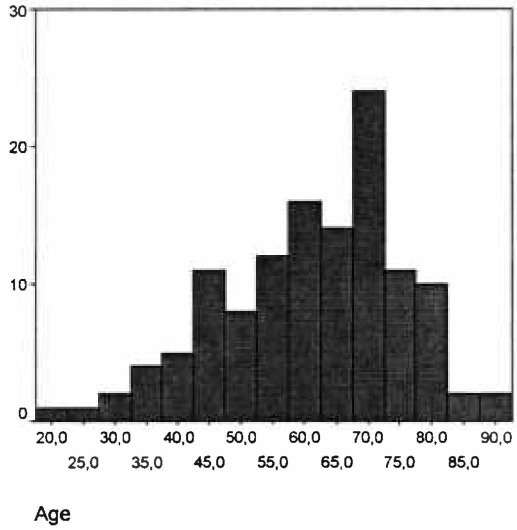

Figure 5.1: Histogram of the patients' age

There were four main initial symptoms reported in the protocol and most patients reported having more than one of them. Of all 123 patients, 29 (23,6%) answered positively in feeling an unspecified local disturbance on their tongue, 93 (75,6%) suffered from pain, 9 (7,3%) reported bleeding and 57 (46,3%) had trouble in swallowing and speaking. Finally, 11 patients (8,9%) reported a different, from the above four, initial symptom. It is apparent that pain and dysphagia-dysarthria, were the most common symptoms, whilst bleeding was the most uncommon one.

For each patient there was a time interval between the beginning of the initial symptoms and his or hers decision to visit a doctor for an examination. As shown in Table 5.2, 82,9% of the patients visited a dentist in the first 6 months and that only 21 patients waited until a year or more had passed.

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	Frequency	Percent	Cumulative Percent
3 Months	38	30,9	30,9
6 Months	64	52,0	82,9
1 Year and more	21	17,1	100,0
Total	123	100,0	

Table 5.2: Frequencies of the patients' time interval from the beginning of the symptoms to their visit to a doctor

There were nine factors considered and many patients reported more than one of them. Smoking, the first factor in consideration, was reported to be the most common one, since there were 76 (61,8%) smokers among the patients. Alcohol was reported by 44 patients (35,8%), while professional reasons were claimed only by 6 patients (4,9%) and family history was found to be of interest only for 6 patients (4,9%). Preexisted leukoplakia was noted in 16 patients (13%), while preexisted lichenoid lesion was less common, since it was noted in only 6 patients (4,9%). Cancer was found to preexist on the mouth's mucosa of 7 patients (5,7%), while it preexisted in other regions of only 3 patients (2,4%). Other precancerous lesion was reported for only one patient (0,8%). There were 15 patients (12,2%) that reported none factor.

The patients, when entering the research, were categorized according to their performance status. According to Table 5.3 , most patients seem to have a normal activity and only 3 (2,4%) seem to be spending a big part of their daily time in bed.

	Frequency	Percent	Cumulative Percent
Normal activity	86	69,9	69,9
Symptomatic-totally ambulant	24	19,5	89,4
Lectual <50% of the day	10	8,1	97,6
Lectual>50% of the day	3	2,4	100,0
Total	96	100,0	

Table 5.3: Patients' performance status

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The site of the primary lesion (S) was also noted in the protocol. Tongue was divided into three parts and many patients reported having lesions on more than one part. There were 20 patients (16,3%) with lesions at the anterior of the tongue. From those 20, 5 had lesions at the middle part of the tongue simultaneously (S_1-S_2), 4 had lesions and at the middle and at the posterior part simultaneously (S_1-S_2-S_3), and only 11 had lesions only at the anterior part of the tongue (S_1). From all patients, 76 (61,8%) were found to have lesions in the middle of the tongue, and from those 57 had lesions only at that part of the tongue (S_2), while 10 of them had simultaneous lesions at the posterior part (S_2-S_3). Finally, 50 patients (40,7%) had lesions at the posterior third of the mobile part or the tongue's base and only 36 of them appeared to have lesions only there (S_3). The following Table 5.4 provides a better view of the site classification of the patients.

	Frequency	Percent	Cumulative Percent
S_1-S_2-S_3	4	3,3	3,3
S_1-S_2	5	4,1	7,3
S_2-S_3	10	8,1	15,4
S_1	11	8,9	24,4
S_2	57	46,3	70,7
S_3	36	29,3	100,0
Total	123	100,0	

Table 5.4: Patients' lesion site

Even though the data give emphasis on lesions found on the tongue, the condition of the rest of the mouth's mucosa was reported too. There were 17 patients (13,8%) found with coexisted leukoplakia, 4 (3,3%) with coexisted lichenoid lesion, 2 (1,6%) with other coexisted pathological situation and only 1 (0,8%) with coexisted Ca of the mouth's mucosa. Finally, there were 101 patients (82,1 %) whose mucosa of the mouth was normal.

The form of the lesion is another characteristic of the patients' situation needed. The following figure pie shows the percentages of each kind. It is apparent

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that most patients are suffering from ulcers (52,8%,i.e. 65 patients) and the second most common kind is the mixed one (30,1%, i.e. 37 patients).

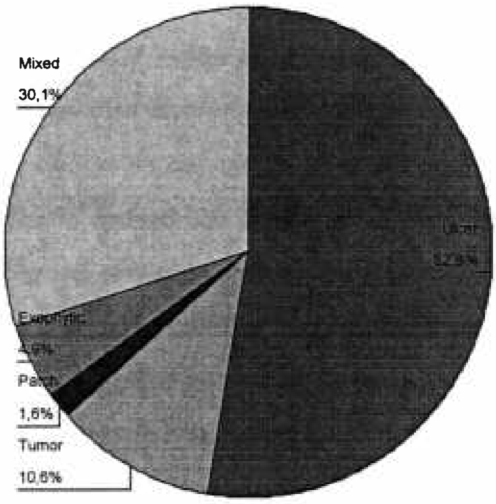

Figure 5.2: Frequencies of the lesions' different kinds of form

The lesion's size (T) is a characteristic needed for the classification and staging of the lesion. With T_1 are coded lesions whose maximum diameter is less or equal to 2 cm, while T_2 represents lesions with maximum diameter between 2cm and 4 cm. The next category is T_3, representing lesions with maximum diameter between 4cm and 6 cm and it is followed by the last category, T_4, with lesions with maximum diameter being more than 6 cm. From Figure 5.3 it is apparent that most lesions belong to T_2 (63 patients). All other three categories share about the same number of patients, since there are 22 patients (17,9%) in T_1, 18 patients (14,6%) in T_3 and 20 patients (16,3%) in T_4.

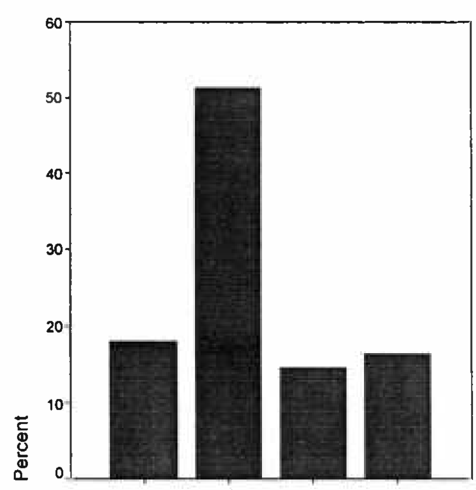

Figure 5.3: Lesion's size coded into 4 categories

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The presence and condition of the associated regional lymph nodes (N) is another characteristic needed for the classification and staging of the patients. With N_0 are coded all the lymph nodes who were found to be clinically negative, while N_1 represents all the homolateral, single lymph nodes whose maximum diameter is less than or equal to 3 cm. The N_2 category is divided into two categories, N_{2a} and N_{2b}. The first one includes all homolateral, single lymph nodes with maximum diameter greater than 3 cm and less than 6cm, whilst the second one includes all homolateral, multiple lymph nodes with none's maximum diameter being greater than 6 cm. The N_3 category is also the sum of other subcategories, N_{3a}, N_{3b} and N_{3c}. N_{3a} includes all homolateral, single or multiple lymph nodes, of which one with maximum diameter greater than 6 cm, N_{3b} includes all bilateral positive lymph nodes, of whom each side is estimated separately, and finally, N_{3c} includes only contra lateral lymph nodes. No patient belongs in the N_X category, that is, no patient shows no evidence for estimation.

In Table 5.5 is shown that most patients are categorized in N_0 (58,5%), while there are only 3 patients (2,5%) in N_3. Out of the 14 patients belonging in N_2, 10 belong in N_{2a} and 4 in N_{2b}. In N_3, just one patient belongs in N_{3a}, while 2 belong in N_{3b}.

	Frequency	Percent	Cumulative Percent
N_0	72	58,5	58,5
N_1	34	27,6	86,1
N_2	14	11,4	97,5
N_3	3	2,5	100,0
Total	123	100,0	

Table 5.5: Presence and condition of the associated regional lymph nodes (N) coded into 4 categories

Distant metastases (M) are also noted in the protocol and is very important that only one patient, out of the 123 that took part in the research, presented a distant metastasis.

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The last characteristic noted in the protocol is the pathology of the lesion (P). The patients are classified according to the classification proposed by Rapidis et al. in 1977. So, in P_0 are all hyperkeratotic lesions showing atypia, in P_1 all carcinomas in situ, in P_2 all basal cell carcinomas. The P_3 is divided into four subcategories. The first one, P_{3a}, includes all verrucous carcinomas. The second one, P_{3b}, is formed by well differentiated squamous cell carcinomas, while P_{3c} includes moderately differentiated squamous cell carcinomas. The last subcategory, P_{3d}, includes poorly differentiated squamous cell carcinomas.

As it can be seen in Table 5.6, no patient belongs in P_0, while most patients are put in P_{3b} (42,3%) and P_{3c} (44,7%).The number of patients belonging in either P_1 or P_2 or P_{3a} is 6 (4,9%), and only 10 patients (8,1%) present poorly differentiated squamous cell carcinomas.

	Frequency	Percent	Cumulative Percent
P_0	0	0	0
P_1 or P_2 or P_{3a}	6	4,9	4,9
P_{3b}	52	42,3	47,2
P_{3c}	55	44,7	91,9
P_{3d}	10	8,1	100,0
Total	123	100,0	

Table 5.6: The pathology of the lesion (P), classified according to the classification proposed by Rapidis et al in 1977

Using T, N and M the researcher can proceed to classification and staging. The patients were separated into four stages according to the TNM proposed in 1997 by the U.I.C.C. and the A.J.C.C.

	Frequency	Percent	Cumulative Percent
Stage 1	16	13	13
Stage 2	47	38,2	51,2
Stage 3	32	26	77,2
Stage 4	28	22,8	100,0
Total	123	100,0	

Table 5.7: TNM staging, according to the TNM proposed in 1997 by the U.I.C.C. and the A.J.C.C.

As it can be seen from Table 5.7, most patients are put into Stage 2 (38,2%). Stages 3 and 4 have about the same number of patients (32 and 28 patients respectively), while Stage 1 has the fewer patients (13%).

TNM is not the only classification and staging system used in the protocol. Data were also analyzed using the STNMP system, proposed by Rapidis et al. in 1977. According to that, patients are separated the way shown in Table 5.8.

	Frequency	Percent	Cumulative Percent
Stage 1	46	37,4	37,4
Stage 2	40	32,5	69,9
Stage 3	22	17,9	87,8
Stage 4	15	12,2	100,0
Total	123	100,0	

Table 5.8: Staging according to the STNMP system proposed by Rapidis et al. in 1977

It is clear that according to the STNMP system patients are categorized differently than according to the TNM. There are more patients in Stage 1 (37,4%) and fewer in Stage 2 (32,5%), Stage 3 (17,9%) and Stage 4 (12,2%). Of course, the most apparent difference in number of patients is in Stage 1, where there is a great increase of 30 patients.

After the classification and staging systems, the protocol notes the various factors used to confirm the diagnosis of each patient. Out of the 123 patients, 38 were

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reported as missing, since their doctors did not fill in the specific variable of the protocol. In the next table, Table 5.9, it is obvious that most doctors proceeded to an investigating operation so as to obtain a sample from the lesion and perform a histological examination (81,2 % of the patients reported not missing). It is also apparent that no doctor preferred to remain at the standard procedures.

Factor for the diagnosis's confirmation	Frequency	Percent	Valid Percent	Cumulative Percent
Physical examination, Standard x-ray, Introspection	0	0	0	0
CT,U/S,P/ISCAN,MRI,FNAC	11	8,9	12,9	12,9
Histological examination from investigating operation	69	56,1	81,2	94,1
Histological examination from final operation	5	4,1	5,9	100,0
Total	85	69,1	100,0	
Missing	38	30,9		
Total	123	100,0		

Table 5.9: Patients' factors for the diagnosis's confirmation

The decisions made by the tumor board were not reported by the doctors for the two thirds of the patients. The doctors who did report the decision, preferred to use codes for the different decisions, so it is in the author's opinion that no information can be provided from the corresponding table, showing the descriptive statistics of this variable.

Next in the protocol is the variable showing the treatment's aim. Since patients present in various conditions, doctors treat each patient separately, aiming each time the best possible outcome for the patient's survival. So, in this data set only two patients were reported missing and from the rest 121, 89 patients (72,4%) were treated aiming their cure. Only one (0,8 %) was treated aiming his or hers rescue, while 19 patients (15,7% of those reported not missing) were treated so as a long termed control of the disease could be achieved. Finally, 12 patients (9,9% of those reported not missing) were treated so as to be relieved.

To treat the patients, doctors use three basic ways, surgery, radiotherapy and chemotherapy. They use them simultaneously, separately or one after another. In the data base used, there were four patients that were reported as missing. From the rest, 94 (79% of those who were reported not missing) were operated, 8 (6,7% of those who were reported not missing) were treated with radiotherapy, and just 2 (1,7% of those who were reported not missing) with chemotherapy. Before surgery, 5 patients (4,2%of those who were reported not missing) were treated with radiotherapy and chemotherapy, and 3 (2,5%of those who were reported not missing) only with radiotherapy. The number of patients treated with only simultaneous radiotherapy and chemotherapy, was 11 (9,2% those who were reported not missing). Finally, after surgery, 39 patients (32,8% of those who were reported not missing) were treated with radiotherapy, and 3 (2,5% of those who were reported not missing) with chemotherapy.

