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NON-INVASIVE BREAST CANCER DIAGNOSIS AND TREATMENT (ES HWANG, SECTION EDITOR)

Ductal Carcinoma In Situ (DCIS): the Importance of Patient-Reported Outcomes (PRO)

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Abstract

Purpose of Review Patient reported outcomes (PROs) are an optimal method for assessing quality of life (QOL), including physical and psychosocial health. This review summarizes PROs frequently assessed in the setting of a DCIS diagnosis.

Recent Findings Health-related QOL has generally been found to be modestly affected in women with DCIS and similar to women with invasive breast cancer. Several studies reported a substantial negative impact on sexual health and body image, including some differences based on surgery type. Some patients experience pain after treatment, although many physical symptoms resolve. The prevalence of anxiety and depression varied based on assessment timing, with symptoms improving overtime. Women with DCIS often overestimate the risks associated both with DCIS and invasive cancer.

Summary PROs provide critical information regarding the experiences of women following a DCIS diagnosis. Continued inclusion of PROs in clinical trials is warranted, further informing treatment decisions and adequately preparing patients for what to expect following treatment.

Keywords DCIS · Quality of life · Physical well-being, · Psychosocial well-being · Risk perceptions

Introduction

As more women undergo mammographic screening, the incidence of ductal carcinoma in situ (DCIS) has increased and now accounts for approximately 15% of current US breast cancer diagnoses [1]. Survival outcomes after treatment for DCIS are excellent, with a large Surveillance Epidemiology and End Results (SEER) study demonstrating 3.3% 20-year breast cancer mortality in women treated for DCIS, regardless of surgery type or use of adjuvant therapy [2, 3].

DCIS has long been treated as a cancer due to potential for progression overtime, with standard therapies similar to those recommended to patients with early stage invasive breast cancer. There is a range of treatment options with excellent clinical outcomes for women with DCIS, with surgery the mainstay of therapy, and additional adjuvant therapy such as radiation and/or endocrine therapy typically recommended to minimize risk of local recurrence. However, these treatments can have a long-lasting impact on certain domains of quality of life (QOL). While efforts are underway to minimize treatment when appropriate for DCIS, increasing numbers of women, particularly young women, are electing to undergo bilateral mastectomy for a unilateral DCIS diagnosis. Data from the National Cancer Database (NCDB) looking at more than two hundred thousand women with DCIS indicates that the rates of bilateral mastectomy tripled from 1998 to 2011 (12.7 to 36.5%) [4]. There are no data to suggest better disease outcomes with this aggressive surgical approach [5], though this procedure is associated with negative QOL outcomes in some studies inclusive of invasive and noninvasive cancer. Radiation and endocrine therapy also have effects that can impact multiple QOL domains [6, 7]. Various efforts are underway to provide individualized treatment recommendations in a safe manner, with genomic assays being utilized to predict risk for local recurrence, such that low-risk women may elect to omit radiation [8]. Efforts to individualize DCIS treatment

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are motivated by the concern for overdiagnosis and that some women may be able to omit some or all standard treatments without negative impact on their overall outcomes [9].

Given excellent clinical outcomes, it is particularly important that women consider the potential QOL sequelae when making decisions about DCIS treatment. Patient reported outcomes (PROs) are an optimal method for assessing QOL, including specific domains of physical health, psychological well-being, sexuality, and body image. Patient knowledge as well risk perceptions are additional endpoints where patient-reported assessments may help inform opportunities to improve risk communication and address inaccurate perceptions regarding recurrence that may cause distress and impact treatment choice [10••], and research suggests there may be even bigger gaps in understanding of risk in Spanish-speaking and English-speaking Latinas [11, 12]. There is evidence that collection of PROs improves both quality of clinical care and outcomes for cancer patients [13, 14••]. Most data addressing QOL is inclusive of both early invasive cancer and DCIS, but women treated for DCIS may not necessarily receive the same therapies as those women with early stage invasive breast cancer and have different outcomes. Thus, understanding the specific impact of a diagnosis in DCIS patients can inform how QOL among patients with noninvasive cancer may or may not differ from the experiences of patients with invasive cancer.

