REVIEW ARTICLE

Survival Analysis in Oral Cancer Patients: A Reliable Statistical Analysis Tool

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ABSTRACT

Clinical trials or follow-up studies sometimes necessitate the long-term monitoring of patients, with an emphasis on crucial events such as mortality, recurrence, severe medication responses, or the advent of new illnesses. These studies cover a range of follow-up times, from a few weeks to several years. Analyzing such data necessitates the use of specialized statistical approaches such as time-to-event analysis and survival analysis. This method is extremely useful in clinical research, providing crucial insights into therapies. The three basic purposes of survival analysis are to determine and analyze survival/hazard functions using survival data, compare these functions, and evaluate how explanatory factors relate to survival time. This methodology is useful for investigating event timing in a variety of situations, notably in clinical studies where event-based data is common. This paper is intended to serve as a primer for researchers, exposing them to the wide range of methods accessible in the discipline of survival analysis. Researchers have the ability to traverse the complex terrain of clinical trial data distinguished by variable follow-up durations, by diving into this approach. The key to survival analysis is its capacity to provide subtle insights into the temporal elements of patient reactions, providing a full view of intervention success. We have taken the cases of oral cancer survival analysis studies and put a light on methods and association used there.

Keywords: Oral cancer, Survival analysis, Survival Rate, Cox Regression, Hazard Ratio

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INTRODUCTION

Oral cancer is a persistent global public health hazard that begins with the vermillion of the lips and progresses to the circumvallated papillae and the junction of the soft and hard palate. It is the eighth most common cancer-related cause of death. Although several advances in therapy, this terrible disease has a miserable survival rate. Every year, over 175000 individuals die from oral cancer, and over 370000 people have been diagnosed with the disorder.[1] WHO recognized worldwide standard "International Classification of Diseases and Related Health Problems (ICD-10)" classifies malignant neoplasms of the head and neck area into the codes C00 to C14.[1,2], divides malignant neoplasms of the head and neck region into the codes C00 to C14. Every code denotes to carcinoma of specific anatomical regions in oral cavity.[2,3]. Nevertheless, the base of the tongue (C01), that is the embryologically posterior one-third of oropharyngeal malignancies, develops from the third branchial arch.[2,4]C01 and C10 OPSCCs are caused by oncogenic forms of the human papillomavirus (HPV).[2,3,5] Five-year survival rates range from 30% to 80%, with significant ethnic disparities.[6] Survival is influenced by genetic predisposition, lifestyle, food habits, and a variety of clinical conditions. Late diagnosis results in lower outcomes, but early discovery improves patient survival dramatically. Smoking tobacco contains tar and nicotine, which impair the innate immune system and make people more susceptible to diseases.[7,8] Alcohol intake is one of the risk factors for oral cancer. Smokeless tobacco involving betel quid chewing and a low-protein diet. Veggies and fruits, inadequate nutrition, marijuana use, poor oral hygiene, and some medications Mutations in the genome.[2,4] TNM and other clinic pathologic prognostic variables for OPSCC stage, overall health status of the patient, co-morbidities, main tumor macrophage content and lymph node metastases have been extensively researched.[9-12] The master cell cycle regulators p53, pRB, and p16 are tumour suppressor genes that play critical roles in cell cycle control and cancer.[13] Age as a prognostic factor has recently been presented. The tumor stage at the time of diagnosis has a significant impact on prognosis. Early detection efforts, as well as understanding the significance of genetic and socio-cultural variables, are crucial in improving the outlook for oral cancer survivors.

Basic Background of survival analysis

Survival analysis is a crucial statistical tool in the field of medicine, particularly for evaluating the prognosis and outcomes of patients with life-threatening disorders.[14] In this review, we look at the uses and relevance of survival analysis in the context of oral cancer patients, examining the insights it gives in understanding disease development, risk factors, therapy efficacy, and total patient survival. Survival analysis is critical in clarifying the complicated dynamics of oral cancer patients' survival, providing doctors and researchers with vital tools for assessing prognosis, identifying risk factors, and evaluating therapy success. Survival analysis will continue to be an important component in improving patient outcomes and determining the future of oral cancer therapy as research advances and new data analytics tools develop.[15] By exploiting these insights, healthcare practitioners will be one step closer to lowering the burden of oral cancer and enhancing the quality of life for patients impacted by this deadly illness.

