Minimally Important Difference for the Expanded Prostate Cancer Index Composite Short Form

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OBJECTIVE To establish a score threshold that constitutes a clinically relevant change for each domain of the Expanded Prostate Cancer Index Composite (EPIC) Short Form (EPIC-26). Although its use in clinical practice and clinical trials has increased worldwide, the clinical interpretation of this 26-item disease-specific patient-reported quality of life questionnaire for men with localized prostate cancer would be facilitated by characterization of score thresholds for clinically relevant change (the minimally important differences [MIDs]).

METHODS We used distribution- and anchor-based approaches to establish the MID range for each EPIC-26 domain (urinary, sexual, bowel, and vitality/hormonal) based on a prospective multi-institutional cohort of 1201 men treated for prostate cancer between 2003 and 2006 and followed up for 3 years after treatment. For the anchor-based approach, we compared within-subject and between-subject score changes for each domain to an external "anchor" measure of overall cancer treatment satisfaction.

RESULTS We found the bowel and vitality/hormonal domains to have the lowest MID range (a 4-6 point change should be considered clinically relevant), whereas the sexual domain had the greatest MID values (10-12). Urinary incontinence appeared to have a greater MID range (6-9) than the urinary irritation/obstruction domain (5-7).

CONCLUSION Using 2 independent approaches, we established the MIDs for each EPIC-26 domain. A definition of these MID values is essential for the researcher or clinician to understand when changes in symptom burden among prostate cancer survivors are clinically relevant. UROLOGY 85: 101–106, 2015. © 2015 Elsevier Inc.

Many of the nearly 3 million prostate cancer survivors in the United States deal with the side effects of prostate cancer treatment.[1,2] Even in the midst of advanced technologies to treat the disease (ie, robotic-assisted surgery and proton beam therapy), urinary, sexual, bowel, and hormonal side effects remain common.[1-6] The Expanded Prostate Cancer Index Composite (EPIC) is a well-established patient-reported outcome (PRO) questionnaire developed to monitor health-related quality of life outcomes among prostate cancer survivors.[7,8] The 26-item version of EPIC, also known as EPIC Short Form or EPIC-26, contains 5 symptom domains (urinary incontinence, urinary irritative/obstructive, sexual, bowel, and vitality/hormonal), scored from 0 (worst) to 100 (best) that can be tracked over time to understand symptom burden, functional outcomes, and the impact of side effect management strategies.[1,8,9]

Although EPIC-26 has proven to be a powerful research tool[1] with its use increasing worldwide, there exists a longstanding challenge in its interpretation; the domain score thresholds that should be considered clinically relevant have not yet been defined. In other words, if a patient's sexual domain score changes from 96 pre-treatment to 90 post-treatment, should this be considered clinically significant, or is it simply statistical noise?

An National Cancer Institute-sponsored working group charged with recommending a core set of symptoms to be assessed using PROs in prostate cancer clinical trials

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cited the definition of these score thresholds, also known as minimally important differences (MIDs), as an essential methodological step in confronting the interpretability challenges of PRO data.[10] In particular, the group questioned whether the commonly used distribution-based statistical threshold of one-half standard deviation is entirely adequate for inferring clinically meaningful change.

Our objective was to use 2 independent approaches (distribution-based and anchor-based methods) to define the MID for each EPIC-26 domain. Our findings provide the necessary context for determining when changes in patient-reported symptoms are likely to be clinically meaningful to patients, providers, researchers, and payers.

METHODS

Study Population

We identified a longitudinal cohort of 1201 men with stage T1 or T2 prostate cancer based on a previously reported multi-institutional study.[1] The men in our study received primary treatment between March 2003 and March 2006 with radical prostatectomy, brachytherapy, or external beam radiotherapy at 1 of 9 university-affiliated hospitals. We examined their longitudinal EPIC-26 data before treatment and for 3 years after treatment. The institutional review boards at each site approved the parent study, and all patients provided written informed consent.