The next variable shown in the protocol is the "type of surgery". There are two main kinds of surgery, the local excision and the complex operation. The local excision was performed on 76 patients (61,8%). The complex operation is divided into four categories, radical lymph excision, modified lymph excision, eclectic lymph excision and two way lymph excision. In the first category there were 8 patients (6,5%), in the second one 12 (9,8%), in the third 40 (32,8% of those reported not missing) and in the fourth 7 (5,7% of those reported not missing).

From the histopathological characteristics of the disease, which are drawn by using a surgical specimen, the first to be presented is the inflammatory reaction. There were 111 patients reported missing, only one patient (8,3% of those reported not missing) presented light reaction, 6 (50% of those reported not missing) presented medium reaction and 5 (41,7% of those reported not missing) intense.

The second characteristic to be presented was the immunological excitation. Out of the 123 patients just one was reported as not missing and that patient presented medium excitation.

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The degree of the histological infiltration of the disease was the next histopathological characteristic. One hundred and one patients were missing in the data set and thus only 22 patients were reported. Out of these 22 patients, 4 (18,2% of those reported not missing) presented perineural infiltration, 2 (9,1% Perineural infiltration) suffered from intravasal deviation, 18 (81,8% of those reported not missing) were noted with infiltration of the surrounding muscles, and 5 (22,7% of those reported not missing) had infiltration on the submandibular salivatory gland.

After having contacted an examination with the help of a microscope, the numbers of estimated and infiltrated lymph nodes were noted on the protocol for each of the patients' surgical specimen. The infiltration of the lymph nodes was afterwards categorized into five levels. From the 123 patients 99 were reported as missing, since they presented no infiltration, and thus all the given information was derived by the remaining 24, who did present infiltration. So, 5 patients (16,7% of those reported not missing) were reported as level 1, 13 patients (54,2% of those reported not missing) as level 2, 10 patients (41,7% of those reported not missing) as level 3, and 4 patients (16,7% of those reported not missing) as level 4. No patient was put in level 5.

Out of the 24 patients found to have infiltrated lymph nodes, 4 were firstly categorized as N_0. This fact means, that these patients were found clear of the disease when examined clinically, but the disease was found to exist histologically.

Only for 11 patients was reported whether there was a capsula's disintegration of the lymph nodes, or not. One (9,1% of those reported not missing) was reported positive, two (18,2% of those reported not missing) negative, and the rest (72,7% of those reported not missing) were reported as unknown.

The last histopathological characteristic that was on the protocol was the "histological type of the squamous Ca". Only 4 patients were this time missing. The majority of the reported patients was separated among the two first categories of the protocol. So, there were 52 patients (43,7% of those reported not missing) with higher differentiation, 53 (44,5% of those reported not missing) with medium differentiation, 12 (10,1% of those reported not missing) with low differentiation, and just 2 (1,7% of those reported not missing) verrucose type. There was no patient with the indifferent type.

After the histopathological characteristics came the "follow up of the patients". Patients' time period of observation was noted and one person was reported as missing. There were 6 patients (4,9% of those reported not missing) observed for less than six months, 41 (33,6% of those reported not missing) for a year, 44 (36,1% of those reported not missing) for three years, and 25 (25,4% of those reported not missing) for more than five years.

For the condition of the disease in its higher interval all patients were reported. So, 60 patients (48,8%) were found alive, clear of the disease locally and negative of distant metastases, 2 patients (1,6%) were alive, revealing a second primary focus, 3 (2,4%) were alive, with field cancerization, 45 (36,6%) had died because of the disease, 9 (7,3%) were dead by other cause, being free of the disease, 3 (2,4%) had died from another cause, and revealed local recidivation or distant metastases, and finally, one (0,8%) was dead because of the disease with field cancerization.

From all 123 patients, 33 appeared to have recurrence, and thus they were further treated. So, 2 (6,1%) were operated, 4 (12,1%) were treated with radiotherapy and 4 (12,1%) with chemotherapy. Another 5 patients (15,2%) were treated simultaneously surgically and with radiotherapy, 2 (6,1%) surgically and with chemotherapy, and 11 (33,3%) with radiotherapy and chemotherapy. From the rest, 3 (9,1%) were treated simultaneously with all three methods, and 2 patients (6,1%) received no further treatment.

After reporting the survival of each patient from all kinds of treatment, the numbers were put together and formed a new variable, the "survival of the patients", counted in months. So, during the observation period, 82 patients (66,7%) managed to survive less or equal to 50 months, 26 (21,1%) survived 51 to 100 months, and 15 (12,2%) lived more than 100 months.

With the above variable, the descriptive part is completed, and the next part of the statistical analysis, with the use of the Kaplan-Meier method, the Cox's regression model, and the chi-square test is presented.

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5.2.2 Statistical analysis of the data with the use of statistical methods

5.2.2.1. Application of the Kaplan-Meier method

The first step in the analysis of the data was to calculate the survival function for each of the variables in the data set and to use test statistics, along with the Kaplan –Meier method, so as to evaluate whether a variable affects the survival of the patients or not. The results of the procedure are shown here. All variables found to have some significance for the patients' survival are presented.

Before presenting the variables, the patients' Kaplan-Meier survival curve was presented. The survival curve is a plot of the Kaplan-Meier's estimate of the survivor function, in which the estimated survival probabilities are constant between adjacent death times and only decrease at each death. The censored observations were 66 and are noted with small crosses.

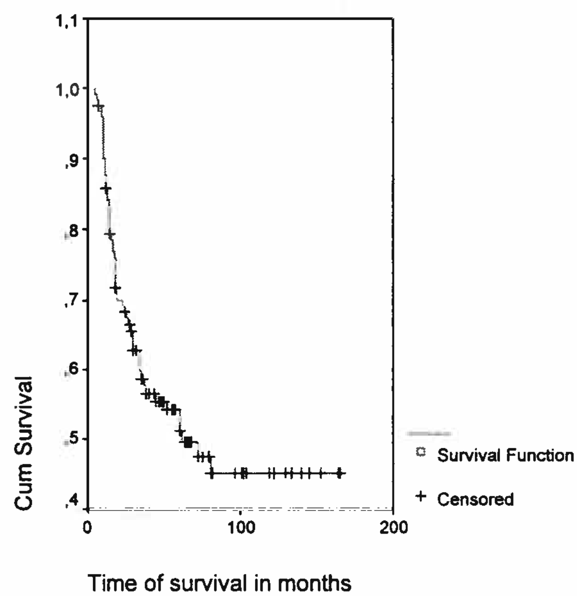

Figure 5.4: Survival curve of the protocol's patients

As it can be seen in the above figure, when the time of survival is 60 months, the probability of surviving is around 0,5.

After checking all five initial symptoms reported in the protocol, only two of them were found to affect the survival of the patients, "bleeding" and "trouble in swallowing and speaking".

As it can be seen in Figure 5.5, all patients that had reported "bleeding" died earlier. The crosses on the figure note the censored patients.

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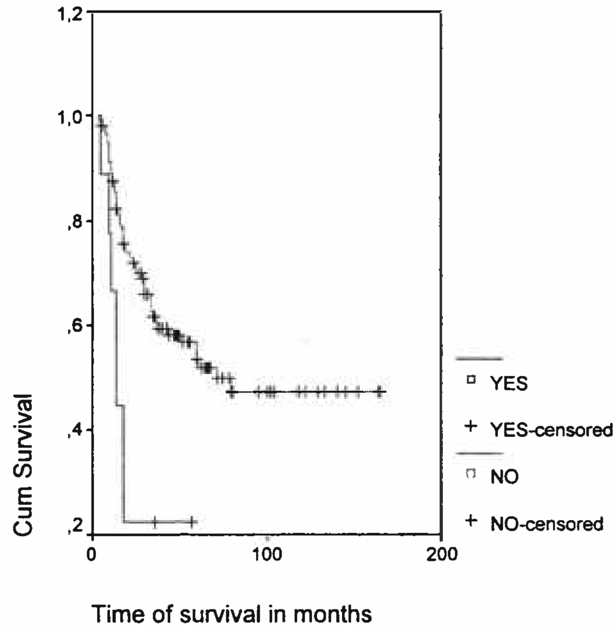

Figure 5.5: Survival function according to initial symptom bleeding

The conclusion is confirmed by the following Table 5.10. The significance value of the logrank test is 0,0029 which is smaller than the alpha level that was chosen, 0,05. So, the null hypothesis of the test is rejected, and there is statistically important difference in the risk of death between those who reported bleeding and those who did not. The other two tests shown on the table confirm the above conclusion, since their significance values are both less than 0,05.

Test	Statistic	Df	Significance
Log Rank	8,85	1	0,0029
Breslow	9,87	1	0,0017
Tarone-Ware	9,53	1	0,0020

Table 5.10: Test Statistics for Equality of Survival Distributions for initial symptom bleeding

In the next figure, Figure 5.6, it is apparent that patients who had complained about having problems with swallowing and speaking, died earlier than those who had not.

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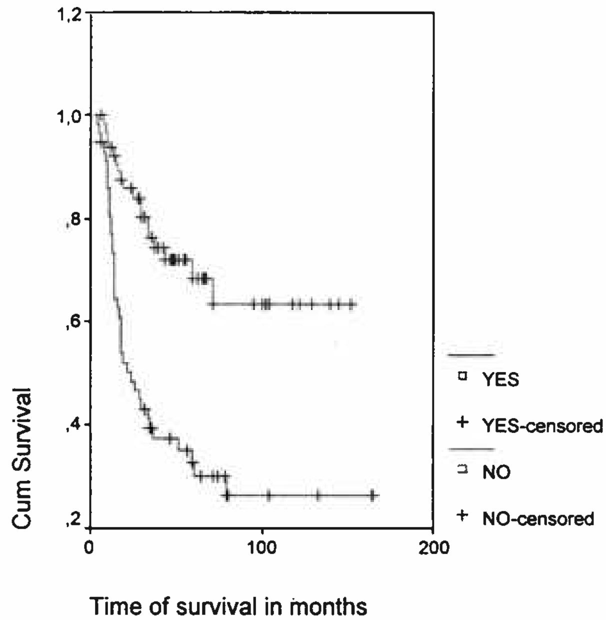

Figure 5.6: Survival function according to initial symptom "trouble in swallowing and speaking".

Table 5.11 provides confirmation of this conclusion since the value of the significance of the corresponding logrank test is 0,00001 , which less than the 0,005, thus rejecting the null hypothesis of the test.

Test	Statistic	df	Significance
Log Rank	19,37	1	0,00001
Breslow	20,06	1	0,00001
Tarone-Ware	20,19	1	0,00001

Table 5.11: Test Statistics for Equality of Survival Distributions for initial symptom "trouble in swallowing and speaking"

There is always a time interval between the beginning of the disease and the first visit of the patient to the doctor. In the next figure, Figure 5.7, it is obvious that those patients that delayed their visit to the doctor for a year or more died earlier. Patients who visited their doctor in six months are the ones shown in the middle of the figure, while the patients shown first are the ones who visited a doctor in three months and managed to survive the longest.

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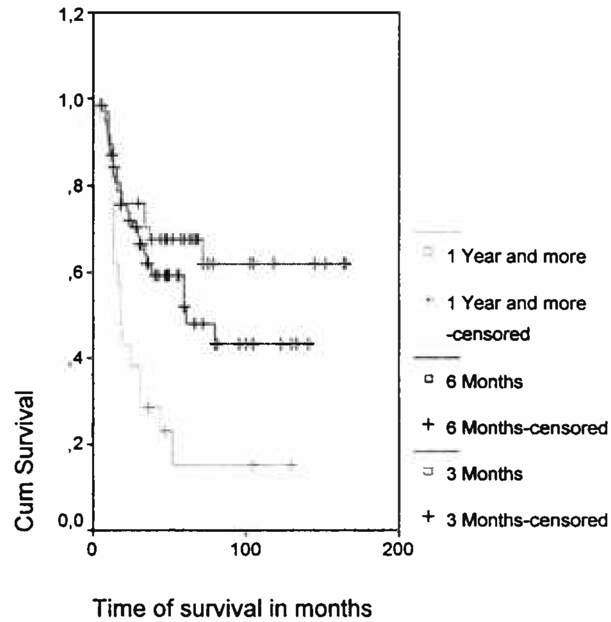

Figure 5.7: Survival function according to the time interval between the beginning of the disease and the first visit of the patients to the doctor.

In the following table, Table 5.12, the statistical tests confirm that there is statistically important difference in the risk of death between the patients categorized in different groups. Specifically, the logrank test's significance value is 0,0006 , a value that is substantially smaller than the alpha level 0,05.

Test	Statistic	df	Significance
Log Rank	14,99	2	0,0006
Breslow	12,12	2	0,0023
Tarone-Ware	13,72	12	0,0010

Table 5.12: Test Statistics for Equality of Survival Distributions for the time interval between the beginning of the disease and the first visit of the patients to the doctor.

From all predispositional factors there was only one that appeared to influence the survival of the patients, "preexisted Ca in other region". As it can be shown in Figure 5.8, patients reported with the factor died earlier than the rest.

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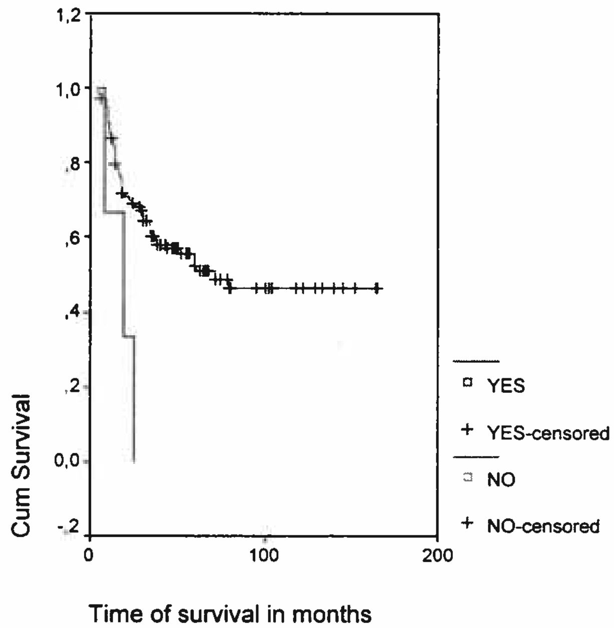

Figure 5.8: Survival function according to predispositional factor "preexisted Ca in other region" .