Survival analysis, additionally referred to as generalized event history analysis, is an applied statistics branch that focuses on analyzing data linked to the timing of events in individual life histories, whether for people or other subjects.[14] It was originally linked to examining the failure of medical therapies for cancer patients and benefitted from considerable resources committed in cancer research.[15] This area of medical statistics posed additional obstacles, particularly when dealing with censored data, in which occurrences were not completely witnessed.

Ad hoc solutions were first utilized to handle these difficulties throughout time, but finally, a unifying concept developed. It included interpreting such data as the result of a dynamic process in time, where each successive day of observation adds new information. This resulted in the creation of tractable statistical models based on continuous modeling of occurrences through time while accounting for previous events. This dynamic temporal structure also gave rise to new statistical notions such as partial probability.

SURVIVAL FUNCTION

The mechanism for survival is a term used in statistics, probability theory, and survival analysis. It is commonly denoted as S (t) or "1 - F (t)". It denotes the likelihood that a given random variable (usually reflecting the duration till an event happens) is larger than a particular value t.

The survival function, which is extensively used in medical studies, engineering, and other areas, gives an understanding of the distribution of time until an event of interest (such as death, failure, or the occurrence of a given event) occurs. It can assist in answering queries such as, "How likely is it that an individual will survive beyond a certain time point?"

S (t) =P (T>t) = the likelihood of living till time t
D (t) =P (T≤t)= Death likelihood at time t (=F(t))
T is a random variable that represents the time of occurrence; t is an integer.
If we recognize it for all i (no censoring), we may estimate S (t) and D (t) using
S(t)E=m(t)/n= percentage of people surviving at time t.
D(t)E=d(t)/n= fraction of people who have died since time t.

Kaplan-Meier Curves

The Kaplan-Meier estimator is the most effective survival function estimate when a data set comprises partial observations.

$t_1<t_2<\cdots<t_n$ are the completed timings in the order
n_i=The total number of individuals identified to be at risk at time (day) t_i, immediately before [ti,ti+1]
d_i=number of individuals who died at period t_i, in [ti,ti+1]
For the individuals alive at the starting of the t_i^{th} time, the likelihood of surviving that period is

$$Pi=\frac{ni-di}{ni}$$

Considering that a patient survived time 1, the likelihood that they would survive time 2 is

$$P_2=\frac{n2-d2}{n2}$$

The probability that (at the outset) a patient survives to time 2 is:

$$P(T>t2) = P(T>t2|T>t1)P(T>t1)$$
$$= \frac{n1-d1}{n1}\frac{n2-d2}{n2}$$

The likelihood of survival in the first two days is:

$$\hat{S}(t)KM = \prod_{ti<T}\frac{ni-di}{ni} = \prod_{ti<T} Pi$$

$$D(t)KM = 1-\hat{S}(t)KM$$

if there are no deaths at time ti, then (ni−di)/ni=1.
If there exist no censoring time ti, Thenn_i-d_i=n_{i-1}
The Kaplan Mayer curve can be adjusted into empirical survival curve.

$$\hat{S}(t)KM = \prod_{ti<T}\frac{ni-di}{ni}$$
$$= \frac{n1-d1}{n1}\frac{n2-d2}{n2}\frac{n3-d3}{n3}\ldots\frac{nk-dk}{nk}$$
$$=\frac{m(t)}{n}$$

Now we shall consider a simple example to consider how Kaplan Mayer curve works. let's consider ti as ordered completed times.
n_i=number of individuals identified to be at risk at time (day) t_i, immediately prior to [ti,ti+1]
d_i=number of individuals who died at time t_i, in [ti,ti+1]

ti	ni	di	Ni-di	$(\boldsymbol{ni-di})/\boldsymbol{ni}$
10	5	0	5	1
15	5	2	3	0.6
20	4	1	3	0.75
25	3	1	2	0.666
30	2	0	2	1
35	1	1	0	0

Time duration	$\hat{S}(t)KM$
[0, 10)	1
[10, 15)	1
[15, 20)	1*0.6=0.6
[20, 25)	0.6*0.75 =1.45
[25, 30)	0.45*0.66=0.297
[30, 35]	0.297*1=0.297

Hazard Function

Hazard function is a key term in survival analysis, a field of statistics that deals with analyzing the time before an event of interest happens. This occurrence might be anything from a patient's death to the failure of a mechanical component. The hazard function, abbreviated as h (t), gives a sense of how the immediate risk of encountering the event evolves over time.

