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Estimating the effect of time on patient-derived measures of quality of life and health state utility

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Introduction

Evaluations of health-related quality of life (HRQoL) and health state utility are commonly conducted cross-sectionally. While cross-sectional estimates are valuable, well-being is seldom constant over the course of a health event, particularly following an acute event like treatment. Assumptions of constant quality of life and/or utility may lead to erroneous conclusions drawn by cost-effectiveness decision models. Regression analysis methods on repeated-measures data may produce estimates of HRQoL and utility that reflect the effect of time. The following exercise demonstrates a use of random-effects regression in time-series HRQoL and utility data to estimate the effect of time in a population of oral cancer patients.

Population and Methods

Study population

Data for this exercise was collected from participants in the Canadian Optically-guided Oral Lesions Surgical (COOLS) Trial. The COOLS Trial is a multi-centre, double-blinded, randomized controlled trial that began recruitment in 2011. Participants in the COOLS Trial were recruited to seven centres across Canada: Vancouver, BC; Calgary, AB; Edmonton, AB; Winnipeg, MB; Toronto, ON; London, ON; and Halifax, NS. People 19 years of age or older with high-grade oral lesions (HGL) or early-stage squamous cell carcinoma (SCC) were eligible for inclusion in the trial. Eligible patients were excluded if they were not candidates for surgery, had concurrent non-oral malignancy diagnosed within the past 3 years, or if their lesion was located at the base of the tongue or the tonsil.

Health-Related Quality of Life Instruments

Participants in the COOLS Trial completed two HRQoL survey instruments at baseline (i.e., prior to surgery), then again at six weeks, three months, and 24 months following their primary treatment. The instruments used for this evaluation were the EuroQoL 5-D (EQ-5D) and the Head and Neck module of the Functional Assessment of Cancer Therapy (FACT-H&N).

The EQ-5D consists of five dimensions describing general health states, and a 100-point visual analogue scale (VAS). The dimensions include: Mobility, Self Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Scores on the EQ-5D were converted to utilities using a set of Canadian tariffs, based on a time trade-off (TTO) exercise. Utilities are commonly expressed as values between 1.0 (perfect health) and 0.0 (a state equivalent to death), although utilities less than zero are possible.

The FACT contains a total of 39 Likert-style questions (scaled 0-4), across five domains. The first four domains of well-being – Physical (PWB), Social/Family (SWB), Emotional (EWB), and Functional (FWB) – comprise the ‘general’ form of the FACT (FACT-G). A fifth domain contains twelve questions specific to head and neck symptoms. The FACT-H&N has a maximum score of 156.

Regression Modelling

Random effects modeling

A random growth curve model was constructed to predict HRQoL. This type of model allows for the estimation of the effect of time on HRQoL, while controlling for the effect of relevant covariates. Time, in a random growth curve model, is expressed as a continuous variable (in days, for this exercise). The model was constructed in SAS 9.4, based on a method developed by Dr. Paul Allison.

Model covariates

COOLS Trial data included in the model falls into two categories: demographic and disease-specific.

Demographic variables include: age, sex, ethnicity, previous cancer history, familial cancer history, ever vs. never smoker

Disease-specific variables include: lesion type (squamous cell carcinoma vs. high-grade lesion), location of lesion (tongue, soft palate, gingiva, buccal mucosa, floor of mouth), interoperative frozen tissue, neck dissection, skin graft, chemotherapy, radiotherapy, adverse event, additional surgery.

Results

Study Sample Characteristics

Demographic and disease-specific variables, as well as patterns of EQ-5D and FACT-H&N responses, are described in the tables below:

Variable	N	%
427		
<i>Demographic Variables</i>		
Age (mean; SD)	61.4	(13.1)
Female sex	167	40
Ethnicity: white	340	81
Previous history of cancer	106	25
Familial cancer history	270	64
Ever smoker	279	66
<i>Disease-Specific Variables</i>		
Lesion Type		
High-Grade (HGL)	181	42
Squamous Cell Carcinoma (SCC)	246	58
Location of primary lesion		
Tongue	272	66
Soft Palate	21	5
Gingiva	31	8
Floor of Mouth	57	14
Buccal Mucosa	29	7
Treatment details		
Interoperative Frozen Tissue	114	28
Neck Dissection	107	26
Skin Graft	84	20
Received Chemotherapy	85	20
Received XRT	27	6
Reported Adverse Event	72	17
Additional Surgery	126	30

