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A Prospective Cohort Study Defining Utilities Using Time Trade-Offs and the Euroqol-5D to Assess the Impact of Cancer-Related Lymphedema

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Abstract

BACKGROUND—The devastating impact of lymphedema on cancer survivors' quality of life has prompted consideration of several changes in medical and surgical care. Unfortunately, our understanding of the benefits gained from these approaches relative to their cost remains limited. This study was designed to estimate utilities for lymphedema and characterize how utilities differ between subgroups defined by lymphedema etiology and distribution.

METHODS—A consecutive sample of 236 subjects with lymphedema seen at a lymphedema clinic completed both a time trade-off (TTO) exercise and the Euroqol 5D. Responses were adjusted in multivariate regression models for demographic factors, comorbidities, and lymphedema severity/location.

RESULTS—Most participants (167 of 236, 71%) had lymphedema as a consequence of cancer treatment; 123 with breast cancer and upper extremity involvement. Mean TTO utility estimates were consistently higher than Euroqol 5D estimates. Unadjusted TTO (0.85; standard deviation [SD], 0.21) and Euroqol 5D (0.76; SD, 0.18) scores diminished with increasing lymphedema stage and patient body mass index (BMI). Adjusted utility scores were lowest in patients with cancer-related lower extremity lymphedema (TTO=0.82; SD, 0.04 and Euroqol 5D=0.80; SD, 0.03). Breast cancer patients also had lower adjusted Euroqol 5D scores (0.80; SD, 0.02).

CONCLUSIONS—Lymphedema-associated utilities are in the range of 0.80. Lower utilities are observed for patients with higher lymphedema stages, elevated BMI, and cancer-related lymphedema. Greater expenditures for the prevention and treatment of cancer-related lymphedema are warranted.

Keywords

lymphedema; health utilities; quality of life; cost; body mass index

Lymphedema is a functionally and medically debilitating condition that is estimated to effect 1.33 per 1000 persons in developed nations.¹ Its hallmark is a swollen, dysfunctional limb, and its etiology, although it may be the product of genetic factors, is most commonly associated with surgical disruption of the body's lymphatic system² and obesity.³ Its incidence is particularly high after the surgical and/or radiation treatment of breast^{4,5} and gynecological⁶ cancers and, given its proclivity to progress to tissue hardening, recurrent infections and ultimately massive limbs, lymphedema remains among the most dreaded sequelae of cancer treatment.⁷⁻⁹

The adverse impact that lymphedema can have on the quality of life (QOL) of cancer survivors, in particular, has prompted consideration of several changes in medical and surgical care. Unfortunately, lack of knowledge of lymphedema's medical, sociological, and economic effects limit our understanding of the potential value that might be gained from these approaches. Of particular concern is that fact that socioeconomically disadvantaged patients may be at higher risk of lymphedema progression, for although private and governmental insurance programs provide coverage for lymphedema complications such as cellulitis, as well as surgical and nonsurgical reductive therapies, they do not provide support for basic maintenance supplies, which are necessary if additional treatments and complications are to be avoided.¹⁰

Some information, however, is available. For example, the economic cost of treating breast cancer survivors with lymphedema has been estimated to be US \$11,000 (2004 dollars) greater than that of their unaffected counterparts.¹¹ Cost, however, is a limited measure. It may be that a cost utility-based appraisal is more appropriate given lymphedema's chronic nature and the finding that its treatment enhances rather than extends patients' lives. More specifically, cost-utility approaches that incorporate utilities as a measure of QOL for various health states are critical to fully appreciate the impact of differing treatment approaches. A utility is a number between 0 and 1 that is assigned to a state of health, with perfect health being valued at 1 and death being valued at 0. To our knowledge, utilities for lymphedema do not exist.

This study was designed to estimate utilities for patients with lymphedema using with both direct (time trade-off [TTO]) and indirect (Euroqol 5-D) methods. The impact of lymphedema etiology, distribution, and stage were also estimated in subgroups defined by these factors.