$$h(t) = \lim_{\Delta t\to 0}\frac{Probability(patientdieattimet+\Delta t|aliveatt)}{\Delta t}$$
$$= \lim_{\Delta t\to 0}\frac{P(T<t+\Delta t|T\geq t)}{\Delta t}$$
$$= \lim_{\Delta t\to 0}\frac{P(t\leq T<t+\Delta t|T\geq t)}{\Delta t}$$
$$= \lim_{\Delta t\to 0}\frac{P(t\leq T<t+\Delta t)}{P(T\geq t)\Delta t}$$
$$= \lim_{\Delta t\to 0}\frac{S(t)-S(t+\Delta t)}{S(t)\Delta t}$$
$$= \lim_{\Delta t\to 0}\frac{S(t+\Delta t)-S(t)}{\Delta t}\frac{1}{s(t)}$$
$$= -S'(t)\frac{1}{s(t)}$$
$$= -\frac{d}{dt}\ln(S(t)$$

$S(t)= \exp\{-\int_0^t h(x)\,dx\}$. if we observe S(t) is 0,No risk of death at time t the curve will be flat.

Discussion

Survival analysis is critical in oral cancer research and treatment. It assists in the evaluation of treatment and adds to personalized patient care by facilitating the knowledge of illness progression. Clinicians and researchers may make educated decisions to enhance the quality of life and outcomes for oral cancer patients by utilizing survival analysis methodologies. This review described the basics of survival analysis and the mathematical algorithm behind it. We described the methods of survival functions, Hazard ratio, and Kaplan-Meier curve by taking examples.

Age remains a determinant in the occurrence, progression, and prognosis of many tumors.[16 19 21 23 24 28 30 42] Head and neck carcinomais typically regarded to be more prevalent among the elderly, associated with cigarettes and alcohol, and mostly occurs in males.2[4 32 37] Researchers noticed that black patients had the lowest rates of survival, which were probably explained by their poor socioeconomic status, which made it challenging for them to get treatment.[38] The potential advantage of leukoplakia screening in lowering OCC mortality by early identification has been revealed by research findings.[17] Statistical analysis revealed that T and N stage and Distant metastasis had already been discovered to be relative survival prognosis factors.[24 27 34]

Table 1: Related study of survival analysis in OSCC patients

Author	Study Design	Country	Follow Up Duration (Years)	Sample Size	Regression Model	Survival curve, comparison methods	Measures of Association/ Effect
Yu-Zhu [16]	Retrospective Study	China	3years	9,474	CPHR	KMM, LRT	HR
Elizabeth L. Yanik [17]	Case-cohort study	USA	7years	479,193	CPHR	NA	HR, OR
Oliveira LR, Ribeiro-Silva A[18]	NA	Brazil	12years	500	CPHR	KMM	OR
Saman Warnakulasuriya [19]	NA	England	7years	5,319	CPHR	NA	HR
Yong-kie Wong[20]	Retrospective study	Taiwan	5years	1010	CPHR	KMM	HR, RR
Kanika Sharma[21]	Retrospective Study	INDIA	8 years	202	CPHR	KMM LPLE	HR
Juliana da Silva [22]Moro	Cross-sectional Study	Brazil	10years	254	CPHR	KMM, LRT	HR
GijsGeleijnse[23]	NA	Netherland and Taiwan	12years	41,633	CPHR	Breslow's Method	HR
Douglas R. Farquhar[24]	Retrospective cohort Study	United States	5years	397	CPHR	SLRT	HR
Elizabeth Bradford Bell[25]	NA	Miami	5years	300	CPHR	KMM	HR
Pratima Agrawal [26]	Retrospective Cohort Study	USA	41years	20271	CPHR	KMM	Sub HR
A. Chandu[27]	Retrospective Study	Australia	11years	116	CPHR	KMM	RR
Balakrishna[28]	NA	INDIA	2years	604	CPHR	HM, LRT	RR
Katarina Zeljic[29]	case-control study	Serbia	5years	232	CPHR	KMM	HR
Eduardo Mendez[30]	NA	USA	4years	119	CPHR	KMM	HR
Shayan Cheraghlou[31]	Retrospective Study	USA	41years	16,030	CPHR	KMM	HR
Yong-Seok Choi[32]	Retrospective Study	Korea	20years	407	CPHR	KMM, LRT	HR
Ling-Yu Kung[33]	cohort study	Taiwan	13years	12,124	CPHR	KMM, LRT	HR
Yuki Sakamoto[34]	Retrospective Study	Japan	17years	388	CPHR	KMM, LRT	HR
Daniella Karassawa Zanoni[35]	Retrospective Study	USA	30years	2,082	CPHR	KMM, LRT	RR
VeralaCentelles[36]	Descriptive Study	Spain	8years	94	CPHR	KMM, LRT	OR
Kirstine Kim Schmidt Karnov[37]	cohort study	Denmark	34years	8,299	CPHR	KMM, LRT	HR