The conclusion drawn from the figure is confirmed by the logrank test's significance result and the results of the other two tests shown in Table 5.13. All three significance values are less than 0,05, showing that there is statistically difference in the risk of death between those who reported the factor and those who did not.

Test	Statistic	df	Significance
Log Rank	6,56	1	0,0104
Breslow	4,73	1	0,0297
Tarone-Ware	5,55	1	0,0184

Table 5.13: Test Statistics for Equality of Survival Distributions for predispositional factor "preexisted Ca in other region"

The performance status of the patients was the next variable concluded to be affective upon the survival of the patients. It is apparent from Figure 5.9 that all patients presenting normal activity were the ones that managed to survive longer. On the other hand patients that passed more than half of their daytime in bed, seem to be the ones that were deceased earlier.

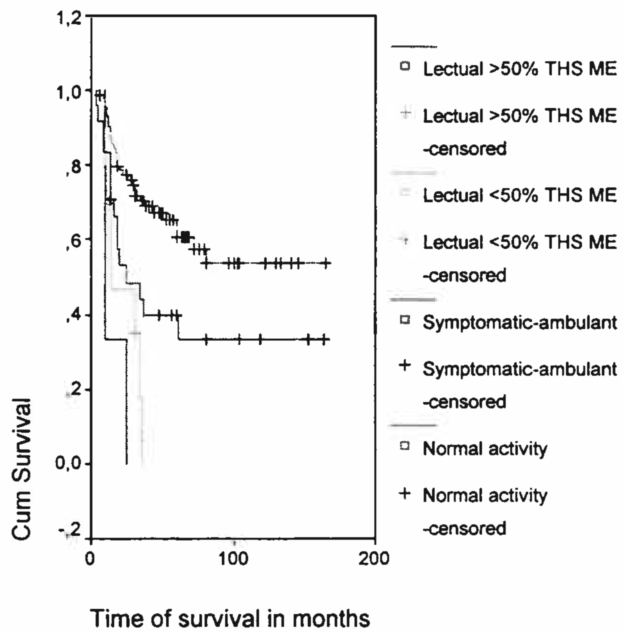

Figure 5.9: Survival function according to the performance status of the patients.

From Table 5.14 it can be noted that all three tests provided significance values less than 0,05. The above shows that there is statistical difference in the risk of death between patients with different performance status.

Test	Statistic	df	Significance
Log Rank	26,30	3	0,00001
Breslow	23,55	3	0,00001
Tarone-Ware	25,01	3	0,00001

Table 5.14: Test Statistics for Equality of Survival Distributions for the performance status of the patients

Looking back at Figure 5.9, it is apparent that there is a notable separation between the patients that had presented normal activity and the rest of the patients. So, the patients can be newly divided into two groups, with first group containing those patients who had presented normal activity, and the second group containing those who had not. From the above separation Figure 5.10 is derived.

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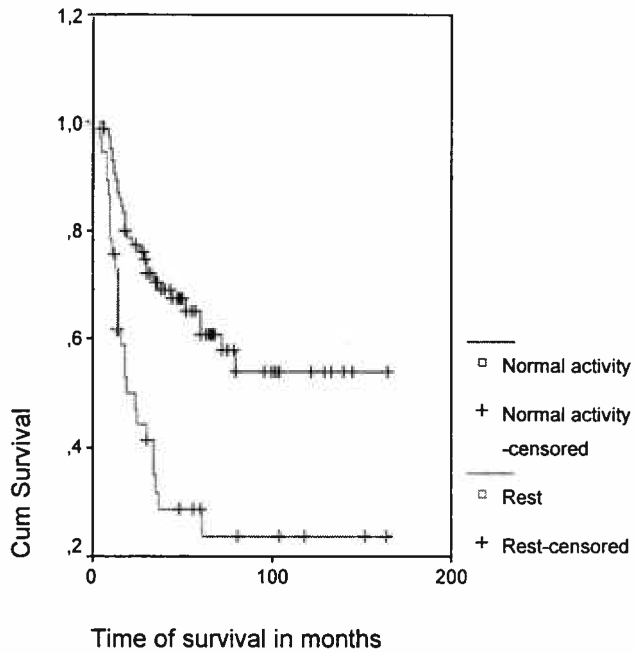

Figure 5.10: Survival function according to the performance status of the patients, when patients are divided according to whether they had presented normal activity or not.

The corresponding table with the significance values of the tests is Table 5.15. As in Table 5.14, all three values are far less than the chosen alpha level 0,05.

Test	Statistic	df	Significance
Log Rank	15,40	1	0,0001
Breslow	16,35	1	0,0001
Tarone-Ware	16,40	1	0,0001

Table 5.15: Test Statistics for Equality of Survival Distributions for the performance status of the patients, when patients are divided according to whether they had presented normal activity or not.

The site of the disease has been proposed by many authors as an additional factor to be used for the patients' staging. In our data the tongue had been divided into three parts: the anterior part, the middle part and the posterior part, which included the posterior third of the tongue and the tongue's base. Two out of these three parts were concluded to affect the survival of the patients, those two parts being the middle part and the posterior part. This result confirmed that site does play a significant role for the survival of the patients and its inclusion to the patients' staging should be considered.

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The next Figure 5.11 shows that patients that did not have lesions in the middle part of the tongue died earlier than the ones that had! Thus, it can be concluded that the middle part of the tongue is a "less dangerous" part for a lesion to appear.

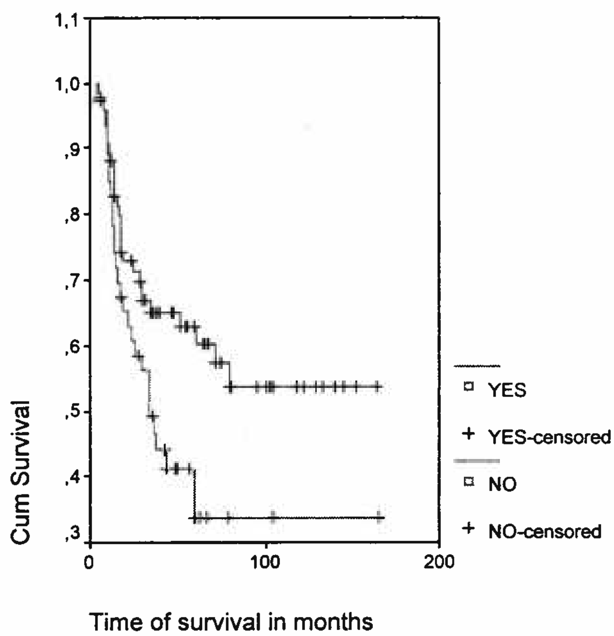

Figure 5.11: Survival function of patients having the disease on the middle part of the tongue

Table 5.16 confirms the conclusion. The value of the significance of the logrank test is 0,0278 and the null hypothesis of the test is rejected, and thus there is statistically important difference in the risk of death between those who had the disease on the middle part of their tongue and those who did not.

Test	Statistic	df	Significance
Log Rank	4,84	1	0,0278
Breslow	3,45	1	0,0631
Tarone-Ware	4,18	1	0,0410

Table 5.16: Test Statistics for Equality of Survival Distributions for patients having the disease at the middle part of the tongue

The other part found to affect the patients' survival was the posterior part. The results for this part are shown in Figure 5.12 and Table 5.17. In the figure, patients with lesions on the posterior part of the tongue appear to have died earlier. The result is confirmed by the significance values provided by the tests. The logrank test's value

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is 0,0385. In a more detailed research, when the third posterior part of the tongue and the tongue's base were explored separately, the logrank test's value for the third posterior third was 0,0682 and the corresponding value for the tongue's base was 0,0062. Thus, one can conclude that the results for the posterior part, as defined in our data set, are based mainly on the affects that lesions have on the tongue's base.

Test	Statistic	Df	Significance
Log Rank	4,28	1	0,0385
Breslow	4,47	1	0,0346
Tarone-Ware	4,44	1	0,0350

Table 5.17: Test Statistics for Equality of Survival Distributions for patients having the disease on the posterior part of the tongue

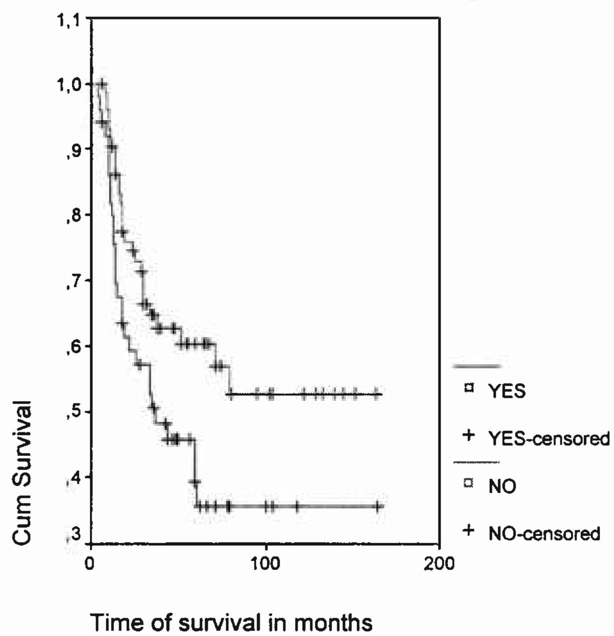

Figure 5.12: Survival function of patients having the disease on the posterior part of the tongue

As it has been mentioned, the anterior part of the tongue was not concluded to affect the survival of the patients. But, the author feels that the following table should be included in the analysis. In Table 5.18, the logrank test's significance value is 0,0631 , which is greater than the alpha level 0,05 , but the other two tests provide values which are both less than the selected values, thus arising doubts about the credibility of the conclusion first made.

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Test	Statistic	df	Significance
Log Rank	3,45	1	0,0631
Breslow	5,75	1	0,0165
Tarone-Ware	4,84	1	0,0278

Table 5.18: Test Statistics for Equality of Survival Distributions for patients having the disease at the anterior part of the tongue

The next variable found to be significant for the survival of the patients, is the aim of treatment. Looking at Figure 5.13, it seems that patients treated aiming their rescue or their relief, died earlier than patients treated aiming their cure or the long termed control of their disease. Of course, this conclusion is understandable, since patients treated for the first two causes are patients closer to death, while patients treated for the last two causes are patients that can more easily saved.

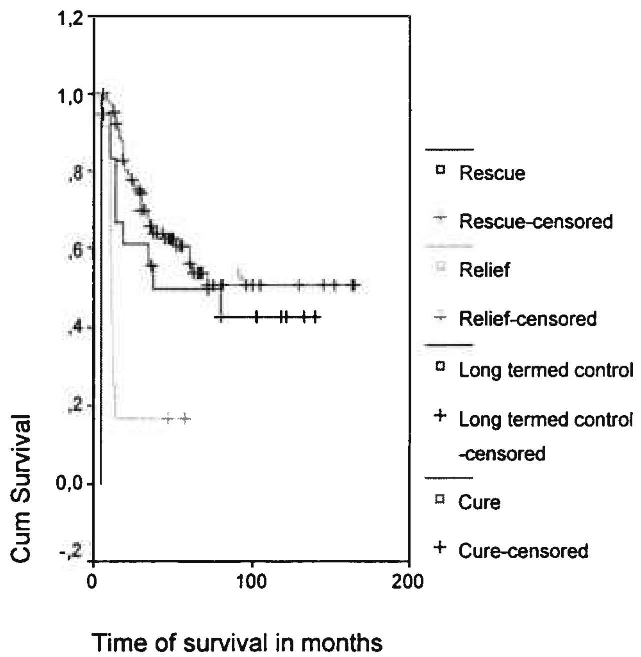

Figure 5.13: Survival function according to the treatment's aim

Table 5.19 shows that the value of the significance of the logrank test is too small and so, there is statistically important difference in the risk of death between patients treated with different aims.

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Test	Statistic	df	Significance
Log Rank	87,93	3	0,00001
Breslow	95,90	3	0,00001
Tarone-Ware	92,56	3	0,00001

Table 5.19: Test Statistics for Equality of Survival Distributions for the treatment's aim, when patients are categorized into four categories

When the four categories of variable "aim of treatment" are separated into two new groups, the first one containing those patients treated for "cure" and "long termed control", and the second one containing those treated for "rescue" and "relief", then Figure 5.14 is obtained. In this figure the discrimination of the patients of the two groups becomes more obvious. Patients in the second group are the ones who died earlier.

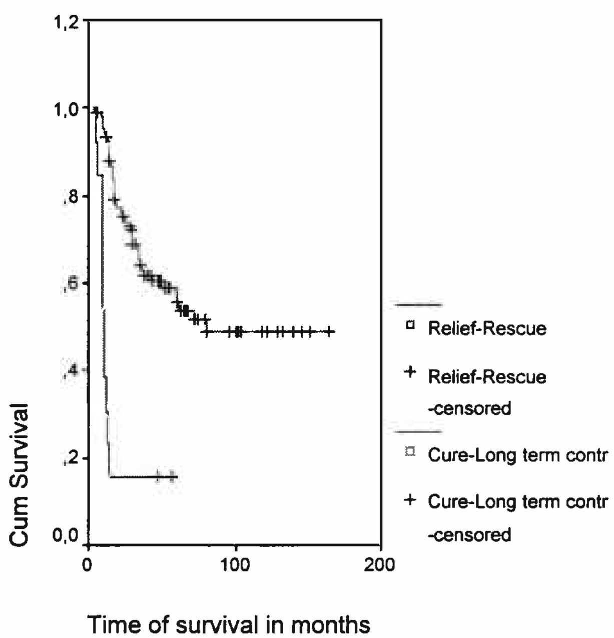

Figure 5.14: Survival function according to the treatment's aim, when patients are categorized into two groups

Table 5.20, is the corresponding one to Figure 5.14. It is apparent that there is statistically important difference in the risk of death between patients in the two groups.

