Calculating Clinical History (Survival) Parameters from the Retrospective Oral Cancer Cohort (ROCC)

Objective: To estimate the "ClinHist" parameters for the model (generally, time to recurrence and death). These estimates must reflect patient treatment type, stage, and other individual characteristics a model entity may potentially have.

- ClinHist_timeRecurrence
- ClinHist_timeDeadOfDisease

Description of patient population:

A retrospective cohort of 886 patients diagnosed and treated with oral cancer was identified from a linkage between the BC Cancer Agency's Oral Biopsy service and the BC Cancer Registry. Members of the cohort, once identified, had their medical charts extracted to determine dates of treatment, recurrence, regional failure, and death (from disease or from another cause). Demographic (age, sex, smoking history, etc.) and clinical characteristics (tumour site, stage, location, etc.) and types of treatment received by each cohort member were also identified and recorded from this chart review – a full list of variables is included in Appendix A.

Each member of the cohort has an identified "date_init" and "date_last" which were considered equivalent to date of diagnosis and death (or censoring). Cohort members who do not have a "date_init" (n = 4) or whose "date_init" and "date_last" were identical (i.e., they contribute zero days to the analysis; n = 26) were removed from the analysis, leaving a final cohort of 856 patients.

Patient demographics

Demographic characteristics of the sample are presented in Table 1. Former and current smokers were considered "ever smokers" and were combined into the same category.

Table 1 – Demographic characteristics of cohort

Variable (N = 856)		Mean	SD/Percent
Age at first treatment		65.6	14.0
Sex	Male	501	58.5%
	Female	355	41.5%
Smoking History	Never smoker	203	23.7%
	Ever smoker	587	68.6%
	Unknown	66	7.7%
Stage at diagnosis	I	319	37.3%
	II	300	35.0%
	III	106	12.4%

	IV	128	15.0%
	Unknown	3	0.4%

Clinical characteristics

Four clinical milestones were identified for each patient, where applicable: 1) date of initial treatment, 2) date of first recurrence, 3) date of second recurrence, and 4) date of death or censoring. Date of initial treatment was defined as the 'date_init' variable in the cohort. Date of recurrence was defined as either 'LR_Date' or 'RR_Date' (locoregional or regional recurrence, respectively), whichever date was the earlier of the two. Date of second recurrence was defined as either 'LR2_Date' or 'RR2_Date', whichever date was the earlier of the two. In cases where a cohort member had a local recurrence *and* a regional recurrence *and* a second recurrence (either local or regional; n = 7), the first two of those dates were taken to be the date of second recurrence. Date of death or censoring was defined as 'date_last' in the cohort datafile.

Overall survival (OS) was measured from date of initial treatment to date of death or censoring. Cohort members who died of oral cancer (N = 282) were considered to have experienced the 'dead of disease' event. Cohort members who did not die (N = 283), or who died of a cause unrelated to cancer (N = 291) were censored at 'date_last'.

Time to First Recurrence (TFR) was measured from the date of initial treatment to date of recurrence. Cohort members who did not experience a recurrence (N = 709) were censored at 'date_last'. Time from First Recurrence to Death (TFRD) was measured from date of recurrence to 'date_last'.

Time to Second Recurrence (TSR) was measured from the date of first recurrence to the date of second recurrence. Only cohort members who had experienced a first recurrence (N = 147) were included in this analysis. Cohort members who did not experience a second recurrence (N = 124) were censored at 'date_last'. Time from Second Recurrence to Death (TSRD) was measured from date of second recurrence to 'date_last'.

Median survival times are presented in Table 2.

Table 2 – Median Time-To-Event Values

Parameter	Value
Overall Survival (N = 856)	
Median (days)	1052
Censored observations (%)	574 (67%)
Time to First Recurrence (N = 856)	
Median (days)	836.0
Censored observations (%)	709 (83%)
Time from First Recurrence to Death (N = 147)	
Median (days)	377
Censored observations (%)	67 (46%)
Time to Second Recurrence (N = 147)	
Median (days)	762
Censored observations (%)	124 (84%)
Time from Second Recurrence to Death (N = 23)	
Median (days)	228
Censored observations (%)	9 (39%)

Treatment characteristics

Treatment type was identified at the time of initial treatment ('prim_tx_type') and at recurrence ('LR_tx_type' and 'RR_tx_type') and grouped into categories. For concurrent therapies (i.e., surgery with adjuvant RT), therapies that occurred within three months of the primary treatment in the absence of recurrence were considered to be given simultaneously. This information is presented in Table 3.