MATERIALS AND METHODS

Setting and Participants

A target sample of 236 consecutive patients seen between March and August, 2006 at the Lymphedema Clinic within the University of Pennsylvania Health System were enrolled at the time of their clinic visits. Diagnostic assessment of lymphedema was performed by a specialist physician (A.L.C.) on the basis of the Common Toxicity Criteria v.3.0 for limb and truncal lymphedema (grade 1-4)¹² and was confirmed by a Lymphology Association of North America¹³ certified physical or occupational therapists. Clinical judgment was corroborated by lymphoscintigraphy in some cases, but this was not required. Patients whose lymphedema diagnoses were in question and those with chronic venous insufficiency, multifactorial edema, phlebolymphedema, lipedema, or lipolymphedema were ineligible for the protocol. Concordance between physician and therapist lymphedema diagnosis and staging was exact. Eligible subjects were required to be 14 years of age, have an intact mental status, and be fluent in English. All subjects who were approached agreed to participate. This study was approved by the University of Pennsylvania Health System Internal Review Board.

Demographics, medical comorbidities, and lymphedema-related data—Data related to patient demographics and medical comorbidities were collected from the University of Pennsylvania Health System electronic medical record, which contains patient self-identified ethnicity, as well as details of all care delivered within the University of Pennsylvania Health System. Lymphedema stage, duration, and distribution, as well as limb circumference measurements and history of cellulitic infections, were collected from the University of Pennsylvania Health System Lymphedema Clinic records. The 3-tier lymphedema staging criteria (I, spontaneously resolving; II, nonspontaneously resolving; III, nonspontaneously resolving with dermal metaplasia) developed by Foldi et al.¹⁴ were used in addition to the Common Toxicity Criteria¹² noted above to classify patients. Lymphedema etiology was designated cancer-related or noncancer. Distinctions were not made between congenital lymphedema, lymphedema praecox, lymphedema tarda, or obesity-related lymphedema among patients with noncancer lymphedema.

All comorbidities recorded at any clinic visit during the year before study enrollment were collected. Because of small numbers ($n < 10$) and/or pathophysiologic similarity, some comorbidities were combined to form larger categories. The final comorbidity categories included hypertension, diabetes mellitus, hypothyroidism, cardiac/pulmonary disorder (excluding hypertension), obstructive sleep apnea, arthritis, chronic pain disorder, gastrointestinal disorder, depression, and neurological disorder. Body mass index (BMI) was calculated as follows: $\text{weight (kg)} \div \text{height (m)}^2$. All patients' heights and weights were measured the day of study enrollment.

Outcomes

Health utility measures—The TTO is an extensively studied approach to utility value estimation that has been used to estimate patient preferences regarding a wide range of chronic conditions.¹⁵ Subjects were questioned about the number of years of their lives in their current health state they would be willing to give up to live in “perfect health.” Two alternatives were presented: 1) live T additional years in perfect health; or 2) live t years in your current health state. A life expectancy of 75 years was used for all patients irrespective of cancer status. Each exercise began with $T = t/2$ and $t = 75$ — patient age. If patients rejected the first alternative, T was lengthened until patients felt indifferent about the 2 alternatives. If patients accepted the first ($T = t/2$) alternative, T was subsequently shortened until they became indifferent. Utilities were defined and calculated as T/t .¹⁶

The EuroQol 5D is a widely used, well-validated instrument that has been evaluated in both Europe and the United States to assess utilities.¹⁷ The instrument contains questions in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Response options for each item include 1) no problems, 2) Some problem or moderate symptoms, and 3) unable to do or extreme symptoms. Patients choose the response that best describes their current experience in each domain, thereby aligning themselves with 1 of 243 possible health states. Euroqol 5D scoring was based on the US weighting system developed by Shaw et al.¹⁸ Weights were determined using a scoring algorithm for STATA.¹⁹

Statistical Analysis

The target sample of 236 was determined by the ability to estimate a mean Euroqol 5D utility with a 95% confidence interval of 0.05 and a sample size of 225. This power calculation was based on an 11-patient pilot-derived standard deviation of 0.19. The 11 patients from the pilot were included in all analyses.

Descriptive statistics were calculated for the total cohort and for subgroups. Trends across ordered groups defined by BMI and lymphedema stage were evaluated using a

nonparametric extension of the Wilcoxon rank sum test developed by Cuzick.²⁰ The Student *t* test and chi-square test were used to compare continuous and binary variables between groups, respectively. Separate univariate linear regression analyses were performed with TTO- and Euroqol 5D-based utility scores as the dependent variable and lymphedema characteristics and medical comorbidities as independent variables. Models were not constructed with the subgroup of patients with upper extremity lymphedema unrelated to cancer because of inadequate sample size (*n* = 3). Standard multivariate model-building techniques were applied, including evaluation of interaction terms. All tests were 2-tailed. *P* values <.05 were considered statistically significant. Analyses were performed with STATA for Windows, version 9.0.

