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Citation: White, I. D., Sangha, A., Lucas, G. & Wiseman, T. (2016). Assessment of sexual difficulties associated with multi-modal treatment for cervical or endometrial cancer: A systematic review of measurement instruments. *Gynecologic Oncology*, 143(3), pp. 664-673. doi: 10.1016/j.ygyno.2016.08.332

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Title: Assessment of Sexual Difficulties Associated with Multi-modal Treatment for Cervical or Endometrial Cancer: a systematic review of measurement instruments

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Abstract

Background: Practitioners and researchers require an outcome measure that accurately identifies the range of common treatment-induced changes in sexual function and well-being experienced by women after cervical or endometrial cancer. This systematic review critically appraised the measurement properties and clinical utility of instruments validated for the measurement of female sexual dysfunction (FSD) in this clinical population.

Methods:

A bibliographic database search for questionnaire development or validation papers was completed and methodological quality and measurement properties of selected studies rated using the Consensus-based **S**tandards for the selection of health **M**easurement **I**nstrument (COSMIN) checklist.

Results: 738 articles were screened, 13 articles retrieved for full text assessment and 7 studies excluded, resulting in evaluation of 6 papers; 2 QoL and 4 female sexual morbidity measures.

Five of the six instruments omitted one or more dimension of female sexual function and only one instrument explicitly measured distress associated with sexual changes as per DSM V (APA 2013) diagnostic criteria.

None of the papers reported measurement error, responsiveness data was available for only two instruments, three papers failed to report on criterion validity, and test-retest reliability reporting was inconsistent. Heterosexual penile-vaginal intercourse remains the dominant sexual activity focus for sexual morbidity PROMS terminology and instruments lack explicit reference to solo or non-coital sexual expression or validation in a non-heterosexual sample. Four out of six instruments included mediating treatment or illness items such as vaginal changes, menopause or altered body image.

Conclusions:

Findings suggest that the Female Sexual Function Index (FSFI) remains the most robust sexual morbidity outcome measure, for research or clinical use, in sexually active women treated for cervical or endometrial cancer.

Development of an instrument that measures sexual dysfunction in women who are infrequently / not sexually active due to treatment consequences is still required to identify women in need of sexual rehabilitation.

Introduction

Worldwide approximately half a million women are diagnosed annually with invasive cervical cancer [1] with 5 year survival rates ranging from >80-90% after treatment for stage 1A/1B disease in developed countries, and a 62% all stage 5 year relative survival across Europe [2]. While rates of cervical cancer in developed countries are in decline, it is estimated that 0.5 million cases of endometrial cancer will be diagnosed worldwide by 2035, with a 5-year survival rate of >80% for stage 1 and a 76% 5 year relative survival for all stages [2,3,4].

Despite treatment advances and improved survival rates, late treatment consequences remain under-recognised and under-reported by health professionals and patients alike [5,6,7,8]. Although reporting of urinary and bowel effects associated with pelvic radiotherapy has become more common, details of treatment-induced female sexual morbidity remain limited [9,10,11]. Published studies suggest that 30-63% of women with cervical cancer experience sexual difficulties after pelvic radiotherapy [12,13]. Furthermore, the type and radicality of pelvic surgery may also influence the extent of sexual recovery achievable [14,15,16]. While fewer studies have focused on sexual function after endometrial cancer treatment [17,18] evidence suggests that this patient population, previously thought to be at low risk, also experience significant sexual dysfunction [19,20].

Treatment-induced physical effects after cervical or endometrial cancer include vaginal dryness, fibrosis, stenosis, shortening, vaginal bleeding, menopausal symptoms, skin reactions, urinary difficulties, disruption to bowel function and infertility [9,13,18, 21]. Furthermore, psychological impacts include anxiety, depression, fear of sexual pain and altered femininity [11,22]. Hence, changes in sexual function and well-being associated with treatment remain important research and clinical outcomes in their own right [11,23,24].

The clinical assessment and management of sexual difficulties after gynaecological cancer remains a frequently overlooked aspect of recovery and rehabilitation, with health professionals and women themselves having difficulty in raising this topic [11,22]. Clearly, the first step towards being able to offer systematic management for the sexual consequences of cancer is timely and accurate clinical assessment [25,26].

The number of health status questionnaires available for measuring patient reported outcomes (PROMS) has increased dramatically over recent decades [26,27]. There is now a range of patient self-report questionnaires developed to assess female sexual dysfunction (FSD) specifically [23,28] or as one dimension of a broader quality of life (QOL) assessment [29,30]. However, many existing questionnaires do not include the full range of organic and psychogenic sexual disruptions encountered after gynaecological cancer treatment.

In general, disease-, treatment-, or symptom-specific questionnaires are better at identifying between-group differences (sensitivity) and changes over time (responsiveness) than generic cancer or sexual dysfunction questionnaires [31]. Nevertheless, the challenge facing clinicians and researchers is to select the most appropriate instrument that demonstrates psychometric rigour [27], reflects the full range of contemporary (DSM V) female sexual dysfunction diagnostic categories commonly encountered in gynae-oncology [32] and has clinical utility in identifying women most likely to benefit from specialist assessment and management [33].

A number of previous reviews have explored the development and use of QOL, symptom assessment and sexual function measures in gynaecological [34,35] or cervical cancer [29,30] survivors, with some discussion of psychometric rigour and/or clinical utility. However, there is a paucity of in-depth systematic reviews conducted to date that specifically evaluate the measurement properties and clinical utility of female sexual dysfunction questionnaires in women treated by pelvic surgery/radiotherapy for cervical and endometrial cancer.