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Test	Statistic	Df	Significance
Log Rank	16,40	1	0,00001
Breslow	13,09	1	0,00001
Tarone-Ware	14,40	1	0,00001

Table 5.20: Test Statistics for Equality of Survival Distributions for treatment's aim, when patients are categorized into two groups

From all the histological characteristics in the protocol the only one found to affect the patients' survival, was the "condition of the surgical margins". From Figure 5.15, the patients with clear surgical margins were the ones who survived the longest, followed by the patients with cancerous cells close to the cut's point. Patients with margins of unknown condition were next, while the patients whose margins were infiltrated died first.

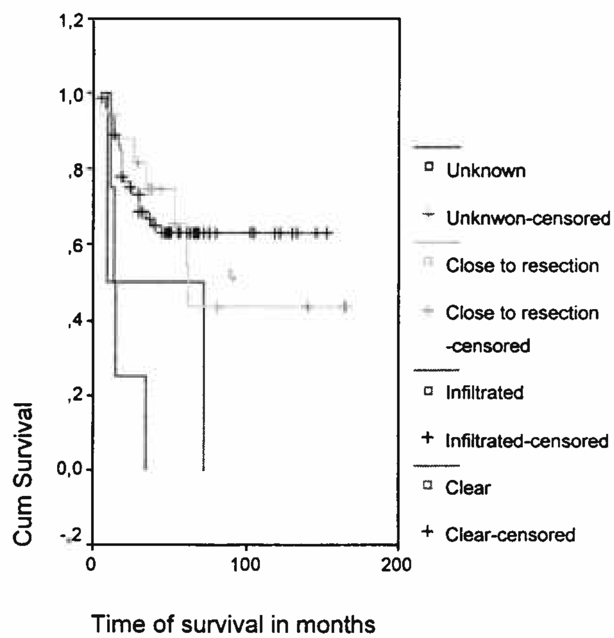

Figure 5.15: Survival function according to the condition of the surgical margins

The corresponding Table 5.21, shows the significance values of the tests. The logrank test provided a very small value, equal to 0,0009, thus the null hypothesis of the test was rejected and there is statistically important difference in the risk of death between patients in different categories.

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Test	Statistic	df	Significance
Log Rank	16,40	3	0,0009
Breslow	13,09	3	0,0044
Tarone-Ware	14,40	3	0,0024

Table 5.21: Test Statistics for Equality of Survival Distributions for the condition of the surgical margins

The next variable that was checked and found to be statistically significant for the patients' survival was the lesion's size. This variable is the one, among others, used for the patients' classification when using the TNM system or the STNMP system. Figure 5.16 reveals that patients noted as T_4, that is patients with any tumor greater than 6 cm in diameter, are the ones that died first. Patients noted as T_2, that is patients with tumors between 2 cm and 4 cm in diameter, are the next shown in the figure, followed by the T_3 patients with tumors between 4 cm and 6 cm in diameter. Finally, patients with tumors less than 2 cm in diameter (T_1) are the ones appearing to have survived longer, since they appear to be at the top of the figure.

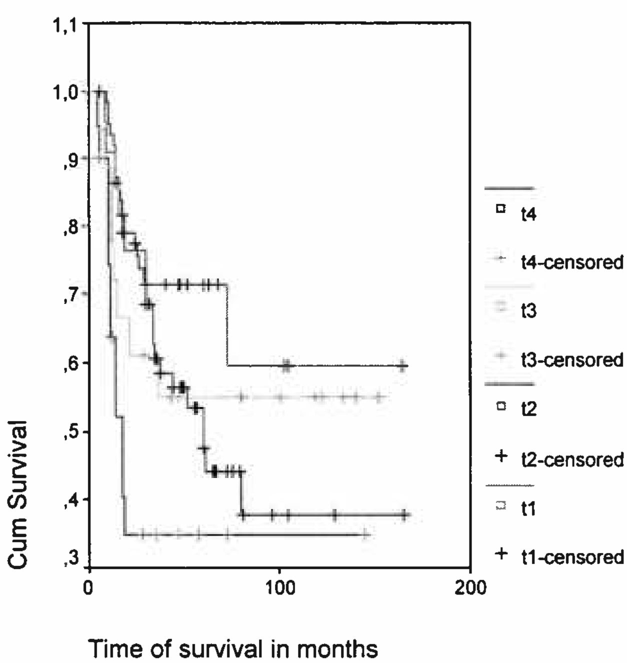

Figure 5.16: Survival function according to the patients' lesions sizes, when they are categorized into four categories

The conclusion that there is statistically important difference in the risk of death between patients belonging in different categories is also shown in Table 5.22, where it can be seen that the logrank test's significance value is 0,0374 which is smaller than 0,05, the alpha level.

Test	Statistic	Df	Significance
Log Rank	8,46	3	0,0374
Breslow	11,92	3	0,0077
Tarone-Ware	10,38	3	0,0156

Table 5.22: Test Statistics for Equality of Survival Distributions for patients' lesions sizes, when patients are categorized into four categories

By looking at Figure 5.16, one can note that patients noted by T_4 are apparently separated from the rest three categories, which cross each other at more than one points. Therefore two new groups can be formed, one containing only the last category, T_4, and another one containing the rest three, T_1, T_2 and T_3. Figure 5.17 reveals that the above separation was right, since the two groups are obviously separated. The same figure also shows that indeed the patients of T_4 category are the ones who died first, and that the T_1, T_2 and T_3 patients "acted similarly" as far as this variable is concerned. The T_1, T_2 and T_3 categories are also to be highly correlated between them, with the significance value of each chi square test being less than 0,0001.

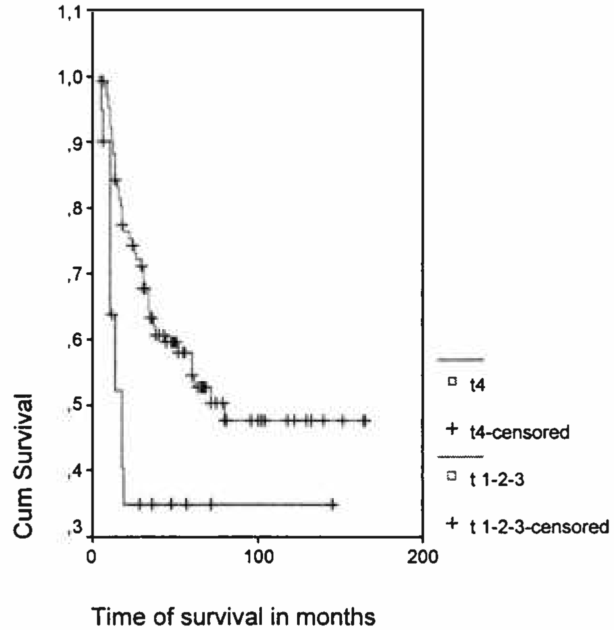

Figure 5.17: Survival function according to the patients' lesions sizes, when they are categorized into two groups

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This newly formed groups seem to have revealed the true relationship between the patients, as far as their lesions' sizes is concerned, as it can be seen in Table 5.23. The significance value of the logrank test is now 0,0067, far smaller than the value 0,0374 which was found using the previous categorization of the patients. The values of the other two tests are also sufficiently smaller.

Test	Statistic	df	Significance
Log Rank	7,34	1	0,0067
Breslow	10,92	1	0,0010
Tarone-Ware	9,45	1	0,0021

Table 5.23: Test Statistics for Equality of Survival Distributions for patients' lesions sizes when patients are categorized into two groups

Patients in the protocol were also classified according to the presence and condition of the associated regional lymph nodes (N), and to the presence or absence of distant metastases (M). While variable M was not found to be statistically significant, variable N, as it can be seen and from Figure 5.18, was indeed found to affect the survival of the patients.

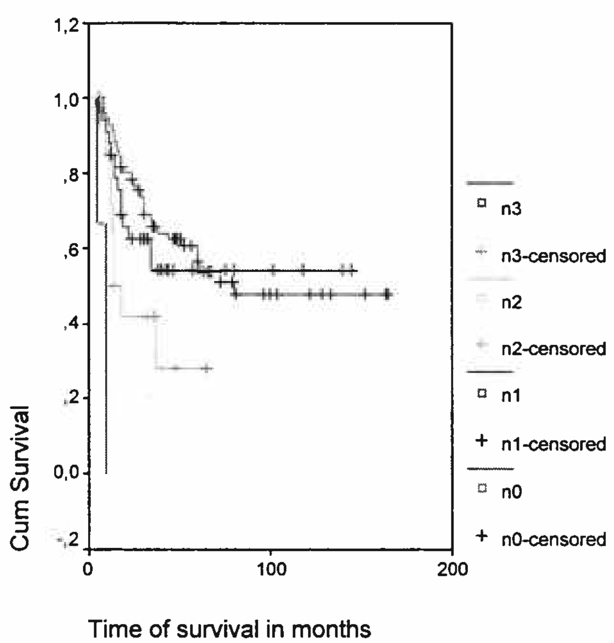

Figure 5.18: Survival function according to variable N, when patients are categorized into four categories

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Patients belonging to the N_3 category are seemed to be the first ones to have died, followed by the ones in N_2. Categories N_1 and N_0 are found at the top of the figure showing that the patients in these categories managed to survive longer than the rest. Since the two categories N_0 and N_1 are crossed in the figure, it can be assumed that they are closely related and therefore one can consider producing a new figure by putting them together.

Table 5.24 shows the corresponding values of the significance tests. The logrank value is 0,00001 and thus the null hypothesis of the test is rejected.

Test	Statistic	df	Significance
Log Rank	42,07	3	0,00001
Breslow	43,10	3	0,00001
Tarone-Ware	42,73	3	0,00001

Table 5.24: Test Statistics for Equality of Survival Distributions for variable N

The following Figure 5.19 is the corresponding figure when categories N_0 and N_1 form one group, and N_2 along with N_3 form another. The logrank significance value is again much smaller than the alpha level. Again the patients in N_2 -N_3 are the ones that died earlier. The two categories in each group are found to be correlated between them, with p-value equal to 0,0001.

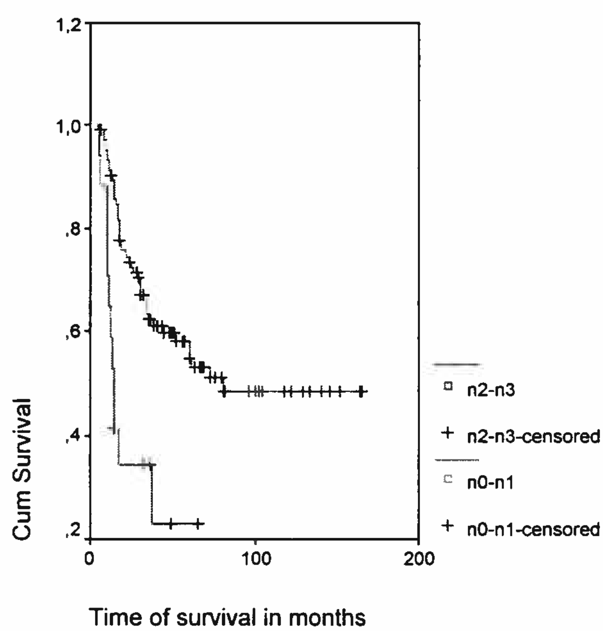

Figure 5.19: Survival function according to variable N, when patients are categorized into two categories

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The next figure, Figure 5.20, provides a different view of the affect that the site of the lesions has upon the survival of the patients. This time the three categories used in the protocol are not taken separately, but simultaneously. So, S_1 stands for patients having lesions only at the anterior part of the tongue, S_2 for patients having lesions only at the middle part of the tongue and S_3 for patients having lesions only at the posterior part of the tongue. The rest of the categories are combinations of the three parts of the tongue, since there were many patients that appeared to have lesions in more than one part of the tongue. Hence, S_2-S_3 indicates all patients with lesions at the middle and posterior part of the tongue and S_1-S_2 indicates all patients with lesions at the anterior and middle part of the tongue. There was no patient that appeared to have simultaneous lesions at the anterior and posterior part. Finally, S_1-S_2-S_3 notes the patients that had lesions at all three parts of the tongue.

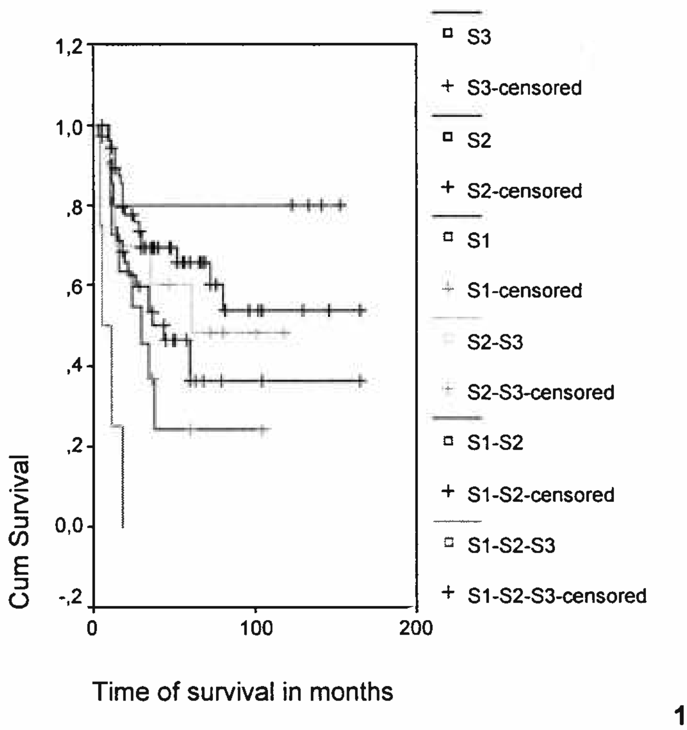

Figure 5.20: Survival function according to site, when patients are categorized into six categories

From the figure, patients with simultaneous lesions at all parts of the tongue seem to be the ones that died earlier, followed by the patients in S_1 category. Next in line are the patients in S_3 category and after them the ones in S_2-S_3. Patients with lesions only at the middle of the tongue are the ones to follow, while the patients that managed to survive the longest are the ones with lesions at the anterior and middle parts. Generally, it is obvious that patients with lesions at the posterior part of the tongue, with or without other simultaneous lesions, are the ones that managed to survive less than the others, while patients with lesions at the middle part of the tongue, with or without other simultaneous lesions, appear once more to be the ones to have survived longer. The surprising new element that is revealed from the figure above, is that patients with lesions only at the anterior part of the tongue seem to have died earlier than others with lesions at parts of the tongue that are assumed to be less curable.