Health-Related Quality of Life

Studies have demonstrated mixed results regarding the impact of DCIS on general health-related physical and psychological QOL (HRQOL) following diagnosis. In a longitudinal study by Partridge et al., Medical Outcomes Study short-form (SF-36) subscale scores for bodily pain and role limitations due to physical and emotional issues improved, while mental health, general health, and vitality decreased significantly, indicating worsening QOL from the time of enrollment (within 6 months of diagnosis) to 18 months [10••]. In contrast, Kennedy et al. found that global QOL (assessed by the European Organization for Research and Treatment Cancer QOL Questionnaire [EORTC-QLQ-C30]) did not change over the first 9 months of follow-up and did not differ by the type of surgery received [15]. Findings from a study that assessed HRQOL an average of 7–10 years post-surgery did not find any differences by surgery type for most domains; however, women who had breast conserving surgery (BCS) without radiation did have higher SF-36 mental health subscale scores, indicating better QOL compared with women who had BCS with radiation and mastectomy with reconstruction [16]. The Wisconsin In Situ Cohort also suggested a potential long-term impact of a DCIS diagnosis on HRQOL [17•]. SF-36 physical and mental component summary (PCS and MCS) scores were similar between women with DCIS and controls without DCIS for the first 10 years of follow-up. However, after 10 years, mental QOL was marginally worse among women with DCIS compared with women less than 2 years from their diagnosis as well as compared with healthy controls [17•]. Nekhlyudov et al. reported greater decreases in the SF-36 domains of role limitations due to physical issues, vitality, and social functioning in DCIS patients vs. controls over a 4-year period, though the magnitude was modest and not clinically meaningful [18]. Long term, QOL recovered and was comparable to women without DCIS; however, having a recent diagnosis (within 6 months vs. > 6 months) was associated with short-term clinically significant decreases in selected QOL SF-36 domains [18].

Studies that have compared HRQOL in women with DCIS and women with invasive breast cancer have been mixed, with some reporting no differences between women who have invasive vs. noninvasive disease patterns, and others reporting more favorable HRQOL in DCIS patients at certain time points. In one study that included several assessment points beginning prior to radiation through 2 years of follow-up, HRQOL (assessed by the EORTC-QLQ-C30) was similar between women with DCIS and invasive cancer, improving overtime for both groups, and was comparable to women without cancer [19]. In another study also covering a 2 year period, HRQOL similarly improved overtime for both DCIS and invasive breast cancer patients, however, selected SF-36 domains, including role limitations due to physical issues, energy/fatigue, and social functioning, were worse in the months after surgery, among women with invasive cancer vs. DCIS; pain and general health were also improved among women with DCIS vs. invasive cancer when assessed at 6 months [20]. As assessed with the SF-12, while mental QOL did not differ between women with and without invasive cancer, Lauzier et al. reported higher PCS scores (indicating better physical HRQOL) among women with DCIS vs. women with invasive cancer who received chemotherapy at 1, 6, and 12 months posttreatment [21]. Another study reported no differences in overall HRQOL (as assessed by the SF-36) between DCIS and invasive cancer patients who were surveyed 2–3 years following treatment; however, selected domains were improved in women with DCIS vs. invasive breast cancer [22].

Collectively, most studies of women with DCIS suggest that overall HRQOL is minimally impacted by treatment, though some women may experience deficits to selected domains.

Physical Well-Being

For many patients who receive treatment for DCIS, long term effects on physical function are limited and appear to return to expected levels within a few years following treatment [20]. A study of more than 1600 DCIS patients compared with controls found no significant differences in physical function at an average of 1.3 years since diagnosis [17•]. A study inclusive of more than 400 women having surgery for early breast cancer (both invasive and DCIS) found that up to 80% of women report some related pain at 4 and 9 months following surgery [23]. However, 20–30% of breast cancer patients develop chronic pain which can persist long after surgery [24]. In another study inclusive of over 400 patients, one-third reported pain to the breast, side of chest, axilla, or arm, a median of 2 years following their DCIS surgery [25•]. In the recent PORTAL study that enrolled over 900 women with a diagnosis of either DCIS or a diagnosis of an atypical breast lesion (atypical ductal hyperplasia or lobular neoplasia), those with DCIS who were treated with surgery reported a higher prevalence of clinically significant breast/chest wall pain compared with women who had been diagnosed with an atypical lesion or had DCIS but did not undergo surgery or radiation (16.5% vs. 9.4%, $p = 0.004$) [26]. When stratified by time from diagnosis, the proportion of women who reported pain within the last month declined significantly overtime among both groups.

