Cost Effective Analysis of Chemotherapy Treatment: A Study of Cancer patients

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Abstract: The present study was carried out to investigate the effectiveness of chemotherapy by monitoring the Quality of Life index of cancer patients. A sample of 114 patients was investigated at IRNUM Hospital Peshawar and their Quality of Life was examined pre and post treatment. The patients were surveyed at the time of their visit to the Hospital for chemotherapy treatment, and their responses were collected through EQ-5D classifier and Time-Trade-Off scale. The Time-Trade-Off responses were regressed on EQ-5D health profile to estimate their Quality of Life index and hence calculate Quality-Adjusted Life Years gained. Study reveals that cancer badly affects the social and personal life of the fatalities, causes an extreme anxiety/depression among the patients and makes them willing to trade off some years of their life for better health conditions. This situation was slightly improved by chemotherapy, which reduce their pain and anxiety, enabling patients to actively participate in social life activities. Analysis of study reveals a negative correlation between age and Quality of Life index, which is a clear indication that the intervention loses its utility as age of the patient increases. Expected life in the improved health conditions declined exponentially indicating chemotherapy is much effective for a shorter period. The average QALY gained is 0.11 for a cost of Rs 115201 PKR per QALY gained. Hence chemotherapy significantly raises the standard of living for cancer patients, but a huge amount has to be paid by them to live their social and personal life in much better environment.

[Muhammad Atif, Qamruz Zaman, Muhammad Iqbal, Muhammad Farooq, Aisha Bibi. **Cost Effective Analysis of Chemotherapy Treatment: A Study of Cancer patients.** *Life Sci J* 2014;11(10s):92-99]. (ISSN:1097-8135). http://www.lifesciencesite.com. 16

Key Words: Quality of Life, QALY, Cost, Cancer, Patients, Chemotherapy

1. Introduction

Statistical methodology plays its part whenever numerical figures enter into the portrait and find an integral place in the situation concerning biological sciences, pharmaceutical industries and medicine. Statistical methods can help in precise comparison of these phenomena by collecting the information in a scientific manner and accurate execution of the randomized experiments. The performance of medication can be assessed by observing two basic components of individual's life, the capability of executing daily life activities such as social, physical, and psychological behavior; and satisfaction with the level of ailment. These two subjective aspects of human behavior i.e. the functioning ability and the satisfaction level collectively are called the health related Quality of Life (Qol) index (Knippenberg et al., 1988; Gotay et al., 1992). This index can be defined in a number of ways related to the context, covering the grounds of policy making, health care units, economics, and international development. Policy makers and economist utilize it for employment and wealth assessment to upraise the standard of living, but in general it is used in clinical research to assess the health improvement occurred as a result of treatment. According to Schipper et al (1988), Qol is the difference between individual's expectations related to his/her own performance in a particular situation and the success to accomplish that task, the wider gap would produce a low index.

The health related determinants of Qol includes cognitive, social, emotional, and physical operation by the patient during disease period and the effect of intervention on his/her status (Leplege et al., 1997) . Thus Qol may be used as a source for comparing the effectiveness of medications and a base for approving a new anti-disease drug. The only problem involved in this indicator is the personal subjective judgment in the calculation process of health profile through EQ-5D classifier (Feld, 1995; Detmar et al., 1998; Muldoon et al., 1998; Velikova et al., 1999). To overwhelm this difficulty, EuroQol group recommended a preference based index for assigning weights to various prominent health conditions (EuroQol Group, 1990). In this process, first the patients mark themselves on a five dimensional EQ-5D classifier consists of Mobility, Self-Care, Leisure, Anxiety, and Pain. Each dimension is categorized in five levels and patients are asked to tick on the best represent able health condition. At the second place of this two parts algorithm, usually consists of visual scale; patients mark themselves on a 20 cm long scale which portrays quantitative measure

