IMPACT OF CANCER ON HEALTH RELATED QUALITY OF LIFE: EVIDENCE USING THE EQ-5D

A. Simon Pickard[1,2]
Caitlyn Wilke[1,2]
Hsiang-Wen Lin[1,2]
Andrew Lloyd[3]

[1]Center for Pharmacoeconomic Research & Dept Pharmacy Practice, College of Pharmacy, Room 164, 833 S. Wood St (MC886), University of Illinois at Chicago, Chicago, IL, 60612 USA;
[2] Department of Pharmacy Administration, College of Pharmacy.
[3]Health Care Analytics Group, United BioSource Corporation, 20 Bloomsbury Square, London, UK

Addresses
A. Simon Pickard, PhD (Corresponding Author)
College of Pharmacy
Rm 164, MC 886
833 South Wood Street
University of Illinois At Chicago
Chicago, Illinois, 60612
Ph: (312) 413-3357
fax: (312) 996-0397
Email: pickard1@uic.edu

Key Words: HRQL, cancer, EQ-5D

In-Text Abbreviations:
CHOP- cyclophosphamide, doxorubicin, vincristine, prednisone; CUA- cost utility analysis; HUI- health utilities index; HRQL- health related quality of life; IPI- International Prognostic Index; IQR- Inter-quartile range; nr- not reported; SD- standard deviation; SEER- Surveillance Epidemiology and End Results; QALY- quality adjusted life year; VAS- Visual analog scale; WHO- World Health Organization

Acknowledgements:
The authors acknowledge funding support from the EuroQol Group Foundation.

ABSTRACT

BACKGROUND AND PURPOSE:

Cancer is one of the most frequent disease-specific applications of the EQ-5D. The objective of this study is to describe the burden of illness associated with various cancer types measured by the EQ-5D and to provide guidance for future studies to increase uniformity and comparability of EQ-5D results.

METHODS:

A structured literature search was conducted on EMBASE and MEDLINE to identify papers using keywords related to cancer and the EQ-5D. Original research studies of patients with cancer that reported EQ-5D results or psychometric properties were included for the review.

Results: Of 57 identified articles, 31 studies were selected for inclusion. EQ-5D scores were reported in multiple studies of prostate cancer (n= 4), breast cancer (n= 4), cancers of the digestive system (n= 7), and Hodgkin and/or non-Hodgkin lymphoma (n= 3). Mean index-based scores ranged from 0.33 (SD 0.4) to 0.93 (SD 0.12) and VAS scores ranged from 43 (SD 13.3) to 84 (SD 12.0) across subtypes of cancer.

CONCLUSIONS:

A substantial body of literature supports the use of the EQ-5D in cancer. EQ-5D index and VAS scores ranged widely due to heterogeneity of treatment protocols, cancer stage, and subtype of cancer. This summary of the available literature on utility-based estimates of HRQL in cancer using the EQ-5D is intended as a resource for outcomes research and economic evaluations in this area.

●●● INTRODUCTION

In 2000, there were 22.4 million individuals living with cancer, 10.1 million new cases diagnosed annually, and 6.2 million deaths worldwide[1]. The lifetime probability of developing cancer in the United States is 46% for men and 38% for women[2]. According to the World Health Organization (WHO), "the average five-year survival rate for cancer patients is 50% in developed countries, 30% in developing countries"[1]. In addition to the uncertainty of survival time, cancer patients must attempt to strike a balance between the physiological benefits of treatment and the negative impact of these therapies on daily life[1]. Assessment of health-related quality of life (HRQL) can help to better understand the physical, mental, and emotional implications of the cancer itself as well as effects of treatments such as chemotherapy, radiotherapy, and/or surgery.

Measurement of HRQL in cancer may be assessed using cancer specific instruments such as the EORTC QLQ-C30[3,4] and the FACIT measurement system[5]. Alternatively, generic HRQL preference-based measures such as the Health Utilities Index (HUI)[6] and EQ-5D[7] may be used. Preference-based measures are advantageous because they are an appropriate means for calculating quality adjusted life years (QALYs) for subsequent application to cost-utility analysis (CUA) and allow for easy comparisons of HRQL burden across different conditions and treatments.

Among the generic measures available, the EQ-5D is widely used and simple to administer and score. A preference-based set of weights are used to convert patient responses to a health state classifier into a single index of HRQL. Each of the five dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression) on the health state classifier has three levels of response: no problems, some problems, or extreme problems. In addition to the self-classifier, the EQ-5D contains a 20 centimeter visual analogue scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) on which an individual places their current health state. The index-based score is typically interpreted along a continuum where 1 represents best possible health and 0 represents dead, with some health states being worst than dead (<0). The ability to convert self classifier responses into a single preference-based score makes the EQ-5D practical for clinical and economic evaluation[7]. Algorithms have been developed based on the preferences of the general United Kingdom population[8], and other country-specific algorithms have been developed for further use[9,10].

It is common, if not usual practice, to include HRQL measures in clinical trials in oncology. Such trials, as well as some cross-sectional studies intended to describe burden of HRQL in a cancer, may include utility-based measures such as EQ-5D which provide quality weights for the calculation of QALYs in econo-

mic evaluation. National catalogs of preference-based scores for chronic conditions have begun to appear in the literature[11]. A catalog of preference-based scores for cancer-related conditions and stages/phases of treatment would be useful to compare of the burden of specific cancers relative to the other health conditions. A catalog of HRQL burden in cancer would help can help to inform utilities assigned to different health state endpoints in decision models for economic evaluations of cancer therapy. Earle and colleagues (2000) previously reported a catalogue of utility weights in oncology[12]. Many advances have occurred since that review, including current practice in economic evaluation as well as a greatly expanded literature using preference-based HRQL measures in cancer[13,14]. A summary of studies that have applied a specific measure such as the EQ-5D to describe the burden of cancer may further support consistency in cost-effectiveness and cost-utility analysis.

This study had 2 objectives. First, the objective was to examine the evidence to support the validity and reliability of the EQ-5D in cancer. Second, we sought to describe the burden of illness associated with various types of cancer in terms of HRQL as defined by the EQ-5D self-classifier and summary scores. A secondary objective was to provide guidance for future studies to increase uniformity and usefulness of results reported in cancer studies using the EQ-5D.

METHODS

DATA COLLECTION AND ASSESSMENT

A computerized search of the current published literature was performed using MEDLINE and EMBASE for years 1988 to January 2006. The search strategy combined medical subject headings and keywords relating to cancer and the EQ-5D as follows: ('cancer'/de OR 'cancer') OR ('oncology'/de OR 'oncology') OR ('neoplasms'/de OR 'neoplasms') AND Euroqol OR 'EQ 5D' OR 'EQ5D'. Author libraries were also hand-searched for references. Only papers which were published in full were included for analysis. The inclusion criteria required that the paper was original research, patients had a diagnosis of cancer, and that the article reported EQ-5D psychometric properties or reported EQ-5D index, visual analog scale, or % dimension scores for cancer patients. There were no language restrictions[15]. Study abstracts that potentially met the inclusion criteria were identified, and full text articles were retrieved for further review[15]. A standardized data abstraction form was developed to facilitate the structured review, which included study design, patient characteristics, intervention information, published source of index-based preference weights and EQ-5D scores. The abstraction form is available upon request. Two of the authors reviewed abstracts of unique citations identified in the literature search (ASP, CTW). Articles mee-

ting the inclusion criteria were abstracted and checked for veracity (CTW, HWL). Any disagreements between the reviewers in screening and selecting the articles for review were resolved by consensus.

DATA ANALYSIS

Studies that reported EQ-5D index-based scores and/or VAS scores were sorted by cancer type and last name of the first author. Studies reporting multiple cancer types were included at the end of the table. Standard deviations were calculated from 95% confidence intervals when not reported directly in the paper. Y-error bars in figures 3-5 represent the 95% confidence interval about the mean score, which was calculated from reported standard deviations.

Psychometric properties presented in table 2 were summarized as follows: type of validity/reliability, comparison performed, and statistical test result. Known-groups comparisons were not included in this summary of psychometric properties unless clearly indicated for the purpose of psychometric evaluation.

An attempt was made to summarize the burden of cancer for each subtype by calculating pooled means across studies. Random effects-based pooled means were calculated using the DerSimonian and Laird method[16] for those types of cancer which had more than one reported mean/standard deviation, first calculating an inverse variance fixed effects pooled mean (1) and tau statistic of heterogeneity (2):

(1)
$$\theta_{IV} = \frac{\sum w_i \theta_i}{\sum w_i}$$

(2)
$$\tau^2 = \frac{Q - (k-1)}{\sum w_i - \left(\frac{\sum w_i^2}{\sum w_i} \right)}$$

Where θ_i is the mean for each individual study, Q is a measure of heterogeneity, k-1 is the degrees of freedom for the studies included in the pooled estimate, and w_i is the weight of each term, calculated as follows:

(3)
$$w_i = \frac{1}{SE(\theta_i)^2}$$

The Dersimonian and Laird random effects pooled mean is calculated with a weight adjusted for τ:

(4)
$$w'_i = \frac{1}{SE(\theta_i)^2 + \tau^2}$$

(5)
$$\theta_{DL} = \frac{\sum w'_i \theta_i}{\sum w'_i}$$

with standard error calculation:

(6)
$$SE(\theta_{DL}) = \frac{1}{\sqrt{\sum w'_i}}$$

Serial assessments of HRQL reported in a paper were included in the results, but only the baseline mean scores were included in pooled mean estimates. This was consistent with the objective of summarizing the burden of illness attributed to different types of cancer without incorporating repeated measurements into the pooled estimate of HRQL burden. When calculable, random effects pooled means were plotted alongside results for each cancer type. The formulas were inputted and statistics calculated with MS Office Excel version 2003.

RESULTS

The electronic search of databases on January 12, 2006 returned 57 papers. An additional 7 articles were identified in personal libraries for a total of 63 articles. Of 46 publications retrieved for review, 34 papers met the selection criteria, 31 which reported an EQ-5D index score, VAS score, and/or responses to the self-classifier system and 12 papers presented evidence of the psychometric properties of the EQ-5D (Figure 1). The number of cancer-related studies that reported HRQL using EQ-5D has increased over the past decade (Figure 2).

Measurement of HRQL using EQ-5D has been performed in a variety of cancer subtypes, severities (tumor/cancer stages), and treatment regimens. HRQL assessments using the EQ-5D were reported primarily in studies of cancer of the breast[11,18-23], digestive system[24-30], Hodgkin and/or non-Hodgkin lymphomas[31-34], and prostate[11,35-38]. Other cancer studies using the EQ-5D included patients with neoplasms of the bones and joints, cranial nerves and other ner-

vous system, multiple myelomas, and lung cancer[39-42]. Some studies did not report the nature/location of the cancer, where patients were characterized as either simply having 'cancer', or stating that multiple types of cancer were grouped together[11,32,43-48]. Of studies reporting mode of administration (n=27, 87%), 30% were on-site self-report, 52% were mailed-out questionnaires, and 18% were administered by in-person interview. The study setting was primarily hospital-based (81% of studies). The majority of studies (57%) involved multiple settings, while 43% were administered at a single setting. Most studies (88%) reported EQ-5D index scores using the York MVH derived algorithm. Study populations varied with respect to therapy, age distribution, and stage of treatment (Table 1).