The corresponding logrank test that confirms that there is statistically important difference in the risk of death between patients belonging in different categories is shown in the following Table 5.25.

Test	Statistic	df	Significance
Log Rank	34,24	5	0,00001
Breslow	33,40	5	0,00001
Tarone-Ware	33,92	5	0,00001

Table 5.25: Test Statistics for Equality of Survival Distributions for the site, when patients are categorized into six categories

The TNM classification and staging system is one of the two systems used in the protocol. When the Kaplan-Meier was applied on the TNM stages, it revealed that there is statistically important difference in the risk of death of the four stages.

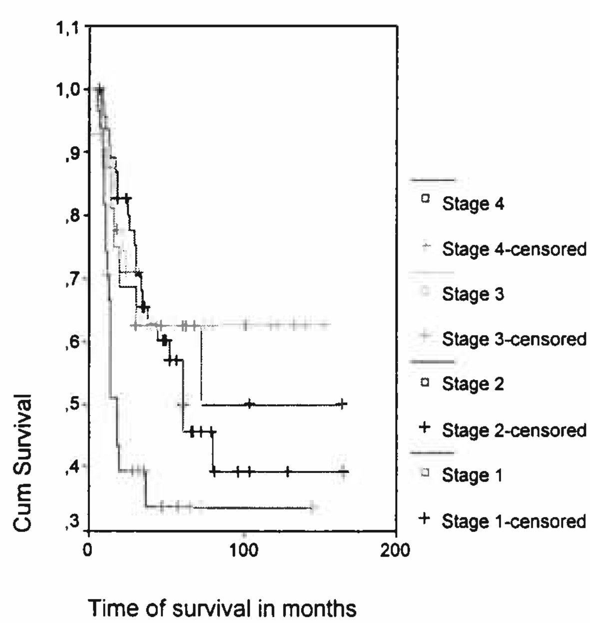

Figure 5.21: Survival functions according to the TNM staging

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The above conclusion is also shown in Table 5.26, where one can see that the significance value provided by the logrank test is 0,0246. With this value the test's null hypothesis is rejected and thus, there is statistically important difference in the risk of death between patients belonging in different stages.

Test	Statistic	Df	Significance
Log Rank	9,39	3	0,0246
Breslow	12,26	3	0,0065
Tarone-Ware	11,02	3	0,0116

Table 5.26: Test Statistics for Equality of Survival Distributions for the TNM staging, when patients are staged into the four TNM stages

In Figure 5.21 it can be seen that all three first stages seem to behave similarly and that they are separated from Stage 4, whose patients are seemed to be the first ones to have died. So, by forming two new groups the next figure is provided. The first group is formed by stages 1 to 3, while the second one is formed only by Stage 4.

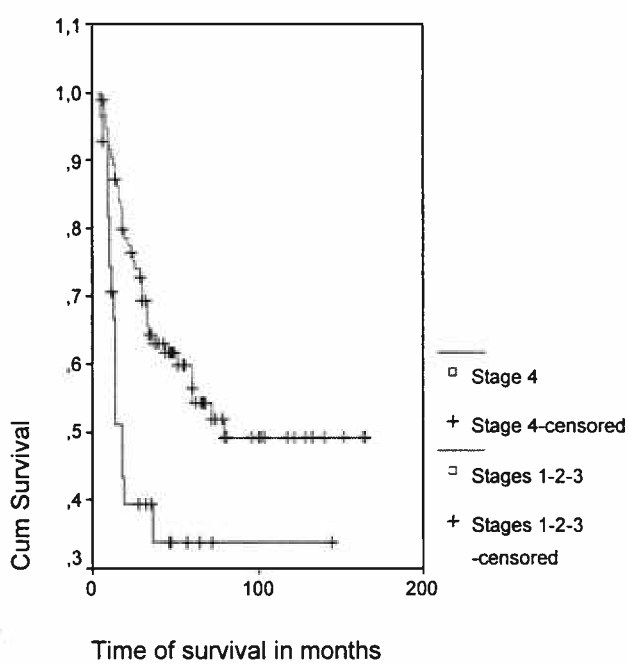

Figure 5.22: Survival functions according to the new separation of the TNM stages

The above Figure 5.22, along with the next Table 5.27, confirm the similar behavior of Stages 1, 2 and 3,(which are correlated between them, with each significance value being less than 0,0001), and the fact that patients of Stage 4 are the ones who were deceased first. The value of the logrank test reveals that there is statistically important difference in the risk of death between patients belonging in the two new groups, and that this difference is more indicating of the patients behaviour, than the one revealed when the four stages had been used. This is shown by the much smaller significance values of the statistical tests.

Test	Statistic	Df	Significance
Log Rank	8,97	1	0,0027
Breslow	12,18	1	0,0005
Tarone-Ware	10,93	1	0,0009

Table 5.27: Test Statistics for Equality of Survival Distributions for the TNM staging, according to the new separation of the TNM stages

As it has been mentioned there were two classification and staging systems used in the protocol. The TNM system was the first one, whereas STNMP was the second one. This system that was proposed in 1977 by Rapidis et al, staged the patients of the protocol into four stages with notable differences from the staging that was provided by the TNM system (Descriptive statistics of the data). In Figure 6.23, though, it can be seen that when the Kaplan-Meier was applied on the STNMP stages, it revealed a similar picture to the one in Figure 15 with the TNM stages.

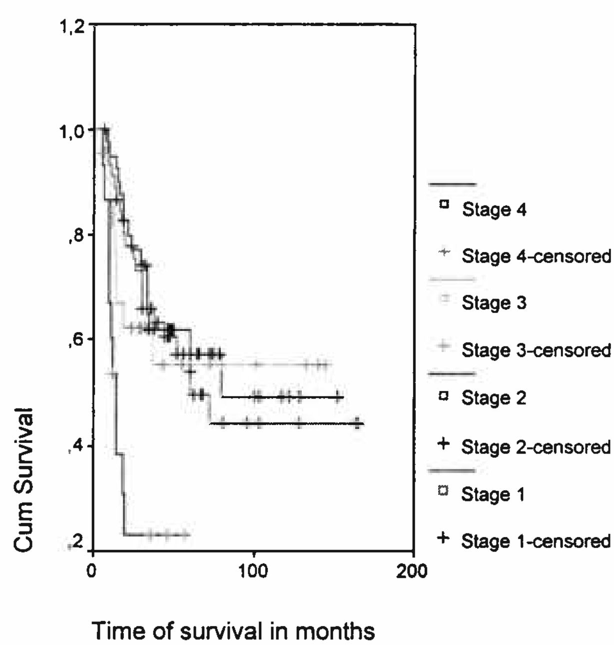

Figure 5.23: Survival functions according to the STNMP staging

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Again, it is obvious that the three first stages cross each other at more than one points, thus allowing a speculation about them having some kind of correlation between them, and that the patients staged in Stage 4 are the ones who died earlier.

In the next table the significance values are presented, all of them being less than 0,05 , the selected alpha level. So, it can be concluded that the null hypotheses of the tests are rejected and there is statistically important difference in the risk of death between patients belonging in different stages of the STNMP.

Test	Statistic	df	Significance
Log Rank	9,39	3	0,0246
Breslow	12,26	3	0,0065
Tarone-Ware	11,02	3	0,0116

Table 5.28: Test Statistics for Equality of Survival Distributions for the STNMP staging, when patients are staged into the four TNM stages

When the first three stages are put together forming a new group, the following figure is provided. The patients of Stage 4, again, are shown to be the ones to have survived less, while the logrank provides a very small significance value, allowing the conclusion that this separation of the stages is a more indicating one. The first three stages that formed the new group, were found to be highly correlated between them (p-value of the chi square tests being less than 0,0001), confirming their common behavior.

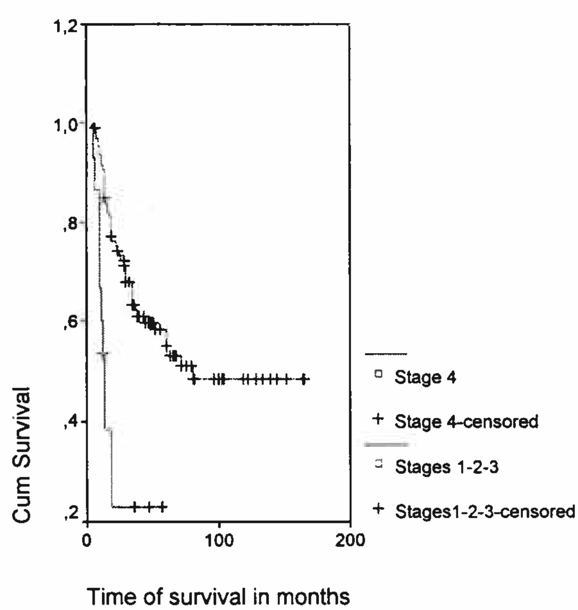

Figure 5.24: Survival functions according to the new separation of the STNMP stages

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Test	Statistic	df	Significance
Log Rank	16,71	1	0,00001
Breslow	19,84	1	0,00001
Tarone-Ware	18,58	1	0,00001

Table 5.29: Test Statistics for Equality of Survival Distributions for the STNMP staging, according to the new separation of the STNMP stages

With the STNMP, the presentation of all the variables found to be affective upon the survival of the patients, by using the Kaplan-Meier method and statistical tests, is completed. The variables included two initial symptoms, "bleeding" and "trouble in swallowing and speaking", and one predispositional factor, the "preexisted Ca in other region". The performance status of the patients and the aim of treatment were also included.

Both systems used for the classification and staging of the patients were found to affect the survival. But, even though, the TNM and STNMP stages were found to be affective, the variables forming the systems were not all found to affect the patients' survival. So, the M variable was not found to affect the survival and the same conclusion was drawn for the STNMP's variable P. On the other hand, variables T, N and S, were all found to affect the patients' survival.

Finally, the time interval between the beginning of the disease and the first visit of the patients to the doctor, was one of the presented variables. Its presence is essential, since its addition to the variables used for classification and staging, was done by Evans et al in 1982.

5.2.2.2. Application of the Cox's proportional-hazards model

After having used the Kaplan-Meier and tests statistics to estimate whether a variable affects the risk of death or not, a second method was used for the same purpose, the Cox's proportional-hazards model.

Before applying the multivariate Cox's proportional-hazards model, univariate models were used for each variable as to reveal all variables affecting the risk of death of the patients.

When the univariate model was applied on all initial symptoms, two were found to negatively affect the survival of the patients, "bleeding" and "trouble in

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swallowing and speaking". Both variables were used in the models as dichotomous variables. So, if X represents variable "bleeding",

$$X = \begin{cases} 0, & \text{if symptom "bleeding" was not reported for the patient} \\ 1, & \text{if symptom "bleeding" was reported for the patient} \end{cases}$$

The corresponding coefficient for "bleeding" was 1,144, with its significant value being 0,003 and the corresponding model was

$$h(t,x) = h_0(t)\exp(1,144x)\,.$$

Thus the estimated hazard for patients with the symptom is exp(1,144)=3,138 of that for patients without it, and there is an increase in the risk of death for patients who appeared to have the symptom.

Similar conclusions were drawn for "trouble in swallowing and speaking". The value of the coefficient was 1,177, while the significant value was less than 0,00001. The estimated hazard for the patients having the symptom is exp(1,177)=3,243, and thus there is an increase in the risk of death of those patients. The above two initial symptoms were also revealed when the Kaplan-Meier method was used.

When the univariate model was applied on the categorical variable of the time interval between the beginning of the disease and the first visit of the patients to the doctor, it revealed that patients delaying less than 6 months or less than 3 months, appeared to have a decrease in the risk of death relatively to patients delaying one year and more.

So, if Y represents the categorical variable, then

$$Y = \begin{cases} 0, & \text{if the patient delayed one year and more} \\ 1, & \text{if the patient delayed less than 3 months} \\ 2, & \text{if the patient delayed less than 6 months} \end{cases}$$

and thus the comparison is done by using the category "one year and more" as the baseline.

More specifically, when comparing to category "one year and more", the coefficient for the category "less than 6 months" was -1,287, with significant value equal to 0,001. Thus the estimated hazard for patients in the "less than 6 months" category is exp(-1,287)=0,276, and there is a decrease in the risk of death of those patients in compare to patients belonging in the "one year and more". Similar conclusions are drawn for patients in the "less than 3 months" category. The

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coefficient is -0,885, with significant value 0,004. The estimated hazard is exp(-0,885)=0,413, and again there is a decrease in the risk of death of these patients in compare to patients in the "one year and more" category.

From all the predispositional factors, only "preexisted Ca in other region" was found to negatively affect the survival of the patients. The factor entered the univariate model as a dichotomous variable, with zero value indicating the absence of the factor and unit value indicating its presence. The corresponding coefficient was 1,405, with significant value equal to 0,02. The estimated hazard for patients reporting the predispositional factor, is exp(1,405)=4,075, and there is an increase in the risk of death of those patients.

When variable "performance status" was investigated as a categorical variable, the comparison was done by using category "lectual >50% of the day" as the baseline. So, if W represents the variable, and

$$W = \begin{cases} 0, & \text{if patient is lectual} >50\% \text{ of the day} \\ 1, & \text{if patient's activity is normal} \\ 2, & \text{if patient is symptomatic-totally ambulant} \\ 3, & \text{if patient is lectual} <50\% \text{ of the day} \end{cases}$$

the following table includes the corresponding coefficients and significance values for the three categories being compared to the "lectual >50% of the day".

Category	Coefficient (b)	Exp(b)	Significance value
Normal activity	-2,066	0,127	0,001
Symptomatic-totally ambulant	-1,331	0,264	0,39
Lectual <50% of the day	-0,641	0,527	0,527

Table 5.30: Coefficients for categorical variable "performance status"

From the table, it can be seen that categories "normal activity" and "symptomatic-totally ambulant" appear to have significant differences in the risk of death from the "lectual >50% of the day" category. For patients in both categories there is a decrease in the risk of death, in compare to the "lectual >50% of the day".

Three ways of treatment were found to affect the survival of the patients, "surgical", "radiotherapy", and "radiotherapy-chemotherapy". All three ways were used separately in univariate models as dichotomous variables.