of the health state. The EQ-5D classify the preferences of various health status, while Time-Trade-Off (TTO) scale collects numerical index of healthiness which are combined together through modeling techniques to estimate a single determinant of Qol (Kind et al., 1994). A massive amount of research work has been conducted to develop an algorithm for interpolating the health status score, but the most commonly used technique for the weighting system of health profile is the development of a main effect linear regression model. The coefficients of such model are estimated, which are the amount of decrement from the weights of full health status and known as "valuation tariff" (Brazier et al., 1993; Kind et al., 1994; Dolan et al., 1995). These tariff valuations are widely used in the cost-effectiveness analysis in clinical trials where the performance of an intervention can be judged in the form of two outcomes via Quantity and Quality of life of patients. One such measure that incorporates these two terms in a single index is the Quality-Adjusted Life Years (QALY) gained, which can be combined together with the cost on medication for cost-effectiveness ratio (Konig et al., 2010) **.** QALY is the arithmetic product of quantity and quality of life to be lived by a patient and is extensively acknowledged as a standard for assessing the cost effectiveness analysis (Gold et al., 1996; McPake et al., 2002; Drummond et al., 2005).

1.1 Need of the study

The process of shared research work done by a network of multidisciplinary researchers belonging to seventeen different kingdoms of Europe resulted in the development of a generic measure EQ-5D instrument. This instrument is widely used in most of the clinical trials and pharmaceutical companies for the cost-effectiveness analysis, and comparison of different interventions in health and medicine (Shaw et al., 2005). But no research work is carried out on this in developing countries in general and Pakistan in particular. Similarly, no clinical researcher used it to estimate the Qol of patients in order to investigate the effects of treatment on them and compare the performance of various anti-disease interventions. So there is a need to introduce this measure in the clinical trials in developing countries like Pakistan and estimate the Qol of patients and the improvement in their health status subsequent to undergone a particular treatment.

1.2 Objectives

The present study was conducted with the following main objectives

1. To estimate quality of life for cancer patients using the EQ-5D and Time-Trade-Off techniques before and after treatment and to investigate the effectiveness of chemotherapy.
2. To test a waiting distribution for the life expectancy of the patients and to estimate the survival function for the life expectancy in the improved health conditions.
3. To estimate the QALY gain for various life expectancy and calculate the cost-effectiveness ratio.

2. Methods and Materials

The patients were surveyed with a set of items containing EQ-5D quality classifier, Time-Trade-Off (TTO) rating scale and the questionnaire including information about demographic factors. Patients died during the study period, refused to respond, and patients with worse than dead category (Negative Qol index) were censored from the data for further statistical analysis.

2.1 Patients and sampling scheme

All patients with various types of tumors and cancer infected cells, who visited the Radiation Therapy Department of the Irnum Hospital Peshawar, were asked to participate in the study. All these patients report themselves on TTO scale and EQ-5D self-evaluation classifier in order to estimate their Qol. Total 114 patients visited the Irnum Hospital Peshawar during the study period; five patients refused to respond, nine died while a substantial number of hundred patients were interviewed. Information was gathered on both scales before and after the treatment. The expected life of patients was estimated with the consent of cancer physicians.

2.2 EQ-5D Questionnaire

EQ-5D is a standard tool for estimating the health related Qol of patients. This was first developed in 1990 by the EuroQol group in order to provide a general measure of the health conditions for clinical trials. Essentially it covers five dimensions of the health profile .i.e. Mobility, Self-Care, leisure Activities, Pain/Discomfort, and Anxiety/Depression. Each aspect is divided into five non overlapping categories abbreviated as EQ-5D-5L. The patient is asked to tick in the most appropriate box representing his/her health status in each of the five health dimensions. Nowadays the levels used are No, Slight, Moderate, Sever, and Extreme Problem numbering from 1 to 5 digits which express the level of selected dimension. These numbers do not have any arithmetical significance but representing the appropriate level. The possible range for each of the five dimension variable is from 1 to 5 where, 1= no problem, 2= slight problem, 3= moderate problem, 4= severe problem, 5= extreme problem. Once the respondents tick the appropriate level these are combined in a vector form to represent the health state of patient. For example if a patient select 1 in mobility, 3 in self-care, 2 in leisure activity, 5 in pain and 4 in anxiety then the state would be represented as 13254. The vector 11111 represent the best logical health state i.e. no problem in any dimension, while the vector

55555 representing the worst possible logical state indicating extreme problems in all.