Outcomes

The primary outcome for this study was the minimally important range for each of the 5 EPIC-26 domains (urinary incontinence, urinary irritative/obstructive, sexual, bowel, and vitality/hormonal). We determined pretreatment, 1-, 2-, and 3-year post-treatment EPIC-26 values for each patient. We based the final MID values on a combination of 2 well-described methods from the survey literature.[11-13]

Distribution-based Approach. First, we used a distribution-based approach to compare changes in EPIC-26 scores to corresponding standard deviations (SDs) for each domain. Previous studies have found that half of an SD and one-third of an SD are appropriate choices for a distribution-based MID cutpoint, with half SD representing a medium-sized effect and one-third SD representing a small effect.[11-13] For this study, we based each domain's SD on the entire cohort's EPIC-26 scores for that domain.

Anchor-based Approach. Second, we used an anchor-based approach to examine within-patient and between-patient EPIC-26 scores corresponding to an external criterion. In general, anchor-based studies compare PRO scores to another subjective assessment, often a global assessment of an external criterion to detect meaningful differences in patient-reported scores.[11] For this reason, we selected the following anchor item from the Service Satisfaction Scale for Cancer Care (SCA) scale[14] (derived from the Service Satisfaction Scale[15]), which was included in the parent study: "In an overall general sense, how satisfied are you with the cancer treatment you received?" The corresponding responses included: completely satisfied, very satisfied, somewhat satisfied, mixed, somewhat unsatisfied, very unsatisfied, and completely unsatisfied. We combined the mixed and unsatisfied groups because of low response levels for those options. The selected global satisfaction item has the highest corrected item-total correlations with the overall 16-item SCA scale (0.82) and the Outcome of Care Satisfaction subscale (0.80).

Statistical Analysis

For the distribution-based approach, we calculated the mean and SD of the EPIC-26 values for each domain at our selected time points (pretreatment, 1, 2, and 3 years), using these to calculate the one-third SD and half SD values corresponding to MID values. For the anchor-based approach, examining changes in response levels to the aforementioned anchor question, we used unadjusted and age-adjusted linear regression to model EPIC-26 changes from pretreatment and cross-sectional results from 1, 2, and 3 years of follow-up. We calculated changes in model-adjusted scores between adjacent anchor-item levels. Finally, we used the distribution- and anchor-based EPIC-26 MID to recommend ranges for clinically meaningful differences in EPIC-26 scores for each domain.[11] For both distribution-based and anchor-based methods, the values derived from the methods previously described were averaged over the time points, with MID values chosen as the predominant range across methods.

All analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC), and all testing was 2 sided. The probability of a type I error was set at .05.

RESULTS

The SD in EPIC-26 domain scores ranged from 8.8 to 27.7 pretreatment and from 12.6 to 31.9 at 3 years. Sexual domain scores tended to have the highest SD at each time point. The corresponding distribution-based one-third and half SD values, analogous to MID values, demonstrated similar variability over time as shown in Table 1. The differences between using a one-third or half SD approach to define MIDs ranged from roughly 2 to 5 EPIC-26 points, with the greatest differences in the sexual domain.

As shown in Table 2, responses varied over time for the cross-sectional SCA anchor item: "In an overall general sense, how satisfied are you with the cancer treatment you received?" Most patients were completely or very satisfied over the study duration. The age-adjusted changes from pretreatment and cross-sectional EPIC-26 domain values between adjacent anchor-level responses over time from primary prostate cancer treatment are shown in the Supplementary Table. The sexual domain again had the highest values.

As illustrated in Figure 1, our EPIC-26 MID estimates are derived from the ranges (recommended best practice[11]) provided by the 2 approaches used in this study. Based on pooled averages from distribution- and anchor-based approaches, we found that the bowel and vitality/hormonal domains had the lowest MID values (both 4-6 EPIC-26 points), whereas the sexual domain had the greatest MID values, ranging from 10 to 12. Urinary incontinence appeared to have a larger and higher MID range (6-9) compared with the urinary irritative/obstructive domain (5-7; Table 3).

