

An Investigation of Quality-of-Life Issues in Patient Treatment Using Enterprise Miner™

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ABSTRACT

Quality-of-Life is a very subjective issue. This study investigates data routinely collected in the Sunbelt Melanoma Trial, a controlled, randomized clinical trial accruing a total of 1370 patients studied longitudinally for a minimal period of 7 years. The data mining procedures of Enterprise Miner will be used to examine the quality-of-life issues.

INTRODUCTION

Quality-of-life in medical care is extremely subjective. Not only does it vary from person to person, but it can vary from one stage in medical treatment to another in the same individual. Therefore, it is important to investigate the meaning of quality-of-life data through the data mining process as provided in Enterprise Miner.

Philosophically, there has been a shift in health care. Increasingly, therapy is designed to improve a patient's quality-of-life, and not just to prolong life. Managed care is shifting from aggressive treatment of individual patients to defining social norms beyond which an individual treatment plan cannot go. The use of quality-of-life criteria is commonly seen in the definition of medication formularies; it is seen most prominently in the rationing of care in Oregon's Medicaid program which defines a list of 500+ diagnoses which will be treated; all other illnesses cannot be reimbursed for treatment. The list of 500+ was defined based upon cost effectiveness and quality-of-life analyses [1]. However, this cost-effectiveness performed by Oregon did not correlate with the academic analysis performed standard decision-making definitions.

In figuring the cost effectiveness, a utility function is defined on the quality-of-life [2-3]. In the past, this utility function was assumed to be linear. Many attempts have been made to define equivalencies in quality, or to define a quality-of-life score. [3] was a retrospective study adjusting survival for quality-of-life based upon a utility function defined in terms of medical criteria. Where patients do have input, the hypothetical scenario is given to them: ten years of perfect health is deemed equivalent to 20 years of impaired health; if you could take a pill which would guarantee ten years of perfect health after which you would immediately drop dead versus having chronic headaches for the next 20 years, would you take the pill?[4]. These types of analysis are somewhat contrived. Patients are asked to make hypothetical decisions that are probably completely different from the ones they will make when actually faced with the decision. Living wills do not permit patients to change their minds. In addition, physicians are usually surveyed multiple times concerning an assessment of risk until the QOL investigator finds a consensus in the results. Unfortunately, physician conception of risk might be far different from reality[5-6.]. These studies did demonstrate that perception was quite different from reality. The result was a substantial cumulative loss to the health care payor. Therefore, the outcomes of these analyses remain primarily of academic rather than practical interest.

The patients themselves must have their judgments solicited concerning their own quality-of-life. Physicians cannot substitute their judgment for that of their patients [7] as their philosophical assumptions are usually vastly different.

The focus must shift to actual clinical data. One of the reasons actual data are not often used is that information concerning quality of life is not routinely collected or thoroughly analyzed [8] This is because there are numerous parameters, collected over long periods of time, and the standard statistical methods are not adequate to work with these data. The Type I error can become excessive when making so many multiple comparisons. However, the inquiry is not necessarily at the point of hypothesis testing; instead the data should be investigated by exploratory data analysis or data mining. The standard questions to be asked in a quality-of-life study for a chronic condition are the following:

- What is the relationship of quality-of-life to treatment?
- Is the additional survival worth the physical impairment caused by treatment?
- When should the drug dose be modified because of a patient's reduced quality-of-life resulting from the high toxicity levels?

These questions do not necessarily have fixed, concrete measures since the parameters of worth, quality, impairment are subjective to each individual patient. Therefore, more exploratory methods should be used in an attempt to make the measurement tools more precise.

The Sunbelt Melanoma Trial is a prospective randomized trial designed to investigate further the effectiveness of the drug interferon alfa-2b for patients with melanoma. In this study, quality-of-life information is routinely collected at all follow-up patient visits.

SEMMA

Enterprise Miner uses the SEMMA process (sample, explore, modify, model, assess). This process will be demonstrated using the quality-of-life information collected in the Sunbelt Melanoma Trial.