2.3 Time-Trade-Off (TTO) scale

Once the patients select their appropriate health state, then these codes need to be converted into numerical health utility value. The most common technique is the TTO approach which is based on the subject consideration of the relative small amount of time willing to sacrifice for the perfect health and avoid poor state of health. TTO is a 20 cm long scale containing about 10 points on it.

The patient is told that you have to trade-off between 10 years of life in the current state or to give up some years and live for a shorter period of time in perfect health conditions. The patient draw a cross line on the number of years S/He would like to live in full health that would be equal to 10 years in the current state. The worst health situation is indicated by 0, while 10 representing the full health status. The person's individual score is then calculated by dividing the number by 10 e.g. if a patient draw a cross line on 8 his/her utility value would be 0.8 and S/He is willing to trade off 2 years for improved health conditions.

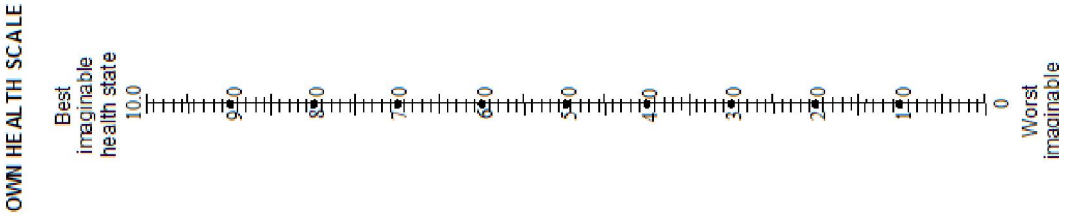

Figure 1: Time-Trade-Off scale

2.4 Single index for Quality of life Assessment

The valuation of health quality describe from the core set of TTO questionnaire and the health state vectors collected from EQ-5D classifier must be combined together to interpolate a single index value of the Qol. An ordinary least square regression model is constructed to regress the TTO valuation (dependent variable) on the dummy variables describing the four levels of each dimension of EQ-5D questionnaire i.e. mobility, self-care, leisure activities, pain, and anxiety (independent variables). Along with these twenty indicator variables, one dependent variable, intercept term and stochastic error term were included in the model. Thus the following regression model is fitted in the literature to estimate the weights associated with the health profile

$$\text{TTO score} = \beta_0 + \beta_1 X_{12} + \beta_2 X_{13} + \beta_3 X_{14} + \beta_4 X_{15} + \beta_5 X_{22} + \beta_6 X_{23} + \beta_7 X_{24} + \beta_8 X_{25} + \beta_9 X_{32} + \beta_{10} X_{33} + \beta_{11} X_{34} + \beta_{12} X_{35} + \beta_{13} X_{42} + \beta_{14} X_{43} + \beta_{15} X_{44} + \beta_{16} X_{45} + \beta 1_7 X_{52} + \beta_{18} X_{53} + \beta_{19} X_{54} + \beta_{20} X_{55} + \varepsilon$$

where β_0 is the weight of health valuation in the full health status (category 11111) and $\beta_1, \beta_2, \ldots, \beta_{20}$ are the tariff valuation and are the decrement from perfect health value of $\beta_0 = 1$.

Variables x_{ij} receive a value equal to 1 if the patient ticks on the particular level of each dimension and 0 otherwise. The coefficient of the corresponding level of each height of EQ-5D is subtracted from the full health coefficient of β_0 =1, for example if we consider the health state vector 21312. We would subtract β_2 (coefficient of moderate problem of mobility), 0 (no problem in self-care), β_6 (extreme problem of leisure activities), 0 (no pain), and β_9 (moderate anxiety) from β_0=1 (full health). The Qol index ranges from -1 to +1 where, negative value corresponds to worst than dead category. In this category the patients agree to trade-off their complete life as they prefer death due to immense pain in their infected body organ and depression related to the disease.

