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Assessing the performance of direct and indirect utility eliciting methods in patients with colorectal cancer: EQ-5D-5L versus C-TTO

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Abstract
Direct and indirect preference-based methods are two main types of utility generating methods which are being frequently used in cost-utility analysis. However, a key question is how do these two methods perform in terms of validity? The aim of this study is to assess the utilities derived from EuroQol five-dimensional 5 level (EQ-5D-5L) as an indirect method and composite time trade-off (C-TTO) as a direct method in patients with colorectal cancer (CRC). A total of 223 patients with CRC were consecutively selected from three cancer centers in Tehran between May and September 2017. The EQ-5D-5L and C-TTO methods were used to estimate utilities in patients. Wilcoxon test was performed to compare utilities between C-TTO and EQ-5D-5L. In addition, intraclass correlation coefficient (ICC) and Bland–Altman plot were used to assess the agreement between the two methods. Bootstrapping quantile regression analysis was performed for comparison coefficient. The mean values of EQ-5D-5L (0.7186 ± 0.1275) for all stages were significantly higher than the C-TTO (0.4180 ± 0.4670) values. Stage 1 had the highest utility in both C-TTO (0.8167 ± 0.2332) and EQ-5D-5L (0.8339 ± 0.0535), whereas stage 4 had the lowest utility (0.1283 ± 0.5530 and 0.6001 ± 0.1220, respectively). As well, the C-TTO underestimates the values in low level of utilities and overestimates in high level of utilities. The overall ICC between the two methods was 0.50. Our study provides some tentative results about the differences between values of EQ-5D-5L and C-TTO, but clearly more work is needed to be done on this issue.

Keywords Utility · EQ-5D-5L · C-TTO · Colorectal cancer

1 Introduction

Colorectal cancer (CRC) was ranked third in terms of incidence and second from mortality perspective with more than 1.8 million new colorectal cancer cases and 881,000 deaths in 2018 (Bray et al. 2018). New interventions in the field of medical treatments

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have increased the survival of CRC patients; however, appearance of these interventions are associated with increasing economic burden on countries' healthcare system. The scarcity of resources makes the economic evaluations an integral part of the decision making process in health sector. Quality Adjusted Life-years (QALYs) are the outcome measure frequently used in economic evaluations. QALYs are calculated through preference-based health-related quality of life (HRQoL) weights in terms of utilities (Ameri et al. 2018).

There are two preference-based methods (direct and indirect) to estimate weights of QALYs. The direct methods (the rating scale (RS), the time trade-off (TTO), and the standard gamble method (SG) are used to directly elicit the value for a given state (Lidgren et al. 2007). The indirect methods are methods for defining and valuing health states that their scoring algorithms are valued in surveys, where general public are asked to assign values to the health states describing which is described by indirect measures. So far, several indirect measures including EQ-5D, SF-6D, HUI, etc. have been developed. The EQ-5D five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) is one of the most commonly used measures to elicit utilities across different diseases.

There is a controversy regarding which methods (direct or indirect) must be applied to estimate the utilities for economic evaluations (Polsky et al. 2001; Peeters and Stiggelbout 2010). Many studies have tried to address this issue by comparing the utilities derived from EQ-5D and TTO in different groups of patients, such as diabetes (Heintz et al. 2012), menopause (Zethraeus and Johannesson 1999), subarachnoid haemorrhage (Polsky et al. 2001), primary open-angle glaucoma (Bozzani et al. 2012), chronic illnesses (Ubel et al. 2003), and breast cancer patients (Lidgren et al. 2007; Perez et al. 2001). The results of the studies showed that there are significant differences in scores between the two methods, as direct methods typically assign the higher utility on dysfunctional health states than indirect methods. The difference is important because it can play an important role in the results of the valuation and subsequently in measuring the effectiveness of the health intervention (Polsky et al. 2001; Heintz et al. 2012; Zethraeus and Johannesson 1999; Bozzani et al. 2012; Ubel et al. 2003; Ratcliffe et al. 2007). Therefore, it is necessary to investigate how these methods behave in specific disease areas. Previous studies in this area have mainly compared the EuroQol five-dimensional 3 level (EQ-5D-3L) values against the conventional TTO (Polsky et al. 2001; Heintz et al. 2012; Zethraeus and Johannesson 1999; Bozzani et al. 2012; Ubel et al. 2003; Ratcliffe et al. 2007). There is some evidence showing that sensitivity of EQ-5D-3L to changes in health is low. The EQ-5D-5L is a new version of EQ-5D that raises the number of response levels from 3 to 5 in each dimension. It is assumed that increasing the response levels will increase the sensitivity of the measure in relation to small change (Round 2018). On the other hand, the conventional TTO has been criticized because it applies different valuation procedures for states worse and better than dead such problems. The C-TTO is a modified version of the conventional TTO that is designed to deal with such a problem (Luo et al. 2013; Oppe et al. 2016). However, data on comparison between the EQ-5D and TTO utilities in cancer patients are limited. Even if there has been any comparative study, they have compared the EQ-5D-3L values against the conventional TTO. To the best of our knowledge, no study has ever been conducted to assess the difference between utilities generated from the C-TTO and EQ-5D-5L in cancer patients. Trying to address these issues, we used C-TTO as a direct method and EQ-5D-5L as an indirect method to generate a utility in patients with CRC and to compare the performance of each method.