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The "surgical" way was found to positively affect the survival of the patients. The coefficient in the model was –1,291, with significant value 0,0001, and the estimated hazard for patients treated only surgically, is exp(-1,291)=0,275.

"Radiotherapy" and "radiotherapy-chemotherapy", were both found to affect the survival of the patients negatively, since there is an increase in the risk of death. The coefficient for the "radiotherapy" model was 1,693, with significance value 0,001, while the coefficient for the

When the categorical variable which includes all possible combinations of the anatomical site of the lesions, was put in a univariate model, the comparison was contacted according to S_3, that is the posterior part of the tongue. Thus, the category S_1-S_2-S_3, which includes all patients with lesions on all three parts of the tongue, was found to negatively affect the survival of the patients in comparison to S_3. The corresponding coefficient of the category was 1,924, and the significance value 0,001. The category S_2, that is the middle part of the tongue, was found to positively affect the survival of the patients in comparison to S_3, with the coefficient being –0,627, and the significance value equal to 0,05.

The presence and condition of the associated regional lymph nodes (N) was another categorical variable that was investigated. The category used as baseline was N_3, and all three other categories of the variable were found to affect the survival positively in compare to the last category. The following table presents the results for variable N.

Category	Coefficient (b)	Exp(b)	Significance value
N_0	-3,085	0,046	0,0001
N_1	-2,912	0,054	0,0001
N_2	-2,129	0,119	0,003

Table 5.31: Coefficients for categorical variable N

For categorical variable "lesion's size", T, the comparison was made to the last category T_4. Again, all other three categories were found to positively affect the survival of the patients in comparison to the baseline category.

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Category	Coefficient (b)	Exp(b)	Significance value
T1	-1,225	0,294	0,009
T2	-0,858	0,424	0,01
T3	-1,021	0,36	-0,031

Table 5.32: Coefficients for categorical variable T

After having applied univariate models on the variables of the protocol, multivariate Cox's proportional hazards models were applied. The most suitable one was chosen and is presented in follow.

In the chosen model there are five variables, two of which are dichotomous, while the rest are categorical. The two dichotomous ones are initial symptom "trouble in swallowing and speaking", and predispositional factor "preexisted Ca in other region". The categorical ones are the "time interval between the beginning of the disease and the first visit of the patients to the doctor", "the presence and condition of the associated regional lymph nodes", and the variable containing all combinations of the anatomical site of the lesions. For the categorical variables the comparisons were made the same way as in the univariate models for each variable.

From the table that follows, it can be seen that for patients who delayed their first visit to the doctor less than 6 or 3 months, there is a decrease in the risk of death in compare to the ones that delayed one year and more. For patients that reported trouble in swallowing and speaking there is an increase in the risk of death, and the same conclusion is made for the predispositional factor in model.

The presence and condition of the associated regional lymph nodes (N), appears to have the same behavior as in the corresponding univariate model. Again, all three categories when compared to the N_3 category, reveal a decrease in the risk of death, thus they affect positively the survival of the patients.

The last categorical variable in the model, the anatomical site S, seems to have a different behavior in the multivariate model than the one it had in the univariate. In this model, only category S_1, that is the anterior part of the tongue, appears to have an increase in the risk of death when compared to the posterior part S_3.

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Variables	Coefficient (b)		Exp(b)	Significance value
Time interval				0,02
Less than 3 months	-1,153	0,413	0,316	0,005
Less than 6 months	-0,531	0,363	0,588	1,44
Trouble in swallowing and speaking	1,214	0,329	3,366	0,0001
Preexisted Ca in other region	2,523	0,703	12,472	0,0001
N				0,0001
N0	-3,927	0,834	0,02	0,0001
N1	-3,317	0,843	0,036	0,0001
N2	-3,205	0,859	0,041	0,0001
S				0,003
S1-S2-S3	0,629	0,662	1,875	0,343
S1-S2	-1,958	1,111	0,141	0,078
S2-S3	-0,399	0,535	0,671	0,455
S1	1,185	0,462	3,271	0,01
S2	-0,406	0,333	0,666	0,222

Table 5.33: Coefficients, Standard errors of the coefficients, significance values of the variables revealed by the final Cox model

5.2.2.3. Application of the chi-square test

The Kaplan-Meier and the Cox's proportional-hazards model, were both used until this moment, to evaluate and reveal, the affect of the protocol's variables upon the patients' risk of death. In this parafigure the chi-square test, which is a hypothesis test, was used for the determination of the various relationships between the variables of the protocol. All revealed relationships are next shown.

5.2.2.3.a. Results from the application of the chi-square-test on all variables except from the two classification and staging systems

The first variable to be investigated was "age". Since this variable was continuous, the patients were divided into three categories, those being less than 50, those from 51 to 70 years old, and those who aged more than 70. Using the new variable, age was found to have a real relationship with variable "performance status". The significance value of the chi-square test was 0,002, but since some of the expected values in the test were found to be less than 5, the likelihood ratio-test was also used. The value of this test was 0,001, thus confirming the chi-square.

The second variable to be searched was "sex". The variable revealed a strong relationship with both "smoking" and "alcohol". The corresponding values were both 0,0001. By looking at both Tables 2 and 3, it becomes clear that men were the ones that were more addicted to the two habits.

	Smoking		
Sex	No	Yes	Total
Woman	32	15	47
Man	15	61	76
Total	47	76	123

Table 5.34: The bivariate table showing the cross-classified variables "sex" and "smoking"

	Alcohol		
Sex	No	Yes	Total
Woman	44	3	47
Man	35	41	76
Total	79	44	123

Table 5.35: The bivariate table showing the cross-classified variables "sex" and "alcohol"

From the tongue's three parts, "sex" was found to have a real relationship with the anterior one, with 0,028 the test's value. The corresponding table showed that women had more frequently lesions at that part of the tongue.

The initial symptoms of the protocol were the next to be checked. The symptoms were first checked between them. "Pain" and "unspecified local disturbance" were found to have a real relationship between them, since the null

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hypothesis of the test was rejected, with the significance value being 0,0001. "Pain" was also found to have a real relationship with "trouble in swallowing-speaking", with 0,039 being the test's significance value. When looking at the corresponding table, it is obvious that the majority of the patients who had trouble in swallowing and speaking, also suffered when they attempted any of the two.

	Trouble in swallowing-speaking		
Pain	No	Yes	Total
No	21	9	30
Yes	45	48	93
Total	66	57	123

Table 5.36: The bivariate table showing the cross-classified variables "Trouble in swallowing-speaking" and "Pain"

"Trouble in swallowing-speaking" also, had a real relationship with each of "unspecified local disturbance" and "bleeding" variables. The significance value for the first chi-square test was 0,0001, whereas the second chi-square had to be confirmed by a likelihood ratio-test, that gave a value equal to 0,021.

After they had been checked between them, the initial symptoms were tested with the other variables of the protocol. So, symptom "bleeding" was found to be related to the anterior part of the tongue, with 0,017 as the test's value this time. Even though, "bleeding" had no relationship to the posterior part of the tongue, with further investigation, it was found that it did have a real relationship with one of the two parts forming that part of the tongue, the tongue's base. The two variables produced a test with 0,004 as its significance value. Both the above chi-square tests were confirmed with the use of the corresponding likelihood ratio-tests.

Finally, "bleeding" was revealed to be related to the variable "lesion's size", and the variable N. The tests' values were both 0,0001 and they were confirmed with the use of likelihood ratio-tests.

The initial symptom "trouble in swallowing-speaking" and the posterior part of the tongue produced a test that rejected the null hypothesis of the chi-square test. The significance value was equal to 0,004. When "trouble in swallowing-speaking" was used in separated tests with the two parts that formed the posterior part of the tongue, it was concluded that the "posterior third of the mobile part" had a real relationship with it, with significance value 0,002. With that in mind, it can be concluded that the relationship between "trouble in swallowing-speaking" and the posterior part of the tongue, was mainly based on the relationship between the initial symptom and the "posterior third of the mobile part". "Trouble in swallowing-speaking" was finally found in real relationship with the variable "size of the lesion". The test's value was 0,043.

The initial symptom "unspecified local disturbance" was found too be really related to "alcohol", with the test's value being 0,017. The symptom was also found to be related to the "posterior third of the mobile part", with the test's value being 0,048 and to variable N, with the test's value being this time 0,019. The chi-square test's value was confirmed by the corresponding likelihood ratio-test's value, 0,016.

The predispositional factors were the next to be investigated after the initial symptoms. They were first looked up between them. The research revealed that "smoking" and "alcohol" were the ones that had a very "strong" relationship, since they had a test significance value equal to 0,0001.

When the factors were checked with other variables, except from the results already mentioned, there were another three results revealed, two having to do with "alcohol" and one with "preexisted leukoplakia" . So, "alcohol" was related to the tongue's base with the test's value being 0,037, and to variable N, with likelihood ratio-test's value equal to 0,003. The last variable was also the one related to "preexisted leukoplakia", with 0,0001 the likelihood ratio-test's value. "Preexisted leukoplakia" was specifically found to be related to N_0 and N_1, with corresponding significance values 0,0001 and 0,008.

When looking for relationships between the tongue's parts, the posterior part was found to be related to both the other two parts. With the anterior part the value of the test was 0,04, whereas the one with the middle part was 0,0001, revealing a more "powerful" relationship.

Except from the relationships mentioned before that had to do with the tongue's parts and other variables, two more relationships existed. The posterior part had a real one with the lesion's size, with the test's value being 0,0001, and the tongue's base had another one with variable N, with likelihood ratio-test's value equal to 0,01 , even though there was no relationship between variable N and the whole third of the tongue.

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5.2.2.3.b. Results from the application of the chi-square-test on the two classification and staging systems

When the chi-square test was applied on the two classification and staging systems, TNM and STNMP, it revealed all the variables that influenced the systems.

So, the TNM system had real relationships with all four initial symptoms, with the corresponding significance values being, 0,018 for the "unspecified local disturbance", 0,012 for the "pain", 0,001 for "bleeding", and 0,021 for "trouble in swallowing-speaking".

TNM was also related to the variable "midinterval from the beginning of the symptoms", with likelihood-ratio test's value equal to 0,015.

From all predispositional factors in the protocol, "smoking", "alcohol", "preexisted leukoplakia" and "preexisted Ca of other region", were the ones to be found related to the TNM system. Their significance values were 0,035 for "smoking", 0,003 for "alcohol", 0,003 for "preexisted leukoplakia" and 0,04 for "preexisted Ca of other region". When the factor "smoking and alcohol" was created, containing all patients that had reported both factors, and then tested with TNM, the test's value was 0,001.

When the three parts of the tongue were considered separately, only the posterior part was found to correlated to the TNM system, with the test's value being 0,034. The relationship was mainly based on the relationship between the tongue's base and the TNM, whose test's value was 0,0001. When the parts were put together in a variable the relationship became stronger, with the value of the test being 0,023. Finally, the TNM was found to be related with the variable containing all the possible combinations of the tongue's parts. This time, the test's value was even smaller, 0,0001. All the above show that the site of the lesion is correlated to the TNM system.

The size of the lesion was also found to be strongly related to TNM, something that was expected, since this variable was one of the variables forming the TNM. The value of the test was 0,0001.

The same happened with the second variable of the TNM, variable N. Again, the relationship was strong and the value of the test was 0,0001.

The second system used, STNMP, was related to three of the initial symptoms. The values of tests were 0,05 for the "pain", 0,0001 for "bleeding", and 0,007 for "trouble in swallowing-speaking".

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STNMP also had a real relationship with variable "midinterval from the beginning of the symptoms", and the significance value was 0,01.

Only two predispositional factors were found to have significance values smaller than 0,05, "alcohol" and "preexisted leukoplakia". The first value was 0,021 and the second one 0,016. Factor "smoking and alcohol" also had a smaller than 0,05 value, when tested with STNMP, that value being 0,017.

Site of the lesion, one of the factors forming the STNMP system, was also found to be related to the system. The posterior part of the tongue was the one found to have a real relationship with STNMP, with test's value 0,004. When all parts were put together the test's value was 0,005, and when all possible combinations of the parts were used in a variable, the value was smaller, 0,001.

The second factor of the STNMP system, size of the lesion, provided a likelihood-ratio test value equal to 0,0001, when checked with the system. This strong relationship was expected.

The same test value was provided by the tests between N and STNMP, and P and STNMP.

In both systems, variable M was not found to have any relationship with either of the tests. This can be explained by the fact, that only one patient in the particular data base, was found to have metastasis. Variable M was also found not to affect the risk of the death of the patients for the same reason. So, it cannot be concluded that the variable is unnecessary for the classification and staging of the patients.

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CHAPTER 6
Conclusions

The conclusions that were drawn from the present research were various. Most of them are confirmed by similar statistical and medical researches, whereas others contradict previous results.

6.1. General conclusions of the research

Even though many authors have concluded that females appear to have a better prognosis and longer survival than males, (Waterhouse, 1974; Easson and Russel, 1968; Easson and Palmer, 1976; Berthelsen et al, 1977; Langdon et al, 1977; Ostman, 1995), this can not be concluded from the present research, which has revealed that there is no statistically important difference in the risk of death of the two sexes. Other researches seem to share the same result with the present one (Binnie et al, 1972).

Age was another variable that has concerned many researchers. Most of them tried to find out whether young patients had a different behavior, as far as their survival was concern , from older patients. Most of the times young patients were considered to be the patients aging less than 40 or 45 years. Like the majority of the researches (Hyam et al, 2003; Veness et al, 2003; Ridge et al, 1998; Pitman et al, 2000; Friedlander et al, 1998), the present one concluded that there was no statistically important difference in the risk of death of the young and old patients. In specific, when the patients were divided into to young and old ones, with the separating age being 40, the logrank test's significance value was 0,1048. When the separating age was 35, the test's value was 0,2238, and when it was 45, the corresponding value was 0,2075.

From the initial symptoms used in the research's protocol two were found to affect the survival of the patients, bleeding and dysarthria-dysphagia, and they were related. The second one was also found to be related to the posterior part of the tongue and the lesion's size, two variables which were found to be correlated. Bleeding was related to the lesion's size too. Having all the above in mind, it can be logically concluded that patients with probably big lesions at the posterior part of the tongue, appear to have trouble in swallowing and speaking. When they do try to perform either of the two activities, they suffer, because the lesions are probably scratched and bleed.