2.5 QALY

The outcomes of medication influence two basic aspects of life, the length to be lived by a patient and standard of their living. Therefore an index is needed to combine these two aspects in a single measure of health to inspect the performance of intervention. Thus, QALY is the arithmetic product of the remaining expected life and the quality lived by a particular patient. A year lived in a full health status is worth 1 utility while death is represented by 0. However a single year lived in less than perfect health condition is assigned a utility value between these two extreme limits. Thus QALY can be calculated as

QALY= Qol*Expected life

where Qol is the quality of life index and expected life means the number of years to be lived in

that particular health state e.g. if an intervention resulted in rising the life expectancy by 3 years rather than dying in the next year but his quality of life fell down to 0.7 (lose some body parts in medication) then the principle of QALY will generate a value equal to 2.1 (3 years of extra life to be lived * quality of 0.7= 2.1).

QALY combines these two factors to analyze the effectiveness of intervention, thus quantity of life may be expressed in terms of life expectancy as

$$\frac{\mathrm{d\,QALY}}{\mathrm{dt}} = \mathrm{P_1(t)Q_1(t) + P_0(t)Q_0(t)}$$

where

$\mathrm{P_1(t)}$ is the proportion of live people and $\mathrm{P_0(t)}$, is the proportion of dead people, similarly $\mathrm{Q_1(t)}$ and $\mathrm{Q_0(t)}$ is the weight of quality of life attached to live and dead people respectively. Hence, the mean QALY gained is estimated by

$$\int_0^l P_1(t)\, Q_1(t) \quad \cdots\cdots\cdots (II)$$

where l is the age of the disease and $\mathrm{P_1(t) = S_1(t)}$

2.6 Statistical tools

A three months study was carried out during 1st June 2012 to 1st September 2013, at radiation therapy department of Irnum Hospital Peshawar. In order to analyze the effectiveness of treatment, paired sample t test was carried out for comparison Qol of before and after chemotherapy treatment. Pearson's correlation coefficient was estimated between Qol and age of the respondents. kalmogrove Smirnove test was used to fit a theoretical waiting time distribution to the expected life of the patients in order to estimate the survival function for the time duration of the remission of disease. QALY was calculated for the cancer patients and the QALY gained due to chemotherapy at all age groups for various life expectancy was calculated. Cost effectiveness ratio was calculated to estimate the amount of money spent by the patients for improved health conditions.

3. Statistical Analysis

The gender wise distribution of the cancer patients surveyed in this study is summarized in Figure 2. It shows that a high number of females i.e. 54 out of 100 patients are the victims of cancer while a considerable number of males (46 out of 100) are suffering with the same disease. Males to females ratio is about 1:1.17 for all 100 cases, which means that there are 117 female cancer patients comparison to 100 male patients in Peshawar district. Almost 39.28% of all female victims suffered from the breast cancer and 10.71% from the reproductive system tumor, while on the other hand only a couple of males reported chest and reproductive system cancer. The males to females sex ratio for breast and reproductive system tumor is 1:14 that is 1400 females suffers from breast cancer for each 100 males. It suggests that one of the prime reasons of such a high percentage in the female patients is the breast and reproductive system tumor.

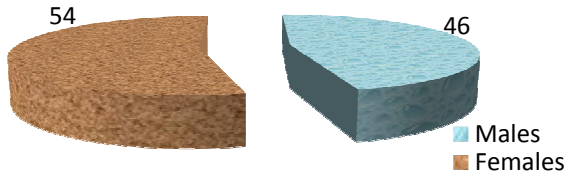

Figure 2: Gender wise distribution of the patients

3.1 EQ-5D

Table 1 summarizes the EQ-5D health profile responses, which suggest that caner badly affect the social and personal life of the patients. As mentioned by the fact that 34% patients have extreme problems in Mobility, 22% and 38% in Self-Care and Leisure activities respectively. Similarly 35% suffering extreme pain in their infected organ, and 34% experiencing extreme anxiety level. A very small proportion of the patients fall in the No Problem category.