2 Materials and methods

2.1 Data collection

255 patients with CRC were recruited using a consecutive sampling method from inpatients and outpatients in surgery, chemotherapy, and radiotherapy wards of three governmental cancer centers (Imam Khomeini Cancer Institute, Shohadaye Tajrish, and Shohadaye Hafte Tir) in Tehran between May and September 2017. Patients were included in the study only once, even if they attended the outpatient clinic repeatedly during the recruitment period. The sample size is described in details elsewhere (Ameri et al. 2019b).

Patients were administered EQ-5D-5L questionnaire and C-TTO questions along with a researcher-made questionnaire to capture demographic characteristics of the patients. The two methods were applied through a face-to-face interview. Furthermore, clinical data were extracted from medical records of the patients. Patients with a previous diagnosis of CRC, being able to communicate in Persian and having no cognitive disorders were eligible to take part in the study. The informed consent was obtained from all patients before participating in the survey.

All interviews were conducted in a meeting between the patient and researcher in patient rooms in hospitals. We also used visual aids in the form of graduated scales to illustrate the length of the different lives for the iteration procedure. Interviews were stopped when the respondent was not able to comprehend the C-TTO task and has no interest to continue the interview process.

2.2 Health related quality of life

2.2.1 EQ-5D-5L

The EQ-5D-5L is a new version of EQ-5D that was introduced by EuroQoL. This version is different from the previous version of EQ-5D-3L in terms of number of levels. The EQ-5D-5L contains 5 dimensions each with five response levels: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression, whereas the EQ-5D-3L has 3 levels for each dimension. The EQ-5D-5L questionnaire describes 3125 potential health states compared with 243 states defined by the EQ-5D-3L questionnaire (van Reenen and Janssen 2015). Iranian EQ-5D-3L value set calculated by TTO for general public (Goudarzi et al. 2019). However, the Iranian value set for EQ-5D-5L has not been developed yet, so we calculated it through the crosswalk algorithm presented by the EuroQoL group (Goudarzi et al. 2019; Van Hout et al. 2012). The validity and reliability of the Persian translation of EQ-5D-5L instrument have been approved by EuroQol group (EuroQol Research Foundation 2017; Ameri et al. 2019a).

2.2.2 Composite TTO

The C-TTO is a combination of the conventional TTO and lead-time TTO. In this approach, for health states better than dead (BTD), the BTD task of the conventional TTO is selected, but for health states worse than dead (WTD), lead-time TTO is used. The value of impaired state h for BTD is calculated using the conventional TTO.

Participants are asked to choose between living in full health for x years followed by death (alternative 1); and living in t years in h (where $x \leq t$) followed by death (alternative 2). Time t is fixed, while time x is varied until the participant becomes indifferent between two alternatives. The value of h, U (h), is determined by x/t. The value of impaired state h for WTD is calculated according to lead-time TTO. The lead-time TTO includes a certain number of years (L) in full health before t years in impaired state h and death. In this approach, the participants are asked to choose between living for x years in full health followed by death (alternative 1); and living for x years in full health followed by t years in h (where $x \leq t + L$) followed by death (alternative 2). Time t and L are fixed, whereas time x is varied until the participant reaches the indifference point between two alternatives. The value of h, U (h), is given by $(x - L)/t$ $(x \leq t + L)$ (Oppe et al. 2016; Janssen et al. 2013).