Table 1. Distribution-based Expanded Prostate Cancer Index Composite Short Form (EPIC-26) standard deviation values corresponding to minimally important differences over time since primary prostate cancer treatment by domain*

	Pretreatment		1-Y		2-Y		3-Y	
EPIC-26 Domain	1/3 SD	1/2 SD	1/3 SD	1/2 SD	1/3 SD	1/2 SD	1/3 SD	1/2 SD
Urinary incontinence	4.3	6.4	7.0	10.5	7.0	10.5	7.0	10.5
Urinary irritative/obstructive	4.6	7.0	5.0	7.5	4.7	7.0	4.2	6.3
Bowel	2.9	4.4	4.7	7.0	4.7	7.1	4.2	6.4
Sexual	9.2	13.8	10.3	15.4	10.5	15.8	10.6	15.9
Vitality/hormonal	3.8	5.7	4.5	6.8	4.8	7.2	3.9	5.9

EPIC, Expanded Prostate Cancer Index Composite; SD, standard deviation.
* For the distribution-based approach, we calculated the mean and standard deviation (SD) of the EPIC-26 values for each domain at our selected time points since primary prostate cancer treatment, using these to calculate the 1/3 SD and 1/2 SD corresponding to minimally important difference values.

Table 2. Service Satisfaction Scale for Cancer Care anchor item responses over time since primary prostate cancer treatment from a cohort of 1201 men

SCA Anchor Item: "In an Overall General Sense, How Satisfied Are You With the Cancer Treatment You Received?"	Time Since Primary Prostate Cancer Treatment		
	1 Y	2 Y	3 Y
Completely satisfied (%)	48.9	44.2	48.2
Very satisfied (%)	43.1	46.5	43.0
Somewhat satisfied (%)	5.8	7.0	6.2
Mixed (%)	0.9	1.0	0.6
Somewhat unsatisfied (%)	0.4	0.5	0.8
Very unsatisfied (%)	0.3	0.5	0.8
Completely unsatisfied (%)	0.6	0.3	0.4

SCA, Service Satisfaction Scale for Cancer Care.

COMMENT

We used distribution- and anchor-based approaches to establish MIDs (ie, clinically relevant) for each EPIC-26 domain. In general, MID estimates were consistent between methods for most domains. Clinically meaningful changes in EPIC-26 scores ranged from 4 to 12 points depending on the domain. We believe the EPIC-26 MID values provided in this study offer the necessary context for determining when changes in symptom burden among prostate cancer survivors are significant. In addition, these findings provide useful endpoints for clinical trials, comparative effectiveness research, and the clinical care of men with prostate cancer after treatment.

The use of EPIC in clinical practice and clinical trials has, in large part, been limited to the realm of clinical epidemiology. At least 2 barriers to its use in real-world practice have been identified. First, the length of EPIC has been cited as a barrier to widespread clinical adoption.[7,16,17] This concern was reduced with the shorter versions of EPIC, including its Short Form (ie, EPIC-26) included in this study, and most recently with the EPIC for clinical practice (EPIC-CP).[17] The EPIC-26 is the most widely used version in clinical studies because of its comprehensive and rigorous delineation of function and bother for each of the relevant domains.[1,7] The subsequent clinical practice version of EPIC, EPIC-CP, further reduced the instrument to a 1-page format with 16 items to facilitate measuring health-related quality of life in the routine practice setting and is highly correlated to the original and Short Forms.[17] Its 16-item, 1-page structure makes ease of use in routine practice straightforward. In addition, our findings are relevant for its scoring, given the high correlation among the EPIC instruments.[16]

A second longstanding barrier is what represents a clinically relevant difference (ie, MID) for each domain of EPIC. Comparisons with other quality of life instruments have revealed cutoffs for symptom severity in different domains,[18,19] although there have never been thresholds for symptom improvement or worsening developed for the EPIC-26 instrument. Our findings, along with recent work in this area using the University of California, Los Angeles-Prostate Cancer Index[20] and EPIC-CP,[16] builds a strong foundation for understanding meaningful differences in PROs among survivors. For example, comparable MID values for the University of California, Los Angeles-Prostate Cancer Index,[20] a precursor of EPIC also scored from 0 to 100, were found for urinary function (8) and bother (9), bowel function (7) and bother (8), and sexual function (8) and bother (11). That the upper bounds of thresholds in our study closely match these values supports construct validity and robustness of the recommended MID levels.