This systematic review evaluates English language instruments for female sexual dysfunction (FSD) in women after pelvic surgery and / or radiotherapy for cervical or endometrial cancer. The COSMIN (**C**onsensus-based **S**tandards for the selection of health **M**easurement **I**nstruments) checklist [36] critically appraised published evidence of the measurement properties of these patient self-report instruments and a summary of the clinical utility of instruments is included. This paper also adheres to PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines [37].

Methods

Search Strategy

The following databases were searched for papers reporting the development or validation of questionnaires measuring sexual (dys)function in women with cervical or endometrial cancer: Embase (1990-2015), MEDLINE (1990-2015), PsycINFO (1990 -2015), CINAHL (1990-2015), BNI (1990-2015), AMED (1990-2015) using Ovid.

As there have been significant developments in treatment for endometrial and cervical cancer, and in the conceptualisation of female sexual [dys]function over recent years, this review focused on full text articles published in the English language from 1990 to 2015.

We used the protocol by Terwee [38] to devise a search strategy with multiple search terms addressing the following instrument dimensions:

1. **The construct of interest:** Sexual [dys]function
2. **Target population:** Female.
3. **Type of instrument:** questionnaire, outcome measure or assessment instrument
4. **Measurement properties:** based on a search filter for finding studies of assessment instrument measurement properties described by Terwee et al [39].

A preliminary search using *cancer* as a search term failed to retrieve a number of relevant papers of which the review team were aware, leading to the selection of wider search parameters to ensure adequate capture of data sources.

This was followed by a systematic search (Table 1) based on a comprehensive list of possible synonyms for each individual search (March 2015). Synonyms combined with the conjunction 'OR' and searches for all four characteristics combined with the conjunction 'AND' obtained a list of references used to search for relevant papers. Reference lists from relevant studies were hand searched and study authors contacted where further information was required.

Study Selection

To meet the inclusion criteria for the review, papers needed to report on the development and / or validation of an instrument measuring sexual (dys)function within an identifiable sample of women treated for either cervical or endometrial cancer. For an instrument to be included, female sexual dysfunction had to be the construct under evaluation within the assessment

instrument, although this could be limited to one domain within a wider quality of life (QOL) instrument.

Exclusion criteria included Quality of Life (QoL) or treatment toxicity studies that did not have a significant focus on sexual dysfunction and papers with a primary focus on sexual history taking or professional / patient communication about sexual impact of illness or treatment or body image. Instruments were also excluded if they measured sexual dysfunction in diseases or treatment effects unrelated to cervical or endometrial cancer, or where results from a cervical or endometrial cancer sub-sample of women was not identifiable [40,41].

Two reviewers (GL and AS) independently assessed the titles, abstracts and reference lists of studies retrieved by the literature search. In addition, IW reviewed lists of included and excluded papers prior to retrieval of full-text articles. Full text articles were then individually reviewed against the inclusion criteria (AS and IW) and in the case of disagreement, a third reviewer (TW) enabled a consensus decision to be reached.

Assessment of methodological quality and data extraction

The rigour of systematic reviews of health status questionnaires is enhanced by the use of methodological quality criteria regarding instrument development and evaluation in order to identify the most valid and reliable questionnaire for research and clinical use [42]. The COSMIN checklist [42] evaluates the methodological rigour of each instrument paper across nine measurement properties. Each property criterion was scored on a 4-point rating scale (i.e. poor, fair, good or excellent) and an overall score for the methodological quality of the reported study determined by taking the lowest criterion rating for that specific measurement property.

Data extraction included relevant data (e.g. design, sample, method, psychometric tests and results) as well as the conceptual scope of instruments in measuring FSD as defined in DSM V and key factors mediating FSD (see Table 4). The data extraction form was piloted to ensure capture of all relevant information.

Data extraction and assessment of (methodological) quality was carried out independently by two reviewers (IW and AS), using criteria agreed in advance, to ensure consistency. In the case of disagreement between reviewers, further discussion ensued to reach consensus with a third reviewer (TW) acting as final arbiter where necessary.

Results

The search strategy generated 707 unique hits; a further 31 articles were identified via reference checking and hand searching. Seven hundred and thirty-eight articles were screened; 650 were excluded with 88 titles and abstracts considered for inclusion.

After reviewing against inclusion and exclusion criteria, a further 75 articles were excluded (see figure 1) and 13 full text papers downloaded. This full text review resulted in the exclusion of a further seven papers, the rationale for which is summarised in Fig. 1.

Characteristics of selected instruments

Six studies reporting the development and/or evaluation of instruments measuring FSD in women treated for cervical and or endometrial cancer were subjected to full data extraction and application of the COSMIN checklist in this systematic review. Two were QoL measures with FSD subscales, developed as disease and treatment specific modules to supplement the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30). The EORTC QLQ CX24 addresses morbidities arising from cervical cancer treatment whilst the EORTC QLQ EN24 is endometrial cancer specific. One FSD measure (FSFI) was validated in a heterogeneous sample of women treated for cancer, including cervical/endometrial cancer, two FSD instruments were specific to gynaecological cancer (SABIS-G and SVQ) and one instrument was validated in a cervical cancer sample alone (GLQ). The characteristics of included studies are summarised in Table 2 and evaluation of the instrument's measurement properties using the COSMIN checklist in Table 3. This paper offers an outline of each instrument prior to synthesis and evaluation of key findings including the conceptual scope (Table 4) and clinical utility (Table 5) of reviewed instruments.