Likelihood and intensity of these symptoms can be increased by radiation [27]. These symptoms can be particularly challenging to treat and are often interwoven with preexisting chronic pain and anxiety level around surgery [28]. Those patients who tend to "catastrophize" (assume the worst will happen) may be disproportionately affected by chronic pain after breast surgery [24, 29].

For those patients who elect for mastectomy with reconstruction, additional surgical procedures can be needed overtime, resulting in longer periods of acute physical discomfort. Women having mastectomy without reconstruction report physical concerns related to pain, fatigue, stiffness, and difficulty with prostheses [30••]. Those patients having mastectomy often undergo axillary evaluation with sentinel lymph node biopsy at surgery, with its resultant impacts of physical well-being. Patients self-report lymphedema as much as 8% of the time following axillary surgery, which is higher than published rates of 3–5% [31, 32]. In this study inclusive of 100 patients with sentinel node negative breast cancers, 49% reported impaired shoulder function and 50% reported pain at 1 year after surgery [31]. A recent meta-analysis that identified risk factors for chronic pain found that local therapy related factors of lymphedema (overall odds ratio [OR]: 2.58, 95% CI 1.93–3.46, $p < 0.00001$), axillary lymph node dissection (overall OR: 1.25, 95% CI 1.04–1.52, $p = 0.02$) and radiation (overall OR: 1.32, 95% CI 1.17–1.48, $p < 0.00001$) were significantly associated with likelihood of chronic pain [33]. Long-term physical symptoms can be challenging to treat and impact other domains of QOL [34].

In general, most women return to baseline physical health within a few years after DCIS treatment. A small but significant percentage of women may go on to develop chronic pain, but the mechanisms behind this remain poorly understood. Studies that have explored the impact of local therapy on physical well-being have largely reported these outcomes in both women with DCIS and women with invasive cancer; more data specific to women treated for DCIS and with longer-term follow-up are needed.

Psychological Well-Being

Several studies have reported substantial levels of psychological morbidity among women with DCIS, including symptoms of anxiety and depression. In one prospective study, the prevalence of anxiety (Hospital Anxiety and Depression Scale [HADS] score ≥ 11) at study baseline was 10% and remained relatively stable overtime (11% at 9 months, 6–8% at 18 months, 7% at 5 years) [10••, 35]. Anxiety (also assessed by HADS) was substantially higher (39.5%) at study baseline in a study by Kennedy et al., likely attributable to its assessment soon after diagnosis (average of 44.7 days), however, decreased to approximately 12% when assessed 6 and 9 months later [15]. Cross-sectional studies that have assessed anxiety at varying timepoints have similarly reported a prevalence of approximately 11–12% [16, 36]. Depression has generally been found to be less common, with clinically abnormal levels ranging from 1–4% in most studies [10••, 16, 35, 36]. Two studies did report higher depression levels: Bluman et al. reported a prevalence of 15% (Center for Epidemiologic Studies Depression Scale [CES-D] score ≥ 16) assessed an average of approximately 2 years following diagnosis, while Kennedy et al. reported a prevalence of 14% (HADS ≥ 11) soon after diagnosis, though this was lower in follow-up (4.7% at 6 months, 7.1% at 9 months) [15, 37]. Using a less conservative threshold (HADS score ≥ 8), Mertz et al. reported a prevalence of 20% and 6% for anxiety and depression, respectively, assessed a median of 2 years after surgery [25•].