As patient-centered cancer care increases in demand, understanding how best to alleviate symptom burden among prostate cancer survivors has important implications for patients, providers, researchers, and payers.[21] The Patient-Centered Outcomes Research Institute methodology core is currently investigating strategies for increasing the use of PROs into electronic health records.[22] Just as normal and abnormal laboratory values are routinely examined in clinical care, PROs should be easily accessed in clinically meaningful contexts to patients and providers. In particular, following EPIC outcomes over time and understanding clinically meaningful differences in their values could facilitate more effective and comprehensive communication between patients and providers regarding clinically meaningful outcomes and thereby improve care quality.

This study identifies thresholds for clinically meaningful differences in patient-reported prostate cancer quality of life outcomes; however, there are several limitations to

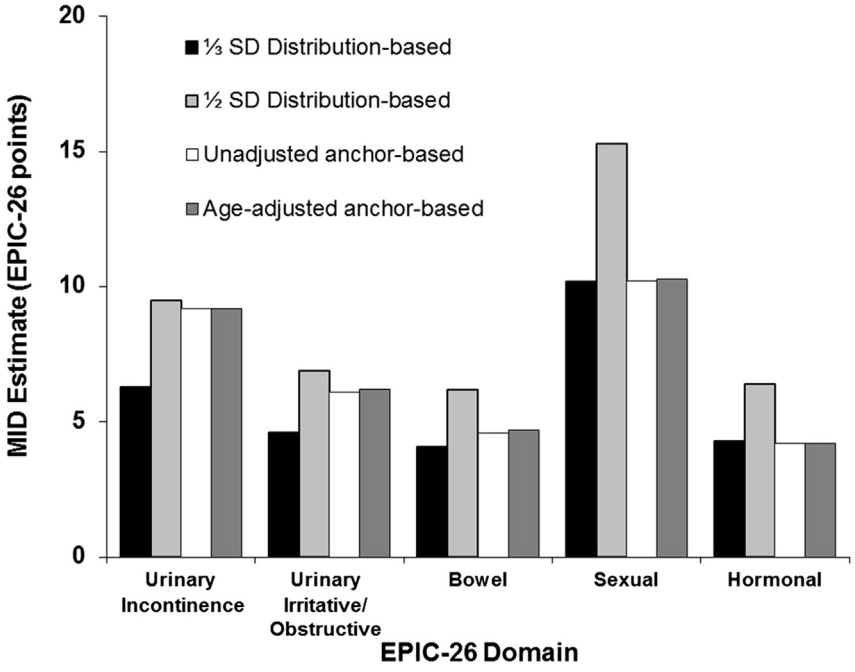

Figure 1. Average Expanded Prostate Cancer Index Composite Short Form (EPIC-26) minimally important difference values using distribution- and anchor-based approaches by domain. EPIC, Expanded Prostate Cancer Index Composite; MID, minimally important difference; SD, standard deviation.

Table 3. Recommended Expanded Prostate Cancer Index Composite Short Form minimally important difference values by domain

EPIC-26 Domain	Minimally Important Difference (EPIC-26 Points)*
Urinary incontinence	6-9
Urinary irritative/obstructive	5-7
Bowel	4-6
Sexual	10-12
Vitality/hormonal	4-6

Abbreviation as in Table 1.
* Based on pooled averages from distribution- and anchor-based approaches.