Female Sexual Function Index (FSFI)

The Female Sexual Function Index is the most widely used research and clinical instrument to measure sexual function in sexually active heterosexual women validated for use in cancer survivors [24]. It is a multi-dimensional measure addressing desire, subjective and objective (lubrication) arousal, orgasm, sexual pain, and sexual satisfaction.

The FSFI consists of 19 items scored on an ordinal Likert scale (0 or 1 to 5). Each subscale has a maximum score of six, resulting in a maximum overall score of 36 for the measure, with high scores indicative of better sexual function and a score of 26 as the clinical cut off for diagnosing FSD [43].

Using the COSMIN checklist (Table 3) the internal consistency reliability score was rated excellent (Cronbach alpha subscale scores 0.85 to 0.94, total score 0.94). Content (and structural) validity were also rated excellent as exploratory factor analysis yielded a factor solution similar to that reported in the original validation studies [28,44]. Five factors accounted for 81.4% of the total variance and corresponded well to the six FSFI domains. In terms of cross-cultural validation, the FSFI has been validated among FSD samples in 8 languages other than English, and in English and Chinese oncology samples to date [45,46].

Limitations of the FSFI are consistent with other measures of sexual (dys)function whereby the validity of instrument scores is undermined when women with little or no recent (past 4 weeks) sexual activity are included. The FSFI scoring algorithm does not distinguish between women who score zero due to sexual difficulties affecting a particular item / domain, versus those who are sexually inactive for reasons unrelated to their cancer treatment [24]. The validation sample comprised predominantly women treated for cervical cancer (59%) and so discriminant validity may warrant further evaluation. Furthermore, longitudinal data is required to demonstrate responsiveness of FSFI scores to change over time.

The conceptual scope of the FSFI addresses all core dimensions of female sexual (dys)function and incorporates solo sexual expression and relationship items, although its validity in non-heterosexual women has not been established.

In terms of clinical utility, the instrument is relatively brief (approx 15 mins to complete), uses standard Likert response options and has an established cut off score (<26) for diagnosis of FSD [43]. However, the instrument does not incorporate mediating factors

prevalent in oncology practice such as specific treatment impacts or intervention use that may be helpful to clinicians in determining management or referral options (Tables 4 & 5).

Sexual Adjustment and Body Image Scale- Gynecologic Cancer (SABIS-G)

The sexual adjustment and body image scale for women with gynaecological cancer measures changes in sexuality and body image arising from diagnosis / treatment, and is based on an outcome measure originally validated in a surgical breast cancer sample [47,48]. SABIS-G is a 7-item measure solely available in English, with three items addressing body image and four related to sexual adjustment. Scores range from 1-5, with higher scores representing better sexual adjustment.

Internal consistency rated excellent (Body Image 0.88, Sexual Adjustment 0.91) but content validity rated only fair as the scope of this instrument includes body image and limited (n=4) sexual adjustment items (Table 4) and hence does not represent a comprehensive measure of FSD. Structural and criterion validity rated excellent as the SABIS-G performed as expected against selected comparator instruments (Table 3).

The SABIS-G demonstrated adequate known groups validity, with women who had cervical cancer or received chemo-radiation scoring lower, as expected, than other disease types / treatment combinations ($p = 0.01 / 0.03$). While intra class correlation (0.89) was excellent (Table 3), overall reliability only scored *fair* as participant stability in the interim test-retest period was not reported.

As the conceptual scope of the SABIS-G does not measure all dimensions of female sexual function (excludes arousal and orgasm) or sexual pain, a common problem after gynaecological cancer treatment, it has limited clinical utility as a comprehensive measure of female sexual dysfunction.

Scoring adopts 5-point Likert scales but calculation of an overall weighted sum of 0-100 for each subscale is complex for rapid clinical use. Furthermore, a cut-off score for clinically significant body image / sexual adjustment difficulties has yet to be determined. Nevertheless, this instrument may represent a suitable brief screening instrument to identify the presence or absence of body image and sexual adjustment concerns prior to more detailed specialist assessment.

European Organisation for Research and Treatment of Cancer Quality of Life

Questionnaire-Cervical Cancer Module (EORTC QLQ CX-24)

The Cervical Cancer Module (EORTC QLQ CX-24) comprises of nine QOL domains, five of which relate to FSD (Table 4) [49].

Internal consistency and structural validity were rated poor according to the COSMIN checklist, due to the use of multi-trait scaling analysis rather than the preferred method of factor analysis [42]. Multi-trait scaling analysis demonstrated high internal consistency for three subscales with satisfactory Cronbach alpha coefficients (Symptom Experience 0.72, Body Image 0.86; Sexual/Vaginal Functioning 0.87). Convergent and discriminant validity scaling errors were below 3%.

Cross-cultural validity rated *poor* (Table 3) as confirmatory factor analysis had not been used to evaluate cross-cultural validity and results from individual countries were not reported. However, the use of item generation and cognitive testing across samples of women from nine European countries, Australia, Brazil, Korea and Taiwan and international expert panel review enhance the instrument's content validity [49]. The CX-24 has been validated in South Asian [50], Korean [51], Chinese [52], Polish [53] and South African [54] samples.