Studies comparing women with DCIS to women with invasive breast cancer have reported mixed findings regarding differences in psychological morbidity between these patients. One study reported levels of psychological distress that were similar between women with invasive and noninvasive breast cancer in the year following diagnosis and treatment [21]. In another study, while overall anxiety and depression scores were comparable between women with DCIS and women with invasive breast cancer who were followed for 2 years, rates of abnormal levels of depression (HADS ≥ 8) increased overtime in women with DCIS at 6, 12, and 18 months vs. women with invasive breast cancer, who demonstrated a pattern of decline [19]. In a recent study that used the Edmonton Symptom Assessment Scale to evaluate psychological outcomes, depression was significantly worse in women with Stage I/II invasive cancer vs. DCIS, while numerically anxiety was worse but differences between groups were not significant when assessed prior to receipt of radiation [38]. A different pattern emerged following radiation, with anxiety significantly worse among the invasive group (inclusive of patients who received chemotherapy and those who did not) compared with the DCIS group, while depression was numerically but not statistically different between groups [38]. When comparing DCIS vs. women with invasive cancer who did not have chemotherapy, anxiety, and depression were again numerically worse when assessed after radiation in the invasive group but between group differences were not statistically significant [38].

Though findings from studies that have compared psychological health outcomes between patients with invasive and noninvasive disease have been mixed, reassuringly, only a minority of women appear to report experience clinically abnormal levels of anxiety and depression following a DCIS diagnosis and treatment.

Sexuality and Body Image

Among the women surveyed by Bluman et al. who were sexually active, half said they had less interest in sex and experienced a decline in sexual activity following their diagnosis, while one-third said they felt sexually unattractive [37]. Challenges related to sexual health were mainly attributed to menopausal side effects, weight gain, and image perceptions following treatment [37]. Among a subset of women enrolled in the prospective DCIS cohort [10••] who reported being sexually active within the last 6 months, appearance, sexual arousal, and sexual satisfaction did not change from baseline through 18 months of follow-up and was comparable to post-menopausal women without cancer [39]. While sexual satisfaction did not differ between women who had mastectomy with and without reconstruction, sexual satisfaction was higher in women who had mastectomy without reconstruction compared with women who did not have a mastectomy [39]. While this study did not find differences by surgery with regard to satisfaction with physical appearance, other studies have reported more differences in body image outcomes with respect to surgery. Body image distress was higher in women who had mastectomy with immediate reconstruction compared with BCS and mastectomy without reconstruction, though the difference between mastectomy groups was borderline significant [15]. Similarly, in a study with longer term follow-up (average of 7–10 years), body image issues were more frequent among women who had mastectomy with immediate reconstruction, with 73% reporting problems with regard to self-consciousness and with feeling less sexually attractive and approximately half dissatisfied with their body as well as perceived their body as less whole and less feminine [16] In contrast, among women who had BCS with radiation, 24 and 31%, reported problems with self-consciousness and sexually attractiveness, and ≤ 25% were dissatisfied with their body, perceived their body as less whole and less feminine [16]. Among women who had BCS without radiation, 16 and 21%, reported problems with self-consciousness and sexually attractiveness, respectively; 21% were dissatisfied with their body, 26% perceived their body as less whole, and 13% as less feminine [16]. Reassuringly, in a small retrospective study inclusive of women who were treated with BCS for their DCIS over a 14-year period, the vast majority of women (94%) reported being satisfied or very satisfied with their cosmetic result [40].

Knowledge and Risk Perceptions

Studies have consistently found that women with DCIS have inaccurate knowledge about their disease and frequently overestimate risks associated both with DCIS and with invasive breast cancer. In one study, 43 and 27% of women expressed uncertainty around the potential for DCIS to spread to other places in the body and the risk of DCIS spreading and one dying if not treated, respectively [36]. In another study, 78% of respondents thought that there was a possibility of DCIS spreading and 28% responded that "DCIS is one of the most serious" types of cancer [37]. Regarding risk perceptions, 61% perceived at least a moderate risk of a cancer recurrence within the next 5 years, with 33% thought they had at least a moderate risk of the DCIS spreading to other parts of the body [37]. In the longitudinal study conducted by Partridge et al., when surveyed at baseline, over half of participants thought they had at least a moderate chance of being diagnosed with DCIS again in the next 5 years, 68% thought they had at least a moderate lifetime risk of being diagnosed with DCIS again [10••]. Risk of developing an invasive breast cancer was similarly overestimated, with 39% perceiving at least a moderate chance of developing invasive breast cancer in next 5 years and 53% perceiving at least a moderate lifetime risk of developing invasive breast cancer [10••]. In this study, perceived risks were similar when assessed at 18 months, however, approximately 6 years after diagnosis, while most risk perceptions did decrease when compared with earlier estimates, they were still relatively high: 32 and 43% perceived at least a moderate 5-year and lifetime chance of being diagnosed with DCIS again, respectively, while 27%