Many authors have suggested that the factor of the delay between the time of the beginning of the symptoms and the time on which the patient appeared to the hospital for diagnosis and treatment, should be added to the classification and staging systems (Evans et al, 1982). In the present protocol this factor corresponds to the variable "midinterval from the beginning of the symptoms". This variable was found to affect the survival of the patients, and its last category, with patients who had delayed one year or more, was found to negatively affect the patients' prognosis. The variable was also correlated to the TNM and STNMP systems. Thus the research's results tend to agree with the above suggestion. But the present results disagree with the observation made by the Evans (1978) that a long delay is advantageous, since patients who delayed the longest are the ones who died earlier.

Alcohol and smoking are the two predispositional factors that are thought, by the majority of the authors, responsible for the oral lesions, with alcohol being the most serious one (Ivanhoe.com; Chen et al, 2000; Neville et al, 2002; Scussy et al, 2000; Shoaf, 2003; Adewole, 2002; Yeole et al, 2000). The present research does not conclude the same. The only predispositional factor revealed was the "preexisted Ca in other region", by both the Kaplan-Meier method and the Cox's proportional hazards model.

Even though alcohol and smoking did not affect the patients' survival, they were both correlated to the TNM system, and alcohol was correlated to the STNMP system as well. Alcohol was also correlated to the tongue's base, which in its turn affected the survival. So, it can be concluded that patients who presented alcohol drinking, presented lesions on the tongue's base, which affected their survival. This last conclusion was also found by other researchers who found out that ethanol, thus alcohol, ratted the size of the basal cell nuclei of the base of the tongue (Simanowski et al, 1995; Maier et al, 1994) and that significant atrophy of the posterior lateral tongue epithelium was presented when 10% solution of absolute alcohol was given to hamsters (al-Damouk, 1993).

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Apart from the tongue's base and the posterior part of the tongue in whole, that were found to negatively influence the survival, the middle part of the tongue was found to affect the survival in a positive manner. This has been confirmed empirically, but it is not yet confirmed clinically.

The necessity of the lesion's site, when the classification and staging is performed, has been pointed out by many researchers (Zhang et al, 2001; Varela-Centelles et al, 2002; Langdon et al, 1977-78; Rapidis et al, 1977). This was confirmed and by this research. Site was found "strongly" correlated to the TNM system and was also statistically significant according to the logrank tests.

When looking at the staging results of the TNM and STNMP, which includes site, it becomes obvious that the two systems, stage much differently the 123 patients of the research. The following Table 6.1 shows that STNMP has placed 46 patients (37,4%) in Stage 1. Out of those 46 patients, 16 (34,8%) were placed in Stage 1 of TNM, 27 (58,7%) in Stage 2 and 3 (6,5%) in Stage 3. A similar situation is presented for Stage 2 of the STNMP. There are 40 patients (32,5%) in Stage 2 of STNMP, and of those 20 (50%) are placed in Stage 2 of the TNM, 18 (45%) in Stage 3, and 2 (5%) in Stage 4. The 22 patients (17,9%) of Stage 3 of STNMP are separated into Stage 3 (10 patients, 45,4%), and Stage 4 (12 patients, 54,6%) of the TNM. The two systems seem to have similar behaviour as far as Stage 4 is concerned, since there are 15 patients (12,2%) in Stage 4 of STNMP, and 14 (93,3%) of them are in Stage 4 of the TNM as well, while just one patient (6,7%) is in Stage 3 of the TNM.

In general, TNM tends to categorize some patients in higher stages than STNMP does.

	STNMP				
TNM	Stage 1	Stage 2	Stage 3	Stage 4	Total
Stage 1	16	0	0	0	16
Stage 2	27	20	0	0	47
Stage 3	3	18	10	1	32
Stage 4	0	2	12	14	28
Total	46	40	22	15	123

Table 6.1: Categorization of the patients according to the two staging systems, TNM and STNMP

In the TNM system, the patients categorized in the T_4 category of the lesion's size, are all put in Stage 4, while in the STNMP system, T_4 is correlated to Stage 4 (the value of test being 0,0001). From the Kaplan-Meier method and the logrank tests it has been made apparent that these patients are the ones who died first. The two stages and the T4 category, are all correlated to the posterior part of the tongue, and especially to the tongue's base (the value of tests being 0,0001). So, it can be concluded that the patients in Stage 4 of the systems, had lesions with maximum diameter larger than 6 cm, situated at the posterior part of the tongue, and most probably at the tongue's base. The creation of such big lesions at this part of the tongue was due to the delay of the symptoms. Since the tumors appeared at spaces that are not easily accessible and apparent to the patients, the last had not become aware of the tumors, until symptoms became too strong.

As it has already been mentioned earlier, the histological characteristics of the intra-oral carcinoma were found by many, to play a significance role to the survival of the patients (Esteban et al, 1998). This research has found only the "condition of the surgical margins" to be statistically significant.

In the present research, 33 patients were found to have recurrence, being the 26,8% of the whole. Out of these 33, 21 were first categorized as N_0, meaning they had clinically, negative lymph nodes, and 6 had lesions at the anterior part of the tongue. But the thing found to have caused the recurrence, was the lesion's size coded as t2, that is when the lesions' maximum diameter was between 2 cm and 4 cm. The significance value of the likelihood-ratio test was 0,009.

The results presented here were the most important ones drawn from the research. It should be noted that the number of patients who took part in this research, 123, might have been proved to be insufficient for the methods which were used, especially for the Cox regression model. This is the reason all results should be considered with caution.

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Appendix

The following protocol was prepared and distributed to patients treated in St. Savvas Hospital with oral squamous cell carcinomas, by Dr. Rapidis A.D. of the Department of Maxillofacial Surgery, of the Greek Anticancer Institute, in the St. Savvas Hospital of Athens.

A. Protocol's form

PROTOCOL

1. Personal data

Surname: ______________________ Name: ____________________

Age during the diagnosis: ______

Sex: male ☐ female ☐

2.Initial symptom

Unspecified local disturbance ☐ Pain ☐ Bleeding ☐

Trouble in swallowing-speaking (dysphagia-dysarthria) ☐ Other ☐

3. Midinterval from the beginning of the symptoms

3 months ☐ 6 months ☐ 1 year and more ☐

4. Predispositional factors

Smoking ☐ Alcohol ☐ Professional reasons ☐

Family history ☐ Preexisted leukoplakia ☐ Preexisted lichenoid lesion ☐

Preexisted Ca of the mouth's mucosa ☐ Preexisted Ca of other region ☐

Other precancerous lesion ☐ None ☐

5. Performance status

Normal activity ☐ Symptomatic-totally ambulant ☐

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Lectual <50% of the day ☐ Lectual >50% of the day ☐ Bed-ridden ☐

6. The disease' s data

I. Site of the primary lesion

Anterior ☐ Middle ☐ Posterior ☐

(Tongue's base ☐ Posterior third of the mobile part ☐)

II. Condition of the rest of the mouth's mucosa

Coexisted leukoplakia ☐ Coexisted lichenoid lesion ☐

Other coexisted pathological situation ☐ Normal ☐

Coexisted Ca of the mouth's mucosa ☐

III. Lesion's size

T_1 ☐ T_2 ☐ T_3 ☐ T_4 ☐

IV. Lesion's form

Ulcer ☐ Tumor ☐ Patch ☐ Exophytic ☐ Mixed ☐

7. Clinical classification

I. T _ N_ M_

II. Cervical levels

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

III. M (Site of the distant metastasis) ____________________

IV. According to STNMP

S ☐ = ___ T ☐ = ___ N ☐ = ___ M ☐ = ___ P ☐ = ___

Total sum ______

8. Staging

I. According to TNM

Stage 1 ☐ Stage 2 ☐ Stage 3☐ Stage 4 ☐

II. According to STNMP

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Stage 1 ☐ Stage 2 ☐ Stage 3 ☐ Stage 4 ☐

9. Factor for the diagnosis's confirmation

☐ Physical examination, Standard x-ray, Introspection

☐ CT, U/S, P/I SCAN, MRI, FNAC

☐ Histological examination from investigating operation

☐ Histological examination from final operation

10. Decision of the tumor board ______________________________

11. The treatment's data

I. Treatment's aim

Cure ☐ Long termed control of the disease ☐

Relief ☐ Rescue ☐

II. Kind of treatment

Surgical ☐ Radiotherapy ☐ Chemotherapy ☐

Presurgical Chemo-Radiotherapy ☐ Presurgical Radiotherapy ☐

Post surgical Radiotherapy ☐ Radiotherapy- Chemotherapy ☐

Post surgical Chemotherapy ☐

III. Type of surgery

Local excision ☐

Complex operation: a) radical lymph excision ☐

b) modified lymph excision ☐

c) eclectic lymph excision ☐

d) two way lymph excision ☐

12. Histopathological characteristics of the disease

I. Surgical specimen' s data

Size of surgical specimen in cm ___

Size of cancerous lesion in cm ___

Size of throat's surgical specimen in cm ___

II. Inflammatory reaction

Light ☐ Medium ☐ Intense ☐

III. Immunological excitation

Light ☐ Medium ☐ Intense ☐

IV. Condition of the surgical margins

Clear ☐ Infiltrated ☐ Close to resection ☐ Unknown ☐

V. Degree of the histological infiltration of the disease

Perineural infiltration ☐

Intravasal deviation ☐

Infiltration of the surrounding muscles ☐

Infiltration of the submandibular salivary gland ☐

VI. Distribution of the lymph nodes

A) Number of the estimated lymph nodes ___

B) Number of the infiltrated lymph nodes ___

C) Infiltration of lymph nodes by level: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

D) Capsula's disintegration of the lymph nodes: yes ☐ no ☐ unknown ☐

VII. Histological type of the squamous Ca

Higher ☐ Middle ☐ Low ☐

Verrucose ☐ Indifferent ☐

13. Follow up of the patients

I. Time period of observation

>5 years ☐ 3 years ☐ 1 year ☐ < 6 months ☐

II. Condition of the disease in its higher interval

Alive, clear of the disease locally and negative of distant metastases ☐

Alive, revealing local recurrence without distant metastases ☐

Alive, revealing local recurrence and distant metastases ☐

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Alive, revealing a second primary focus ☐

Alive, with field cancerization ☐

Dead because of the disease ☐

Dead by other cause, being free of the disease ☐

Dead by other cause, and revealed local recurrence or distant metastases ☐

Dead because of the disease with field cancerization ☐

14. Recidivation of the disease

I. Free of the disease time interval between the surgery and the local recidivation of the disease in months ___

II. Free of the disease time interval between the surgery and appearance of throat's disease in months ___

III. Free of the disease time interval between conservative treatment and local recidivation or recidivation of the lymph nodes in months ___

IV. Treatment of the local recidivation and the throat's disease

Surgical ☐ Radiotherapy ☐ Chemotherapy ☐

Surgical-Radiotherapy ☐ Surgical- Chemotherapy☐

Surgical-Radiotherapy- Chemotherapy ☐ Radiotherapy- Chemotherapy ☐

None ☐

15. Survival (in months)

Duration of survival from the surgery ___

Duration of survival from the radiotherapy ___

Duration of survival from the chemotherapy ___

Duration of survival from the local recidivation ___

Duration of survival from the recidivation of the lymph nodes ___

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B. Medical terminology of the protocol's variables

All the proceeding terms were taken from a previous research contacted by **Kritikou E. and Petros S.** in **2000**, based on the same data base, before the last follow up of the patients was performed.

2. Initial symptom

Unspecified local disturbance: Underlying disturbance reported by the patient, the nature of which can not be defined exactly.

1. Predispositional factors

Professional reasons: Exposure of the patient, because of his profession, to an environment which is characterized by the presence of known or probable carcinogenic substances.

Family history: Presence of cancer at the patient's parents, brothers or sisters, or at the parents of the patient's parents.

Leukoplakia: A white patch attached to the mucosa of the mouth.

Mucosa: The covering tissue of the oral cavity and of every inner cavity of the body.

Lichen: Lesion of the skin-mucosa of the body, with no known reason for its appearance, which appears periodically in various forms.

Other precancerous lesion: The rest of the lesions that are or are thought to be precancerous.

Preexisted Ca: Preexisted cancerous lesion that is not associated anatomically to the tongue.

1. Performance status

Symptomatic-totally ambulant: The patient suffers from known health problems that do not affect his or her activities.

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Lectual <50% of the day: The patient suffers from health problems that keep him or her in bed less than the 50% of the daytime.

Lectual >50% of the day: The patient suffers from health problems that keep him or her in bed more than the 50% of the daytime.

Bed-ridden: The patient suffers from health problems that do not allow him or her to leave bed.

1. The disease' s data

III. Lesion's size

T_1 : Lesions whose diameters are less or equal to2 cm

T_2 : Lesions whose diameters are between 2 cm and 4 cm

T_3 : Lesions whose diameters are between 4 cm and 6 cm

T_2 : Lesions whose diameters are equal or more than 6 cm

IV. Lesion's form

Ulcer : The destruction of the mucosa's structure and the progressive creation of painful tissue remains.

Tumor: Lesion in the form of a pump, separated from the rest of the mucosa.

Patch: Lesion in the form of a patch.

Exophytic: Lesion that stands up with up normal, wrinkled surface, and in various shapes, looking like cauliflower lesion.

7. Clinical classification

I. TNM: The TNM classification and staging system as it was proposed in 1997 by the U.I.C.C. and the A.J.C.C.

<u>Classification:</u>

<u>T</u>

T_x: There is no evidence for estimation

T_0: There is no primary tumor

T_{IS}: Ca in situ

T_1: Maximum diameter $\leq$2cm

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T_2: Maximum diameter ≤ 4 cm

T_3: Maximum diameter > 4 cm

T_4: Tumor > 4cm at large infiltration heading for occupation of the igmorium, the tongue's base, the throat's skin.

<u>N</u>

N_X: There is no evidence for estimation

N_0: Clinically, negative lymph nodes

N_1: Homolateral, single lymph node with maximum diameter ≤ 3 cm

N_{2a}: : Homolateral, single lymph node with maximum diameter >3 cm and < 6cm

N_{2b}: : Homolateral multiple lymph nodes with none's maximum diameter being > 6 cm

N_{3a} : Homolateral, single or multiple lymph nodes, of which one with maximum diameter > 6 cm

N_{3b}: Bilateral positive lymph nodes. Each side is estimated separately.