Table 1: EQ-5D Responses Before Chemotherapy

Dimension/Level	Mobility	Self-Care	Leisure	Pain/Discomfort	Anxiety/Depression
No Problem	9	9	2	9	10
Slight Problem	14	10	5	14	6
Moderate Problem	17	27	22	24	21
Severe Problem	26	32	33	18	29
Extreme Problem	34	22	38	35	34

Table 2 Indicates that the health status of the patients was improved by chemotherapy treatment, as only 8% complain about extreme problems in Mobility of their body parts. After treating the only 7% have extreme problems in Self-Care activities and 14% in Leisure activities, like wise 17% and 24% suffering from Pain and Anxiety respectively. After the treatment most of the patients fall in No or Slight problem in each dimension.

Table 2: EQ-5D Responses After Chemotherapy

Dimension/Level	Mobility	Self-Care	Leisure	Pain/Discomfort	Anxiety/Depression
No Problem	19	35	20	5	26
Slight Problem	34	22	28	30	20
Moderate Problem	27	22	26	22	16
Severe Problem	12	9	15	26	14
Extreme Problem	8	7	14	17	24

3.2 Time-Trade-Off (TTO)

Table 3: Time-Trade-Off Descriptive

TTO	N	Mean	S.E Mean	S.D
Before	100	4.5	0.252	2.51
After	100	2.32	0.145	1.44

Table 3 elicit TTO responses that were collected through a visual scale and it was observed that the patients agreed to trade-off an average of 4.5 years for the improved health conditions that would be considered equivalent to the 10 years in current health. After the radiation therapy there health status was so improved that they decide to trade-off only 2.32 years of their life for full health.

3.3 Regression model for estimating quality of life

A simple linear regression of main effects is fitted to the data and the coefficients of the model are estimated, the following model gives the decrement coefficients which are to be subtracted from $\beta_0 = 1$ to estimate the Qol values for each health state. The regression model for quality before chemotherapy is:

$$\text{TTO valuation} = \beta_0 + 0.089X_{12} + 0.14X_{13} + 0.17X_{14} + 0.19X_{15} + 0.14X_{22} + 0.18X_{23} + 0.26X_{24} + 0.21X_{25} + 0.19X_{32} + 0.24X_{33} + 0.20\ X_{34} + 0.27X_{35} + 0.12X_{42} + 0.17X_{43} + 0.22X_{44} + 0.30X_{45} + 0.15X_{52} + 0.21X_{53} + 0.27X_{54} + 0.32X_{55}$$

where β_0 is the coefficient of full health and $\hat{\beta}_i$ are the decrement coefficients.

In a very identical manner the regression model for regressing the TTO valuation after chemotherapy on twenty state vectors dummy variables representing the levels of mobility/self-care/leisure-activities/pain/anxiety for estimating Qol is given by:

$$\text{TTO valuation} = \beta_0 + 0.063X_{12} + 0.045X_{13} + 0.079X_{14} + 0.069X_{15} + 0.097X_{22} + 0.083X_{23} + 0.063X_{24} + 0.089X_{25} + 0.085X_{32} + 0.074X_{33} + 0.037\ X_{34} + 0.073X_{35} + 0.027X_{42} + 0.050X_{43} + 0.060X_{44} + 0.045X_{45} + 0.069X_{52} + 0.021X_{53} + 0.055X_{54} + 0.065X_{55}$$

Table 4 gives the overall Qol for 100 patients ahead and subsequent to chemotherapy. The average Qol for patients before the treatment was 0.3227 ($\pm$0.1263), while after curing the disease their standard of living was improved to 0.6620 ($\pm$ 0.1368). A significant improvement occurred as a result of medication where the difference in the Qol was 0.3393, with t statistic value of 19.71 and p value <0.05 suggesting chemotherapy is an effective treatment for curing the cancer. It is clear from Figure 3 that the Qol index falls in the range of 0.6 to 0.8 for most of the patients after chemotherapy, whereas is was below 0.5 most of the time before treatment.