Primary treatment type (i.e., the treatment approached used for the first presentation of the oral cancer) was collapsed into four categories: surgery alone, surgery with radiotherapy, other adjuvant treatment (including brachytherapy, chemotherapy, and chemoradiotherapy), and no treatment. Treatment at time of recurrence was collapsed into four categories: surgical management, non-surgical management (i.e., any curative treatment that does not include surgery), palliative care, and no treatment.

Table 3 – Treatment Received by Cohort

Parameter	N	%
Primary Treatment Type (N = 856)		
Surgery Alone	406	47.43
Surgery + RT	125	14.60
Other Adjuvant Treatment	310	36.21
No Treatment	15	1.75
Recurrence Treatment Type (N = 147)		
Managed Surgically	62	42.18
Managed Non-Surgically	48	32.65
Managed Palliatively	20	13.61
No Treatment	17	11.56
Had Second Recurrence	23	2.3

Statistical Regression Methods

Survival times (in days) were fit to a Weibull regression model using the LIFEREG Procedure in SAS 9.4. A Weibull distribution was chosen as it allows for estimation of baseline hazard as well as proportional hazard, making it ideal for use in this type of analysis. Akaike Information Criterion (AIC) and Bayes' Information Crierion (BIC) statistics suggested that a Weibull approximation fit the cohort data similarly to a Gamma or Lognormal approximation.

Age, sex, and smoking status were chosen as demographic covariates in the regression analysis. Stage at diagnosis was collapsed into three categories: stage I, stage II, and advanced stage (III and IV) – cancers of unknown stage were excluded from the analysis. Treatment type, both primary and recurrence, were also included in the model.

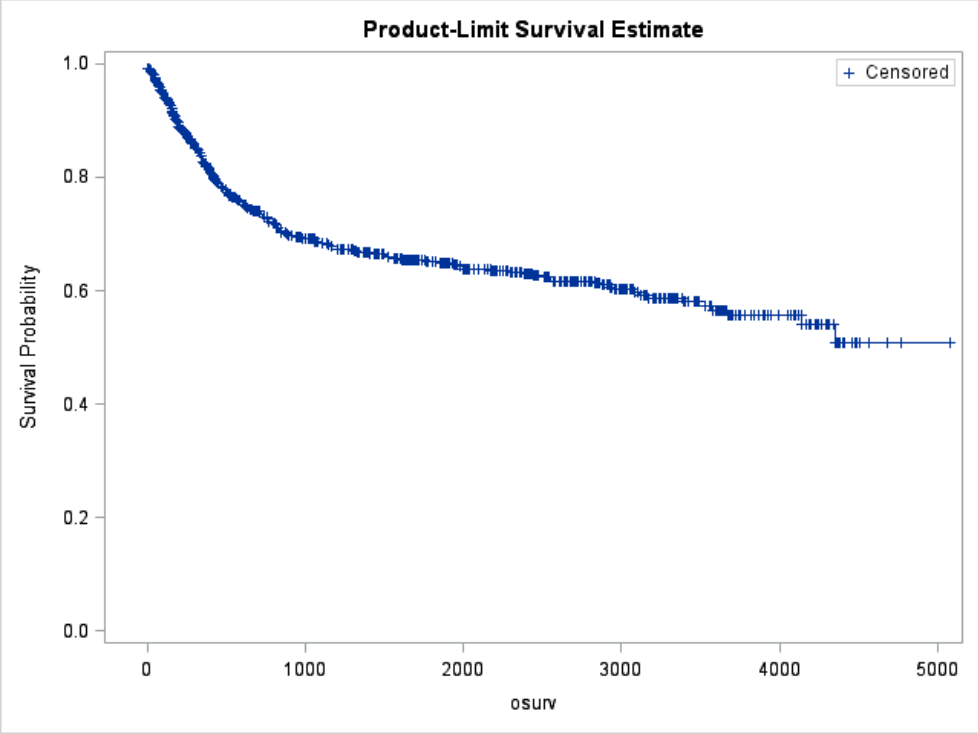
It is worthwhile to note that the results of this regression should not be taken to suggest that a given type of treatment is more effective than another. This analysis assumes that each patient was recommended the most appropriate type of treatment for their individual clinical presentation, and that they enjoyed the maximum survival benefit from whatever treatment they received.