CPHR - Cox's Proportional Hazards Regression; KMM - Kaplan-Meier Method; SLRT - Stratified Log-Rank tests; HM- Hakulinen Method; LRT- Log-Rank tests; KMM PLE - Kaplan-Meier Method - product limit estimator; HR – Hazard Ratio; OR – Odds Ratio; RR – Relative Risk

Table 2: Prognostic and genetic risk factors associated with OSSC

Prognostic Factor	Survival Rate	Reference
Old age (HR=1.712), Black Color (HR=1.466), 1st malignant primary indicator (HR=0.636)	NA	16
After diagnosis of Leukoplakia in months (HR ≥ 3 months=24.1, with prior leukoplakia diagnosed at regional/distant stage (OR=0.36, HR=0.76)	NA	17
r p53 immunoexpression (OR=2.91), age (OR=3.94), and anatomic localization (OR=1.21)	5yrs-28.6%	18
Age(45+HR=1), Stage (Metastasis-2.57), Treatment-(Investigative surgery only-1.61)	5 yrs-43%	19
Sociodemographic factors include religious belief-Without Religious Belief (RR-2.057), Marital status-widow/widower or Divorce-(RR-1.528)	5 yrs-63.24%	20
Age->50(HR-1.652), Grade-Poorly Differentiated-(HR-4.128) pN3 stage (HR-2.417), pT4 stage (6.815), and the presence of extracapsular extension (HR-5.773)	5 Yrs-66.6%	21
Anatomical location (oropharynx p=0.03)	5yrs-42%	22
Age (≥70 years-HR-2.16), Stage (Advanced stage-HR-2.18), Location-(Hard palate HR-1.65), Grade (Poorly or undifferentiated-2.63) Treatment (Surgery+Radio+chemo) HR-2.29	NA	23
Age (45+)- prior alcohol history (HR-1), and prior tobacco history 10+ Years (HR-1.5), T stage-(HR-13.2), N stage-(HR-2)	NA	24
Salads (HR= 0.72) or other vegetables (HR-0.68), CD44 levels (Salivary Biomarkers) (solCD44 ≥8.1 vs.<8.1 HR= 4.57)	NA	25
Insurance (Medicaid SHR=1.87), Primary cancer site (Floor of mouth SHR=1.53), Lymph Node (N3 SHR=2.74), Tumour Size (SHR=1.00)	NA	26
LocaRecurrance RR=3.1, Regional Recurrance RR=6.9, Distantmetastasis RR=5.0, Perivascular spread RR=7.2	5Yrs-83.3%	27
age65 +(RR-2.5), Clinical extension (Distant-RR-11.2), Marital Status-(widowed/separated RR-1.1, Sub-site (Retromolar Area-RR-2.2)	5yrs-39.7%	28
CYP24A1 rs2296241 gene polymorphism (HR-1.538, OR-0.281), VDR FokI (HR-0.615), Stage-(HR-2.774), Nodal Status-(HR-2.977), Tumour size-(HR-2.636), Age-(HR-1.307)	NA	29
Age (HR=3.31), Sex (HR=1.66-6.58), Stage (HR=5.43), LAMC2 gene expression	NA	30
Age>80(HR=2.207), Sex-male (HR=1.127), Site-Palate (HR=1.072), Late Stage (HR=1.899), Late stage (HR=1.899), High Grade (HR=1.335), Treatment (Surgery+Chemo HR=1.840)	NA	31
T4 stage (HR=1.088), Node Metastasis (N+, HR=2.010, TNM Stage (Advanced HR=1.363), Perineural in-vasion (P+, HR=1.888), Smoking History (yes HR=1.251)	5yrs-70.7%	32
Alcohol Abuse (AHR=10.63), Anxiety (AHR=5.978), Sleep Disorder (AHR=3.109), Subsequent Depression (HR=2.224)	NA	33
Prognosis of the patient wiith pN2c Necks (Os T Stage (HR =2.753), DSS T Stage (HR=3.883))	NA	34
Age (RR=1.857), Tobacco Use (RR=1.131), Positive Margin status (RR=1.753), Vascular Invasion (RR=1.288), Perineural Invasion (RR=1.259), pT4(RR=1.807), pN3(RR=3.116)	5yrs-64.4%	35
age of the patient, TumorSize (OR=1.06)	5Yrs-44%	36
age (HR=1.03), sex (HR=0.85),	5yrs-38%	37