To estimate the utilities, first, each patient completed EQ-5D-5L to determine their health states, and then C-TTO was applied for the same state. The C-TTO was done through several phases: first, patients were faced with health states BTD where they had to choose between x years of full health (Life A) and years of current health status which is equal to the years of survival time of each stage (Life B) ($x \leq$ years of survival time of each stage). Time x is varied until the participant's selection between the Life A and Life B are indifferent. Based on CRC survival rates in Iran, four time periods were used, including x: 4, 3, 2, and 1 year for patients with stage 1, 2, 3, and 4, respectively; and it was 3 years for patients with unknown stage. For example, if a patient in stage 1 CRC, whose years of survival time are 4 years, could not differentiate between 3 years in Life A and 4 years living in Life B, then the value of that health state would be 0.75 (3/4) (Fig. 1a). For health status that patients prefer to die immediately rather than survive in life B; the lead-time TTO approach was used. In this case, patients had to choose between x years (L) in full health followed by death (Life A); and x years (L) in full health followed by years of current health status and death (Life B). For example, if a patient in stage 1 CRC reaches an indifference point between the amount of time '3 years' in Life A and Life B, the health state value is − 0.25 (3, 4)/4 (Fig. 1b). X was varied systematically in 6 months for patients in stage 1 and 4 months for stages 2 and 3, and 1 month for stage 4 in 'ping-pong' fashion until the point of indifference was reached for the patient.

2.3 Statistical analysis

The distribution of EQ-5D-5L and C-TTO utility scores was not normal ($p < 0.05$ by Kolmogorov–Smirnov test); therefore, Wilcoxon test was performed to compare utilities

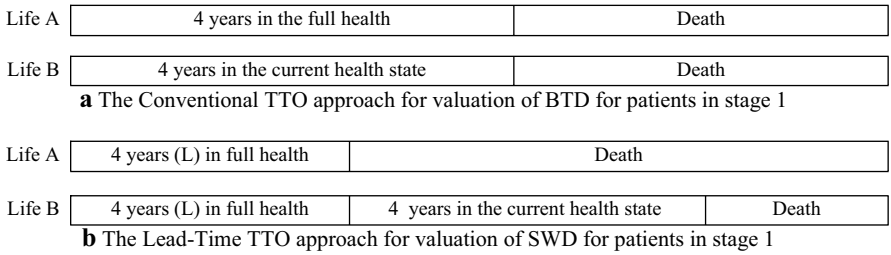

Fig. 1 The composite time trade-off

between C-TTO and EQ-5D-5L. To assess the degree of agreement between the two methods, the ICC and Bland–Altman plot were used. Since the results of normality tests (Kolmogorov–Smirnov test) showed no normal distribution; therefore, we used bootstrapping quantile regression for comparison coefficient. The analysis was performed using the C-TTO and EQ-5D-5L utility scores as the dependent variables and the levels of EQ-5D-5L dimensions and stages as independent variables. Analyses were performed with STATA version 14.0

3 Results

Of 252 patients who completed the EQ-5D-5L questionnaire, 223 patients completed the interview process for the C-TTO question (88.50%). 29 incomplete interviews were excluded from the final analysis including 16 men and 13 women; 16, 9, and 4 patients with stages 3, 4, and 2, respectively. The mean age (59.1 years) of non-responders to the C-TTO question was higher than those who answered the C-TTO question (55.2 years). Only the patients who answered all questions in both methods were included in the analysis. Reasons for interview failure included refusal to participate due to lack of interest, unacceptable questions, religious belief, and difficulty in comprehending the C-TTO task. Patients' characteristics are summarized in Table 1.

The results of the Wilcoxon test revealed that the mean utility difference within each stage was significant for two methods (Table 2).