perceived at least a moderate chance of developing invasive breast cancer in the next 5 years, and 38% thought they had at least a moderate lifetime risk of developing invasive breast cancer [10••, 35]. Approximately one-quarter perceived at least a moderate risk of DCIS recurring in other parts of the body, a perception that did not change substantially over follow-up [10••, 35]. Differences have also been seen between Latinas and English-speaking white women. In one study, English-speaking and Spanish-speaking Latinas (vs. English-speaking white women) were significantly less likely to understand that DCIS is not a threat to one's life (OR, 95% CI 0.6, 0.4–0.9 and 0.5, 0.3–0.9, respectively) [12].

Studies inclusive of women with noninvasive and invasive breast cancer have general found risk perceptions to be similar when comparing between groups [22, 41, 42]. The challenges of cancer risk communication are well-established; given that overestimation of risks associated both with DCIS and with invasive breast cancer is common, employing strategies, such as simple language and pictograms, to assist with conveying this information may help improve both knowledge and perceptions around risk [43].

Conclusion

Given the modest oncologic benefits of DCIS treatment in patients with low-risk disease, and potential for QOL (Table 1) to be impacted following treatment, it is important to understand how women make DCIS treatment decisions. A recent SEER- Medicare Health Outcomes Survey (SEER-MHOS) study found that women age ≥ 65 with DCIS who reported symptoms consistent with a major depressive disorder had higher odds of undergoing BCS without radiation vs. BCS with radiation (adjusted OR: 2.04, 95% CI, 1.04–4.00, $p = 0.04$) [44]. Pre-diagnosis mental QOL as measured by the MOS-SF-36/Veterans Rand-12 was not associated with local therapy treatment however worse pre-diagnosis physical QOL was associated with lower odds of mastectomy (vs. BCS with radiation, OR: 0.71, 95% CI, 0.54–0.95, $p = 0.02$) [44].

Women with DCIS generally have excellent clinical outcomes as well as a variety of options for treatment to include surgery, radiation, endocrine therapy, and potential for monitoring. Ongoing prospective trials of active surveillance for low risk DCIS, including COMET, LORD, and LORIS will provide more information on HRQOL, psychological outcomes, and risk perceptions among women who undergo guideline concordant care vs. active surveillance for DCIS [45–47]. If trials of active surveillance demonstrate equivalent oncologic outcomes to standard therapy for DCIS, PROs may provide women with additional information with which to make treatment decisions. It is both encouraging and important that both patients and providers have expressed interest in using tools designed to optimize communication of DCIS treatment information and risk [48]. Future efforts aimed toward developing, testing, and disseminating these tools may further improve decision-making around DCIS treatment. **It is critical that these tools be accessible to women of diverse races and ethnicities and in a variety of languages.** Additionally, continued inclusion of PROs in breast cancer clinical trials that measure short and long-term patient-centered outcomes will be needed in order to provide comprehensive information regarding outcomes following a DCIS diagnosis, better informing treatment decisions as well as adequately preparing patients for what to expect following diagnosis and treatment, and through survivorship.

Table 1 PRO domains and summary of findings

PRO domain	Summary of findings
Health-related quality of life	Overall HRQOL is minimally impacted by DCIS treatment, though some women may experience deficits to selected domains.
Physical well-being	Most patients return to baseline within a few years following treatment though a small but significant percentage develop chronic pain.
Psychological well-being	A minority of women experience clinically abnormal levels of anxiety and depression following a DCIS diagnosis and treatment, with anxiety more common than depressive symptoms.
Sexuality and body image	Breast conserving surgery is typically associated with fewer body image concerns than mastectomy, though a substantial minority of women who have breast conserving surgery report image-related issues. Prospective data suggests sexuality is stable overtime and comparable to postmenopausal women without cancer.
Knowledge and risk perceptions	Overestimation of breast cancer associated risk is relatively common; simple language and pictograms may help improve knowledge and understanding of risk.

PRO, patient-reported outcome

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Compliance with Ethical Standard

Conflict of Interest The authors declare that they have no conflicts of interest.

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