Limitations of the EORTC QLQ CX-24 include absent test-retest reliability and instrument responsiveness data, together with a high non-response rate (>60%) for the sexual / vaginal functioning sub-scale, representing sexually inactive women.

In terms of clinical utility, the QLQ CX-24 can be completed in approximately 15 mins and has a simple Likert scoring system, although the instrument-scoring template requires linear transformation to a 0-100 scale. As this is a QOL instrument, clinical cut off scores for diagnostic purposes are not appropriate.

The QLQ CX-24 does not include sexual desire, subjective arousal or orgasm, nor does it include items related to the relationship or partner, and as such does not represent a comprehensive measure of female sexual (dys)function. However, as a disease-specific QOL module, it does include a number of important disease / treatment related mediating factors encountered in gynae-oncology (Table 4).

European Organisation for Research and Treatment of Cancer Quality of Life

Questionnaire-Endometrial Cancer Module (EORTC QLQ EN-24)

The Endometrial Cancer Module (EORTC QLQ EN-24) is a QOL measure developed for use in women treated for endometrial cancer [55]. The measure consists of 13 subscales including four subscales related to sexual/vaginal problems, sexual interest, sexual activity and sexual enjoyment.

Multi-trait scaling analysis confirmed a hypothesised 13-subscale structure with internal consistency ranging from 0.74-0.86. Psychometric properties of the initial hypothesised scale for sexual functioning was poor, therefore sexual interest, sexual activity and sexual enjoyment were retained as 3 x single-item scales and sexual /vaginal problems as one multi-item scale. As with the CX24, application of the COSMIN checklist led to a *poor* rating for both internal consistency and structural validity (Table 3) as the preferred analytical method, factor analysis, had not been used [42].

Despite an *excellent* rating for content validity using the COSMIN checklist, with item generation derived from literature review, patient and health professional interviews and expert panel consultations, the authors acknowledge that this QoL instrument does not represent a comprehensive measure of female sexual function [55].

COSMIN criteria rated reliability *fair*, as details of time lapse and stability of participants between test-retest measurement points was absent (Table 3). Correlations ranged from 0.81-0.92 for multi-item scales and from 0.72-0.97 for single item scales and criterion validity rated as *good* (Table 3).

As with the CX-24, use of the COSMIN criteria rated cross-cultural validity *poor* as confirmatory factor analysis was not undertaken and results from individual country samples not reported. However, item generation and cognitive testing was undertaken in samples of women from 8 European countries, Australia and Taiwan together with international expert panel consultation [55] and the EN-24 subsequently validated for use in a Polish sample [56].

Known group comparison of the sexuality single items discriminated between patient groups with high versus low Karnofsky performance scores, but no between group difference found for sexual/vaginal problems and sexual enjoyment scales.

In respect of clinical utility, the EN-24 measures sexual desire, objective arousal (lubrication), sexual satisfaction, sexual pain and some mediating factors (Table 4). However, like the CX-24, it omits subjective arousal, orgasmic changes and does not include partner items or pre-treatment comparators.

The instrument can be completed in approximately 15 mins, but the scoring template requires reverse scoring for two items, linear transformation to a 0-100 scale and calculation of mean scores for multi-item scales in accordance with the scoring manual. As this is a QOL instrument, clinical cut off scores for diagnostic purposes are not appropriate.

Future studies are required to evaluate the responsiveness of the instrument and, as with other instruments reviewed, it is not suitable for sexually inactive women, irrespective of cause, having observed a 74% non-completion rate for sexuality subscales.

Sexual function-Vaginal changes Questionnaire (SVQ)

The sexual function-vaginal changes questionnaire (SVQ) consists of 27 items [57]. Twenty core items measure sexual interest, lubrication, vaginal dimensions, dyspareunia, intimacy, sexual activity, orgasm, sexual problems in partner, sexual satisfaction and body image.

Seven additional change items are included to capture the patient's perception of changes between pre-treatment and post-treatment levels of sexual and vaginal problems.

Five scales hypothesised were intimacy (IN), sexual interest (SI) and global sexual satisfaction (GS), with two additional scales for sexually active respondents: vaginal changes (VC) and sexual functioning (SF). Internal consistency (Cronbach's alpha 0.76-0.83 for subscales) and structural validity rated *fair* in accordance with COSMIN guidelines, as the percentage and specific management of missing data items was not reported. Furthermore, the authors observed potential local dependency between the SF and GS scales.

Content validity was rated *excellent*, although authors noted that the terminology used may be inherently heterosexist and excluded solo sexual expression.

Reliability was rated *poor* as inter-rater reliability (patient response scores versus research interview observer scores for same items) was only reported for a sub-set of patients in study 1 (n=75) and no test-retest reliability results given for the main validation sample (study 2 n=257). While responsiveness to change was not reported in this main validation paper,

evidence of satisfactory sensitivity and responsiveness was reported previously [58]. This instrument was validated in a cervical cancer patient sample and, as with other instruments reviewed, two subscales could only be answered by women who had been sexually active in the last month.

In terms of cross-cultural validation, the instrument was backwards and forwards translated from Danish to English as per EORTC translation guidelines, for validation in a Danish sample. More recently the SVQ has been validated in a sample (n=75) of Hong Kong Chinese women with gynaecological cancer [59].