A wide range of mean/median EQ-5D scores were reported in the literature (Table 3). The lowest five EQ-5D index scores reported occurred in the following populations: cancer-related anorexia cachexia syndrome patients measured at baseline[44], multiple myeloma patients discharged after high dose chemotherapy[41], patients receiving palliative treatment for oesophageal carcinoma[26], patients with Hodgkin or non-Hodgkin lymphoma 14 days post-autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation[33], and elderly non-Hodgkin lymphoma patients with age-adjusted IPI of 2-3 at baseline, prior to treatment with CHOP chemotherapy[31]. Low scores were not related solely to one particular type of cancer, but rather varied according to treatment type and patient subgroup (Figures 3 - 5).

Most studies of cancer patients that reported psychometric properties of the EQ-5D investigated construct validity of the EQ-5D, typically through correlations with cancer-related clinical characteristics or with cancer-specific HRQL measures (Table 2). Evidence of validity and reliability were reported most frequently in breast and prostate cancer studies as well as studies that combined cancer types. Convergent validity was the most common property assessed, typically reported in the form of association with another measure using Pearson's correlation coefficient. Comparisons were made between the EQ-5D and Musculoskeletal Tumor Society functional evaluation system (MTSS), TTO measurements, Functional Living Index- Cancer (FLIC), EORTC- QLQ C-30, SF-36, and simple VAS scales.

Of the 69 EQ-5D index-based scores shown in Figures 3, 4, and Table 3, 26 studies (37.7%) did not report a standard deviation. Of studies that reported EQ-5D index or VAS scores, 7 out of 31 studies (22.6%) did not report standard deviations (Figure 5). The random effects pooled mean of prostate cancer EQ-5D mean index scores was 0.756 (SE 0.07) and 0.785 (SE 0.05) for cancers of the digestive system. Insufficient statistical data were available from articles in other cancer types to enable the calculation of pooled mean summary scores. For instance, only one breast cancer study and no Hodgkin's or Non-Hodgkin lymphoma studies reported standard deviations for mean EQ-5D index scores,

precluding the estimation of fixed or random effects pooled means. In examining the dimension-specific burden of disease among studies that reported percentage of problems by dimension, usual activities and anxiety/depression tended to be more adversely affected by cancer (Figures 6 – 10).

••• DISCUSSION

The available literature on the HRQL burden of cancer using EQ-5D has greatly expanded in recent years. This trend is consistent with the acceptance of patient reported outcomes and quality of life as a routine measures to be incorporated into clinical trials, and of the EQ-5D as one of the international standard metric of health status. The catalog of preference-based summary scores based on the EQ-5D index-based and VAS reported in this paper for cancer-related conditions elaborates upon the more general catalogs of scores reported by Sullivan *et* al[11] and Tengs[51]. Cost-utility analyses rely heavily on generic measures such as the EQ-5D for the determination of quality adjusted life years (QALYs). This review expands upon Earle *et* al's (2000) examination of cost-utility assessment in the field of oncology, with an exclusive focus on studies using the EQ-5D[12]. The EQ-5D index values found in Figures 3 and 4 could be used to calculate QALYs in a similar fashion to compliment the previous paper.

The number of studies published on the various types of cancer mirrored their relative prevalence. Breast cancer was the most prevalent cancer worldwide in 2000, followed by colorectal cancer and prostate cancer[1]. This review found studies of those types of cancer to be the most common among the literature that included the EQ-5D.

As would be expected, cancer patients had lower index and VAS scores when compared to the studies of the general population using the EQ-5D. Across all cancer studies, the median index scores summarized was 0.75 (IQR 0.61 - 0.84) and median VAS score was 71.5 (IQR 60.3 - 76.7), much lower than mean scores reported for the US general population of 0.87 (SD 0.01)[52] and 82 (SD 14) with median score 85[53], respectively. A general population survey from Alberta, Canada reported an index-based mean score of 0.914 (SD 0.15) and VAS mean score of 84.8 (11.6) for individuals with no medical problems. That study also reported mean estimates index-based mean score of 0.77 (0.20) and VAS of 70.4 (SD 19.6) for community-based individuals with cancer,[54] similar to the average burden observed in studies included in this review. Among the cancer studies reporting problems according to dimension, usual activities, pain/discomfort and anxiety/depression were the greatest sources of burden.

Psychometric properties, when reported, supported the use of the EQ-5D in the various types of cancer. There was evidence of agreement between results reported by the EQ-5D and those reported by both generic and specific

measures of HRQL in cancer populations. The validity and test-retest reliability of the EQ-5D was generally supported. Several studies used relationships between EQ-5D and other measures to support their validity, evidence that the EQ-5D is recognized as one of the standards in the field of HRQL and patient-reported outcomes in oncology.

Much heterogeneity in scores was observed across studies. Differences in HRQL burden between cancer studies was not solely attributed to subtype of cancer, as the diverse range of mean/median scores could have been due to stage of illness, treatment phase, and non-cancer related sample characteristics such as co-morbid conditions and age as well as other unmeasured factors. In addition, not all studies used the same algorithm to calculate index-based scores. The choice of algorithm used to convert self-classifier scores will affect the index score presented, as seen in Hamashima et al's study on rectal cancer in Japan, which reported index scores calculated by both the Ikeda and Dolan algorithms[24]. Country specific scoring would be most useful to decision makers in health care that use evidence from CUA to guide allocation of resources. For enhanced comparability between studies in the literature, however, a "common currency" for calculating EQ-5D index-based scores for the classifier may be a worthwhile consideration. The expanding body of literature in cancer studies that employ the EQ-5D suggests that the EuroQol group establish an oncology repository for EQ-5D scores for the continuance of this review. While only a handful of studies reported HRQL values according to stage of disease and level of toxicity at present, a repository would be important resource to those who wish to model cancer-related endpoints in economic evaluations of health care interventions.

Statistics for group level data as commonly reported in the literature is not conducive to meta-analysis. Studies often reported only medians, or means unaccompanied by standard deviations. We calculated pooled mean estimates for several types of cancer, but acknowledge there were substantial and statistically significant heterogeneity between pooled studies, and many studies could not be included in a pooled mean estimate due to the absence of a reported mean and standard deviation. In addition to statistical heterogeneity, substantial differences in study designs and patient demographic and clinical characteristics were noted.

In summary, the number of published studies reporting the use of EQ-5D in cancer has increased in recent years. The broad range of EQ-5D index-based and VAS mean scores in these studies likely reflects some systematic variance attributable to stage of treatment protocols, progression of disease, and type of cancer in addition to patient characteristics such as age. The report of both mean (standard deviation) and median (interquartile range) EQ-5D scores in studies of cancer would facilitate comparisons burden of HRQL between studies and conditions. There is an emerging interest in health state preferences as

experienced by patients with the condition which may represent a future area for research using the EQ-5D in cancer. There continues to be much opportunity for research using EQ-5D in cancer that would fill gaps in knowledge relating to values associated with cancer stage by type of cancer; values associated with common sites of metastases within various types of cancer; and values for common treatment-induced toxicities.

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Table 1: Description of study characteristics

Cancer Type [Cancer Details]	Author, Year [Reference No]	Study design	Disease/ treatment stage	Treatment regimen	Patient subgroup	% M/ % F	Mean Age (SD)	Age Range
BONJNT	Lee *et al*, 2003[39]	Cross-sectional: evaluation of another HRQL measure	Active treatment	Previous operation on tumors; maintaining ability to walk	60/40	34	14-74	
BRN	Van Rojen *et al*, 1997 [40]	Quasi-experimental non-randomized intervention trial	Active treatment	Comparison of microsurgery and radiotherapy with Gamma Knife	Microsurgery	51/49	52 (11)	
					Radiotherapy	34/66	55 (14)	
BRE [Stage II and III]	Conner-Spady *et al*, 2005 [19]	Longitudinal	Active treatment	FAC chemotherapy : 4 cycles (repeated every 21 days); increased dose mitoxantrane, vinblastine, & cyclophosphamide; local radiotherapy				
BRE	Jansen *et al*, 2004 [20]	Cross-sectional	Post treatment	38% reported previous adjuvant chemotherapy		1/99	57 (11)	
BRE	Polsky *et al*, 2002 [21]	Longitudinal	Active treatment		Choice in	See original paper treatment for stratified age distribution		
					No choice in treatment	See original paper for stratified age distribution		
	Verkoojen *et al*, 2002 [22]	Quasi-experimental non-randomized intervention trial	Pretreatment	Study: Large core needle biopsy Control: Open breast biopsy		0/100 0/100	57 58	
GI- CoRe	Hamishama *et al*, 2002 [24]	Cross-sectional	Post treatment-postoperative			54/46	69 (12)	
GI-CoRe	Norum *et al*, 1997 [25]	Posttest-only Control Group Design	Active treatment	Study: Adjuvant chemotherapy (5-fluorouracil and levamisole) + surgery Control: surgery alone		44/56	Med: 62	36-76
GI- ESO	Homs *et al*, 2004 [26]	Randomized control trial	Long Term Treatment	12 Gy brachytherapy (intraluminal radiotherapy)		75/25	69 (13)	
				Ultraflex stent		80/20	69 (11)	
GI- ESO	Wildi *et al*, 2004 [27]	Cross-sectional	Pretreatment; Active Treatment			16/84	64	46-83

Table 1: Description of study characteristics

Cancer Type [Cancer Details]	Author, Year [Reference No]	Study design	Disease/ treatment stage	Treatment regimen	Patient subgroup	% M/ % F	Mean Age (SD)	Age Range
GI-CoRe [with liver metastasis]	Krabbe *et al*, 2004 [28]	Prospective cohort	Active treatment; Post treatment	All patients had laparotomy. Group I: surgical liver resection with or without additional ablative therapy Group II: local ablative therapy alone Group III: no treatment (no surgery could be performed)				
GI	McMillan *et al*, 1999[29]	Randomized control trial	Active treatment	Study: Megestrol acetate & ibuprofen		55/45	72	50-90
				Control: Megestrol acetate & placebo		63/37	69	52-88
GI	O'Gorman *et al*, 1998 [30]	Cross-sectional	Active treatment	Overnight fasting before testing	Weight Stable	55/45	70	49-84
HdNk [Oral cavity and pharynx; Head and neck]	Schneider *et al*, 2000 [49]	Cross-sectional	Active treatment	Home enteral nutrition		63/37	56 (25)	
NHL [Stages II, III, IV]	Doordujin *et al*, 2005 [31]	Longitudinal	Active treatment	Cyclophosphamide, doxorubicin, vincristine, prednisone chemotherapy		56/44	72	65-84
HOD	Norum *et al*, 1996 [34]	Retrospective cohort: cost utility analysis	Post treatment	Radiotherapy (10); chemotherapy (16); Radiotherapy and chemotherapy (16)		43/57	38	15-70
HOD, NHL	van Agthoven *et al*, 2001 33	Randomized control trial	Active treatment	Induction chemotherapy (DHAP & VIM course); Randomized to PBSCT or ABMT; Another DHAP course and high-dose conditioning chemotherapy	PBSCT	68/32	Med: 49	18-64
					AMBT	48/52	Med: 46	18-63
MTMY	Uyl-de Groot *et al*, 2005 [41]	Longitudinal	Active treatment	2 courses VAD or vincristine, adriamycin, & methyl prednisone chemotherapy; HDM followed by transplantation of whole blood; collection of r-met Hu G-CSF mobilised peripheral blood progenitor cells by leukopheresis; high-dose chemotherapy; reinfusion of previously collected peripheral stem cells		64/36	53 (8)	