N_{3c}: Only contra lateral lymph node(s)

<u>M</u>

M_0: There is no evidence of distant metastases

M_1: Distant metastases are present

<u>Staging:</u>

<u>Stage 1:</u> $T_1N_0M_0$

<u>Stage 2:</u> $T_2N_0M_0$

<u>Stage 3:</u> $T_3N_0M_0$

T_1 or T_2 or $T_3N_1M_0$

<u>Stage 4:</u> T_4N_0 or N_3M_0

Every T, N_2 or N_3M_0

Every T, every N, M_0

II. Cervical levels: The lymph nodes of the region of the throat, where the cancer of the tongue chooses to show up in the form of metastasis, are classified anatomically into 5 levels. The levels are symbolized using the latin numbers I, II, III, IV and V.

IV. According to STNMP: The STNMP classification and staging system as it was proposed by Rapidis et al in 1977.

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Classification:

S

S_1: Lip-Skin

S_2: Lip-Mucous Membrane

S_3: Tongue

S_4: Cheek

S_5: Palate

S_6: Floor of the mouth

S_7: Alveolar Process

S_8: Antrum

S_9: Central Ca of Bone

T

T_1: Tumor less than 2 cm in diameter

T_2: Tumor between 2 cm and 4 cm in diameter

T_3: Tumor between 4 cm and 6 cm in diameter and/or extending beyond the primary region, and/or through adjacent periosteum

T_4: Any tumor greater than 6 cm in diameter and/or extending to involve adjacent structures

N

N_0: No palpable nodes

N_1: Equivocal node enlargement

N_2: Clinically palpable homolateral regional node(s) not fixed

N_3: As N2, but fixed

N_4: Clinically palpable contra lateral or bilateral node(s) not fixed

N_5: As N4, but fixed

M

M_0: No distant metastases

M_1: Clinical evidence of distant metastases without definite histological and/or radiographic confirmation

M_2: Proven evidence of metastases beyond the regional nodes

P

P_0: Hyperkeratotic lesion showing atypia

P_1: Carcinoma in situ

P_2: Basal cell carcinoma

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P_{3a}: Verrucous carcinoma

P_{3b}: Well differentiated squamous cell carcinoma

P_{3c}: Moderately differentiated squamous cell carcinoma

P_{3d}: Poorly differentiated squamous cell carcinoma

Value of each category of the variables:

S	T	N	M	P
$S_1=4$	$T_1=0$	$N_0=0$	$M_0=0$	$P_0=0$
$S_2=6$	$T_2=10$	$N_1=10$	$M_1=30$	$P_1=5$
$S_3=8$	$T_3=20$	$N_2=20$	$M_2=40$	$P_2=5$
$S_4=10$	$T_4=35$	$N_3=30$		$P_{3a}=5$
$S_5=12$		$N_4=40$		$P_{3b}=10$
$S_6=14$		$N_5=50$		$P_{3c}=15$
$S_7=16$				$P_{3d}=20$
$S_8=18$				

Staging:

Stage 1: 0-30

Stage 2: 31-50

Stage 3: 51-70

Stage 4: >70

9. Factor for the diagnosis's confirmation

Introspection: The examination of inner organs with the use of micro cameras that allow the inspection of regions that are not directly visible.

Histological examination: Study of a tissue part with the use of a microscope at the level of the cells.

Investigating operation: Examination of a lesion's part for the investigation of its nature.

Final operation: Examination of the lesion's hole after the its complete removal.

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10. Decision of the tumor board

Council for tumors: A medical council, formed by doctors specialized in different, relevant subjects, with the purpose to achieve the best possible approach of the patient and to determine, the best for the patient's survival, treatment schedule.

11. The treatment's data

I. Treatment's aim

Cure: Usually, for cancer cure means a five-year survival.

Long termed control of the disease: Survival of the patient for a relatively long time interval, that is longer than six months.

Relief: A curative approach that aims the patient's relief from a torturing symptom (trouble in breathing, trouble in swallowing etc).

Rescue: Instant curative approach that aims the rescue of a patient close to death.

III. Type of surgery

Local ectomy: The abstraction of the cancerous lesion, along with a part of the its surrounding, healthy tissues.

Complex operation: The abstraction of the lesion, along with a part of the throat's tissue, which contains and other anatomical parts, such as salivary glands and muscles, and mainly the lymph nodes.

Radical lymph ectomy: The abstraction of all the throat's levels that belong to the throat's corresponding part to the lesion, along with other anatomical parts.

Modified lymph ectomy: Like the radical one, but with keeping some of the anatomical parts.

Eclectic lymph ectomy: The abstraction of some lymph node levels (not all of them).

Two way lymph ectomy: An operation in both parts of the throat.

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12. Histopathological characteristics of the disease

I. Surgical specimen' s data

Surgical specimen: Part of the tissue facts that is abstracted from during the surgical operation from the rest of the body, and sent for histological examination.

Surgical specimen: The hole part of tissue sent, coming from both the tongue and the throat's region.

Size of cancerous lesion: Size of the lesion found on the tongue.

Size of throat's surgical specimen: Size of the surgical specimen of the throat, that contains a variety of tissues and anatomical parts.

II. Inflammatory reaction: The reaction of a group of cells of the defensive system, which react to the attempt of entry in the body, of any foreign subject.

III. Immunological excitation: This a higher reaction of the body's defenses than the inflammatory reaction, and it contains four types of reaction.

IV. Condition of the surgical margins

The surgical abstraction of the cancerous lesion has to be done in a safe range of healthy tissues (about 1 cm around the lesion). Even though, this can be performed clinically, under the microscope it is not always possible.

Clear limits: The surgical specimen's limits, during the examination with the microscope, do not contain cancerous cells in a safe distance (about 1 cm).

Infiltrated limits: The surgical specimen's limits contain cancerous cells (in fact, the ectomy was made inside the cancerous lesion).

Close to resection: The surgical specimen's limits do not contain cancerous cells, but are very close to the cut's point (less than 1 cm).

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Unknown: The limits' situation can not be determined using a microscope or it is not mentioned in the histological report.

VI. Distribution of the lymph nodes

Number of the estimated lymph nodes: The total number of the lymph nodes that are in throat's surgical specimens under the microscope.

Number of the infiltrated lymph nodes: The total number of the lymph nodes that are in throat's surgical specimens under the microscope and are found to be infiltrated.

Infiltration of lymph nodes by level: The infiltrated lymph nodes, at which level of the throat are put.

Capsula's disintegration of the lymph nodes: If the cancerous cells have or have not invaded or passed through the "membrane" that surrounds the lymph nodes. If they have, then it most possible that cancer has been spread to the surrounding tissues.

VII. Histological type of the squamous Ca

Ca: Cancer

Differentiation: Stages from which all cells have to pass so as to form the various tissues of the human body.

Higher differentiation: The cancerous cells look a lot like the normal squamous cells.

Middle differentiation: The cancerous cells look less like the squamous ones.

Low differentiation: The cancerous cells look a little like the squamous cells.

Verrucose: Special histological type of the squamous cancer, with special architectural structure of the cells, and sometimes with macroscopic-clinical image.

Indifferent: The cancerous cells do not look like the squamous ones at all.

13. Follow up of the patients

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II. Condition of the disease in its higher interval

Local recurrence: Appearance of cancerous lesion around the ectomy's limits of the primary lesion of the tongue.

Recurrence of the lymph nodes: Appearance of cancerous invasion into the corresponding lymph nodes.

Distant metastases: Appearance of cancerous invasion, from a squamous cell, beyond the tongue or the lymph nodes.

Second primary focus: Second cancerous lesion, of the same histological image that appears simultaneously or after a while, in another position of the oral mucosa or the tongue. Between the primary and the new position there is a "bridge" of healthy tissues.

Field cancerization: Multiple primary focuses of squamous cancer in various positions of the oral mucosa, that reveal problems in the genes of the patient.

C. The protocol's coding used in the data base

1. Personal data

Age during the diagnosis: age

Sex: sex

male=1 , female=0

2.Initial symptom

Unspecified local disturbance= initial 1

Pain= initial 2

Bleeding= initial 3

Trouble in swallowing-speaking (dysphagia-dysarthria)= initial 4

Other= initial 5

3. Midinterval from the beginning of the symptoms= interval

3 months= 1

6 months= 2

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1 year and more= 3

4. Predispositional factors

Smoking= factor 1

Alcohol= factor 2

Professional reasons= factor 3

Family history= factor 4

Preexisted leukoplakia= factor 5

Preexisted lichenoid lesion= factor 6

Preexisted Ca of the mouth's mucosa= factor 7

Preexisted Ca of other region= factor 8

Other precancerous alleosis= factor 9

None= factor 10

5. Performance status= perfom

Normal activity= 1

Symptomatic-totally ambulant=2

Lectual <50% of the day= 3

Lectual >50% of the day= 4

Bed-ridden= 5

6. The disease' s data

I. Site of the primary lesion

Anterior= thesi 1

Middle= thesi 2

Posterior= thesi 34

Posterior third of the mobile part= thesi 3

Tongue's base thesi 4

II. Condition of the rest of the mouth's mucosa

Coexisted leukoplakia= katasta 1

Coexisted lichenoid lesion= katasta 2

Other coexisted pathological situation= katasta 3

Normal= katasta 4

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Coexisted Ca of the mouth's mucosa= katasta 4

III. Lesion's size= megethos

T_1= 1

T_2= 2

T_3= 3

T_4= 4

IV. Lesion's form= morfi

Ulcer= 1

Tumor= 2

Patch= 3

Exophytic= 4

Mixed= 5

7. Clinical classification

T_1= t1	N_0= n0	M_0= m0
T_2= t2	N_1= n1	M_1= m1
T_3= t3	N_2= n2	
T_4= t4	N_3= n3	

II. Cervical levels

1= epipedo 1

2= epipedo 2

3= epipedo 3

4= epipedo 4

5= epipedo 5

III. M (Site of the distant metastasis)= m1thesi

IV. According to STNMP

S= s

T= t

N= n

M= m

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P= p

Total sum= sumstnmp

8. Staging

I. According to TNM= tnm

Stage 1= 1

Stage 2= 2

Stage 3= 3

Stage 4= 4

II. According to STNMP= stnmp

Stage 1= 1

Stage 2= 2

Stage 3= 3

Stage 4= 4

9. Factor for the diagnosis's confirmation= parbeb

Physical examination, Standard x-ray, Introspection= 1

CT, U/S, P/I SCAN, MRI, FNAC= 2

Histological examination from investigating operation= 3

Histological examination from final operation= 4

10. Decision of the tumor board =apofasi

11. The treatment's data

I. Treatment's aim= skopth

Cure= 1

Long termed control of the disease= 2

Relief= 3

Rescue= 4

II. Kind of treatment

Surgical= ther 1

Radiotherapy= ther 2

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Chemotherapy= ther 3

Presurgical Chemo-Radiotherapy= ther 4

Presurgical Radiotherapy= ther 5

Post surgical Radiotherapy= ther 6

Radiotherapy- Chemotherapy= ther 7

Post surgical Chemotherapy= ther 8

III. Type of surgery

Local excision = type 1

Complex operation: a) radical lymph excision= type 2
b) modified lymph excision= type 3
c) eclectic lymph excision= type 4
d) two way lymph excision= type 5

12. Histopathological characteristics of the disease

I. Surgical specimen' s data

Size of surgical specimen in cm= stoix 1

Size of cancerous lesion in cm= stoix 2

Size of throat's surgical specimen in cm= stoix 3

II. Inflammatory reaction= flemgon

Light= 1

Medium= 2

Intense= 3

III. Immunological excitation= anosol

Light= 1

Medium= 2

Intense= 3

IV. Condition of the ectomy's limits= katastas

Clear= 1

Infiltrated= 2

Near to ectomy= 3

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Unknown= 4

V. Degree of the histological infiltration of the disease

Perineural infiltration= bathmos 1

Intravasal deviation= bathmos 2

Infiltration of the surrounding muscles= bathmos 3

Infiltration of the submandibular salivatory gland= bathmos 4

VI. Deviation of the lymph nodes

E) Number of the estimated lymph nodes= lempha 1

F) Number of the infiltrated lymph nodes= lempha 2

G) Infiltration of lymph nodes by level:

1= dihth 1

2= dihth 2

3= dihth 3

4= dihth 4

5= dihth 5

In another level= dihth 6

H) Capsula's disintegration of the lymph nodes:

yes= 1

no= 2

unknown= 3

VII. Histological type of the squamous Ca= typeca

Higher= 1

Middle= 2

Low= 3

Verrucose= 4

Indifferent= 5

13. Follow up of the patients

I. Time period of observation= periodos

>5 years= 4

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3 years= 3

1 year= 2

< 6 months= 1

II. Condition of the disease in its higher interval= katastfu

Alive, clear of the disease locally and negative of distant metastases= 1

Alive, revealing local recurrence without distant metastases= 2

Alive, revealing local recurrence and distant metastases= 3

Alive, revealing a second primary focus= 4

Alive, with field cancerization= 5

Dead because of the disease= 6

Dead by other cause, being free of the disease= 7

Dead by other cause, and revealed local recurrence or distant metastases= 8

Dead because of the disease with field cancerization= 9

14. Recurrence of the disease

I. Free of the disease time interval between the surgery and the local recurrence of the disease in months= upotrop 1

II. Free of the disease time interval between the surgery and appearance of throat's disease in months= upotrop 2

III. Free of the disease time interval between conservative treatment and local recurrence or recurrence of the lymph nodes in months= upotrop 3

IV. Treatment of the local recurrence and the throat's disease= upotrop 4

Surgical= 1

Radiotherapy= 2

Chemotherapy= 3

Surgical-Radiotherapy= 4

Surgical- Chemotherapy= 5

Surgical-Radiotherapy- Chemotherapy= 6

Radiotherapy- Chemotherapy= 7

None= 8

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15. Survival (in months)

Duration of survival from the surgery= epib104

Duration of survival from the radiotherapy= epib204

Duration of survival from the chemotherapy= epib304

Duration of survival from the local recurrence= epib404

Duration of survival from the

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