As shown in Table 2, the mean values of EQ-5D-5L for all stages were significantly higher than the C-TTO values. Stage 1 had the highest utility in both methods (EQ-5D-5L = 0.8339 and C-TTO = 0.8167), whereas stage IV had the lowest utility (EQ-5D-5L = 0.6001, and C-TTO = 0.1283). As can be seen in Table 2 for stage 4, the C-TTO leads to lower QALY weights, while EQ-5D-5L has consistent pattern. The relationship between the two methods within stage 1 and unknown stage has the highest and lowest ICC values, respectively. The distribution of scores on the EQ-5D-5L and C-TTO has been illustrated in Fig. 2. Figure 3 presents the Bland–Altman plots that were obtained by plotting the distribution of differences between the C-TTO and EQ-5D-5L utilities (y axis)

Table 1 Demographic and clinical characteristics of the patients (N = 223)

Characteristics	N (%)
Age (years), mean ± SD	55.2 ± 12.98
Female	71 (31.84%)
AJCC stage classification	
Stage I	18 (8.07%)
Stage II	36 (16.14%)
Stage III	109 (48.88%)
Stage IV	52 (23.32%)
Unknown	8 (3.59%)
Treatment status	
Chemotherapy	134 (60.09%)
Radiotherapy	36 (16.14%)
Surgery	13 (5.83)
Non service	40 (17.94)

Table 2 Utilities for the five stages derived from EQ-5D-5L and C-TTO (N = 223)

Stage	TTO N (mean ± SD [95% conf. interval])	EQ-5D-5L N (mean ± SD [95% conf. interval])	ICC
I	18 (0.8167[a] ± 0.2332 [0.7007–0.9327])	18 (0.8339 ± 0.0535 [0.8072–0.8605])	0.47
II	36 (0.5117[a] ± 0.3873 [0.3806–0.6427])	36 (0.7833 ± 0.0870 [0.7539–0.8128])	0.38
III	109 (0.4414[a] ± 0.4088 [0.3638–0.5190])	109 (0.7310 ± 0.1126 [0.7096–0.7524])	0.40
IV	52 (0.1283[a] ± 0.5530 [0.0256–0.2823])	52 (0.6001 ± 0.1220 [0.5668–0.6347])	0.33
Unknown	8 (0.6625[a] ± 0.2722 [0.4349–0.8901])	8 (0.7650 ± 0.0563 [0.7179–0.8121])	0.15
Total	223 (0.4180[a] ± 0.4670 [0.3563–0.4796])	223 (0.7186 ± 0.1275 [0.7018–0.7354])	0.50

[a] $p < 0.0001$ (significantly different between two instruments for each instrument); *ICC* intraclass correlation coefficients

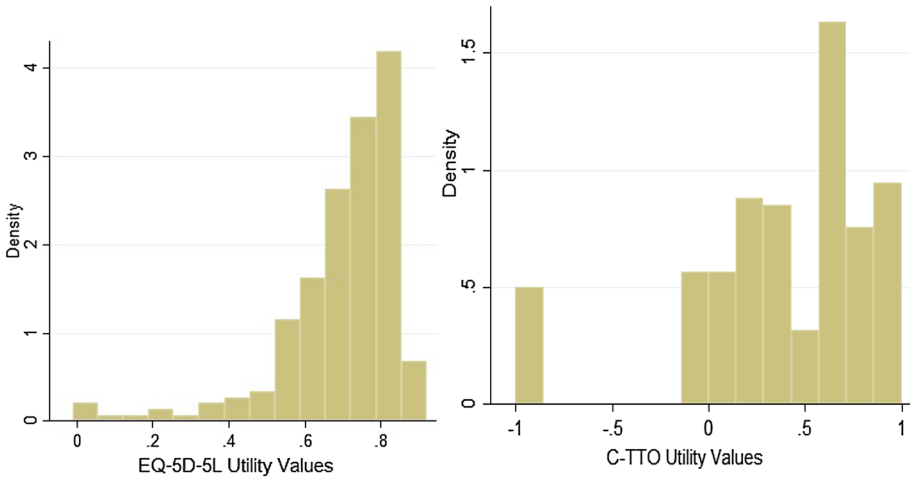

Fig. 2 Utility values of EQ-5D-5L and C-TTO for each stage

versus the C-TTO and EQ-5D-5L mean for utilities (x axis). The Bland–Altman plot for the mean difference of C-TTO and EQ-5D-5L utilities was −0.3006 ± 0.3959 SD.

3.1 The bootstrapping quantile regression analysis

The results of the regression analysis on C-TTO and EQ-5D-5L values are shown in Table 3. Model 1 of EQ-5D-5L showed that, compared to other health sates, scores of EQ-5D-5L values were lower for health state that was worse. In Model 2, the stage variable was added to Model 1, and stages 2, 3 and 4 for EQ-5D-5L and for C-TTO were significant. Findings obtained from Model 1 and Model 2 of the EQ-5D-5L showed that there are monotonic coefficients in all dimensions of the EQ-5D-5L, that is, health states that were worse had lower scores. However, it was not for models of C-TTO in the dimensions mobility, self-care, and usual activity.