Table 1: Description of study characteristics

Cancer Type [Cancer Details]	Author, Year [Reference No]	Study design	Disease/ treatment stage	Treatment regimen	Patient subgroup	% M/ % F	Mean Age (SD)	Age Range
PRO [Non-metastatic]	Bertaccini *et al*, 2003 [37]	Cross-sectional	Stage not reported			100/0	68 (7)	
PRO	Korfage *et al*, 2005 [38]	Prospective cohort	Active treatment	Prostatectomy		100/0	62 (5)	49-74
			Radiotherapy		100/0	68(6)	49-82	
PRO	Sandblom *et al*, 2001 [36]	Cross-sectional	Active treatment; Post treatment; Long term treatment			77(8)		
PRO	Sandblom *et al*, 2004 [35]	Cross-sectional	Active treatment; Post treatment; Long term treatment			76 (10)		
LUNG	Trippoli *et al*, 2001 [42]	Cross-sectional	Active treatment; Post treatment	See original paper for previous surgery, radiotherapy, and chemotherapy regimens		93/7	62 (9)	
GEN	Ananth *et al*, 2003 [43]	Case-control	Active treatment; Long term treatment		Palliative Care	38/63	57 (14)	
					Oncology	48/52	59 (13)	
					General Practice	37/63	57 (15)	
GEN [Stomach; Colon and rectum; Pancreas; Lung and bronchus; Breast; Ovary; Uterine; Head and neck]	Mantovani *et al*, 2004 [44]	Quasi-experimental non randomized intervention trial	Active treatment	Polyphenols, p.o. pharmaconutritional supplement, metroxiprogesterone acetate		40/ 60	58 (9)	
HOD (n=9); NHL (n=15); MTMY (n= 32); LEU (n=15)	Slovacek *et al*, 2005 [45]	Cross-sectional		Previous autologus/ allogenous hematopoletic stem cell transplantation		71/29	56	
Low-risk [includes LUNG, BRE, PRO, BRAIN, female genital system]; ESO; STO; CoRe	Ravasco *et al*, 2002 [46]	Prospective cohort	Active treatment	Radiotherapy		66/34	63 (11)	33-86

Table 1: Description of study characteristics

Cancer Type [Cancer Details]	Author, Year [Reference No]	Study design	Disease/ treatment stage	Treatment regimen	Patient subgroup	% M/ % F	Mean Age (SD)	Age Range
BRE;	Sullivan *et al*, 2005 [11]	Cross-sectional			Cancer of Breast		64	
PRO					Cancer of Prostate		70	
SKIN					Cancer of the Skin		66	
GEN [Does not include breast, prostate, skin cancers]					Other Cancers		44	
GI- CoRe; HOD	Norum *et al*, 1996 [32]	Cross-sectional	Post treatment					
GEN [GI (n=3); LUNG (n=1); BRE (n=17); PRO (n=2); BRAIN (n=1); LEU (n=1); Female genital system (n=1); undisclosed (20)]	Weze *et al*, 2004 [47]	Prospective cohort	Complementary care	Gentle touch- 4 sessions; See original paper for other regimens		31/66	Med:57	24-80
GEN	Desandes *et al*, 2005[48]					36/64	55 (13)	

See Appendix 5 for Abbreviations

Table 2: Summary of studies examining validity and reliability of EQ-5D in cancer

Cancer Type	Author, Year [Reference]	Reliability	Validity	Responsiveness
BONJNT	Lee *et al* , 2003 [39]	Internal consistency: Cronbach a for full EQ-5D = 0.71.	• Convergent validity: MTSS and EQ-5D related dimensions compared using Pearson correlation. Moderate to strong correlations (Range: 0.39-0.6). • Discriminant validity: MTSS and EQ-5D related dimensions compared using Pearson correlation. Lack of discrimination in all but Pain dimension of MTSS.	
BRE	Conner-Spady *et al*, 2001[18]		• Construct validity: FLIC and EQ-5D compared. Similar patterns of change over time. wk to 8 wk post HDC is moderate (0.66).	Effect Size for EQ-5D index. Baseline to 3 wk post HDC is large (1.16); 3
BRE	Gerard *et al*, 1999[23]	Test-retest: 40% agreement (within. 1 of the mean difference) after 4 wks for valuations of false positive and true negative and 26% agreement for true positive and false negative breast screening scores. Internal consistency: Condition ranking and EQ-5D score % agreement compared. True negative : 69.2%, False positive: 30.7%. Between site agreement: TTO = EQ-5D tested by F- ratios for between-site variation. Failed to reject the null.	• Convergent validity: EQ-5D and TTO compared for short term and long term of true negative (tn) and false positive (fp) % agreement. Short term: 32% (tn), 18% (fp); Long term: 20% (tn), 22% (fp). Paired ranks: Short-term agreement between EQ-5D and TTO. tn>fp: 56.7%; tn≥fp: 31.2%; tn=fp: 5.6%. Disagreement in 7.6%.	
GI-CoRe	Krabbe *et al*, 2004[28]		• Convergent validity: EQ- 5D index and EORTC QLQ C-30 compared. Effect sizes comparable for corresponding domains. past surgery increases.	Effect size: moderate to large for SC, UA, MO and PD dimensions and small for AD. Effect size decreases as time
HOD	Norum *et al*, 1996[34]		• Convergent Validity: Simple VAS scores and EQ-5D scores compared. High correlation reported, but Pearson correlation not given.	

Table 2: Summary of studies examining validity and reliability of EQ-5D in cancer

Cancer Type	Author, Year [Reference]	Reliability	Validity	Responsiveness
PRO	Bertaccini *et al*, 2003[37]		• Construct validity: Bonian Satisfaction Profile-Prostate Cancer compared to EQ-5D using Pearson correlation. Items with r≥ 0.5 ($p<0.005$) selected for BSP-PC. • Known-groups: Bonferroni post hoc test comparing prostate cancer with healthy subjects and other diseases. Significant difference from healthy (M=0.84 vs. M=0.94, $p<0.001$) but not significant from other diseases (M=0.84 vs M=0.85, p=1).	
PRO	Sandblom *et al*, 2004[35]		• Predictive validity: Score of EQ-5D VAS predicted by regression. Items with $p<.01$ significance for prediction included: worst pain last week, Died before 31 December 2000, Age (years), Health-care availability and palliative treatment.	
LUNG	Trippoli *et al*, 2001[42]		• Construct validity: EQ-5D results compared to other studies. Found comparable with Kurtz, Magione, and Wang studies. • Convergent validity: Pearson correlation used to compare EQ-5D index, EQ5D VAS, and SF-36 domains. Strong index correlation with VAS($r = 0.54$). Moderate to strong relationship for SF-36 domains and index score (range: .35-.732) with highest correlation for SF-36 physical functioning; moderate to strong relationship for EQ-VAS and SF-36 domains (range: .401-.685) with highest correlation for SF-36 Vitality.	
GEN	Ananth *et al*, 2003[43]	Test-retest reliability: $k > 0.7$ for patients tested ($n = 16$).		

Table 2: Summary of studies examining validity and reliability of EQ-5D in cancer

Cancer Type	Author, Year [Reference]	Reliability	Validity	Responsiveness
HOD, NHL, MTMY, LEU	Slovacek *et al*, 2005[45]		• Discriminant validity: HRQL difference in patients with different number of diseases and higher age at hematopoietic stem cell transplantation.	
GI-ESO	Ravasco *et al*, 2002[46]		• Content validity: worse mobility and usual activities scores associated with malnutrition or reduced energy; Strong correlation between nutritional intake post- radiotherapy and improvement with QOL.	
GI-CoRe; HOD	Norum *et al*, 1996[32]		• Convergent validity: EQ-5D index compared with EORTC QLQ-C30 and simple VAS scale. High correlation ($p < 0.0001$ for r^2).	
GEN	Desandes *et al*, 2005[48]		• Convergent validity: EQ-5D index and Patient Judgments of Hospital Quality compared using Pearson correlation. Low correlation ($r^2 = 0.10 – 0.16$).	

Table 3: Summary of EQ-5D assessments reported in cancer studies

Author, Year (Reference No)	Cancer type: Subgroup [Reference]	n	Index mean (SD)	VAS mean (SD)	% MO	% SC	% UA	% PD	% AD	Scoring Algorithm	Author Comments	Reviewer Comments
Lee*et al*, 2003[39]	BONJNT	49	0.68 (0.22)	73 (19)						Dolan 1997, United Kingdom (UK)		Concentration on the Musculoskeletal Tumor Society Functional Evaluation System.
Van Rojen *et al*, 1997[40]	BRAIN: Microsurgery; 1 of 2	53	0.77 (0.18)							Dolan 1997, UK		EQ-5D not a main focus.
	BRAIN: Radiosurgery; 2 of 2	92	0.89 (0.15)									
Conner-Spady *et al*, 2001 [18]										Dolan 1997, UK		Some data presented below was given in this preliminary paper.
Conner-Spady *et al*, 2005[19]	BRE-Baseline: Pretreatment; 1 of 7	48	0.78 (0.18)		1-98 2-2 3-0	1-98 2-2 3-0	1-60 2-38 3-2	1-56 2-44 3-0	1-31 2-64 3-4	Dolan 1997, UK		The EQ-5D index results are taken from the same cohort as the characteristics presented above.
	BRE: 1st day of 3rd FAC cycle; 2 of 7	48	0.75 (0.18)		1-96 2-4 3-0	1-90 2-10 3-0	1-44 2-52 3-4	1-35 2-65 3-0	1-46 2-52 3-2			
	BRE: 3 wk post HDC; 3 of 7	48	0.61 (0.29)		1-64 2-36 3-0	1-85 2-15 3-0	1-15 2-52 3-33	1-40 2-58 3-2	1-51 2-42 3-7			
	BRE: 6 mo post HDC; 4 of 7	45	0.79 (0.19)		1-93 2-7 3-0	1-100 2-0 3-0	1-40 2-53 3-4	1-47 2-53 3-0	1-51 2-42 3-7			
	BRE: 12 mo post HDC; 5 of 7	40	0.84 (0.19)		1-88 2-12 3-0	1-100 2-0 3-0	1-73 2-25 3-3	1-48 2-53 3-0	1-60 2-35 3-5			
	BRE: 18 mo post HDC; 6 of 7	36	0.84 (0.13)		1-92 2-8 3-0	1-97 2-3 3-0	1-66 2-34 3-0	1-47 2-53 3-0	1-61 2-39 3-0			
	BRE: 24 mo post HDC; 7 7 of 7	37	0.89 (0.13)		1-92 2-8 3-0	1-97 2-3 3-0	1-76 2-24 3-0	1-62 2-38 3-0	1-68 2-30 3-3			