Survival Analysis

Overall Survival

Age, stage at diagnosis, and treatment type were all significantly associated with overall survival.

Figure 1 – Overall Survival in Days



Total	Failed	Censored	Percent Censored
856	282	574	67.06

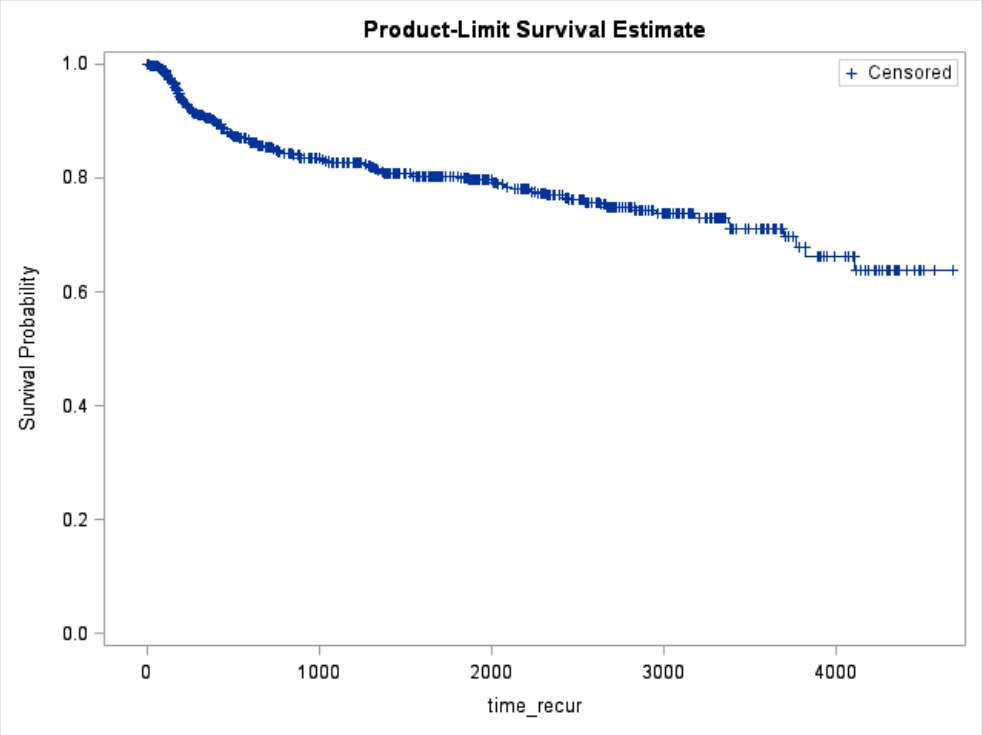
Table 4-1: Overall Survival Regression Coefficients

Parameter		Estimate	SE	95% Confidence Limits			Pr > ChiSq
Intercept		12.1050	0.5397	11.0473	–	13.1628	<.0001
Sigma		1.4102	0.0720	1.2760	–	1.5585	
Age		**-0.0364**	**0.0074**	**-0.0509**	**–**	**-0.0219**	**<.0001**
Sex	Male	Ref.					
	F	0.2028	0.1874	-0.1645	–	0.5701	0.2792
Smoking	Never	Ref.					
	Ever	-0.2358	0.2160	-0.6591	–	0.1875	0.2750
Stage	**I**	**Ref.**					
	II	**-0.5226**	**0.2471**	**-1.0070**	**–**	**-0.0382**	**0.0345**
	Adv	**-1.3667**	**0.2584**	**-1.8733**	**–**	**-0.8602**	**<.0001**
Treatment Type	**Surgery Alone**	**Ref.**					
	Surgery + RT	**-0.9073**	**0.2673**	**-1.4312**	**–**	**-0.3834**	**0.0007**
	Other	**-0.9437**	**0.2268**	**-1.3882**	**–**	**-0.4992**	**<.0001**
	No Treatment	**-3.0385**	**0.5296**	**-4.0765**	**–**	**-2.0005**	**<.0001**