The general trend in studying quality-of-life is to define a quality-of-life score and a cutpoint so that above the cutpoint a patient has good quality and below the cutpoint the patient has poor quality-of-life [9]. There are usually subscales that relate to physical and psychological domains as well as functioning in daily routines. Such a score assumes that the relationships between patient characteristics are linear. However, quality-of-life means different things at different stages of life. Most people will give different responses before and after diagnosis, and a different response after treatment. As discussed in [10], quality-of-life can even differ in a clinical trial or in a different treatment setting. Instead of defining a score, data mining can be used to investigate the meaning behind many of the patient responses.

This paper will demonstrate how the data mining techniques of Enterprise Miner can be used to examine the meaning of quality-of-life data. The question is whether all the quality-of-life data should be reduced to a single score.

SAMPLING

In July, 1997, patients were initially enrolled into a clinical trial, the Sunbelt Melanoma Trial, to test the use of the drug interferon alpha-2b in the treatment of patients with melanomas. It is a multi-center trial (over 40 centers currently) with anticipated patient accrual of 1370 over a 3-year period. The melanoma is surgically removed and sentinel lymph nodes tested. If cancer is detected in the sentinel lymph node by standard pathology methods (serial sectioning and immunohistochemistry for S-100), the remaining regional lymph nodes are removed. Patients who test negative by routine pathology are further tested using polymerase chain reaction (PCR) analysis of melanoma-specific mRNA expression. The clinical trial is also intended to determine the sensitivity and specificity of the test. Based upon the outcomes, patients are placed into the following treatment arms:

- I. SLN test positive, randomized to observation
- II. SLN test positive, randomized to interferon alfa-2b
- III. SLN test positive, multiple positive nodes, interferon

- IV. alfa-2b, not randomized
- V. PCR test positive, randomized to observation
- VI. PCR test positive, randomized to lymph node dissection only
- VII. PCR test positive, randomized to lymph node dissection plus interferon alfa-2b
- VIII. PCR test negative, not randomized, observation

A block randomization scheme was used to assign patients into treatment arms. Treatment III is not randomized because it consists of patients with multiple positive SLN lymph nodes and the condition is considered too serious to warrant observation only; I and II are limited to patients with one positive node. Treatment VII is not randomized since the condition is regarded as too minor to warrant more aggressive treatment. Once started, treatment with interferon alpha-2b is to continue for one year. The duration of the clinical trial is ten years so that a minimum of 7 years of data will be collected for each patient enrolled in the study. Patients are asked questions concerning quality-of-life at baseline, and again at each follow-up visit. Follow-up will occur every three months for the first two years, every 4 months for year 3, every 6 months for years 4 and 5, and annually thereafter. At this point in time there are a sufficient number of patients accrued (545) with approximately half (248) reaching the 9-month follow-up point.

The quality-of-life information was collected in a 1-page form. The decision was made to limit the form to 1-page so that it would be easy to fill out and medical centers would not be reluctant to take the time to have it done. It was designed to be easy for patients to complete. It was also designed to allow patients to provide somewhat subjective answers concerning life quality; an issue which is subjective in any case. The questions are given in Table 1.