Table 3: Summary of EQ-5D assessments reported in cancer studies

Author, Year (Reference No)	Cancer type: Subgroup [Reference]	n	Index mean (SD)	VAS mean (SD)	% MO	% SC	% UA	% PD	% AD	Scoring Algorithm	Author Comments	Reviewer Comments
Gerard *et al*, 1999 [23]		440										EQ-5D scores were speculative from women eligible for breast cancer screening.
Jansen *et al*, 2004 [20]	BRE: Chemo + choice in treatment; 1 of 4 **	54	0.84	77						Dolan 1997, UK	Nonresponders were slightly older and treated with chemotherapy less frequently	Choice in treatment was reported by the patient. The 3rd purpose of this study "whether the proportion of treatment choice is related to satisfaction with the assigned tx, experienced chemotherapy burden and current QOL" is related to our study purpose.
	BRE: No chemo + choice in treatment; 2 of 4**	28	0.74	69								
	BRE: Chemo + no choice in treatment; 3 of 4**	105	0.82	75								
	BRE: No chemo + no choice in treatment; 4 of 4 **	174	0.83	77								
Polsky *et al*, 2002 [21]	BRE: Choice in treatment; 1 of 2)	566		79 (16						Dolan 1997, UK		
	BRE: No choice in treatment; 2 of 2	117		75 (17)								
Verkoojen *et al*, 2002 [22]	BRE: Before needle biopsy; 1 of 4*	30	0.73	80						Dolan 1997, UK		
	BRE: After needle biopsy; 2 of 4*	30	0.71	80								
	BRE: Before open breast biopsy; 3 of 4*	27	0.69	80								
	BRE: After open breast biopsy; 4 of 4*	27	0.61	76								
Hamishama *et al*, 2002 [24]	GI-CoRe: Stoma; Ikeda; 1 of 4	72	0.87 (0.16)	72 (16)	2/3-20	2/3-7	2/3-29	2/3-21	2/3-14	Ikeda 1999, Japan		

Table 3: Summary of EQ-5D assessments reported in cancer studies

Author, Year (Reference No)	Cancer type: Subgroup [Reference]	n	Index mean (SD)	VAS mean (SD)	% MO	% SC	% UA	% PD	% AD	Scoring Algorithm	Author Comments	Reviewer Comments
	GI-CoRe: No Stoma; Ikeda; 2 of 4	38	0.84 (0.17)	70 (15)	2/3-26	2/3-13	2/3-32	2/3-34	2/3-24			
	GI-CoRe: Stoma; Dolan; 3 of 4	72	0.87 (0.22)								Dolan 1997, UK	
	GI-CoRe: No Stoma; Dolan algorithm; 4 of 4	38	0.84 (0.19)									
Norum *et al*, 1997[25]	GI-CoRe	62	Med: 0.78) (0.33 to 1								Dolan 1997, UK	
Homs *et al*, 2004 [26]	GI-ESO: All patients post treatment; 1 of 3*		0.42 (0.36)	59							Dolan 1997, UK	No significant difference between EQ-5D scores of the 2 treatments; Baseline cores for these patients are below the population norms.
	GI-ESO:; Brachytherapy 2 of 3	101	47 (13)									
	GI-ESO: Stent Placement; 3 of 3	108	43 (13)									
Wildi *et al*, 2004 [27]	GI-ESO: SEER Stage 0; 1 of 4	50	0.93 (0.12)									
	GI-ESO: SEER Stage 1; 2 of 4		0.6 (0.29)									
	GI-ESO: SEER Stage 2; 3 of 4		0.71 (0.21)									
	GI-ESO: SEER Stage 3; 4 of 4		0.69 (0.31)									
Krabbe *et al*, 2004 28	GI-LIV : Baseline pre-surgery; 1 of 3	75	0.84 (0.12)	75 (14)	1-89	1-100	1-76	1-83	1-61	Dolan 1997, UK		Post 3 months also reported. EQ-5D is comparable to disease-specific HRQL.
					2-10 3-0	2-0 3-0	2-21 3-3	2-17 3-0	2-36 3-3			
	GI-LIV: Post 1/2 month; 2 of 3	74	0.68 (0.23)	58 (19)	1-55	1-78	1-19	1-38	1-69			

Table 3: Summary of EQ-5D assessments reported in cancer studies

Author, Year (Reference No)	Cancer type: Subgroup [Reference]	n	Index mean (SD)	VAS mean (SD)	% MO	% SC	% UA	% PD	% AD	Scoring Algorithm	Author Comments	Reviewer Comments
					2-39 3-5	2-18 3-4	2-42 3-39	2-61 3-1	2-13 3-0			
	GI-LIV: Post 6 months; 3 of 3	69	0.84 (0.11)	75 (14)	1-81	1-97	1-64	1-71	1-78			
					2-18 3-0	2-3 3-0	2-35 3-1	2-29 3-0	2-22 3-0			
McMillan *et al*, 1999 [29]	GI :MA+ placebo; 1 of 2	38	Med: 0.63 (-0.1 to 1.00)							Dolan 1997, UK	Significant improvement in EQ-5D score of ibuprofen group ($p<.05$), values not shown.	
	GI: MA+ ibuprofen; 1 of 2	35	Med: 0.69 (-0.26 to 1.01)									
O'Gorman *et al*, 1998 [30]	GI: Weight Stable; 1 of 2	22	Med: 0.85 (0.03 to 1.00)							Dolan 1997, UK	No significant difference in EQ-5D between groups.	
	GI: Weight Losing; 2 of 2	97	Med: 0.52 (-0.26 to 1.00)									
Doordujin *et al*, 2005 [31]	NHL: Baseline, aaIPI 0-1; 1 of 4	63	0.74							Dolan 1997, UK		Little focus on EQ-5D; After 2nd and 4th CHOP cycle reported as well.
	NHL: Baseline, aaIPI 2-3; 2 of 4	53	0.44									
	NHL: post 6th CHOP cycle, aaPI 0-1; 3 of 4	54	0.69									
	NHL: post 6th CHOP cycle, aaPI 2-3; 4 of 4	44	0.53									

Table 3: Summary of EQ-5D assessments reported in cancer studies

Author, Year (Reference No)	Cancer type: Subgroup [Reference]	n	Index mean (SD)	VAS mean (SD)	% MO	% SC	% UA	% PD	% AD	Scoring Algorithm	Author Comments	Reviewer Comments
Norum *et al*, 1996 [34**]	HOD	42	0.78	80						Dolan 1997, United Kingdom		
van Agthoven *et al*, 2001 [33]	NHL, HOD: PBSCT, Day before transplantation; 1 of 4*	62	0.75	68						Dolan 1997, United Kingdom		Two time points not presented in this table.
	NHL, HOD: ABMT, Day before transplantation; 2 of 4*	29	0.78	66								
	NHL, HOD: PBSCT, 14 days post transplantation; 3 of 4*	62	0.53	55								
	NHL, HOD: ABMT, 14 days post transplantation; 4 of 4*	29	0.42	50								
Uyl-de Groot *et al*, 2005 [41]	MTMY: Baseline; 1 of 4	25	0.52 (0.33)							Dolan 1997, United Kingdom	Not based on a pretreatment baseline, so this study probably underestimate improvements in quality of life.	There were a total of 7 time points reported; Baseline, T3, T5, T7 in table.
	MTMY: discharge HDM; 2 of 4	24	0.38									
	MTMY: discharge PSCT]; 3 of 4	14	0.66									
	MTMY: 12 mo followup; 4 of 4	12	0.69									
Bertaccini *et al*, 2003 [37]	PRO: Healthy; 1 of 3	57	0.94 (0.02)							Dolan 1997, UK	Significant difference in patients with prostate cancer vs. healthy individuals, but not significant compared to individuals with other diseases.	EQ-5D used primarily to ensure the validity of Bonian Satisfaction Profile- Prostate Cancer.
	PRO: Prostate Cancer; 2 of 3	103	0.84									
	PRO: Other Diseases; 3 of 3	101	0.85 (0.02)									

Table 3: Summary of EQ-5D assessments reported in cancer studies

Author, Year (Reference No)	Cancer type: Subgroup [Reference]	n	Index mean (SD)	VAS mean (SD)	% MO	% SC	% UA	% PD	% AD	Scoring Algorithm	Author Comments	Reviewer Comments
Korfage *et al*, 2005 [38]	PRO: Prostatectomy -pretreatment; 1 of 6*	127	0.89 (0.15)	79 (17)						Dolan 1997, UK		Data from Rotterdam study; Time point at 12 months not in this table.
	PRO: Prostatectomy post-6 mo; 2 of 6*		0.91 (0.16)	84 (12)								
	PRO: Prostatectomy, post-52 mo; 3 of 6*		0.88 (0.16)	81 (13)								
	PRO: Radiotherapy, pretreatment; 4 of 6*	187	0.81 (0.20)	72 (17)								
	PRO: Radiotherapy-post 6 mo; 5 of 6*		0.83 (0.21)	76 (17)								
	PRO: Radiotherapy-post 52 months; 6 of 6*		0.76 (0.23)	74 (16)								
Sandblom *et al*, 2001 [36]	PRO	1243			1-62	1-87	1-75	1-38	1-66	Dolan 1997, UK		EQ-5D results in graphical form, by age.
					2-36	2-11	2-18	2-57	2-32			
					3-15	3-2	3-7	3-5	3-2			
Sandblom *et al*, 2004 35	PRO: Died of PRO by 31 Dec 2001; 1 of 2	66	0.538 (0.32)	54 (22)						Dolan 1997, UK		Patients dying of other causes not presented in this table.
	PRO: Still Alive 31 Dec 2001; 2 of 2	1076	0.77 (0.25)	70 (20)								
Trippoli *et al*, 2001 [42]	LUNG	92/94	0.58 (0.33)	58 (2)						Dolan 1997, UK	Good agreement with Wang, Kurtz, & Mangione studies.	Scores were divided by gender, surgery, chemotherapy, radiotherapy metastasis, age, and time since diagnosis.
Ananth *et al*, 2003 [43]	GEN: Palliative Care; 1 of 3*	64	0.52 (0.18)							Dolan 1997, UK		EQ-5D incorporated into another questionnaire.
	GEN: Oncology; 2 of 3*	56	0.67 (0.19)									