RESULTS

Two hundred thirty-six patients met the screening criteria for study participation, and all agreed to enroll in the study. Among the 236 study subjects, only 29 (11%) of subjects were interviewed at the time of their initial evaluation. The remaining 210 (89%) subjects were receiving or had completed lymphedema treatment when interviewed. Demographics and lymphedema characteristics for the cohort are displayed in Table 1. As the table shows, participants ranged in age from 16 to 89 years. Subjects were disproportionately female (90.3%), reflecting the preponderance of breast cancer patients (*n*=128). Almost ¾ were Caucasian; ¼ were African American. Of the remaining 3, 1 self-identified as Hispanic and 2 as Asian.

Patients with lymphedema of a noncancer cause were about 10 years younger and had the condition for a longer period of time (mean of 10.6 years vs 4.4 years) than those with cancer-related lymphedema. The number of cellulitic infections documented since the time of lymphedema diagnosis was higher in patients with lymphedema unrelated to cancer (mean, 2.3; standard deviation [SD], 5.7) versus cancer-related lymphedema (mean, 1.1; SD, 2.8) (*P* = .02), and in those with lower extremity (mean, 2.1; SD, 5.1) versus upper extremity (mean, 0.9; SD, 2.7) (*P* = .02) lymphedema.

More than 70% of the study participants were over-weight (BMI ≥ 25 kg/m²), with almost half meeting the criteria for being obese (BMI ≥ 30 kg/m²) and 30% meeting the criteria for being morbidly obese (BMI ≥ 35 kg/m²). Eleven (5%) subjects had BMIs >60 kg/m². BMI was significantly higher in patients with noncancer lymphedema (39.0 kg/m²; SD, 15.6) than in those with cancer-related lymphedema (29.4 kg/m²; SD, 7.0) (*P* < .0001) as well as in patients with lower extremity lymphedema (35.9 kg/m²; SD, 14.3) versus those with upper extremity lymphedema (29.7 kg/m²; SD, 7.6) (*P* < .0001).

Unadjusted Utility Estimates

Unadjusted utilities estimated using TTO averaged 0.85 (SD, 0.21), whereas those determined from the Euroqol 5D averaged 0.76 (SD, 0.18) (Table 2). Overall, TTO-based utility scores, except in subjects with cancer-related lower extremity lymphedema, were significantly higher than those derived from the Euroqol 5D. Patients with upper and lower extremity lymphedema had similar utilities when estimated using the same method; TTO 0.87 (SD, 0.22) versus 0.84 (SD, 0.20) and Euroqol 5D 0.77 (SD, 0.17) versus 0.75 (SD, 0.19), respectively. Similarly, lymphedema etiology did not strongly influence the unadjusted utility estimates. Utilities for lower extremity lymphedema were noted to be 0.82 (SD, 0.04) for TTO and 0.80 (SD, 0.03) for the Euroqol 5D in cancer patients and 0.85 (TTO; SD, 0.02) and 0.73 (Euroqol 5D; SD, 0.03) for noncancer lymphedema patients.

Unadjusted utility scores differed between TTO and Euroqol 5D estimation methods in all but 28 patients, with a mean absolute difference of 0.17 (SD, 0.15). For 48 patients, Euroqol

5D scores were greater than TTO scores, whereas for 160 patients TTO scores were greater. Almost half the sample ($n = 111$), was unwilling to trade time for “perfect health.” However, among these patients, Euroqol 5D scores averaged 0.82 (SD, 0.15) with almost 10% being <0.5 .

Unadjusted utility values derived with both estimation techniques decreased with increasing lymphedema stage for the total cohort and for patients with lower extremity noncancer lymphedema (Table 2). Similar trends were not detected in subgroups lacking patients with stage III lymphedema (upper extremity lymphedema and lower extremity cancer-related lymphedema). For patients with cancer-related lymphedema, the difference in utility estimates between those with stage I and II lymphedema were minimal. Increasing BMI was strongly associated with reduced utility scores irrespective of the estimation approach in the study cohort as a whole (Table 3). Demographic factors were otherwise not associated with utility estimates.