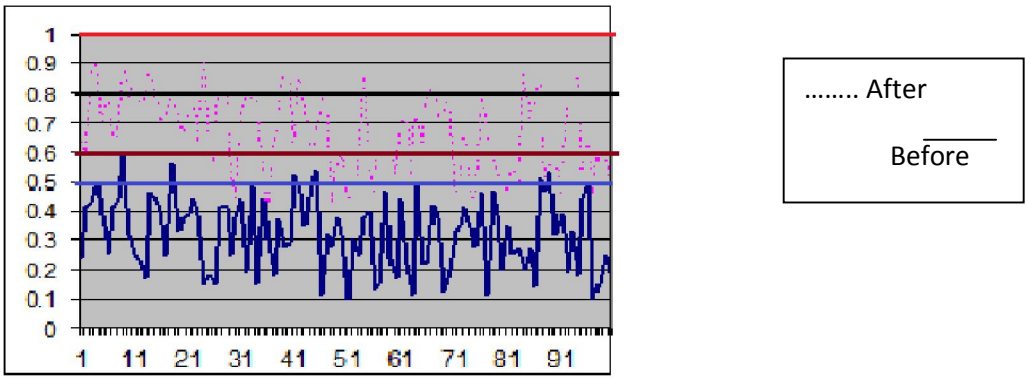

Figure 3: Qol Index before and after chemotherapy

Table 4: Descriptive Statistics of QOL

	N	Minimum	Maximum	Mean	Standard deviation Deviation
Before Treatment QOL	100	.10	.59	.3227	.12625
After Treatment QOL	100	.40	.90	.6620	.13684

Table 5 gives Pearson correlation coefficient between the age of the respondent and their Qol before and after treatment. The correlation before the treatment is -0.131 with a p-value of 0.195 while after curing the disease the coefficient becomes -0.371 with p-value 0.00014, suggesting that there is a significant negative correlation between the Qol after the treatment and age of the patient. While on the other hand Qol before the treatment and age of the respondent is insignificant.

Table 5: Correlation coefficient

Factor	Correlation	P-Value
Age*Before Treatment Qol	-0.131	0.195
Age*After Treatment Qol	-0.371	0.00014

3.4 Survival Function for Life Expectancy

Table 6 revealed that the expected life follows an exponential distribution with mean 3.43 years. The maximum absolute difference between these two is 0.053 with a chi-square test statistic value of 0.582 and p-value 0.887. This distribution of life expectancy is further used for estimating the survival function of the life expectancy in the improved health conditions and hence QALY is estimated using Equation-I:

$$\mathbf{f(t)} = \frac{\mathbf{1}}{\mathbf{3.43}} \mathbf{e}^{\frac{-\mathbf{t}}{\mathbf{3.43}}}$$

$$\mathbf{S(t)} = \mathbf{e}^{\frac{-\mathbf{t}}{\mathbf{3.43}}} \quad \ldots\ldots\ldots\ldots\ldots\ldots \mathbf{II}$$

Table 6: Kalmogrove Smirnove Test

Factors	Expected life	Maximum Difference	Chi-Square	P-value
Exponential parameter	3.43	0.053	1.518	0.87

The survival probabilities are calculated using the survival function given in Equation-II. Figure 4 illustrate the survival curve of the patients.