Time to First Recurrence (TFR)

Treatment type was related to recurrence time, with patients requiring RT experiencing recurrence at an earlier average date than other patients.

Figure 2 – Time to First Recurrence in Days



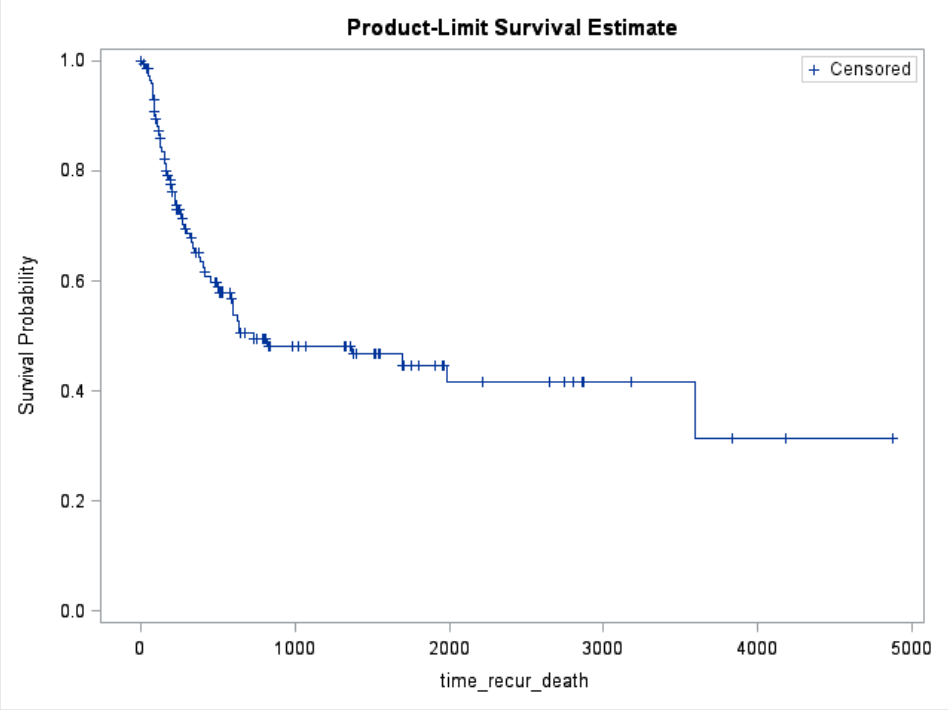
Total	Failed	Censored	Percent Censored
856	147	709	82.83

Table 4-2: Time to First Recurrence Regression Coefficients

Parameter		Estimate	SE	95% Confidence Limits			Pr > ChiSq
Intercept		10.3039	0.6232	9.0824	–	11.5254	<.0001
Scale		1.3754	0.0961	1.1994	–	1.5773	
Age		-0.0087	0.0092	-0.0267	–	0.0093	0.3425
Sex	M	Ref.					
	F	0.2774	0.2476	-0.2079	–	0.7626	0.2626
Smoking	Never	Ref.					
Smoking	Ever	- 0.1331	0.2843	-0.6902	–	0.4241	0.6397
Stage	T1	Ref.					
	T2	-0.3536	0.2810	-0.9043	–	0.1971	0.2082
	adv	-0.3102	0.3396	-0.9759	–	0.3555	0.3611
Treatment Type	Surgery Alone	0.0000					
	Surgery + RT	**-0.9004**	**0.3145**	**-1.5167**	–	**-0.2840**	**0.0042**
	Other	-0.4612	0.2938	-1.0371	–	0.1147	0.1165
	No Treatment	28.3841	63509.82	-124449	–	124505	0.9996