Adjusted Utility Estimates

The results of the linear regression analyses for TTO and Euroqol 5D scores are summarized in Table 4. Utilities were lowest among cancer survivors with lower extremity lymphedema (TTO 0.82 [SD, 0.04]; Euroqol 5D 0.80 [SD, 0.03]). Breast cancer patients had adjusted Euroqol 5D scores of 0.80 (SD, 0.02). Cardiac/pulmonary disorders, among the various comorbidities, were most consistently inversely associated with utility scores. Notably BMI, the number/rate of cellulosic infections, lymphedema duration, and lymphedematous involvement of the dominant upper extremity were not associated with adjusted utility values by either estimation approach (data not shown).

DISCUSSION

In this cross-sectional study of patients with lymphedema because of cancer and noncancer causes, mean unadjusted utility values were 0.76 when assessed using the Euroqol 5D compared with 0.85 for TTO, and diminished further in the presence of higher lymphedema stages and obesity. Adjusted utility values were lowest for patients with cancer-related lymphedema, and these values were significantly lower than reported values for cancer survivors without lymphedema.^{21–25}

This study is the first to our knowledge to assess the utility scores of patients with lymphedema. The overall findings that lymphedema, and particularly severe lymphedema, is associated with lower utilities are not surprising given previous reports of poor QOL among lymphedema patients^{26–29}; however, several additional observations can be made. First, utilities elicited using the TTO methodology were significantly higher than those elicited using the Euroqol 5D. Second, although, unadjusted TTO- and Euroqol 5D-based utility scores decreased with increasing BMI, BMI was not significantly associated with adjusted utility values. Third, neither the presence of lymphedema-related medical complications (ie, recurrent cellulitis) nor lymphedema location was associated with utility values. The potential implications of these findings are discussed below.

Lymphedema Stage and Utility Scores

There was a strong association between adjusted Euroqol 5D scores and lymphedema stage for the total cohort and for the subgroup of patients with lower extremity lymphedema unrelated to cancer. The diminishing adjusted Euroqol 5D estimates of 0.94 for stage I, 0.82 for stage II, and 0.70 for stage III align with reports of greater functional and psychological morbidity with higher lymphedema stages.^{30,31} Comparison of these utilities with reported utilities for disease-free survival after breast cancer (0.959–0.989)^{21,22,24,32} and melanoma

(0.960)^{25,33} treatment highlights the degrading effect of higher lymphedema stages and argues persuasively for the need to prevent lymphedema progression.⁷

Discrepancies in TTO and Euroqol 5D Utility Scores

The seemingly small difference between mean TTO and Euroqol 5D utility estimates of 0.09 becomes noteworthy when projected over the almost half a million affected patients in the United States. For this reason, it is important to consider which utility estimation method best approximates patients' real world choices. It could be argued that the TTO exercise, by allowing patients to consider their total lymphedema "lived experience," may capture subtle dimensions of the health state (eg, the tedium of maintenance activities), whereas the Euroqol 5D, which is limited to 5 dimensions, cannot. However, if such adverse, subtle factors influenced patients' valuations during the TTO exercise, one would expect TTO-based utilities to be lower than Euroqol 5D-based utilities, not the converse.

A more likely explanation for the discrepancy noted has been suggested by previous authors, namely upward biasing of TTO scores.³⁴ The finding that almost half the sample was unwilling to trade time, and that $\frac{2}{3}$ of these patients scored below 0.85 on the Euroqol 5D, suggests inflation of TTO scores at odds with patients' true preferences because of loss aversion bias.^{34–36} Prior work appears to be relevant to our findings, as cancer patients, in particular, may be more averse to relinquishing time when considering their personal conditions.^{37–40} These considerations suggest that Euroqol 5D scores may align more closely with patients' true preferences.