Table 1. Questions Concerning Quality-of-Life

1. Prior to diagnosis of your melanoma, were you? Unemployed Employed Retired
2. Prior to diagnosis of your melanoma, what percent of time were you absent from work (if employed)? 0% 1-10% 26-50% 51-75% more than 75%
3. Prior to diagnosis of your melanoma, what percent of the time were you unable to go about your normal daily routine? 0% 1-10% 26-50% 51-75% more than 75%
4. Prior to diagnosis of your melanoma, you frequently felt weak irritable tired depressed forgetful feverish anxious confused hungry sad nervous
5. Prior to diagnosis of your melanoma, you frequently had nausea constipation diarrhea headaches muscle or joint aches shortness of breath swelling loss of appetite other problems, explain _____
6. Prior to diagnosis of your melanoma, your weight was _____ lb.
7. In the year prior to diagnosis of your melanoma, have you applied for or received: disability benefits Social Security Medicare Medicaid Welfare Benefits disability insurance benefits
8. In the year prior to the diagnosis of your melanoma, have you had any of the following major changes in your life? Marriage divorce Separation Breakup with significant other New relationship with significant other Loss of job Change job New job Change address File for bankruptcy
9. Prior to diagnosis of your melanoma, how would you rate your overall physical condition? **Very Poor** 1 2 3 4 5 6 7 8 9 10 **Excellent**
10. Prior to diagnosis of your melanoma, how would you rate your overall quality of life? **Very Poor** 1 2 3 4 5 6 7 8 9 10 **Excellent**

To test for the reliability of the survey instrument, Cronbach's alpha was computed at 0.835 for standardized variables. Therefore, the measurement instrument is fairly reliable.

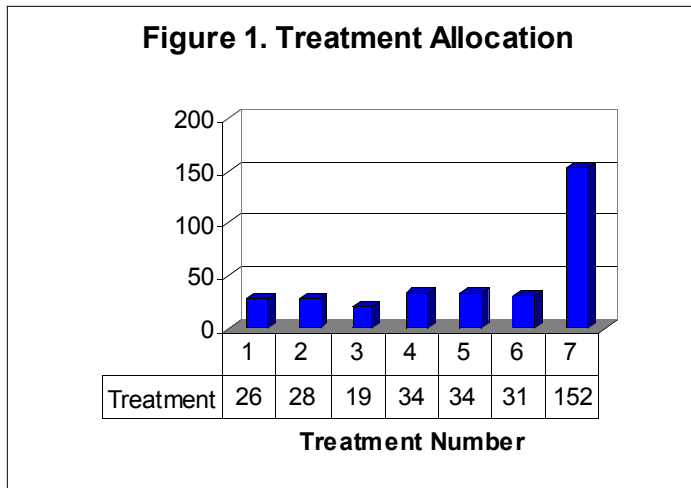
EXPLORE

There are relatively the same number of patients assigned to treatments 1,2 and to treatments 4-6. The distribution into treatments is shown in

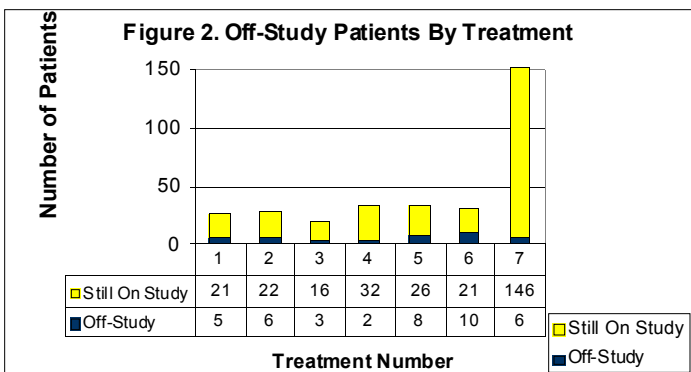
Figure 1.

Because of the nature of the disease, over 30% of the patients in treatment VI are refusing treatment and are going off-study as shown in Figure 2.

There were no statistically significant differences between treatment groups at baseline with the exception of physical condition and quality-of-life. However, differences were shown