keep in mind. First, the study did not include patients on active surveillance, an increasingly popular treatment option among men at low risk of dying of their disease as there would not have been sufficient changes in EPIC scores to examine MID.[23] Caution in applying this to men on active surveillance is warranted; nevertheless, knowing which side effect management strategies work best in terms of meaningful and measureable differences in EPIC-26 outcomes will remain relevant for men treated for the disease. Second, we only used 2 approaches to estimate the EPIC-26 MID values for each domain[11,12,20]; however, the consistency between these well-vetted approaches is reassuring.[11] Third, the estimates derived in this study are from a nonrandomized prospective study raising generalizability concerns in terms of pretreatment function and treatment selection. This limitation applies to all observational studies where a subset of the population is enrolled in a nonrandom fashion. The parent study attempted to address this through enrollment at multiple institutions using a standardized protocol. Fourth, there may be some concern that a 10-point improvement in the lower range of a domain score (eg, 30-40) represents a larger proportional increase compared with that in the upper range of a domain score (eg, 80-90). Fortunately, the approaches used to estimate the EPIC-26 MID values provide thresholds across the entire range of domain scores from 0 to 100. We feel the MIDs in this article and based on raw differences indicate when a clinically meaningful change in the patient's state has taken place, thereby adding a helpful threshold for interpreting EPIC-26 results. However, we recognize that for individuals, the perception of whether the change is truly important may differ based on where on the scale they fall.

In conclusion, our findings provide the necessary context for determining when changes in patient-reported symptoms using the EPIC-26 are likely to be clinically meaningful to prostate cancer patients, their providers, researchers, and payers. In doing so, this study provides useful endpoints for clinical trials, comparative effectiveness research, and the clinical care of men with prostate cancer.

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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2014.08.044.

EDITORIAL COMMENT

The Expanded Prostate Cancer Index Composite Short Form (EPIC-26) for determining health-related quality of life (HRQOL) is widely used in clinical research, based on its extensive validation and psychometric properties.[1] However, there is a lack of available minimal important difference (MIDs) values, also known as domain score thresholds, for determining the clinical significance of changes in urinary incontinence, urinary irritative or obstructive, bowel, sexual, and hormonal symptoms. The lack of these thresholds makes it difficult to interpret the effects obtained. The present study is important in filling this gap by providing these values for prostate cancer survivors. Having the MID values available for the EPIC-26 domain scores will not only facilitate interpretation of clinically significant symptom changes in research studies, but will also assist in the clinical management of HRQOL, including treatment side effects.

This study has a number of strengths that buttress the utility of the findings obtained. First, in line with recommendations in the literature,[2] 2 major approaches to estimating MIDs were used, that is, distribution- and anchor-based, and the resulting values were averaged to arrive at MID estimates. Second, the MIDs of the 2 approaches were strikingly consistent, supporting their validity. Third, MID ranges were used rather than single values, enabling clinicians to choose a higher or lower threshold value depending on the clinical context.[3] Fourth, assessments were obtained at pretreatment and at 1, 2, and 3 years post-treatment, providing a fairly inclusive time frame to capture important changes in HRQOL. Fifth, results were based on data collected on a large cohort of early-stage prostate cancer patients (n = 1201), thereby strengthening the generalizability of study results.

The authors acknowledge certain limitations to the study. Additional concerns include the fact that a single anchor was used rather than multiple anchors. Furthermore, this anchor was a patient-reported outcome rather than a clinical variable and therefore likely to share patient-reported outcome—related measurement error with the EPIC-26 domain scores.[4] Second, the anchor was a single Likert rating scale item (ie, "In an overall sense, how satisfied are you with the cancer treatment you received?"), which constrains the utility of the assessment. Third, the validity of the anchor was somewhat questionable, because only correlations with the overall 16-item Service Satisfaction Scale for Cancer Care and the Outcome of Care Satisfaction subscale were reported; in addition, the correlations of the anchor with the EPIC-26 domain scores were not reported.[5]

Nonetheless, the consistency of the MIDs reported across the 2 estimation approaches, as well as the other strengths of the study, warrant utilization of the reported MIDs in both research and clinical settings. The results are particularly relevant to early-stage prostate cancer patients who have undergone prostatectomy, brachytherapy, or external beam radiotherapy, the patient population under study. Future research is needed to both strengthen and to extend the evidence base for the EPIC-26 threshold scores, notably studies that use alternative approaches to MID estimation,[6] as well as studies that assess patients on active surveillance regimens, and studies that evaluate patients at more advanced clinical stages who are receiving other therapeutic regimens (eg, hormonal therapy). The authors are to be commended for advancing the field and contributing to the literature and clinical applications of HRQOL and symptomatology in prostate cancer survivors.

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