Time from Recurrence to Death

Figure 3 – Time From Recurrence to Death in Days



Total	Failed	Censored	Percent Censored
147	67	80	54.42

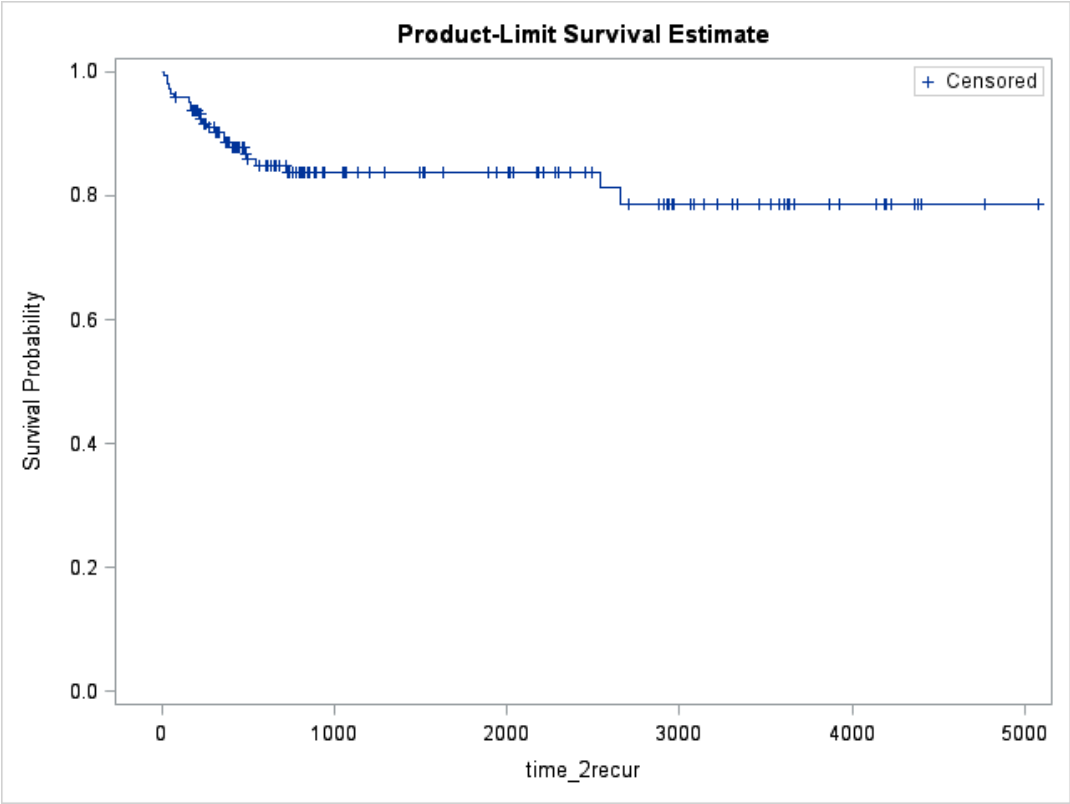
Table 4-3: Time From Recurrence to Death Regression Coefficients

Parameter		Estimate	SE	95% Confidence Limits	Pr > ChiSq
Intercept		9.2803	0.9231	7.4712 – 11.0895	<.0001
Scale		1.2543	0.1201	1.0398 – 1.5132	
Age		-0.0123	0.0134	-0.0386 – 0.0140	0.3588
Sex	M	0.0000			
	F	-0.5217	0.3190	-1.1468 – 0.1035	0.1019
Smoking	Never	Ref			
	Ever	-0.5840	0.3900	1.3485 -0.1804	0.1343
Recurrence Treatment	**Surgical**	**0.0000**			
	Non-Surgical	**-1.0934**	**0.4074**	**-1.8918 – -0.2949**	**0.0073**
	Palliative	**-2.7061**	**0.4510**	**-3.5901 – -1.8222**	**<.0001**
	No Treatment	**-1.7166**	**0.5271**	**-2.7496 – -0.6836**	**0.0011**

Time to Second Recurrence

Time to second recurrence was not statistically associated with any of the parameters in the model.