Lymphedema and BMI

That patient BMI influences lymphedema incidence and severity is well established,^{3,41} and it is not surprising that BMI correlated inversely with unadjusted lymphedema utilities. However, the finding that the associations between lymphedema utilities and BMI were no longer significant after adjusting for medical comorbidities is noteworthy and may suggest that obese patients' lower lymphedema utilities are due to nonlymphedema comorbidities. A notable concern is the strong association between obesity-related complications and higher BMI, such that including both variables in the models may be problematic. Such modeling limitations may explain the surprisingly high adjusted utilities for patients with non-cancer lower extremity lymphedema, 0.93 TTO and 0.94 Euroqol 5D. These high utilities are the reverse of expected, because this subgroup included the highest proportion of patients with stage III lymphedema, 36%, and therefore should have included more patients with degraded health states.^{30,31}

Utilities and Lymphedema Characteristics

As yet there are scant data relating the preferences, health status, and QOL of patients with lymphedema to specific lymphedema characteristics other than stage. Several factors, at face value, would seem to impact lymphedema utilities, such as bilateral involvement, frequency of cellulitis, involvement of a dominant upper extremity, and lymphedema distribution. The finding that these factors did not influence subjects' evaluation of their health states as measured with utility assessments is notable and challenges assumptions regarding the influence of specific lymphedema characteristics. Further work is needed to understand the dimensions of lymphedema health states that most trouble patients for integration into care delivery models.

Limitations

This study has several limitations. One is that although the overall sample and upper extremity, cancer-related lymphedema subgroup were sufficient to allow utility estimation

with reasonable precision, the smaller sample sizes of some of the subgroups (eg, cancer-related lower extremity lymphedema) limit the inferences that can be made regarding these patients. (Table 5 provides estimates of the sample sizes required to estimate mean Euroqol 5D utilities at various 95% confidence interval widths for each subgroup and the total sample.)

The lack of distinction between newly diagnosed lymphedema patients and those with longer standing and perhaps stably maintained lymphedema limits inferences that can be drawn regarding the importance of these issues. These data also shed no light on whether utility scores improve with lymphedema treatment. An important next step will be to estimate the change in utilities associated with conventional lymphedema treatments to support cost-utility analyses of current lymphedema treatments.

Another potential limitation is that the utilities were elicited from the patients' perspective rather than a societal perspective. Utility weights are often determined by requesting unaffected individuals (societal perspective) to evaluate health states portrayed with written vignettes, voice recordings,⁴² or video clips⁴³ or by having affected patients rate their health state. There are ample precedents for all of these approaches.⁴⁴ Although the latter estimation technique may be more appropriate for lymphedema, because unaffected individuals may be unfamiliar with dimensions of a relatively uncommon health state, the converse could be argued, because affected individuals may be less willing to devalue their current health states.

Conclusions

Lymphedema reduces health utilities, particularly at higher stages (II and III) and when associated with elevated BMI. Adjusted lymphedema utilities are lowest among cancer survivors, and lymphedema risk-reducing cancer treatment modifications may be justified from a cost-utility perspective. Greater expenditures for the prevention and treatment of cancer-related lymphedema are warranted.

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Table 1

Demographics, Cancer-Related Information, and Medical Comorbidities of the Study Cohort and Subgroups Defined by Lymphedema Location and Etiology