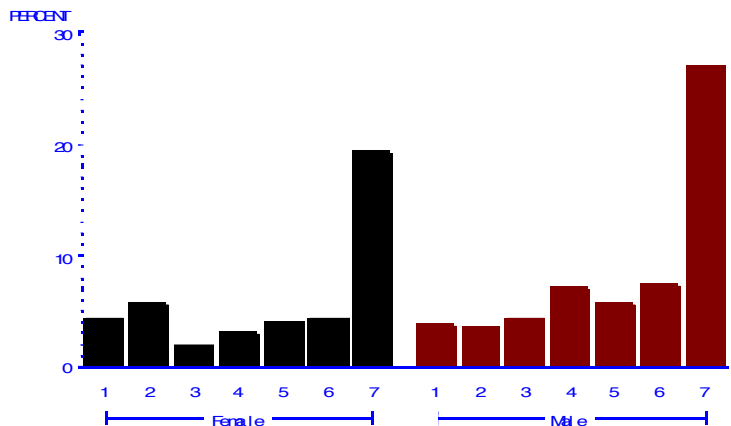


at the follow-up time periods. In addition, differences in treatment versus patient demographics were investigated. Over 90% of the patients were Caucasian; therefore, race was not investigated as a factor. Gender is of interest since a higher rate of severe side effects are often reported in females. Although not statistically



significant, there was a slight difference in distributions between genders in the treatment assignments (Figure 3).

Figure 3. Comparison of Treatment to Gender



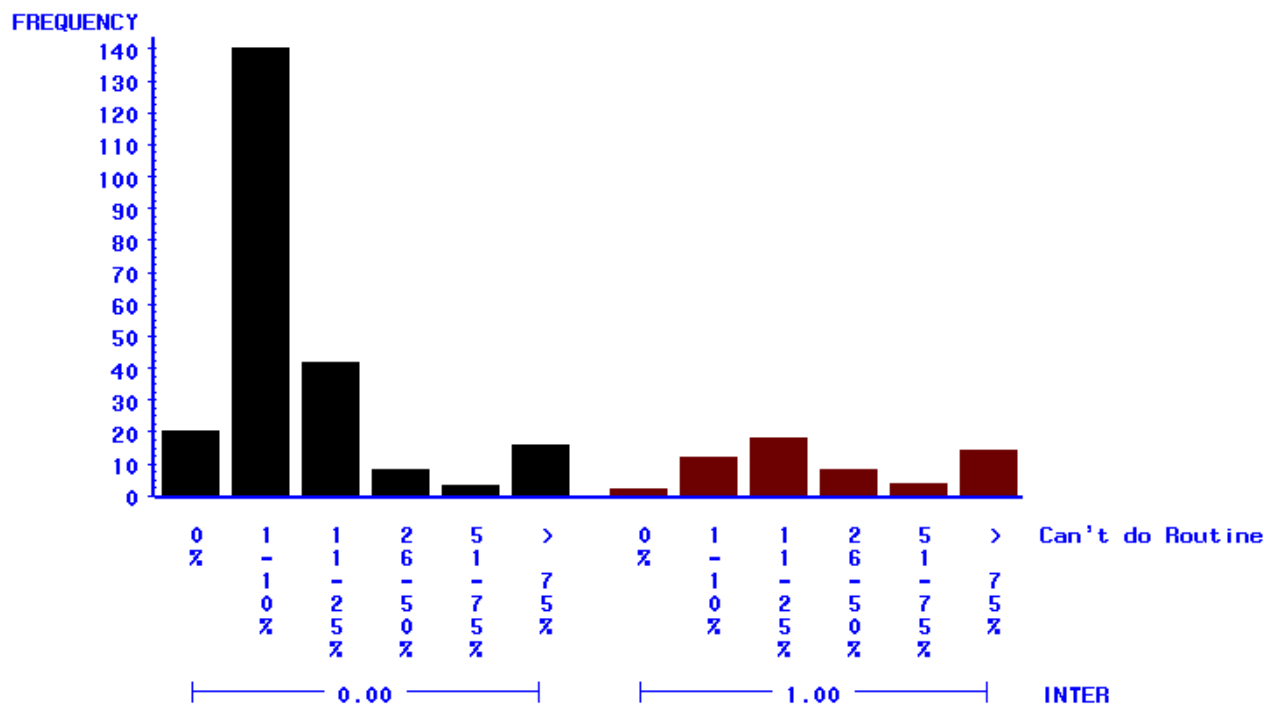
quality-of-life information was made. There were not statistically significant differences. Although not conclusive, this is a strong indication that gender will not have to be examined as a factor in future analyses.