Figure 4 – Time to Second Recurrence in Days



Total	Failed	Censored	Percent Censored
147	23	124	84.35

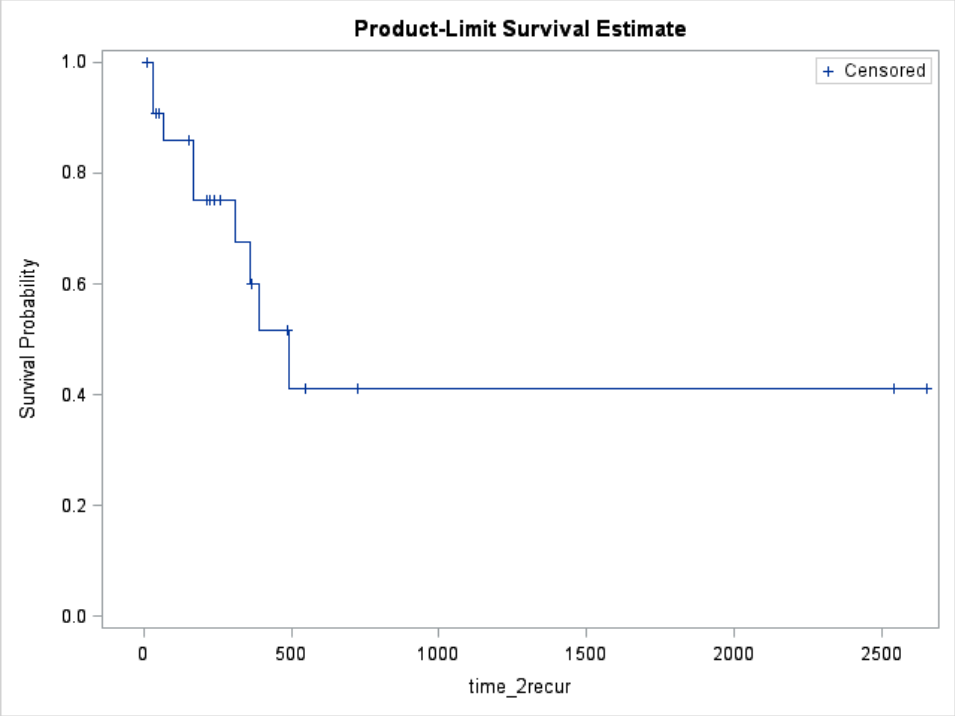
Table 4-4: Time To Second Recurrence Regression Coefficients

Parameter		Estimate	SE	95% Confidence Limits			Pr > ChiSq
Intercept		10.2014	2.3781	5.5405	–	14.8623	<.0001
Scale		1.9706	0.3723	1.3608	–	2.8537	
Age		-0.0058	0.0356	-0.0756	–	0.0640	0.8697
Sex	M	Ref.					
	F	1.1526	0.9755	-0.7595	–	3.0646	0.2374
Smoking	Never	Ref.					
	Ever	0.1752	0.9612	-1.7088	–	-2.0591	0.8554
Recurrence Treatment	Surgical	0.0000					
	Non-Surgical	1.1131	1.0785	-1.0007	–	3.2269	0.3020
	Palliative	2.4629	2.1279	-1.7077	–	6.6336	0.2471
	No Treatment	-0.3380	1.2823	-2.8514	–	2.1753	0.7921

Time from Second Recurrence to Death

Women in the sample had shorter survival time than men, but this may be due to the small number of observations rather than being a true effect.

Figure 4 – Time From Second Recurrence to Death in Days



Total	Failed	Censored	Percent Censored
23	9	14	60.87

Table 4-5: Time From Second Recurrence to Death Regression Coefficients

Parameter		Estimate	SE	95% Confidence Limits	Pr > ChiSq
Intercept		5.9464	2.4339	1.1761 – 10.7167	0.0146
Scale		1.2485	0.3036	0.7751 – 2.0110	
Age		0.0355	0.0409	-0.0447 – 0.1156	0.3855
Sex	M	Ref.			
	F	**-2.4923**	**0.9150**	**-4.2857 – -0.6989**	**0.0065**