From a clinical perspective, the SVQ does not have a published scoring template or a clinical cut-off score for diagnostic purposes and no participant completion times or acceptability were reported, although the Chinese validation paper average completion time was 13 minutes [59]. Furthermore, this instrument includes clinically relevant mediating factors including vaginal changes, body image concerns, partner interest in sexual contact and pre-treatment sexual function comparator items (Tables 4 & 5).

Gynaecologic Leiden Questionnaire (GLQ)

The Gynaecologic Leiden Questionnaire measures sexual function and vaginal changes for women with gynaecological cancer [60]. There are three domains within the questionnaire; Female Sexual Complaints (FSC) three items; Female Sexual Function (FSF) four items; Female Orgasm (FO) one item.

The validation sample consisted of 66 cervical cancer patients, 66 women attending a sexology service and 66 controls (n=198). Inter-scale correlations computed for the three groups ranged from 0 to 0.53, although results indicated that GLQ subscales did not measure totally independent constructs. According to COSMIN criteria, the measure rated as *good* for internal consistency (0.73 to 0.80) and structural validity, (total variance explained by the three-factor structure was 71% for the ONCO group). Test re-test reliability of 0.78-0.93 (mean 2.8 weeks, SD1.7, range 1-8 weeks) was rated as *good*, but was only tested in the control group. Responsiveness was rated *fair* as, while subscale scores demonstrated sensitivity to change before and after cervical cancer treatment, stability of other factors likely to affect sexual function during this time was not reported.

Scores from the three subscales differentiated well between women treated for cervical cancer, those attending the sexology service and control group participants. However, the GLQ rated *poor* for hypothesis testing, no *a priori* hypotheses were stated and appropriate comparator measures used solely in the sexology clinic sub-sample. Although the questionnaire was translated into English, the instrument has only been validated in a Dutch language sample to date.

In terms of clinical utility, the GLQ scoring system is not easy to use and, as with all but one of the reviewed instruments, no clinical cut off score is available to date.

The measure contains a number of clinically relevant mediating factors including vaginal changes and partner items, but may not be fully inclusive of solo sexual expression or same sex sexual activity. Furthermore, in the final validated 8-item measure, subjective arousal and orgasm, independent of intercourse, were not included. As with other instruments reviewed, this measure does not adequately evaluate the concept of sexual dysfunction in women who are sexually inactive.

Discussion

When identifying a suitable instrument for sexual morbidity research in oncology, researchers primarily consider which patient-reported outcome measures (PROMS) generate the most valid and reliable data. Currently there is no single self-report measure in use within cancer clinical trials that incorporates broader (physical, emotional and relational) aspects of sexual health or well-being for people of either gender affected by cancer [61].

Selection of an instrument for clinical use, where assessment informs decisions about clinical management and onward referral, means that there should be no clinically important omissions and items / domains should represent contemporary definitions of female sexual dysfunction as well as being valid and reliable from a psychometric perspective [32]. While disease-specific QOL instruments with sexuality sub-scales may be useful to screen for the presence of treatment-induced sexual difficulties- they often lack the measurement precision on which to base diagnostic or clinical management decisions.

Furthermore, while female sexual (dys) function after cancer treatment has some anatomical and physiological constants, this complex and multi-faceted concept is a social construct. The

assessment (or measurement) of FSD must therefore evolve in scope, definition and terminology across cultures and across time. Hence research and clinical instruments developed and in common use in earlier published studies are not always fit for purpose regarding current norms for sexual attitudes, behaviour, identities, relationships or in relation to the impact of contemporary multi-modal cancer treatment.

Recognition of the limitations in many self-report measures of sexual function and satisfaction for people affected by cancer has led to important American and European instrument development initiatives. The US National Institutes of Health PROMIS network have validated a suite (SexFS v.2.0) of customisable self-report items and domains for use in cancer and other male and female populations, sexually active with and without a partner [40,41]. Furthermore, the EORTC Quality of Life Group is developing a sexual health module suitable for all primary diagnostic groups in oncology. This new EORTC module addresses the limited scope of previous site-specific QoL modules [61].

It is interesting to note that despite four [24,49,55,57] of the six instruments achieving an “excellent” rating for content validity (Table 3), five [47,49,55,57,60] of the six instruments reviewed omitted one or more dimension of female sexual function. The QLQ CX-24 omits sexual desire, only the FSFI includes items addressing both subjective and objective aspects of sexual arousal, and half of the instruments reviewed [47,49,55] do not evaluate orgasmic changes (Table 4).

While the instruments measured global sexual satisfaction, or satisfaction with specific aspects of sexual response, *distress* or *bother* associated with sexual changes or difficulty was explicitly measured by the SVQ alone, in keeping with latest DSM V diagnostic criteria for sexual disorders [32]. The presence or absence of emotional distress (or bother) associated with changes in sexual function or expression is an important clinical diagnostic threshold for management decisions. Hence, as sexual inactivity is not itself problematic, clinical and research instruments should measure the extent to which people are distressed or avoid sexual contact because of changes in sexual function or well-being [62].