Table 3: Summary of EQ-5D assessments reported in cancer studies

Author, Year (Reference No)	Cancer type: Subgroup [Reference]	n	Index mean (SD)	VAS mean (SD)	% MO	% SC	% UA	% PD	% AD	Scoring Algorithm	Author Comments	Reviewer Comments
	GEN: General Practice; 3 of 3*	67	0.75 (0.15)									
Mantovani *et al*, 2004 [44]	GEN: Baseline; 1 of 4	25	0.33 (0.4)	44 (2.2)						Not reported	EQ-5D index improved at 4 months; VAS improved at 1 and 2 months.	
	GEN : After 1 month; 2 of 4	25	0.45 (0.3)	56 (2.2)								
	GEN: After 2 months; 3 of 4	18	0.59 (0.3)	62 (2)								
	GEN: After 4 months; 4 of 4	12	0.54 (0.3)	62 (2)								
Slovacek *et al*, 2005 [45]	HOD, NHL, MTMY, LEU: 0 Assoc. Diseases; 1 of 3*	30	0.84 (0.16)	76 (12)						Dankova 2001,Czech Republic	influence of polymorbidity, age, and religion on EQ 5D index and Visual Analog Scale are statistically significant (P<.01).	Results also summarized by belief in God
	HOD, NHL, MTMY LEU: 1 Assoc. Diseases 2 of 3*	13	0.75 (0.19)	72 (18)								
	HOD, NHL, MTMY LEU: 2 Assoc. Diseases; 3 of 3*	14	0.71 (0.15)	66 (13)								
Ravasco *et al*, 2002 [46]	GI –ESO; 1 of 5	6			1-83 2-17 3-0	1-66 2-17 3-17	1-0 2-50 3-50	1-67 2-33 3-0	1-50 2-33 3-17		Recommendation that Euroqol should be used as a routine in such patients, since quality of life is a major outcome.	Only end results reported to conserve space. Patients grouped as "high risk" or "low risk".
	GI –STO; 2 of 5	5			1-100 2-0 3-0	1-100 2-0 3-0	1-40 2-60 3-0	1-80 2-20 3-0	1-80 2-20 3-0			
	GI-CoRe; 3 of 5	46			1-63 2-22 3-15	1-89 2-7 3-4	1-26 2-41 3-33	1-83 2-15 3-2	1-16 2-43 3-41			
	HdNk; 4 of 5	23			1-53 2-30 3-17	1-48 2-30 3-22	1-5 2-43 3-52	1-83 2-13 3-4	1-0 2-48 3-52			

Table 3: Summary of EQ-5D assessments reported in cancer studies

Author, Year (Reference No)	Cancer type: Subgroup [Reference]	n	Index mean (SD)	VAS mean (SD)	% MO	% SC	% UA	% PD	% AD	Scoring Algorithm	Author Comments	Reviewer Comments
	GEN: Low Risk; 5 of 5	45			1-94 2-4 3-2	1-100 2-0 3-0	1-94 2-2 3-4	1-89 2-7 3-4	1-84 2-9 3-7			
Schneider *et al*, 2000 [49]	HdNk	11	0.54 (0.33)	56 (2.3)						Dolan 1997, UK		Small sample size for cancer.
Sullivan *et al*, 2005 [11]	BRE; 1 of 4	236	0.81							Shaw 2005, United States	Concern about ceiling effects and potential lack of discrimination.	Disutility of condition reported for all groups; 25%, 50%, and 75% EQ-5D scores also given.
	PRO; 2 of 4	171	0.77									
	GEN: Other Cancer; 3 of 4	132	0.85									
	SKIN; 4 of 4	505	0.82									
Norum *et al*, 1996 [32]	GI-CoRe; HOD**	98	0.79 (0.23)	80 (20)								
Weze *et al*, 2004 [47]	GEN: Pre-treatment; 1 of 2	35			1-38 2-62 3-0	1-74 2-23 3-3	1-14 2-63 3-23	1-20 2-71 3-9	1-9 2-77 3-14	Dolan 1997, UK		Info on MO, SC, and UA was only found in a bar graph.
	GEN: Post- treatment; 2 of 2				1-50 2-47 3-3	1-74 2-26 3-0	1-14 2-69 3-17	1-23 2-66 3-11	1-34 2-57 3-9			
Desandes *et al*, 2005 48	GEN			62 (19)								

* index scores were transformed within tables to a 0-1 scale for consistency
** VAS scores were transformed within tables and figures to a 0-100 scale for consistency
See Appendix for abbreviations