The results of estimated regression coefficients showed that the C-TTO and EQ-5D-5L coefficients were different. In general, the coefficients of EQ-5D-5L were smaller than C-TTO. These results showed that the difference between C-TTO and EQ-5D-5L value

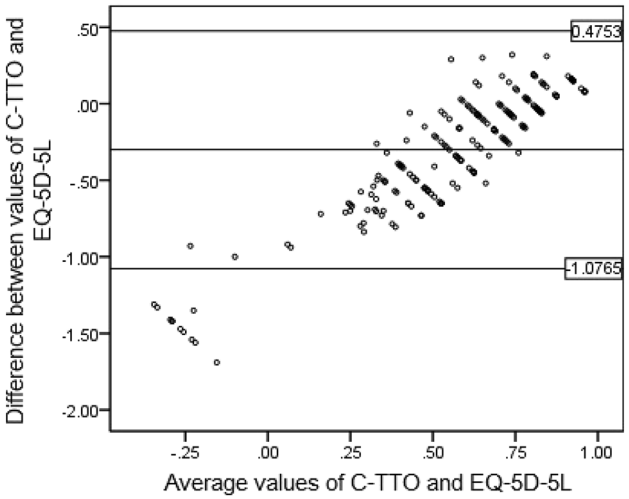

Fig. 3 Bland–Altman plot of mean utility difference between C-TTO and EQ-5D-5L (95% limits of agreement, −1.0765 to 0.4753)

scores was greater for more severe health states. Findings on the impact of the different dimensions on the health state score showed that the dimension "self-care" had the greatest impact on the EQ-5D-5L values followed by dimension "mobility". In the C-TTO, the dimension "self-care" had the greatest impact followed by dimension "pain/discomfort".

4 Discussion

To the best of our knowledge, this is the first study that assesses the performance of the C-TTO and EQ-5D-5L in CRC patients (Polsky et al. 2001; Heintz et al. 2012; Zethraeus and Johannesson 1999; Bozzani et al. 2012; Ubel et al. 2003; Ratcliffe et al. 2007). The calculation of utility scores is the key component of a cost-utility analysis. The direct and indirect methods are used to calculate utilities; however, the difference between these methods are a controversial issue. In this study, we focused on the difference between utilities calculated by the direct method (C-TTO) and indirect method (EQ-5D-5L) in patients with CRC. We used EQ-5D-5L weights that were derived from EQ-5D-3L using crosswalk algorithm. The EQ-5D-3L value sets in this study were originally developed from Iranian general public using TTO method. On the other hand, we used C-TTO method to obtain utilities from patients with different stages of colorectal cancer.

Our study has three important findings. First, when comparing mean values of utilities obtained by both methods, the difference of utilities between indirect and direct methods was significant, as the mean value of EQ-5D-5L was 0.718 while the mean value of C-TTO was 0.418, and this figure exceeds the minimally important difference (MID) (0.074) (Walters and Brazier 2005). However, the pattern of difference varied in the range of utilities as illustrated in Bland–Altman plot. This plot showed that for more severe states, the C-TTO, in comparison with EQ-5D-5L, underestimates the values, but conversely as states get healthier, the C-TTO overestimates the values. Potentially, there might be some reasons for

Table 3 Regression analysis on composite time trade-off (C-TTO) values and Iranian version of EQ-5D-5L