There is clearly a difference in outcomes with the use of treatment. Consider the baseline value for the percent of time the patient was unable to go about a normal routine (Figure 4).

The baseline values have the same distributions. However, at follow-up the distributions change (Figure 5).

There is a shift toward a greater inability to perform the daily routine. However, the shift is much more pronounced in the treatment group. To examine further the changes in quality-of-life resulting from treatment, chi-square tests were performed to examine for trends.

Figure 4. Comparison of Treatments Concerning the Ability of Patients to Perform Routine.



The following table gives the p-values for differences between treatments at 3,6, and 9 months follow-up (using chi-square tests) in Table 2.

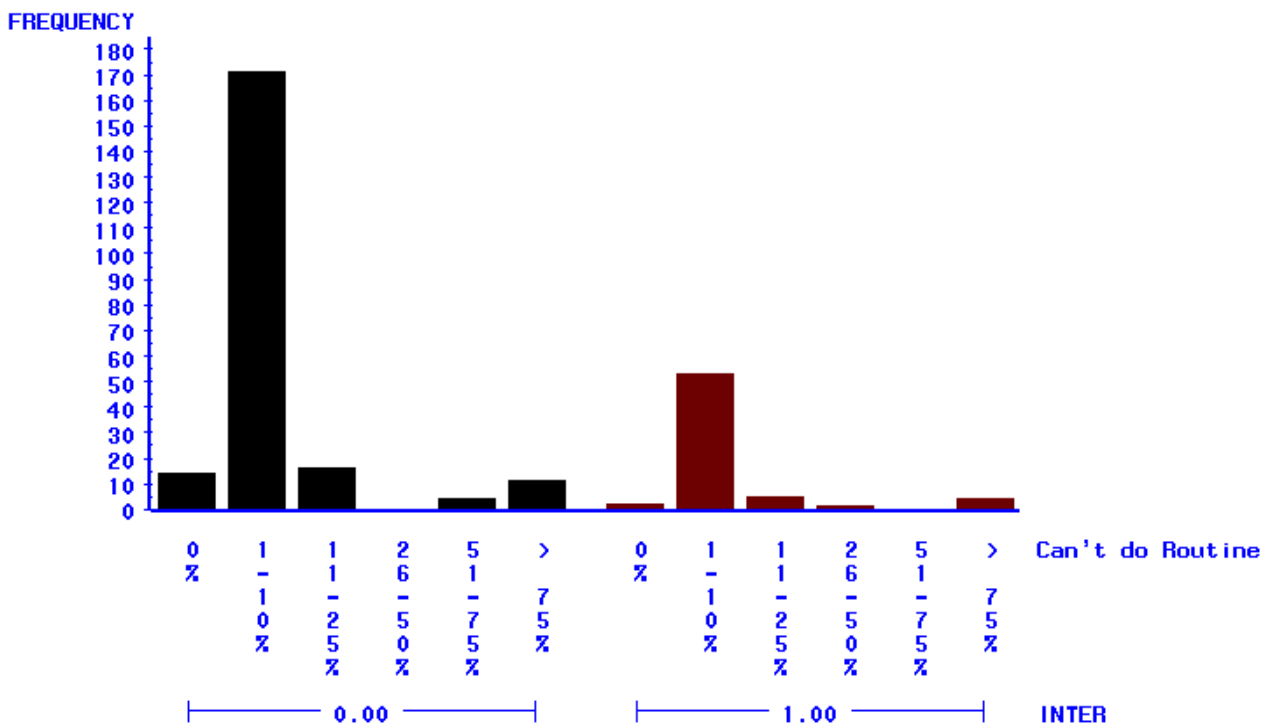
Characteristic	Base	3-Month	6-Month	9-Month
Percent time Absent from work	0.944	0.018	0.099	0.017
Percent time not able to do routine	0.448	0.001	0.004	0.001
Weak	0.101	0.001	0.001	0.011
Irritable	0.824	0.032	0.001	0.001
Tired	0.21	0.001	0.001	0.001
Depressed	0.78	0.9	0.002	0.05
Forgetful	0.142	0.932	0.103	0.002
Feverish	0.199	0.001	0.001	0.011
Anxious	0.252	0.068	0.006	0.978
Confused	0.115	0.521	0.001	0.014