Factor	All		Noncancer Lower Extremity		Cancer Lower Extremity		Noncancer Upper Extremity		Cancer Upper Extremity		Multiple Loci	
	Mean or No. (%)	SD	Mean or No. (%)	SD	Mean or No. (%)	SD	Mean or No. (%)	SD	Mean or No. (%)	SD	Mean or No. (%)	SD
Patient demographics												
No.	236		66		28		3		124		15	
Age, y	55.6	14.6	48.4	14.7	58.3	14.1	41.7	16.0	58.9	13.4	58.3	13.5
Percent female	213(90.3%)		53 (80.3%)		25 (89.3%)		3(100.0%)		122 (98.4%)		10(66.7%)	
BMI	32.2	11.2	38.9	15.6	29.1	7.2	32.0	2.1	29.5	7.1	31.1	12.0
Obese	115(48.7%)		41 (62.1%)		9(32.1%)		2 (66.7%)		57 (46.0%)		6 (40%)	
Race												
Caucasian	175(74.2%)		45 (68.2%)		26 (92.9%)		1 (33.3%)		91 (73.4%)		12 (80%)	
African American	58 (24.6%)		21 (31.8%)		2(7.1%)		2 (66.7%)		31 (25.0%)		2 (13.33%)	
Asian	2 (0.8%)		0.0		0.0		0.0		1 (0.8%)		0.0	
Hispanic	1 (0.4%)		0.0		0.0		0.0		1 (0.8%)		1 (6.7%)	
Cancer and lymphedema characteristics												
Stage of lymphedema												
I	35(14.8%)		9(13.6%)		4 (14.3%)		1 (33.3%)		19(15.3%)		2 (13.3%)	
II	174(73.7%)		33 (50.0%)		23(82.1%)		2 (66.7%)		105(84.7%)		11 (73.3%)	
III	27 (11.4%)		24 (36.4%)		1 (3.57%)		0.0		0.0		2 (13.3%)	
Duration of LE, y	6.2	8.1	11.1	11.7	6.6	8.1	1.0	0.0	4.1	4.3	3.0	2.9
No. of cellulitic infections since LE onset	1.4	3.9	2.4	5.8	1.4	2.4	0.0	0.0	0.9	2.7	1.5	3.6
Cancer-related												
Cancer-related	167(70.8%)										14(93.3%)	
Breast	128(54.2%)				0.0				123(99.2%)		5 (33.3%)	
Melanoma	9 (3.8%)				7 (25.0%)				0.0		2 (13.3%)	
Gynecological	17(7.2%)				16(57.1%)				0.0		1 (6.7%)	
Other ^d	13(5.5%)				5 (17.9%)				1 (0.79%)		6 (40.4%)	
Stage IV cancer	17(7.20%)				5 (17.9%)				11 (8.9%)		1 (6.7%)	
Patients with unilateral arm lymphedema												

Factor	All	Noncancer Lower Extremity		Cancer Lower Extremity		Noncancer Upper Extremity		Cancer Upper Extremity		Multiple Loci	
		Mean or No. (%)	SD	Mean or No. (%)	SD	Mean or No. (%)	SD	Mean or No. (%)	SD	Mean or No. (%)	SD
Interarm circumferential difference, %											
LE affects dominant arm											
Medical comorbidities											
Cardiac/pulmonary disorder	39(16.5%)		7(10.6%)		7 (25.0%)		2 (66.7%)		19(15.3%)		4 (26.7%)
Arthritis ^b	42 (17.8%)		13(19.7%)		4 (14.3%)		0.0		24(19.4%)		1 (6.7%)
Diabetes mellitus	21 (8.9%)		8(12.1%)		1 (3.6%)		0.0		11 (8.9%)		1 (6.7%)
Hypertension	57 (24.2%)		16(24.2%)		5 (17.9%)		0.0		33 (26.6%)		3 (20.0%)
Depression	20 (8.5%)		3 (4.6%)		2(7.1%)		1 (33.3%)		12 (9.7%)		2 (13.3%)
Gastrointestinal disorder	26 (11.0%)		4(6.1%)		3 (10.7%)		1 (33.3%)		16(12.9%)		2 (13.3%)
Nonarthritic chronic pain disorder ^c	41 (17.4%)		8(12.1%)		4 (14.3%)		1 (33.3%)		27(21.8%)		1 (6.7%)
Hypothyroidism	27 (11.4%)		6(9.1%)		2(7.1%)		0.0		6 (4.8%)		3 (20.0%)
Obstructive sleep apnea	15(6.4%)		11 (16.7%)		1 (3.6%)		0.0		2 (2.42%)		0.0
Neurological disorder	37(15.7%)		17(25.8%)		4 (14.3%)		0.0		15(12.1%)		1 (6.7%)

SD indicates standard deviation; BMI, body mass index; LE, lymphedema.

^aOther cancers indicate prostate, lymphoma, lung, and Merkel cell.

^bOsteoarthritis, systemic arthropathy.

^cFibromyalgia, interstitial cystitis, migraine headaches, myofascial pain syndrome, and chronic low back pain.