Sexual inactivity over the instrument recall period (usually 4 weeks) is an important research and clinical consideration affecting the validity of most sexual morbidity instruments. Scoring inconsistencies or lower scoring validity occurs when sexually inactive participants are

included, as the instrument cannot distinguish between low scoring women sexually inactive as a direct consequence of treatment / disease induced sexual difficulties, versus those sexually inactive for unrelated reasons. Baser et al [24] remark that it is important from a psychometric perspective that any scale score of zero to an item explicitly relates to the severity of dysfunction assessed by those items / scales. Some of the instrument structures (SVQ and EORTC modules) offer a reduced item or domain set for sexually active respondents. However, this instrument structure may result in significantly reduced sample numbers of sexually active women for individual domain or item validation purposes [49, 55]. Clinically, the normal recall period of 4 weeks may be too short, particularly for older women / couples who are sexually active but at intervals in excess of 4 weeks.

In using the COSMIN checklist as recommended [27,42] we found that none of the papers reported measurement error, data on responsiveness was available for only two instruments [58,60] and half of the papers reviewed failed to report on criterion validity [24, 57, 60]. Furthermore, test-retest reliability reporting was inconsistent, with a tendency to omit details of time lapse and stability of participant's health status between measurement points (Table 3). Cross-cultural validity for EORTC instruments achieved a *poor* rating, despite being the only instruments in which cross-cultural development / cognitive testing was routinely included at the instrument development stage [63]. The *poor* COSMIN rating arose from failure to report results from individual countries and an inadequate sample size for some country sub-groups [42].

Clinical Utility

In reviewing the conceptual scope of these instruments, only the SVQ and SABIS-G included pre-treatment sexual function comparisons, despite clinical recognition that pre-treatment sexual function or well-being is frequently affected by presenting disease symptoms (e.g. vaginal bleeding / sexual pain) and hence rarely represents a true baseline measure [22]. Four [49,55,57,60] of the six instruments included commonly encountered mediating treatment or illness effects (Table 4) such as vaginal changes, menopause and altered body image or femininity. Despite the use of PROMS to monitor changes in severity or duration of symptoms over time, particularly in response to an intervention, none of the instruments included items regarding the effect of therapeutic aids. When considering management and

referral options it is often helpful for clinicians to review compliance and efficacy of biomedical strategies (HRT, lubricants, moisturisers, and dilators), sexual aids (vibrators, clitoral vacuum devices) or specialist services (gynaecologist, sexual counselling, and medical sexology).

Although partner and relationship items were absent from both QOL instruments, this important contributory factor to women's sexual recovery was included in the content of the four sexual morbidity instruments reviewed. Sexual morbidity PROMS terminology continues to privilege heterosexual penile-vaginal intercourse as the dominant sexual activity. None of the instruments reviewed were explicitly inclusive of solo sexual expression, nor validated in a sample of non-heterosexual women.

As open access and remote (on-line / mobile apps / telephone clinics) follow-up systems are used increasingly to manage service access for the exponential increase in cancer survivors, within finite resources, clinicians will need to become more familiar with the selection and use of self-report measures for remote monitoring of treatment late effects and their management [26]. Hence, adequate investment in the development and integration of automated IT systems to collect and analyse "real time" PROMS data will be increasingly important if patients and clinicians are to benefit fully from routine PROMS data use.

The ideal clinical instrument should be brief and easy to complete and score to minimise burden for the patient and health professional, while still generating meaningful data [34].

None of the instruments reviewed exceeded 24 items, but only two [49,55] out of six papers reported completion time and participant feedback on ease of use (Table 5).

Five [47,49,55,57,60] of the six instrument scoring templates were complex or time-consuming for self or clinical interpretation and the absence of a clinical cut-off score for all but one instrument (FSFI) limits diagnostic and clinical management utility. However, all of the instruments have some application in both remote monitoring systems or as a vehicle for structured clinical discussion given the low levels of routine assessment of FSD, even in high-risk patient groups [11,64].

Conclusion

The findings of this review suggest that the Female Sexual Function Index (FSFI) remains the most robust female sexual morbidity outcome measure, for research or clinical use, in sexually active women treated for cervical or endometrial cancer. However, development of

an instrument that measures sexual dysfunction in women who are infrequently / not sexually active due to treatment consequences is still required to identify women in need of further support and sexual rehabilitation.

Increasing the use of valid and reliable sexual morbidity PROMS in routine clinical practice, and in survivorship research, is imperative if we are to improve the identification and management of treatment-induced sexual difficulties associated with current and emerging treatments. While female sexual difficulties remain an embarrassing and challenging aspect of recovery after cancer for many clinicians and patients, the appropriate use of validated screening tools and PROMS such as the FSFI may yet prove invaluable in helping to target self-management strategies and scarce sexual rehabilitation resources to women and couples most in need.

Conflict of Interest Statement

There are no conflicts of interest to disclose for any authors of this paper.

Acknowledgements

Dr. Isabella D. White received a clinical research fellowship grant from Remedi and MacMillan Cancer Support charities to undertake a PROMS development study that informed the focus of this systematic review. The funding bodies were not involved in the conduct of this systematic review or in the preparation of this manuscript for publication.