Characteristic	Base	3-Month	6-Month	9-Month
Hungry	0.587	0.044	0.397	0.011
Sad	0.691	0.464	0.001	0.411
Nervous	0.167	0.044	0.034	0.213
Nausea	0.674	0.001	0.506	-----
Constipation	0.704	0.017	0.003	0.39
Diarrhea	0.996	0.044	0.014	0.002
Headache	0.126	0.001	0.016	0.078
Muscle	0.892	0.001	0.026	0.001
Shortness of breath	0.504	0.009	0.249	0.075
Swelling	0.811	0.788	0.385	0.177
Appetite	0.674	0.001	0.036	0.39
Weight Change	0.721	0.001	0.527	0.163
Physical Condition	0.027	0.001	0.001	0.391

As the 9-month values only had 45 observations, the p-values are somewhat questionable and need to be validated when more data become available. It is troubling that there are differences in quality-of-life and physical condition at baseline. However, it must be recalled that treatments 3 and 7 are not randomized. If the analysis is divided between randomized and non-randomized patients, the results are as follows:

Characteristic	Base	3-Month	6-Month	9-Month
Physical Condition	0.001	0.373	0.057	0.915
Quality-of-Life	0.001	0.255	0.775	0.915

Figure 5. Comparison Between Treatments at Follow-up.



This can be subdivided to examine both characteristics with respect to the interferon alfa-2b:

Characteristic	Base		3- 3-Month	
	With Drug	Without Drug	With Drug	Without Drug
Physical Condition	0.273	0.322	0.694	0.436
Quality-of-Life	0.001	0.255	0.269	0.233

As a future analysis, it is of interest to determine whether patients on interferon improve in overall quality-of-life once the interferon treatments are completed.

MODIFY

There is no question that treatment is having an impact on patient quality-of-life. The QOL parameters were examined at baseline, at 3, 6, and 9-month intervals. To determine the impact of interferon, the 7 treatment groups were divided into interferon (treatments 2,3,6) and no interferon (treatments 1,4,5,7). The 1-10 scale of physical condition and quality-of-life was condensed into categories: <5.5 and >5.5.

In addition, the variables concerning life changes such as marriage, job change, etc. were not considered for the purpose of analysis. Fewer than 1% of responses were checked so that there is virtually no discriminating ability in those variables.

MODEL

Both factor analysis and cluster analysis were performed on the dataset. The cluster analysis divided the parameters into five different clusters (Table 4).

Since the clusters are relatively easy to label, the cluster analysis tends to validate the quality-of-life survey (construct validity). The reliability will be tested with additional data. Similarly, a factor analysis was performed resulting in 6 factors (Table 5).