Table 2

Unadjusted TTO and EQ-5D Utility Estimates for the Study Cohort and Subgroups Defined by Lymphedema Location, Etiology, and Stage

Subgroup	No.	Time TTO Mean (SD)	Range	EQ-5D Mean (SD)	Range	<i>p^a</i>
All						
All stages	236	0.85 (0.21)	0.05–1.00	0.76 (0.18)	0.17–1.00	<.0001
Stage I	35	0.89 (0.19)	0.30–1.00	0.81 (0.18)	0.20–1.00	
Stage II	174	0.85 (0.22)	0.05–1.00	0.77 (0.16)	0.17–1.00	
Stage III	27	0.78 (0.21)	0.33–1.00	0.63 (0.23)	0.20–1.00	
<i>p^b</i>		.01		.001		
Upper extremity lymphedema noncancer						
All stages	3	0.83 (0.29)	0.50–1.00	0.66 (0.44)	0.17–1.00	
Stage I	1	1.0 (0.0)	1.00	0.83 (0.0)	NA	
Stage II	2	0.75 (0.35)	0.50–1.00	0.58 (0.59)	0.17–1.00	
Stage III	0	NA	NA	NA	NA	
<i>p^b</i>		.48		1.00		
Upper extremity lymphedema cancer						
All stages	124	0.87 (0.22)	0.05–1.00	0.77 (0.16)	0.20–1.00	<.0001
Stage I	19	0.87 (0.21)	0.36–1.00	0.77 (0.21)	0.20–1.00	
Stage II	105	0.87 (0.22)	0.05–1.00	0.77 (0.15)	0.31–1.00	
Stage III	0	NA	NA	NA	NA	
<i>p^b</i>		.75		.89		
Lower extremity lymphedema noncancer						
All stages	66	0.85 (0.19)	0.33–1.00	0.73 (0.21)	0.20–1.00	.0001
Stage I	9	0.96 (0.8)	0.77–1.00	0.90 (0.12)	0.71–1.00	
Stage II	33	0.86 (0.19)	0.45–1.00	0.78 (0.17)	0.31–1.00	
Stage III	24	0.78 (0.21)	0.33–1.00	0.61 (0.22)	0.20–0.84	
<i>p^b</i>		.02		<.0001		
Lower extremity lymphedema cancer-related						

Subgroup	No.	Time TTO		EQ-5D		<i>P</i> ^a
		Mean (SD)	Range	Mean (SD)	Range	
All stages	28	0.82 (0.21)	0.30–1.00	0.80 (0.13)	0.38–1.00	.52
Stage I	4	0.78 (0.33)	0.30–1.00	0.83 (0.21)	0.60–1.00	
Stage II	23	0.83 (0.20)	0.50–1.00	0.79 (0.13)	0.38–1.00	
Stage III	1	0.86 (0.0)	0.86	1.0 (0.0)	NA	
<i>P</i> ^b		.93		.63		

TTO indicates time trade-off; EQ-5D, Euroqol 5D; SD, standard deviation; NA, not available.

^a *P* value for Student *t* test comparing mean TTO and EQ-5D utility estimates.

^b *P* value for test for trend across ordered groups defined by lymphedema stage.

TTO and EQ-5D Utility Estimates for the Study Cohort and Subgroups Defined by Lymphedema Etiology and Increasing Degrees of Obesity

Table 3

Subgroup	All Patients		TTO		Cancer-Related Lymphedema		All Patients		EQ-5D		Cancer-Related Lymphedema	
	Mean (SD)		Noncancer Lymphedema	Mean (SD)	Mean (SD)		Mean (SD)		Noncancer Lymphedema	Mean (SD)	Mean (SD)	
All patients	0.85 (0.21)		0.85 (0.20)		0.86 (0.22)		0.76 (0.18)		0.72 (0.23)		0.78 (0.16)	
BMI <35 and 35	0.79 (0.20)		0.75 (0.22)		0.83 (0.19)		0.67 (0.21)		0.63 (0.21)		0.71 (0.21)	
BMI <35 and 30	0.86 (0.20)		0.92 (0.16)		0.84 (0.21)		0.74 (0.17)		0.76 (0.22)		0.74 (0.15)	
BMI <30 and 25	0.88 (0.22)		0.90 (0.12)		0.88 (0.24)		0.83 (0.12)		0.86 (0.12)		0.82 (0.13)	
BMI <25	0.89 (0.22)		0.95 (0.12)		0.87 (0.24)		0.82 (0.14)		0.84 (0.18)		0.81 (0.13)	
Probability	$P<.0001^a$		$P=.001^a$		$P=.039^a$		$P<.0001^a$		$P<.0001^a$		$P=.006^a$	

TTO indicates time trade-off; EQ-5D, Euroqol 5D, SD, standard deviation; BMI, body mass index.