Explanatory variable	EQ-5D-5L				C-TTO			
	Model 1		Model 2		Model 1		Model 2	
	β	SE	β	SE	β	SE	β	SE
Mobildity								
Level 2[a]	−0.0956*	0.00073	−0.07541*	0.00041	−0.14615	0.008451	−0.19875	0.00923
Level 3	−0.10992*	0.00091	−0.08912*	0.00067	−0.1162*	0.00119	−0.12838*	0.01432
Level 4	−0.11204*	0.00117	−0.10912*	0.00102	−0.4611	0.00196	−0.53832	0.03598
Level 5	−0.13346*	0.00217	−0.18174*	0.00231	−0.3893*	0.00315	−0.30048*	0.03891
Self-care								
Level 2	−0.09587*	0.00081	−0.08648*	0.00071	−0.12887	0.00132	−0.14103	0.10486
Level 3	−0.11312*	0.00135	−0.10363*	0.00124	−0.13138	0.01989	−0.14918	0.02854
Level 4	−0.14373*	0.00192	−0.13164*	0.00176	−0.47241*	0.00279	−0.48028*	0.19865
Level 5	−0.20262*	0.00389	−0.17395*	0.00224	−0.38180*	0.04013	−0.36871*	0.21354
Usual activity								
Level 2	−0.06908*	0.00047	−0.06721*	0.00061	−0.0914	0.00687	−0.12234*	0.07873
Level 3	−0.09128*	0.00063	−0.10443*	0.00074	−0.37492	0.00115	−0.33123*	0.09862
Level 4	−0.12987*	0.00098	−0.12154*	0.00108	−0.12348	0.00276	−0.19231	0.11589
Level 5	−0.13467*	0.00132	−0.16439*	0.00213	−0.39499	0.01388	−0.49876*	0.13631
Pain/discomfort								
Level 2	−0.06742*	0.00041	−0.06874*	0.00040	−0.13416	0.01176	−0.15416*	0.07813
Level 3	−0.09323*	0.00063	−0.09705*	0.00059	−0.14931	0.00321	−0.11408*	0.09985
Level 4	−0.11307*	0.00099	−0.18317*	0.00189	−0.31234	0.00213	−0.34343*	0.18976
Level 5	−0.1135*	0.00108	−0.19439*	0.00232	−0.41332	0.01367	−0.58944*	0.21814
Anxiety/depression								
Level 2	−0.04781*	0.00038	−0.06767*	0.00034	−0.07121	0.006770	−0.09453*	0.06743
Level 3	−0.07513*	0.00041	−0.09894*	0.00051	−0.12349	0.00107	−0.19025*	0.19732
Level 4	−0.13217*	0.00123	−0.12909*	0.00098	−0.28135	0.00214	−0.29146*	0.10254
Level 5	−0.19615*	0.00171	−0.20594*	0.00198	−0.41941	0.003445	−0.42378*	0.23124
Stage[b]								
II			−0.00132*	0.00063			−0.10871*	0.09812
III			−0.00166*	0.00068			−0.32165*	0.11876
IV			−0.00339*	0.00081			−0.39211*	0.12345
Unknown			0.00037	0.00024			−0.00217	0.09207
Intercept	0.91731*	.00018	0.91523*	0.00132	0.83862*	0.47898	0.91897*	0.09360
R^2	99.97%		99.98%		41.12%		42.23%	

*$p < 0.05$

[a]Baseline category: Level 1

[b]Baseline category: Stage I

these differences. One reason can be due to using crosswalk algorithm for converting EQ-5D-3L to EQ-5D-5L values. Results of researches showed that value scores based on crosswalk are less reliable than scores obtained from the general public-preference based value sets (Golicki et al. 2014, 2015). Another reason for this difference may arise from basic method that is used to derive value sets for EQ-5D-3L. The conventional-TTO was applied

to calculate EQ-5D-3L value sets, while we carried out C-TTO to directly obtain patients' utilities. Moreover, another reason for this discrepancy could be the source of valuation, which is general public for EQ-5D value sets and CRC patients for C-TTO. Other studies have proven that, in comparison with patients, general public usually assign higher values to a given condition (Badia et al. 2001; Johnson et al. 1998). This statement can be tracked even in Bland–Altman plot as in low levels of utility, where the state is severe, the EQ-5D under estimates the values. As utility increases and the states get closer to general public's health status, the C-TTO values exceed the EQ-5D.

Second, there is the difference between the C-TTO and the corresponding EQ-5D-3L in terms of the number of coefficients turned out to be statistically significant and monotonic variation of coefficients. If the utility measure on the 5 levels of either of the 5 dimensions is regressed for EQ-5D-5L; then, the results are going to be all significant and monotonic within each dimension. This is caused because of the weight assignments of the EQ-5D-5L. For C-TTO, some of the coefficients of dimensions mobility, self-care, and usual activity were non-significant, and changes in the coefficients of the dimensions mobility, self-care and pain/discomfort were no-monotonic. This difference can be explained by different distribution patterns of utilities. The distribution pattern of the EQ-5D-5L was unimodal, while the distribution of the C-TTO utilities had a bimodal pattern.