Table 4. Results of PROC VARCLUS

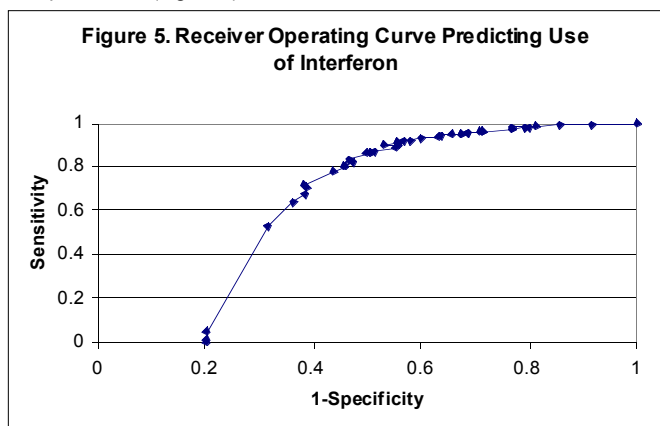
Cluster	Cluster Label	Variables	Correlation With Own Cluster	Correlation With Next Closest Cluster
1	Physical 1	Absent Percent Percent of Routine Weak Tired Feverish Headache Muscle Shortness Swelling Nausea	0.1980 0.3710 0.4488 0.4763 0.4601 0.4870 0.4362 0.3432 0.0797 0.5440	0.0465 0.0925 0.1745 0.1804 0.2263 0.1918 0.1006 0.0841 0.0422 0.1026
3	Physical 2	Diarrhea Appetite Constipation	0.6292 0.6292 0.6052	0.0565 0.0913 0.0536
2	Overall Quality	Physical Condition Quality-of-Life Weight Change	0.9134 0.9134 0.2290	0.1114 0.1175 0.0193
4	Emotiona l 1	Forgetful Anxious Confused Sad Nervous	0.5385 0.3169 0.5355 0.5494 0.5953	0.2438 0.1579 0.1753 0.2727 0.1197
5	Emotiona l 2	Irritable Depressed Hungry	0.6833 0.5066 4126	0.2890 0.1964 0.0597

Table 5. Results of PROC FACTOR

Factor	Factor Label	Variables	Factor Loadings
1	Emotional	Depressed	0.71789

Factor	Factor Label	Variables	Factor Loadings
		Anxious Confused Sad Nervous Irritable Hungry	1.00000 0.60023 0.85277 0.46137 0.67290 0.95520
2	Physical 1	Weak Diarrhea Appetite Constipation	0.40397 1.00000 0.78704 1.00000
3	Physical 2	Tired Forgetful Feverish Headache Muscle Aches Shortness of Breath	0.35169 0.65151 0.72309 0.34799 0.77718 1.00000
4	Overall Quality	Physical Condition Quality-of-Life	1.00000 0.99679
5	Routine	Percent Absent Percent of Routine	1.00000 0.72061
6	Physical 3	Swelling Weigh change	0.97474 1.00000

In a logistic regression, the same patient characteristics were statistically significant as given in the chi-square analysis in predicting the use of the treatment interferon. However, there is some question as to the appropriateness of the logistic regression because of the lack of independence of the characteristics, particularly since some of them correlate highly as demonstrated in the factor and cluster analyses. For this reason, other classification techniques which do not make linear assumptions should be used (kernel density discriminant analysis, neural network analysis). Also, the area under the receiver operating curve is only equal to 0.77 (Figure 5).



Because logistic regression is a poor discriminator, other methods were used to improve the ability of the model to predict outcomes. This includes the techniques of discriminant analysis as provided in PROC DISCRIM and Neural Network Analysis as provided in Enterprise Miner. The data were randomly partitioned into 80% training/20% testing subsets for this purpose. The results are as follows (Table 6)

Table 6. Comparison of Classification Methods

Method	Misclassification for Training Set	Misclassification for Validation Set
Linear Discriminant	0.2431	0.3021
Kernel Density r=2	0.7016	0.7083
Kernel Density	0.4995	0.5208

Method	Misclassification for Training Set	Misclassification for Validation Set
r=6		
Kernel Density r=8	0.3980	0.3854
Kernel Density r=9	0.4423	0.5000
Neural Network Analysis	0.0085	0.0595

In this particular dataset, it is clear that neural network analysis is the superior method of classification.