Figure 1: Summary of Article Retrieval

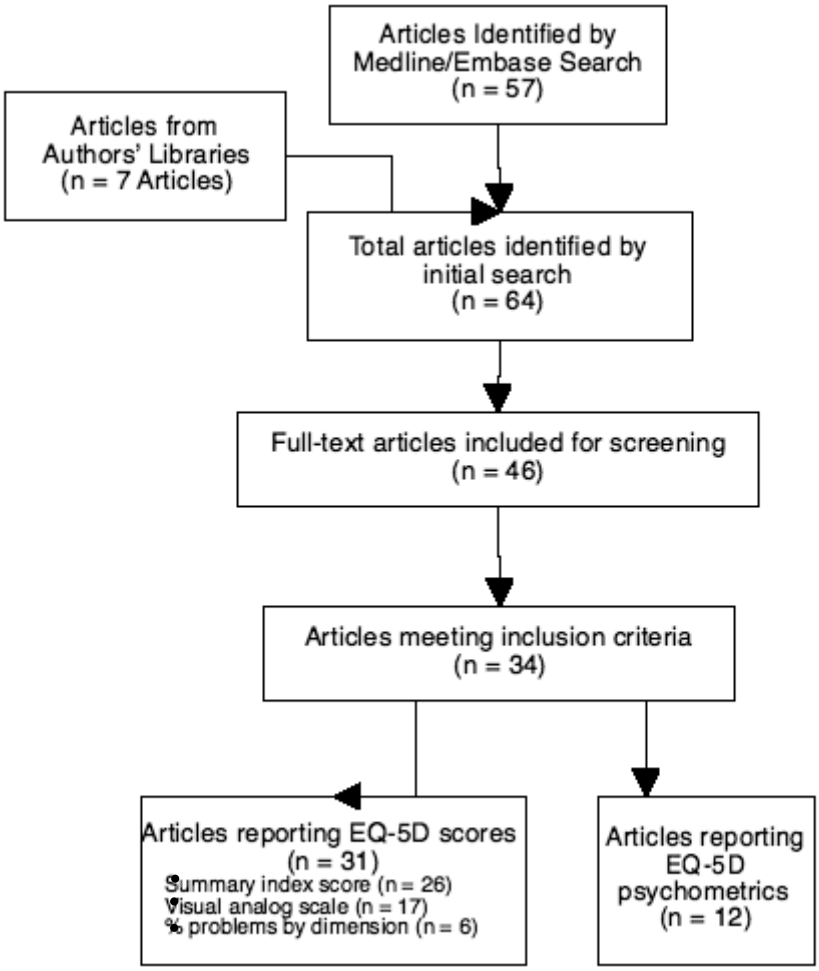


Figure 2: Trends in Publications of Cancer Studies using EQ-5D

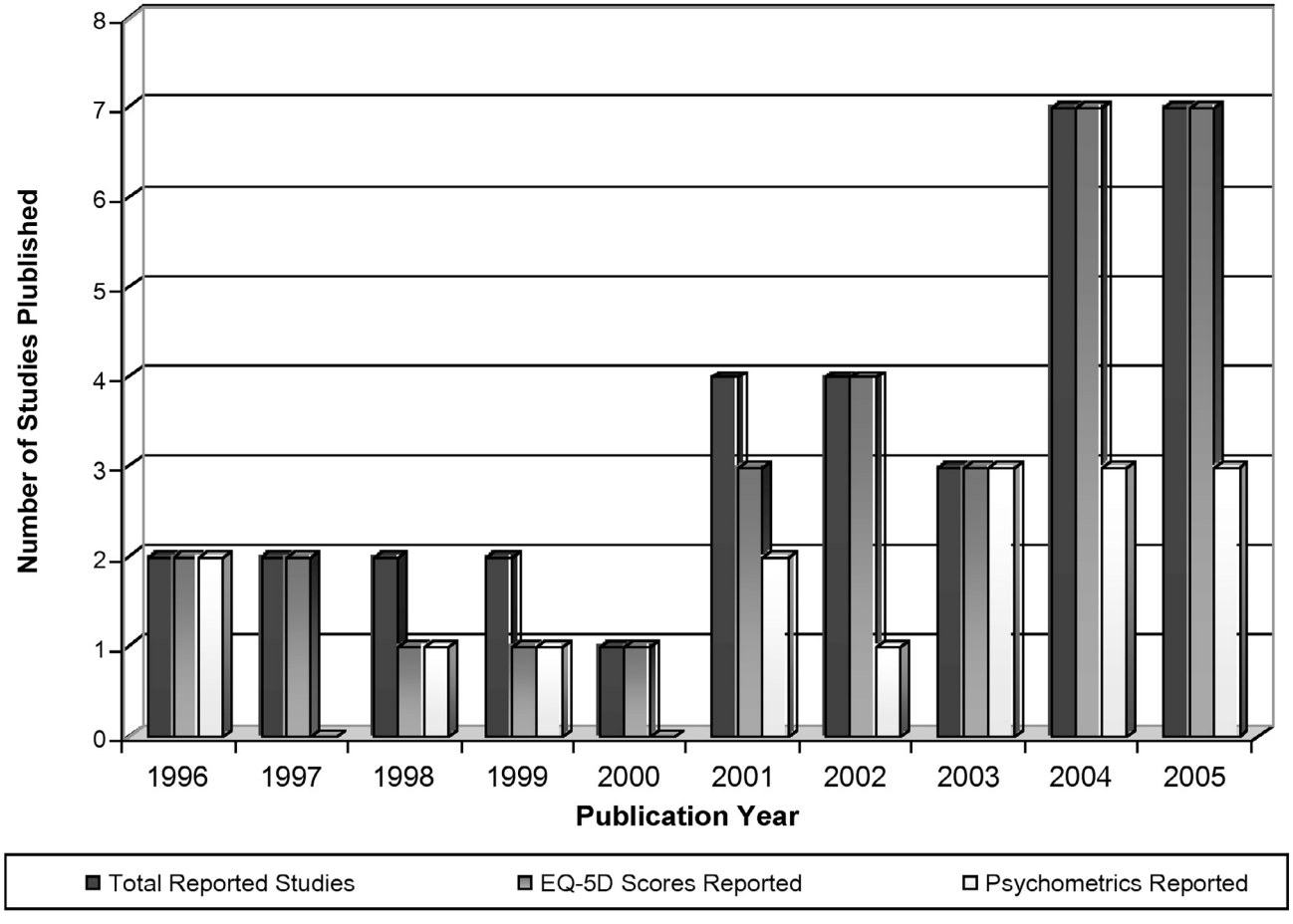
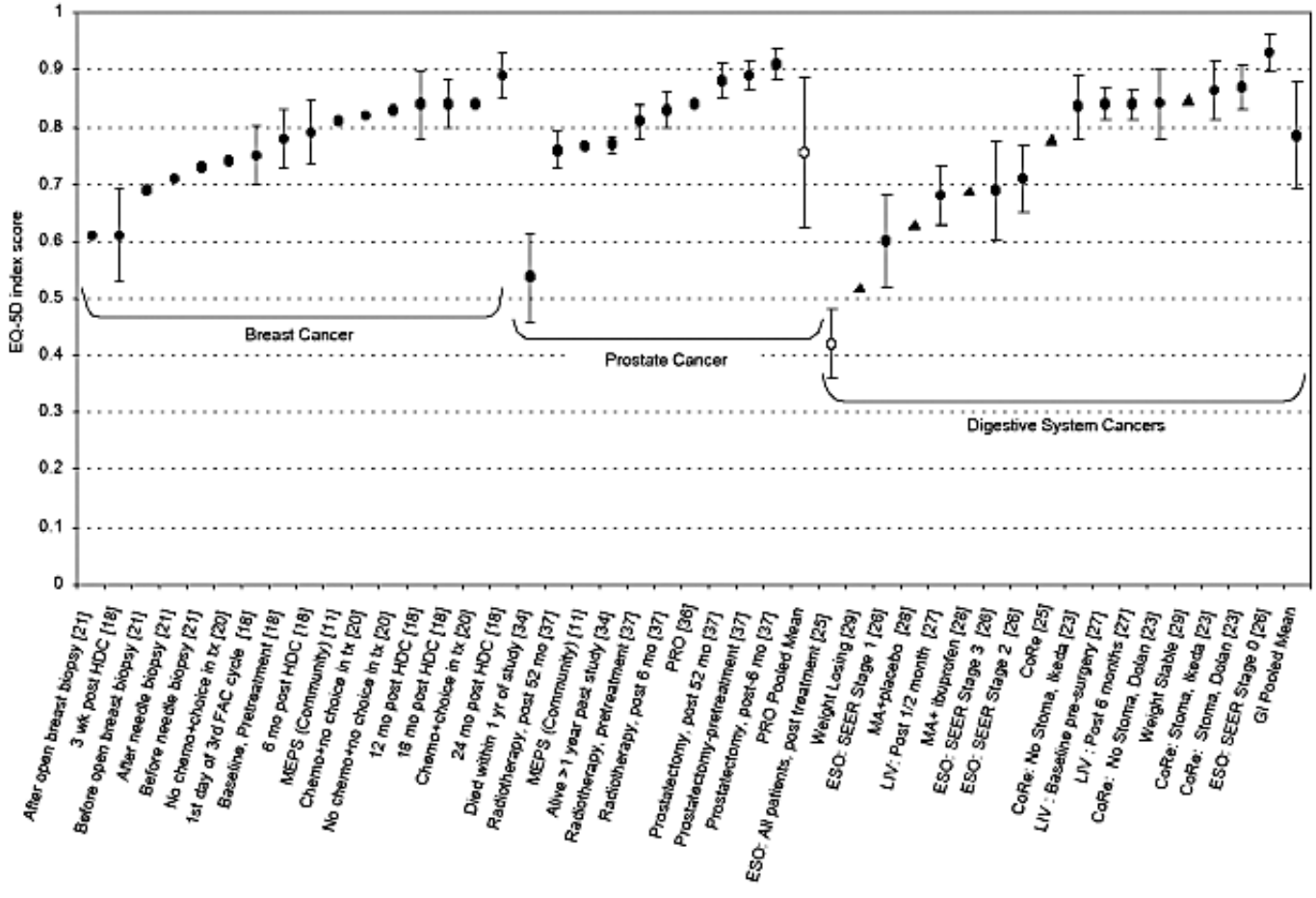
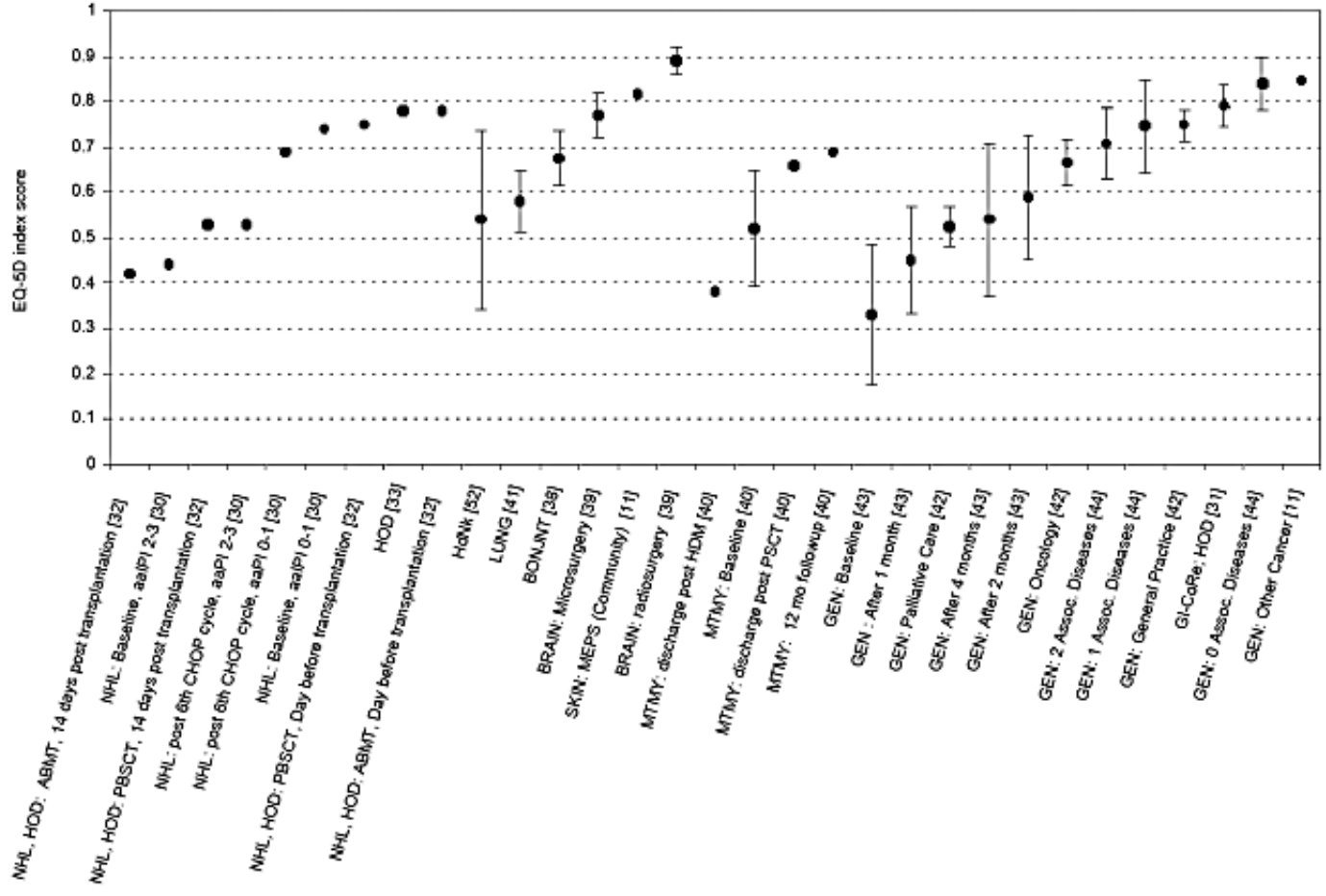


Figure 3: EQ-5D Index Mean/Median Scores for Breast, Prostate and Digestive System Cancers



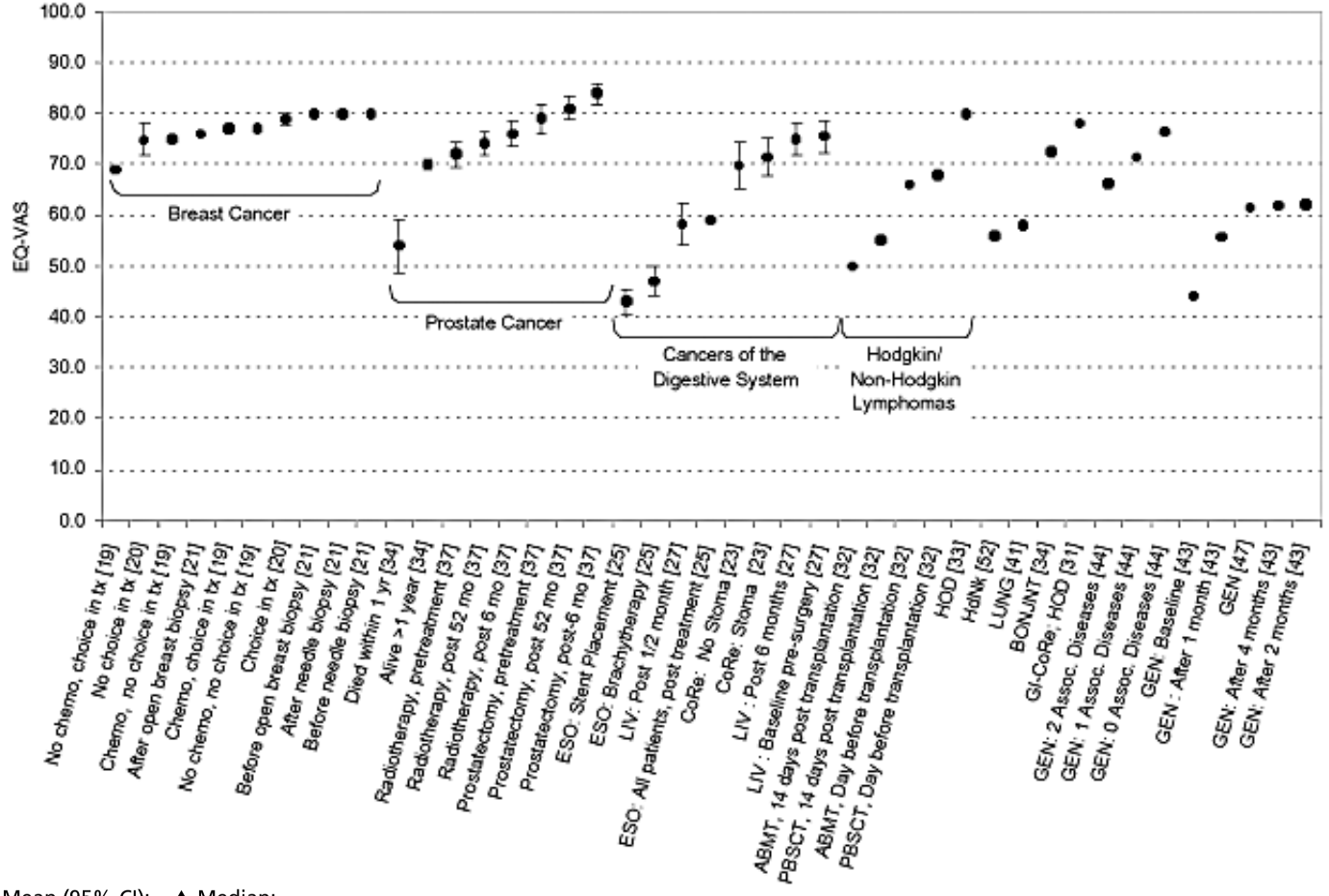
● Mean (95% CI); ▲ Median; ❍ Pooled mean