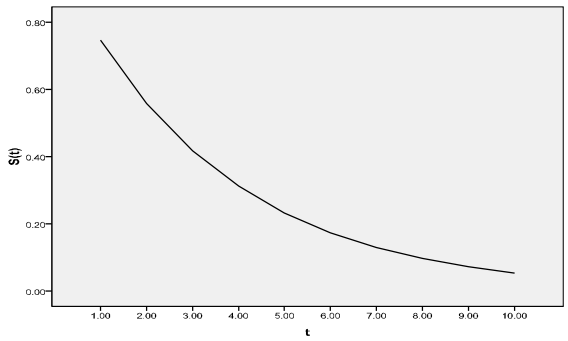

Figure 4: Survival Curve

3.5 Quality Adjusted Life Years Gain

Life expectancy in the improved health condition for the patients was estimated with the harmony of clinical researchers by analyzing the conditions of the patient and performance of the intervention. It was pointed out that the minimum expected life in improved health status was one year while maximum time of was ten years, with an average life expectancy of 3.43 years. Using equation -I QALY was calculated for life expectancy of 2, 3, 5, and 10 years expected life. Table 7 gives the Average QALY gained and the cost per QALY gained by the patients.

Table 7: Cost per QALY

Life expectancy	Average QALY gained	Cost Per QALY gain
Two years	0.19	27710 PKR
Three Years	0.15	36946 PKR
Five Years	0.079	70151 PKR
Ten Years	0.017	326000 PKR

4. Results and conclusion

This study investigates the effectiveness of chemotherapy treatment carried out for curing the cancer tumor and a group of 100 patients who visited the IRNUM Hospital Peshawar were interviewed. This group of patients was subjugated by mostly females, because of their common exposure to breast and reproductive system tumors. Male subjects were

observed in the mouth and stomach cancer category because of the excessive use of the tobacco products by the youth.

The responses of EQ-5D classifier was an indication that mostly the cancer patients had problems in the mobility and they could not move their body parts freely because of immense pain in the infected organ. Due to this massive pain and discomfort in the body they are unable to perform their self-care and leisure activities such as eating, washing, walking, etc. Due to these factors the patients are feeling extreme anxiety and depression regarding their health and standard of living that's why they are willing to trade-off some years of their life for better health conditions. Data from TTO scale elicited that on average patients were agreed to trade-off 4.5 years for improved health status in order to feel less pain and anxiety and perform daily life activities more often. These conditions were improved by chemotherapy where patients felt relatively less pain and became able to perform these activities more regularly. This could be observed from TTO as well, because only 2.23 years of life are trade-off by the patients after chemotherapy. Qol of the cancer patients was estimated by regressing the TTO responses on twenty dummy variable and was observed that the average Qol before chemotherapy was 0.3227 while after it was improved to 0.6620. This was an indication that chemotherapy treatment significantly increased the overall standard of living of the patients by reducing their pain and anxiety and stopped the tumor from spreading out faster. Analysis of student's t distribution signified that the treatment was effective at all age groups but there is no correlation found between age of the patient and their Qol before treatment. On the other hand significant negative correlation was observed between age and Qol after chemotherapy. This clarified that chemotherapy was more effective at the lower ages and lost its utility as the age of the patients increased. In the same way the expected life of the patients in the improved health status also decline exponentially with an average life expectancy of 3.43 years after chemotherapy. A very low proportion of the patients will survive in the improved health for 10 years or more, a high risk of striking of the disease is associated with patients, as the time of treatment increased.

Additional cost on the treatment of chemotherapy was estimated and it was observed that each patient paid an average amount of Rs 5547 PKR for their improved health status. The cost effectiveness ratio suggested that this average cost increased as the time after chemotherapy increased because the patients had to use different kind of drugs in order to survive in the improved health conditions. The QALY gained was highest where 0.22 utility per year is gained at additional cost of Rs 27710 PKR per QALY when the expected life in improved conditions was considered to be two years. For ten years of life expectancy the QALY gained reduced to 0.017 utility per year for a cost of Rs 326000 PKR per QALY and continued decreasing as the expected life increased with additional charges.

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6/6/2014