Since the quality-of-life parameters do provide a predictive marker for treatment, PROC FASTCLUS was used to examine the patients themselves. First, the patients taking interferon were investigated. Originally, the maximum number of clusters was set at 5. However, two of the clusters defined had so few observations that the maximum number of clusters was reduced to three. The baseline values are almost exclusively contained within one cluster strongly indicating that the use of interferon and its impact on patient health is the primary factor in clustering observations. The patient characteristics separating clusters are defined as follows:

Cluster Number	Number of Observations	Characteristics
1	25	Quality-of-Life < 5, Physical Condition < 5, Weak, Tired, Headache, Muscle Aches; About half also experience fever, anxiety, nervousness, and weight change
2	84	Baseline Observations; Quality-of-Life > 5, Physical Condition > 5 No indication of physical symptoms
3	27	Quality-of-Life > 5, Physical Condition > 5 Experiencing some symptoms: tired and about half with muscle aches

A total of 23 out of 78 patients experience discomfort with serious impact upon their quality-of-life while taking the interferon. Another 9 patients experience some discomfort with only modest impact on quality-of-life. Of the 23 patients with serious impact, 7 indicate improvement in quality-of-life from < 5 to > 5 as time of treatment increases from 3 months to 9 months.

Similarly, PROC FASTCLUS was used on the patients not taking interferon. There were also three clusters defined as follows:

Cluster Number	Number of Observations	Characteristics
1	25	Initial Followup; Quality-of-Life < 5, Physical Condition < 5; A few (not quite half) experiencing characteristics: weak, tired, depressive
2	113	Observations beyond baseline; Quality-of-Life > 5, Physical Condition > 5; No indication of physical symptoms
3	330	Baseline Observations; Quality-of-Life > 5, Physical Condition > 5; No indication of physical symptoms

Of the 20 patients in cluster 1, approximately 8 indicate an improvement in quality-of-life beyond the first 3-month followup visit.

ASSESS

There is a quality-of-life marker for the use of interferon in treatment; patients with interferon have a reduced quality-of-life. In fully one third of patients, this reduction can be severe in the early period. By the six-month follow-up, patients indicate an increased quality-of-life regardless of treatment. As some patients become more used to interferon, they indicate an improved quality-of-life. Other patients continue with a low quality-of-life. There are two questions which need to be answered as a result of this analysis:

1. Patients are treated with interferon for one year. After that year, does quality-of-life improve?
2. Is quality-of-life considered in making interferon dose-reduction decisions.

These questions will be answered once the Sunbelt Melanoma Trial has a sufficient number of patients.

A third question will have to be answered at the end of the clinical trial:

3. Is the increased survival from interferon treatment worth the decreased quality-of-life during the time of treatment?

To answer this question, the amount of increased survival (or disease-free survival) using the treatment needs to be measured. It is not enough to demonstrate a significant log-rank statistic. In this case, data mining will be important to weight costs versus benefits.

CONCLUSION

A search through Medline using key words related to quality-of-life and interferon treatment yield just one significant publication [11] in addition to [3]. This paper did not use an empirical data; instead it developed a Markov model using simulated patients in a clinical trial. Assumptions involving risk, outcomes, and quality were built into the model to determine whether interferon was cost-effective.

Cost-effectiveness requires that quality-of-life be reduced to one score which can be used in a linear analysis of outcomes. However, quality-of-life in medical treatment is a complex and subjective issue which must be investigated using a variety of data mining techniques to determine the actual meaning of the collected data. Only in this way will it be possible for patients to make informed choices concerning treatment. The analysis must examine quality outcomes along with physical outcomes.

Since each patient has different standards and attitudes toward quality-of-life, a simple score will have relatively little meaning to individuals, although useful in making sweeping recommendations for cost effectiveness. As it is used in other areas such as marketing [12], data mining provides a way to tailor medical decisions to an individual patient.

Enterprise Miner provides a quick way to routinely use multiple methods of analysis to investigate the data. Just partitioning the data becomes relatively simple. Otherwise, it is a long, involved, complex process.

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ACKNOWLEDGMENTS

The Sunbelt Melanoma Trial is funded through Schering-Plough Pharmaceuticals. Patricia B. Cerrito is funded through the National Science Foundation for investigations in data mining applied to clinical databases.

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