^a *P* value for test for trend across ordered groups defined by BMI.

Table 4

Multivariate Linear Regression Models of TTO and EQ-5D Scores by Lymphedema Etiology and Location Adjusted for Medical Comorbidities

Statistic	Upper Extremity Lymphedema Cancer-Related (n = 124)		Lower Extremity Lymphedema Noncancer (n = 66)		Lower Extremity Lymphedema Cancer-Related (n = 28)		Entire Cohort (n = 236)	
	TTO	EQ-5D	TTO	EQ-5D	TTO	EQ-5D	TTO	EQ-5D
Constant								
95% CI	0.93	0.80	0.93	0.94	0.82	0.80	0.91	0.84
	0.88 to 0.99	0.77 to 0.84	0.88 to 0.97	0.84 to 1.05	0.74 to 0.91	0.75 to 0.85	0.88 to 0.94	0.79 to 0.90
Cardiac/pulmonary disorder^d								
Coefficient	-0.11	-0.12	NS	-0.18	NS	NS	-0.11	-0.10
P	.043	.003		.007			.003	.001
95% CI	-0.22 to -0.003	-0.19 to -0.04		-0.31 to 0.05			-0.17 to -0.04	-0.16 to -0.04
Depression								
Coefficient	NS	-0.12	-0.19	-0.22	NS	NS	-0.16	-0.15
P		.012	.036	.026			.001	.000
95% CI		-0.21 to -0.03	-0.36 to -0.01	-0.42 to 0.03			-0.26 to -0.07	-0.23 to -0.08
Arthritis^b								
Coefficient	NS	NS	-0.19	-0.17	NS	NS	-0.08	-0.06
P			.000	.002			.024	.031
95% CI			-0.29 to -0.09	-0.28 to 0.07			-0.15 to -0.01	-0.12 to .01
Obstructive sleep apnea								
Coefficient	NS	NS	-0.25	NS	NS	NS	-0.16	NS
P			.000				.004	
95% CI			-0.35 to -0.15				-0.26 to -0.05	
% difference in arm circumference								
Coefficient	-0.003	NS	NA	NA	NA	NA	NA	NA
P	.024							
95% CI	-0.006 to -.0004							
Lymphedema stage^c								
II								
Coefficient	NS	NS	NS	-0.12	NS	NS	NS	-0.03

Statistic	Upper Extremity Lymphedema Cancer-Related (n = 124)		Lower Extremity Lymphedema Noncancer (n = 66)		Lower Extremity Lymphedema Cancer-Related (n = 28)		Entire Cohort (n = 236)	
	TTO	EQ-5D	TTO	EQ-5D	TTO	EQ-5D	TTO	EQ-5D
<i>P</i>				.038				.301
95% CI				−0.24 to 0.01				−0.09 to 0.03
III								
Coefficient	NS	NS	NS	−0.24	NS	NS	NS	−0.17
<i>P</i>				.000				.000
95% CI				−0.36 to −0.12				−0.25 to −0.09
<i>P</i>	.006	.001	.000	.000			.000	.000
Adjusted <i>R</i> ²	0.07	0.10	0.43	0.45			0.14	0.18
<i>R</i> ²	0.09	0.11	0.45	0.49			0.15	0.20

TTO indicates time trade-off; EQ-5D, Euroqol 5D; CI, confidence interval; NS, not significant; NA, not available.

^aCoronary artery disease, congestive heart failure, cardiac dysrhythmia, chronic obstructive pulmonary disease, and/or asthma.

^bOsteoarthritis, systemic arthropathy.

^cRelative to stage I lymphedema.

Table 5
Sample Sizes Required for EQ-5D Utility Estimates at Different Distances From the Mean to the 95% CI Based on Sample SDs

Subgroup	Cancer-Related Lymphedema	Study No.	Sample SD	Sample Size, Width of 95% CI	
				0.1	0.06 0.04
All subjects		236	0.18	53	141 314
Upper extremity	No	3	0.44	300	827 1860
	Yes	124	0.16	42	112 249
Lower extremity	No	66	0.21	71	191 426
	Yes	28	0.13	29	75 165

EQ-5D indicates Euroqol 5D; CI, confidence interval; SD, standard deviation.