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Table / Figure Legends

Table 1: Summary of Full Search Strategy

Table 2: Summary of included studies

Table 3: Instrument Measurement Properties: Methodological Evaluation (COSMIN)

Table 4: Conceptual scope of Instrument: extent to which instrument measures dimensions of FSD and includes key mediating factors

Table 5: Clinical Utility Criteria

Figure 1: Flow chart for search strategy

Research Highlights

- No instrument reviewed included all pertinent physical, emotional and relational impacts on sexual well-being after cancer
- Measuring sexual dysfunction in women who are not sexually active due to treatment consequences remains problematic
- The Female Sexual Function Index is the most suitable PROM for sexual morbidity measurement in gynae-oncology practice

Figure 1: Flow chart for search strategy

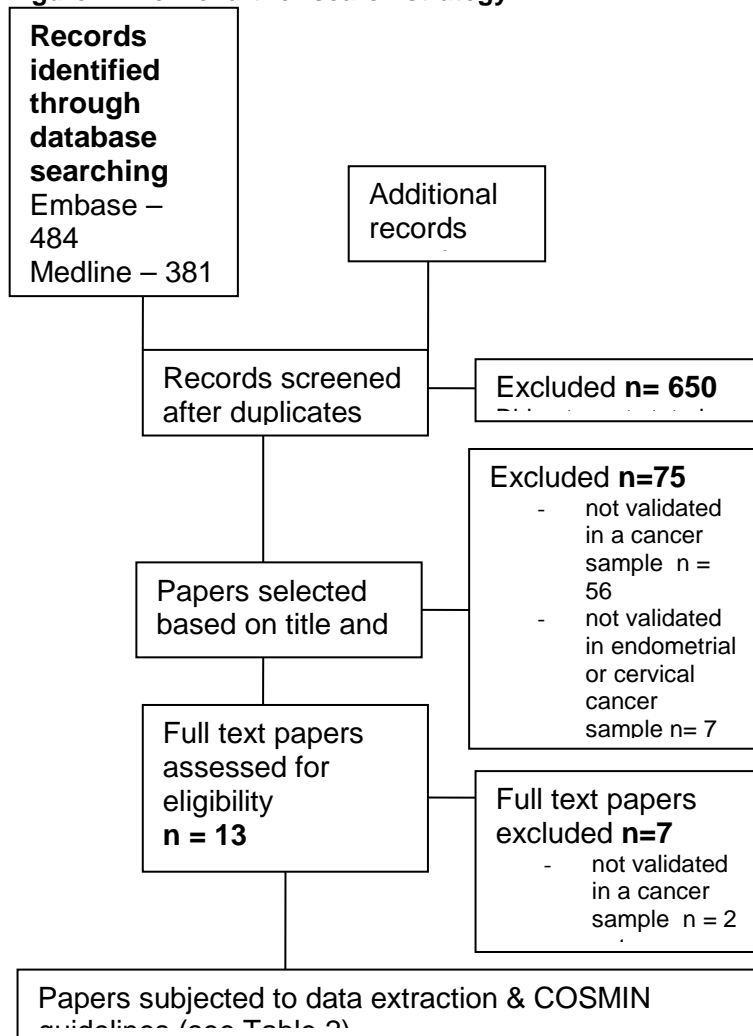


Table 1: Summary of Full Search Strategy

<p>("quality of life" OR "health related quality of life").ti,ab</p> <p>OR (Sex* OR "Sexual difficult*" OR "Sexual dysfunc*" OR "Sexual funct*" OR "Sexual morb*" OR "Sexual behav*").ti,ab</p> <p>AND (Questionnaire OR Measure* OR Instrument OR Assessment OR Tool OR outcome OR "Outcome assessment" OR "Outcome measure*").ti,ab</p> <p>AND (Validation AND stud* OR Psychometr* OR Valid* OR Reliab* OR Reproducib* OR "Reproducibility of results" OR "Discriminant analysis" OR Coefficient OR "internal consistency" OR alpha OR item OR correlation* OR factor AND analys* OR subscale OR multi-trait OR error OR sensitiv* OR responsive* OR Rasch OR Cronbach* AND alpha OR factor AND structure OR test AND retest).ti,ab</p> <p>AND (Female OR Women OR Woman).ti,ab</p> <p>All searches [Limit to: English Language and Female and Humans and Publication Years 1990-2015]</p>
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Table 2: Summary of included studies

Measure	Study Details (authors, date)	Country of Origin	Cancer or disease specific measure	Assessment focus: FSD or QOL measure	Assesses only sexually active patients	Domain Names (number of items)	Total number of items	Recall period	Study Population	Age range of sample (years)
FSFI [24]	Baser, Yuelin & Carter (2012)	USA	Cancer	FSD	Yes- women with no recent sexual activity excluded	Desire (2) Arousal (4) Lubrication (4) Orgasm (3) Satisfaction (3) Pain (3)	19	Past 4 weeks	Gynaecological, Cervical Cancer & Bone Marrow Transplant	18-50
SABIS-G [47]	Ferguson, Urowitz, Massey et al. (2012)	Canada	Gynaecological Cancer	FSD (sexual adjustment) & Body Image	No	Sexual Adjustment (4) Body Image (3)	7	Since treatment	Gynaecological	20-76
EORTC QLQ CX-24 [49]	Greimel, Vlastic, Waldenstrom et al. (2006)	7 European countries, Austria, Australia & Taiwan	Cervical Cancer	QOL	Yes- sexually active to answer sexual / vaginal function items	Sexual/Vaginal Functioning (4) Sexual Worry (1) Sexual Activity (1) Sexual Enjoyment (1) Menopausal symptoms (1) Body Image (3) Symptom Experience (11) Lymphoedema (1) Peripheral Neuropathy (1)	24	Past week for symptom / other items Past 4 weeks for sexual items	Cervical Cancer	37-65
EORTC QLQ EN-24 [55]	Greimel, Nordin, Lanceley et al. (2011)	7 European countries, Austria, Australia & Taiwan	Endometrial Cancer	QOL	Yes- sexually active to answer sexual/ vaginal problem	Sexual/ Vaginal Problems (3) Sexual Interest (1) Sexual Activity (1) Sexual Enjoyment (1) Body Image (2) Lymphoedema (2)	24	Past week for symptom / other items Past 4 weeks for sexual items	Endometrial Cancer	35-87