Instrument	Baseline		6-week		3-month		24-month	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
EQ-5D	0.81	0.17	0.82	0.16	0.84	0.17	0.88	0.14
EQ-5D VAS	76.9	18.5	76.9	17.4	78.1	17.9	81.2	15.0
FACT								
Physical Subscale	24.4	4.3	23.5	4.4	24.1	5.0	24.8	3.8
Social/Family Subscale	21.3	5.6	21.7	5.3	22.0	5.3	22.2	5.3
Emotional Subscale	17.7	4.4	19.1	4.1	19.6	4.1	20.1	3.9
Functional Subscale	20.6	6.4	19.8	6.2	20.9	6.4	22.0	5.7
Head & Neck Subscale	35.5	6.7	33.6	6.6	35.1	6.8	36.3	6.3
Total FACT-G	84.0	15.3	84.1	15.8	86.5	16.2	89.2	14.2
Total FACT H&N	119.5	19.7	117.7	21.2	121.6	20.9	125.6	18.9

The sample was mostly white and predominantly male. The majority of the lesions were located on the tongue. Many participants required more than one surgery, which is common in this disease area.

Participants reported improvements across all measures of HRQoL and utility over the course of 24 months, with a slight dip at the six-week mark (aggregate EQ-5D and FACT-H&N differences were not significantly lower at six weeks vs. baseline). Response rates were 85%, 89%, and 59% at six-week, three-month, and 24-month follow-up respectively. 55 participants died during follow-up; 9 of whom died before their 3-month visit. The trial is ongoing, and many participants have not reached 24 months follow-up yet.

Regression Modeling

Demographic and disease-specific variables, as well as patterns of EQ-5D and FACT-H&N responses, are described in the table below (values in red are statistically significant):

Lesions developing in the buccal mucosa were associated with lower EQ-5D scores than those on the tongue. Patients receiving a skin graft in their primary surgery had lower utility, as did those whose disease required additional surgery.

FACT-H&N scores were significantly lower in those whose lesions developed in the soft palate or floor of the mouth, compared to the tongue. No treatment variable was significantly associated with HRQoL, aside from receiving additional surgery.

Time was significantly associated with scores on both the EQ-5D and the FACT-H&N, when controlling for the effect of the other covariates. The pattern of significant association did not change when participants who died were excluded from the analysis.

Variable	EQ-5D		FACT-H&N	
	Estimate	SE	Estimate	SE
Intercept	0.898	0.0347	125.45	4.48
<i>Demographic Variables</i>				
Age (mean; SD)	-0.00031	0.00052	0.024	0.067
Female sex	-0.015	0.014	-0.50	1.81
Ethnicity: white	0.010	0.017	0.60	2.25
Previous history of cancer	-0.0037	0.016	-1.79	2.02
Familial cancer history	-0.021	0.014	-2.02	1.81
Ever smoker	-0.013	0.015	-0.82	1.96
<i>Disease-Specific Variables</i>				
Lesion Type				
High-Grade (HGL)		Ref.		Ref.
Squamous Cell Carcinoma (SCC)	-0.015	0.016	-0.76	2.04
Location of primary lesion				
Tongue		Ref.		Ref.
Soft Palate	-0.049	0.031	-9.30	0.021
Gingiva	0.036	0.025	4.01	0.22
Floor of Mouth	0.0012	0.020	-5.37	2.60
Buccal Mucosa	-0.069	0.026	-5.35	3.34
Treatment details				
Interoperative Frozen Tissue	-0.015	0.018	-3.83	2.33
Neck Dissection	0.011	0.027	0.93	3.44
Skin Graft	-0.061	0.021	-5.11	3.55
Received Chemotherapy	0.0093	0.021	1.00	2.66
Received XRT	-0.042	0.031	-7.36	4.04
Reported Adverse Event	-0.019	0.018	-2.36	2.33
Additional Surgery	-0.045	0.015	-5.59	1.97
Time (days)	0.000087	0.000012	0.0081	0.0013

Conclusion

Regression models using repeated-measures HRQoL data can yield useful insights into the factors affecting disease recovery. This technique can also be used to estimate the effect of continuous time on health state utility, which has potential applications for decision analytic models that include time (i.e., Markov or discrete event models). These applications and their implications on cost-effectiveness will be explored in future research.

The COOLS Trial is expected to reach full data acquisition by next year.

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