yrs – years

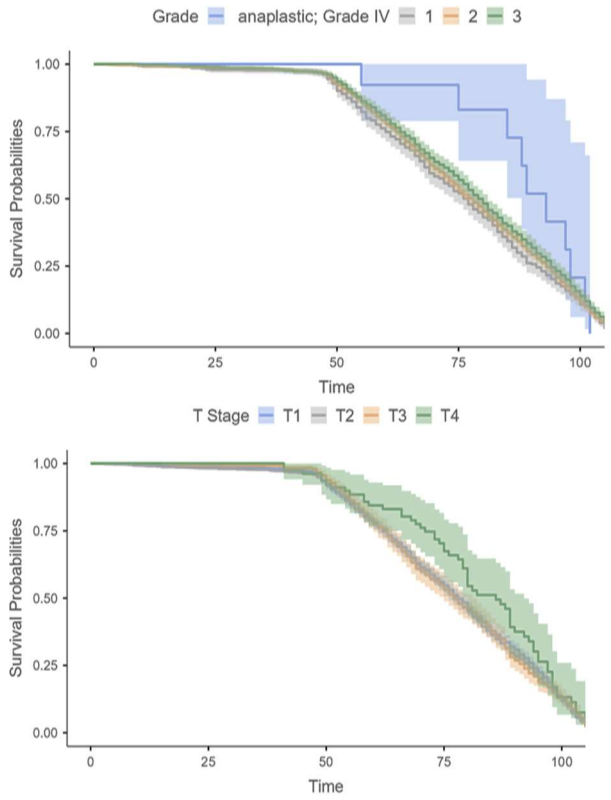

Figure 1: A graphical Representation of Kaplan – Meier curve

T4 stage, in which the tumour invades nearby structures such as the mandible, tongue, musculature, maxillary sinus, and skin, and N3 stage, in which metastasis in a lymph node >6cm in largest dimension, are risk factors. Extracapsular Spread has been described as a predictor of survival and recurrence, with an increasing relative risk of mortality with T stage. A significant marker of local recurrence and distant metastasis, extranodal expansion in metastatic lymph nodes is associated with poor prognosis of OCC.[39] CYP24A I gene polymorphism, r p53 immunoexpression and VDR FokI polymorphism is associated with poor survival rate among different populations.[18 29] Model containing LAMC2 alone was found to be the worst OSCC-specific Survival.[30] Sociodemographic factors involving marital status where single , widow/widower, or divorced/separated were found to have poor prognosis.[20] Additionally, these results demonstrated that eating green salads and vegetables was linked to decreased CD44 levels and greater survival in OSCC patients.[25] Some study also suggests that early detection and treatment of depression in oral cancer patients is essential.[33] Furthermore, individuals with oropharyngeal cancer who are HPV positive have a better prognosis than those who are HPV negative. This trait is connected to the low proportion of mutation found in these tumors, which results in better treatment responses and higher survival rates.[40] Nevertheless, an increasing number of young individuals with HNSCC have been observed worldwide. The prevalence of OSCC has been increasing in recent years, particularly among adolescents and young adults. According to earlier research, the most prevalent significant locations implicated in OSCC differ by geographic area. The mucous membrane of the oral cavity is more susceptible in Asian countries, including South Asia, Sri Lanka, and others, where 40% of oral cancers are detected in the buccal mucosa, due to the widespread practice of men and women chewing smokeless tobacco.[41]

Conclusion

Performing survival analysis is crucial in identifying and controlling oral cancer, which is a severe and sometimes deadly illness. It gives critical information about the duration remaining before an event of interest, such as mortality or recurrence, happens. This evaluation assists medical professionals and scholars in determining the prognosis of oral cancer patients, which aids in selecting therapies and patient counseling. Survival analysis allows for the recognition of risk variables and their influence on patient outcomes by accounting for censoring (cases where the event has not occurred by the conclusion of the trial) and including other covariates such as age, stage, and treatment methods. This data informs the creation of personalized treatment plans and contributes to medical research developments. Finally, survival analysis provides significant tools to healthcare providers in order to improve patient outcomes.

Abbreviation

OSSC**:** Oral squamous cell carcinoma
OR: Odds Ratio
HR: Hazard Ratio
RR: Relative Risk
OS: Overall survival
DSS: Disease Specific survival
SHR: Sub hazard ratio
AHR: Adjusted Hazard Ratio
HNSSC: Head and neck squamous cell carcinoma
HPV: Human papillomavirus

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