					items	Urological Symptoms (4) GI symptoms (5) Back / pelvic pain (1) Muscular / joint pain (1) Peripheral Neuropathy (1) Hair Loss (1) Taste Changes (1)				
SVQ [57]	Jenson, Klee, Thranov et al. (2004)	Denmark	Cervical, Endometrial & Ovarian Cancer	FSD	Yes- sexual / vaginal function items only answered by sexually active patients	Sexual Interest (1) Intimacy (2) Sexual Functioning (3) Vaginal Changes (4) Global sexual satisfaction (2) Plus 8 non-scoring items	20 (plus 7 change items)	Past 4 weeks	Cervical Cancer	23-80
GLQ [60]	Pieterse, Ter Kuile, Maas et al. (2008)	Netherlands	Cervical	FSD	Yes- female orgasm & female sexual complaints domains only answered by sexually active patients	Female Sexual Complaints (3) Female Sexual Function (4) Female Orgasm (1) Plus 3 non-scoring items	11	Not reported	Cervical cancer, sexology clinic attendees, healthy volunteer control group	21->60

Table 3: Instrument Measurement Properties: Methodological Evaluation (COSMIN)

Measure	Internal consistency	Reliability	Measurement Error	Content Validity	Structural validity	Hypothesis Testing*	Cross-cultural validity	Criterion validity	Responsiveness
FSFI [24]	Excellent	Not reported	Not reported	Excellent	Excellent	Good	Not reported	Not reported	Not reported
SABIS-G [47]	Excellent	Fair	Not reported	Fair	Excellent	Fair	Not reported	Excellent	Not reported
EORTC QLQ CX-24 [49]	Poor (multi-trait scaling analysis)	Not reported	Not reported	Excellent	Poor (no factor analysis)	Poor	Poor (didn't use CFA)	Good	Not reported
EORTC QLQ EN-24 [55]	Poor (multi-trait scaling analysis)	Fair	Not reported	Excellent	Poor (no factor analysis)	Good	Not reported	Good	Not reported
SVQ [57]	Fair	Poor (only inter-rater)	Not reported	Excellent	Fair	Not reported	Not reported	Not reported	Reported in Jensen et al 2003
GLQ [60]	Good	Good	Not reported	Not reported	Good	Poor	Not reported	Not reported	Poor

* According to COSMIN guidance *Hypothesis Testing* refers to whether hypotheses were created a priori and whether the direction and expected magnitude of correlations were stated in the journal papers [36].

CFA = Confirmatory Factor Analysis

Table 4: Conceptual scope of Instrument: extent to which instrument measures dimensions of FSD and includes key mediating factors

Measure	Dimensions of FSD									Mediating Factors				
	Sexual Desire	Sexual Arousal (Subjective / Objective)		Orgasm	Sexual Satisfaction	Sexual Pain	Solo sexual expression	Relationship / partner	Body image / femininity	Distress / Bother	Pre-treatment comparator of sexual function	Treatment Impact (s) on altered sexual wellbeing	Sexual Aids Use	Specialist Service Use
		Sub	Obj											
FSFI [24]	•	•	•	•	•	•	•	•	X	X	X	X	X	X
SABIS-G [47]	•	X	X	X	•	X	X	•	•	X	•	X	X	X
EORTC QLQ CX-24 [49]	X	X	•	X	•	•	X	X	•	X	X	•	X	X
EORTC QLQ EN-24 [55]	•	X	•	X	•	•	X	X	•	X	X	•	X	X
SVQ [57]	•	X	•	•	•	•	X	•	•	•	•	•	X	X
GLQ [60]	•	X	•	•	•	•	•	•	X	X	X	•	X	X

Key:

- Concept measured
- X Concept not measured

Table 5: Clinical Utility Criteria

Measure	Length of instrument	Completion time (mins)	Complexity	Patient self-report or researcher administered	Clinical cut off scores	Patient or HCP user ease of use feedback	Score (out of 6)
FSFI [24]	19 items	Not reported	Likert (5 item response)	Patient self-report	Cut off score \leq 26 considered diagnostic of FSD	Not reported	5
SABIS-G [47]	7 items	Not reported	Likert (5 item response), scoring system complex	Patient self-report	No	Not reported	2
EORTC QLQ CX-24 [49]	24 items	< 15 mins	Likert (4 item response) scoring system complex	Patient self-report	Not applicable	Majority completed under 15 mins and 90% of sample reported questions are clear and easy to understand	4
EORTC QLQ EN-24 [55]	24 items	15 mins	Likert (4 item response), scoring system complex	Patient self-report	Not applicable	Majority completed under 15 mins and 90% of sample reported questions are clear and not upsetting	4
SVQ [57]	20 items	Not reported	Likert no scoring template	Patient self-report	No	Feasible for self-assessment and high participation rate	3
GLQ [60]	11 items	Not reported	Likert (5 item response) scoring system complex	Patient self-report	No	Not reported	2