Third, the mean value of C-TTO was 0.342 lower than the mean value of EQ-5D-5L. This result differs from the findings of the only available study by Lidgren et al., in patients with breast cancer. They found that the TTO values were higher than the corresponding EQ-5D-3L values for all stages of patients with breast cancer (Lidgren et al. 2007). The difference can be due to different survival rates of breast and colorectal cancers. The survival rate of colorectal cancer patients is lower than that of the breast cancer patients. The colorectal cancer patients might assume that after they complete their treatment, they will remain in the current state of health for less than 5 years, while Swedish breast cancer patients survive more than 10 years after primary breast cancer diagnosis in approximately 80% of the cases (Lidgren et al. 2007). The low survival rate of colorectal cancer patients might make them more willing to trade time for an increase in quality of life, because they believe that an increase in quality of life will not occur in this short time. Another reason for lower mean of C-TTO values in comparison with the mean of TTO values calculated in the study by Lidgren et al. can be related to condition of this disease. During the data collection period, it was noticed that some patients had substantial differences in the EQ-5D-5L value compared to their TTO score. When these patients were asked to answer their C-TTO question, the majority answered that even though they did not have a more severe health state, they did not want to be in the same state, because this disease could affect the patient's family members and relatives, too. For Swedish breast cancer patients, the majority answered that even though they were not in full health, they did not want to sacrifice any time, since this would shorten their time together with their family (Lidgren et al. 2007).

This result is also inconsistent with the findings of a study by Kristina et al. on general population and another study by Zethraeus et al. on patients with hormone replacement therapy. They found that the TTO values of the actual health state were higher than the EQ-5D-3L values for the same health states (Zethraeus and Johannesson 1999; Burström et al. 2006). Such inconsistency in the results of the studies sparks the idea that when respondents are trading the years, they do not only consider the values of healthy life years in relation to the number of years in disease state. In other words, they may consider the absolute number of life years they are going to sacrifice. That is to say that the absolute number of years they have been offered to sacrifice matters. In addition, in

case of long survival, there are more available years to sacrifice using C-TTO scenario. Therefore, they may resist to sacrifice more than a given number of years. And consequently, this idea puts forward the hypothesis that respondents judge about the value of traded life years in relation to common life expectancy in their own context. Following this idea, the results of the present study also is not similar to the results reported by Bozzani et al. on utilities obtained from TTO and EQ-5D in patients with primary open-angle glaucoma. They present that TTO values were bigger than that in EQ-5D. This could be because due to the fact that patients with primary open-angle glaucoma consider themselves only temporarily dysfunctional health state (Bozzani et al. 2012). This finding of our study is in line with the results observed of utilities obtained from TTO and EQ-5D-3L in epilepsy patients. Kang et al. found that utilities obtained from TTO were lower than EQ-5D-3L. They pointed out that 50% of the survey respondents in TTO method chose immediate death rather than stay in the current state (Kang et al. 2014).

The present study has some limitations that are worth mentioning. First, since the three selected centers are the largest centers for treatment of cancers in Iran and are located in Tehran; therefore, many patients are admitted to these centers from all over Iran. Therefore, most of the studied patients did not live in Tehran. This issue imposes economic and emotional burden of caring on patients and had an impact on TTO values. Considering the disproportioned distribution of patients across stages and bearing in mind that this difference may be rooted in some socio-economic differences among patients; therefore, the results of this study should be used cautiously. It is recommended to run similar studies with quite large sample sizes and in other groups of diseases to confirm the generalizability of our findings. Another limitation is related to using crosswalk as a method to calculate value sets for the EQ-5D-5L. The value scores based on crosswalk are less reliable than scores obtained based on the general public-preference based value sets. However, using the crosswalk algorithm to generate EQ-5D-5L value sets is the only available technique at the moment for countries that do not have the EQ-5D-5L value sets based on their own context.

5 Conclusion

According to the results, the C-TTO and EQ-5D-5L values were different, but these differences were lower for relatively good health states. For more severe health states, the C-TTO values tended to be lower than the EQ-5D-5L values. Our study provides some empirical results about the difference between values of EQ-5D-5L and C-TTO. These differences could have influenced the conclusions of an economic evaluation, so clearly more work is needed to be done on this issue.

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Compliance with ethical standards

Conflict of interest The authors have stated that they have no conflict of interest.

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