Figure 4: EQ-5D Index Mean/Median Scores for All Other Cancer Types



● Mean (95% CI);

Figure 5: Visual Analog Scale Mean/Median Scores for All Cancer Types



● Mean (95% CI); ▲ Median;

Figure 6: Distribution of Responses to Mobility Dimension of EQ-5D

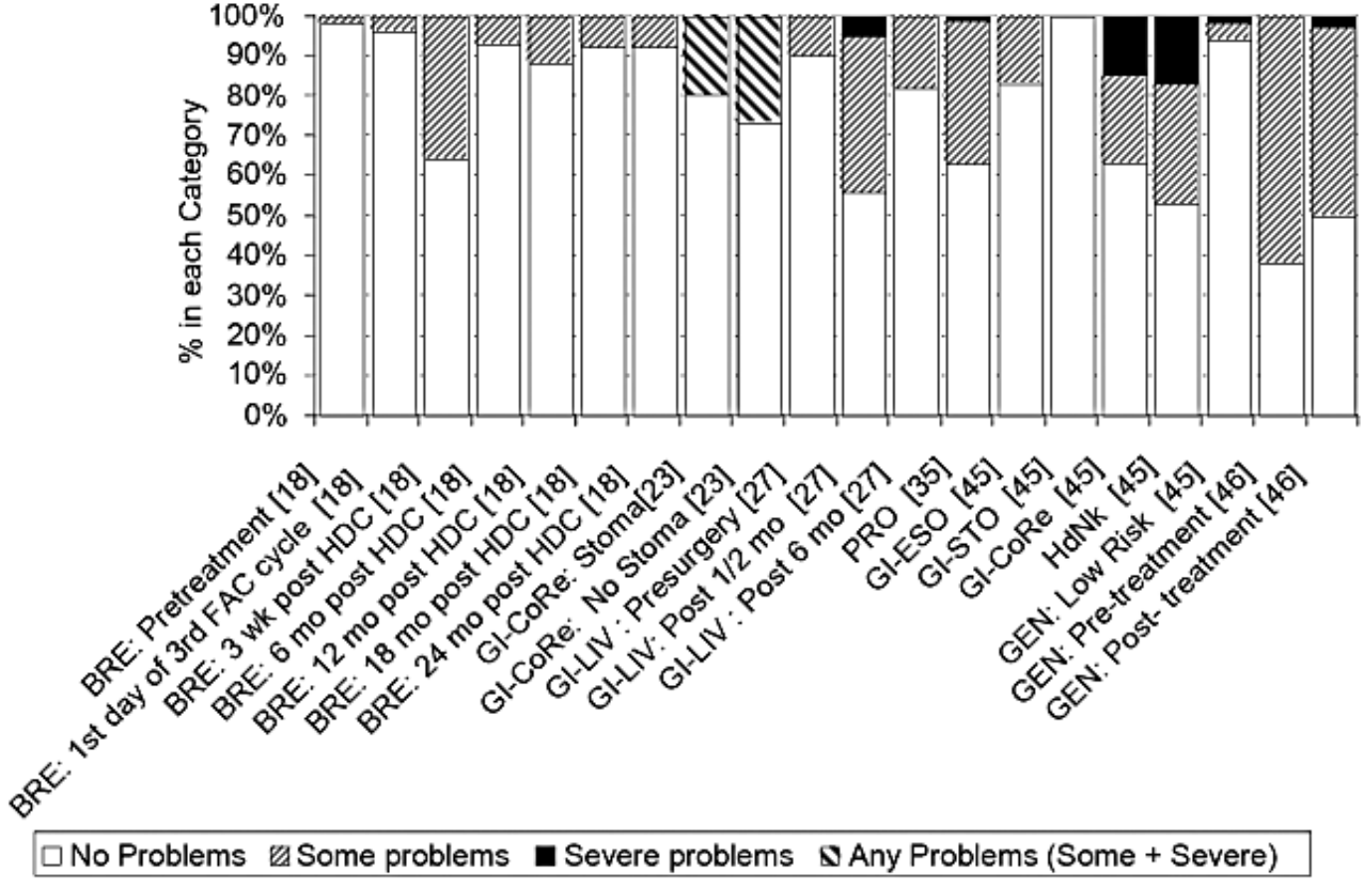


Figure 7: Distribution of Responses to Self Care Dimension of EQ-5D

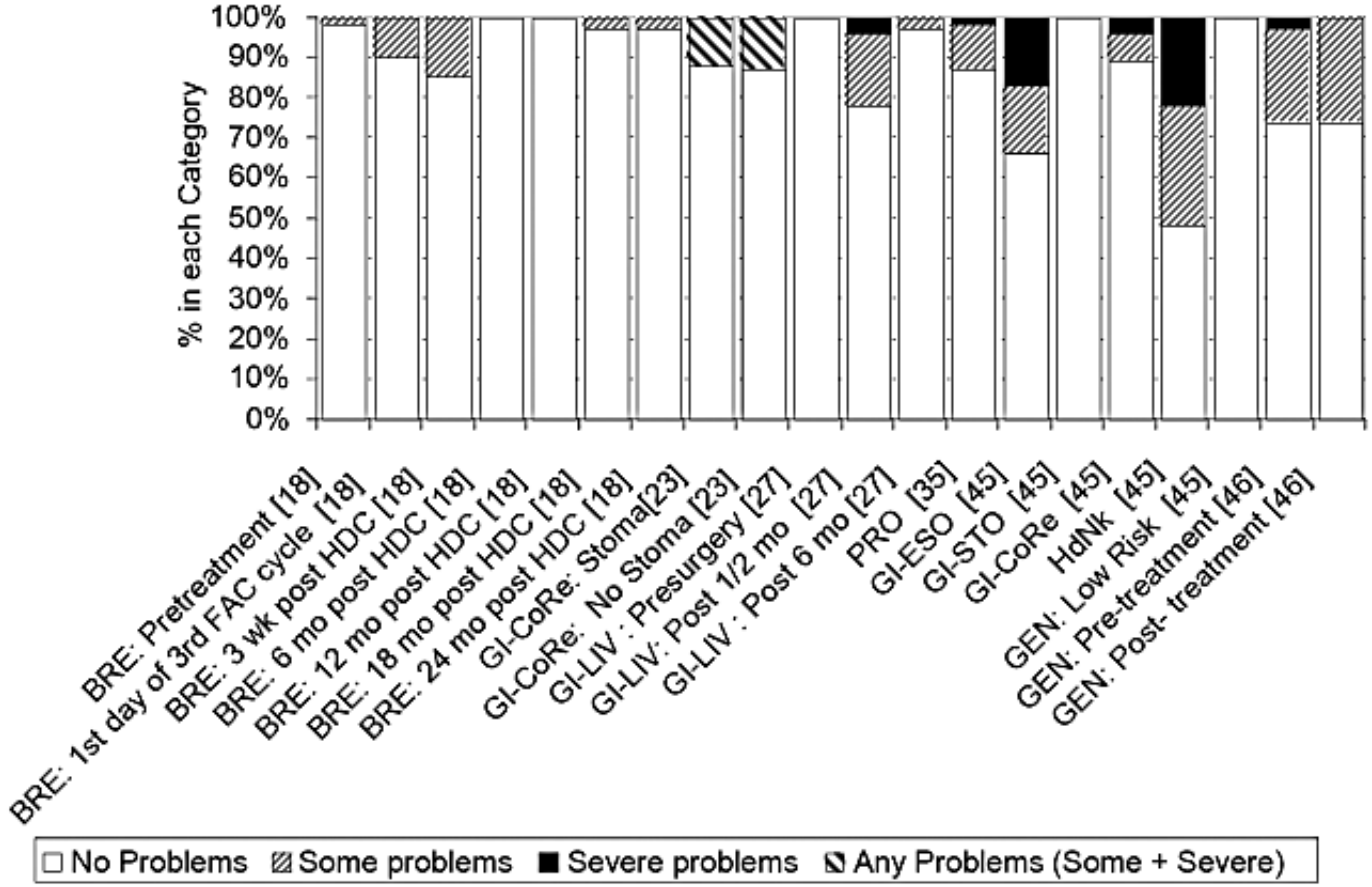


Figure 8: Distribution of Responses to Usual Activities Dimension of EQ-5D

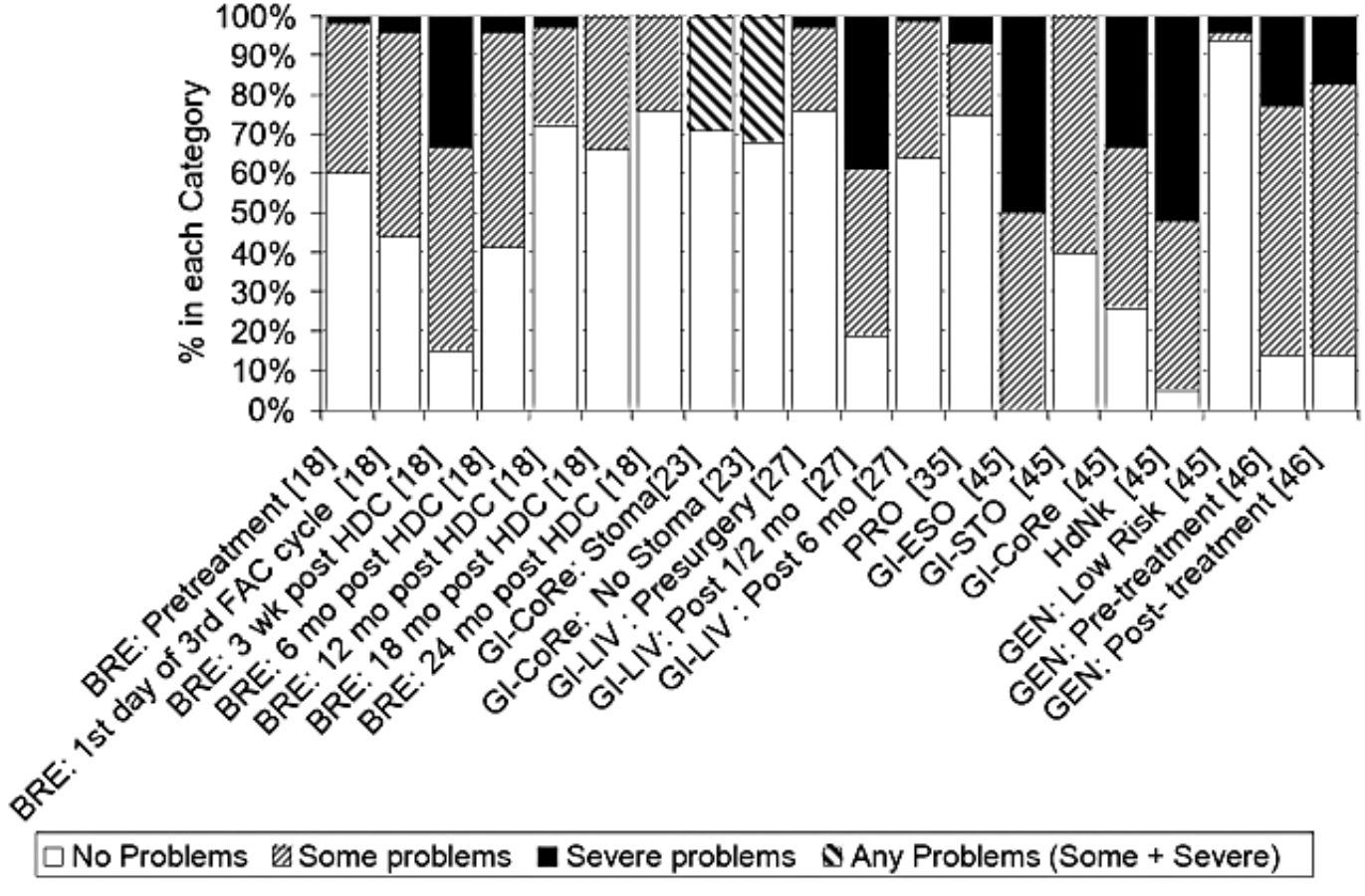


Figure 9: Distribution of Scores for Pain/ Discomfort Dimension of EQ-5D

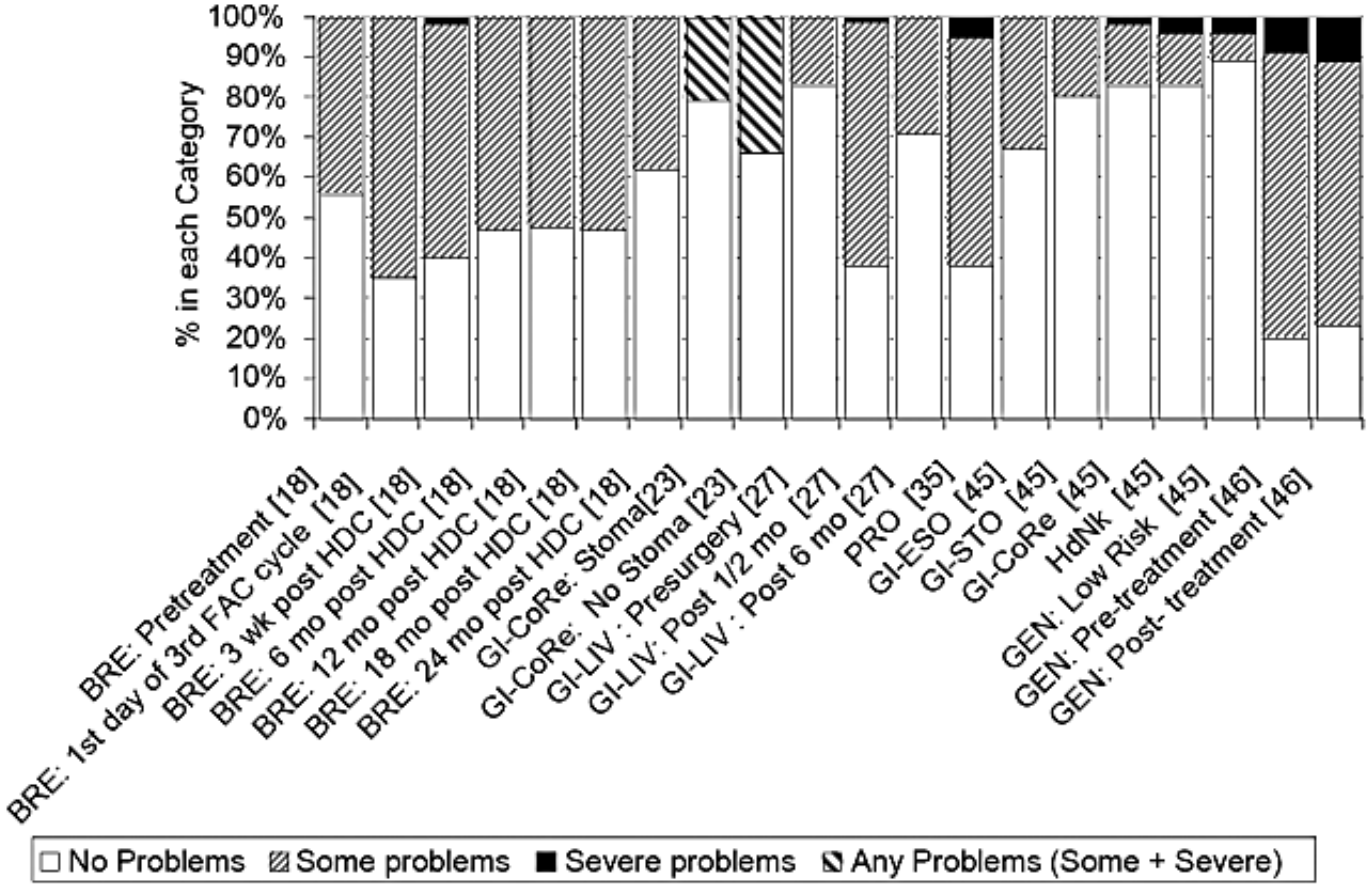
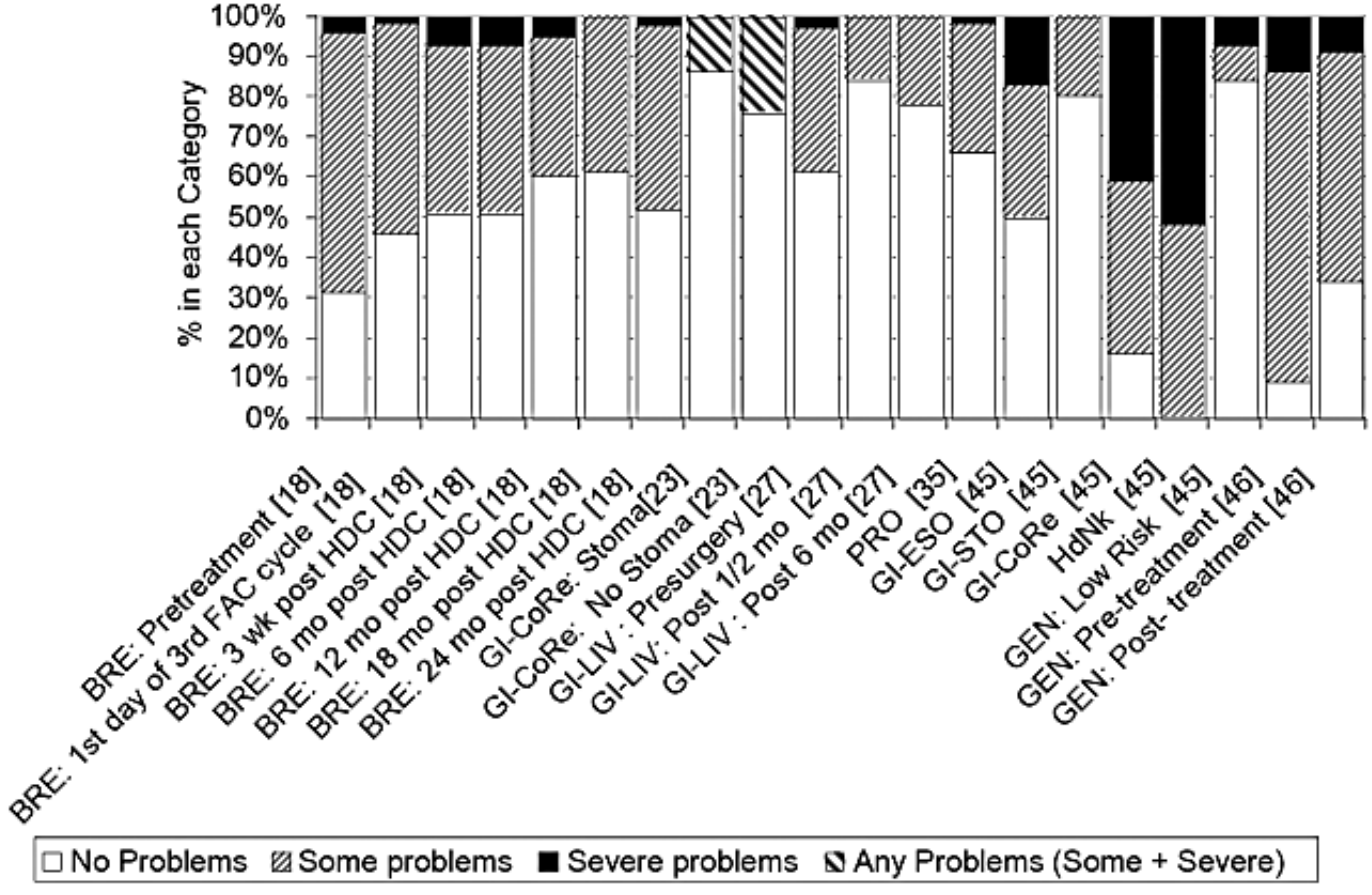


Figure 10: Distribution of Scores for Anxiety/ Depression Dimension of EQ-5D



●●● APPENDIX 1:

ABBREVIATIONS USED IN TABLES/FIGURES

Cancer Types

BONJNT	Bones and joints
BRE	Breast
GI	Digestive System
CoRe	Colon and Rectum (Colorectal)
ESO	Esophagus
LIV	Liver
STO	Stomach
NHL	Non-Hodgkin Lymphoma
HOD	Hodgkin's Disease
MTMY	Multiple Myeloma
PROS	Prostate
LUNG	Lung
GEN	General cancer – no type specified
LEU	Leukemia
HdNk	Head and Neck

Study Abbreviations

aaIPI	age-adjusted International Prognostic Index
ABMT	autologous bone marrow transplantation
Assoc.	associated
chemo	chemotherapy
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
DHAP	cisplatin, cytarabine, dexamethasone
HDC	High dose chemotherapy
HDM	high-dose melphalan
FAC	Fluorouracil, adriamycin, cyclosphosphamide
FLIC	Functional Living Index- Cancer
MA	Megestrol acetate
Med	Median
MTSS	Musculoskeletal Tumor Society functional evaluation system
PBSCT (PSCT)	peripheral blood stem cell transplantation
SEER	Surveillance Epidemiology and End Results
TTO	time tradeoff
Tx	treatment
VAD	vincristine, adriamycin and dexamethason
VAS	visual analog scale
VIM	etoposide, ifosfamide, methotrexate