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Long-term patient-reported distress in locally advanced cervical cancer patients treated with definitive chemoradiation

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ABSTRACT

Background and purpose: To evaluate longitudinal patient-reported distress in cervical cancer patients treated with definitive chemoradiation (CRT).
Materials and methods: Between 2011 and 2016, consenting cervical cancer patients treated with definitive CRT who completed ≥ 2 revised Edmonton Symptom Assessment System (ESAS-r) questionnaires at clinical visits, including baseline, were included. A linear mixed model was used to assess the longitudinal trend in ESAS-r. A minimal clinically important difference (MCID) for total ESAS-r score was defined as a change of 3-points for improvement and 4-points for deterioration. The proportion of patients with an MCID over time was described using moving averages. To test for changes, mixed effects logistic models were fitted, each of which included patient-specific random intercepts and random slopes.
Results: 67 patients were eligible for analysis (736 ESAS-r assessments). Median (range) follow-up was 24 months (range: 15–45) and compliance at 12 months was 60% (40/67). There was a significant decrease in ESAS-r scores over time. Baseline ESAS-r was strongly predictive of ESAS-r at follow-up ($p < 0.001$). The proportion of patients with an MCID for improvement from baseline significantly increased over time ($p < 0.001$) and the proportion with an MCID for deterioration significantly decreased over time ($p < 0.001$). No predictors for distress were found.
Conclusions: Long-term cervical cancer survivors experience distress that significantly improves over time to an extent expected to be clinically meaningful for patients. Implementing cervical cancer specific patient-reported outcome tools into practice could better inform patient needs.

1. Introduction

The standard treatment for locally advanced cervical cancer includes external beam radiation (EBRT) with concurrent cisplatin followed by brachytherapy. Although treatment and technological advancements, such as chemotherapy, MR-guidance and interstitial techniques, have improved cervical cancer outcomes, late toxicities are prevalent and increase with time [1–3]. As clinical outcomes improve, it is imperative to acknowledge and assess the impact of treatment on patients' quality of life (QoL) to direct comprehensive survivorship planning.

Patient-reported outcomes (PROs) capture the patient's perspective and can enhance the patient-clinician partnership by improving communication, patient satisfaction and complementing physician-reported toxicities [4–6]. The integration of PROs into oncological practice has multiple benefits such as improved symptom monitoring, decreased emergency room admissions, prolonged time on active treatments, as well as improved health-related QoL and survival [7–9].

Distress, defined as "a multifactorial unpleasant emotional experience of a psychological, social and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment," is prevalent in cancer patients [10]. The Edmonton Symptom Assessment System (ESAS) is a widely accepted and validated screening tool for patient-reported distress [11–13]. The ESAS revised version (ESAS-r) evaluates 9 commonly experienced physical (pain, tiredness, nausea,

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drowsiness, loss of appetite, well-being, dyspnea), and psychological symptoms (depression, anxiety) [12].

Cervical cancer survivors treated with radiation suffer from social, physical and psychological morbidities and have an inferior QoL in comparison to healthy or surgical cohorts [14–16]. A poor QoL is associated with worse mental health, decreased spiritual well-being and physical complaints [17–19]. Many studies have explored QoL in cervical cancer survivors; however, in these studies treatments and disease stages were heterogeneous and often lacked a baseline evaluation, which is critical to provide an individualized comparison point [2,6,17–21]. Limited studies exist that specifically evaluate distress in cervical cancer patients treated with definitive chemoradiation (CRT) with a baseline assessment. Evaluating the prevalence of patient-reported distress in this population will inform survivorship planning and facilitate early, targeted interventions, which could translate into improved QoL.

The primary objective was to describe longitudinal patient-reported distress in locally advanced cervical cancer survivors treated with definitive CRT in whom a baseline score was available and predict distress using baseline information.

2. Materials and methods

2.1. Study population

Patients with biopsy-proven International Federation of Gynecologists and Obstetricians (FIGO) stages IB-IVA cervical cancer treated with definitive CRT including MR-guided brachytherapy from November 2011 to September 2016 were identified. Patients were eligible for inclusion if they were $\geq$ 18 years old, provided research consent and completed ESAS-r in English with a baseline assessment and at least one additional follow-up questionnaire. Baseline was defined as before or within 14 days of the EBRT start date to avoid the confounding impact of acute radiation-related toxicites. The University Health Network Research Ethics Board approved this study.

Patients were treated with 3-dimensional, conformal pelvic EBRT with concurrent cisplatin followed by brachytherapy. There were several modifications to brachytherapy techniques throughout the study period. Single tandem Pulse-Dose Rate (PDR) brachytherapy was used until February 2014, with a transition to High-Dose-Rate (HDR) brachytherapy with exclusive use of HDR after January 2015. In July 2014, interstitial techniques were introduced, either in conjunction with a ring and tandem or a Syed-Neblett (Best Medical, Springfield, USA) perineal template. Contouring, planning and dose reporting for target volumes and organs at risk (OARs) were per the Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) guidelines [22–23]. Treatment plans were calculated in BrachyVision v8.6 (Varian Medical Systems) prior to February 2014 and then Oncentra v4.5 (Elekta Medical Systems). All treatment plans underwent peer-review at weekly quality assurance rounds.

2.2. Data collection

The ESAS-r was introduced into gynecologic oncology clinics at our institution in 2011 [11–12] (Appendix). Patients are asked to complete the ESAS-r on touch-screen computer kiosks, iPads or paper while in the clinic waiting room as part of routine clinical care prior to each appointment with their oncologist, including at consultation (baseline), upon treatment completion and prior to follow-up visits. Follow-up appointments were at the discretion of the treating oncologist and based on institutional guidelines.

The ESAS-r comprises 9 commonly experienced cancer symptoms with the severity of each symptom rated from 0 ('symptom is absent') to 10 ('worst possible severity'). The minimal clinically important difference (MCID) is defined by the patient's perspective and refers to the smallest change to the ESAS-r which patients would be expected to detect. The MCID for total ESAS-r score has been defined as a 3-point decrease for improvement, 4-point increase for deterioration and changes less than these cut-offs are considered stable [24]. The ESAS-r data for all patients seen in gynecologic oncology clinics from November 2011 to September 2016 were obtained from our internal e-cancer database. Patient eligibility was confirmed through data obtained from a radiation anthology database and the Distress Assessment and Response Tool (DART) database.

Patient demographics (age at diagnosis, date of birth, date of diagnosis, disease histology and FIGO stage), treatment characteristics (chemotherapy, treatment start and completion dates, brachytherapy dose rate and technique) and radiotherapy dosimetric data (doses to targets and OARs) were extracted. Clinical outcomes and late toxicity were prospectively recorded at point-of-care by the treating radiation oncologist using the Formatted Anthology Syntopic Tick sheet method [25]. Toxicity was graded according to the common toxicity criteria for adverse events (CTCAE v4.0). These endpoints were retrospectively reviewed and confirmed with medical records to ensure accuracy.

2.3. Data analysis

Descriptive statistics were used for patient demographics, treatment details, dosimetric variables and toxicity. Total and individual ESAS scores were described longitudinally using spaghetti plots and summarized using locally weighted scatterplot smoothing (LOWSS) curves including all patients at all available time points. Pearson correlation coefficients between individual ESAS scores were presented in a correlogram using *corrplot* [26]. The change in the proportion of patients with an MCID for improvement, deterioration and stability over time were described using moving averages.

To test for changes, generalized linear mixed effects logistic models were fitted, each of which included patient-specific random intercepts and random slopes. Age, stage, nodal involvement, brachytherapy technique and physician-reported toxicity were

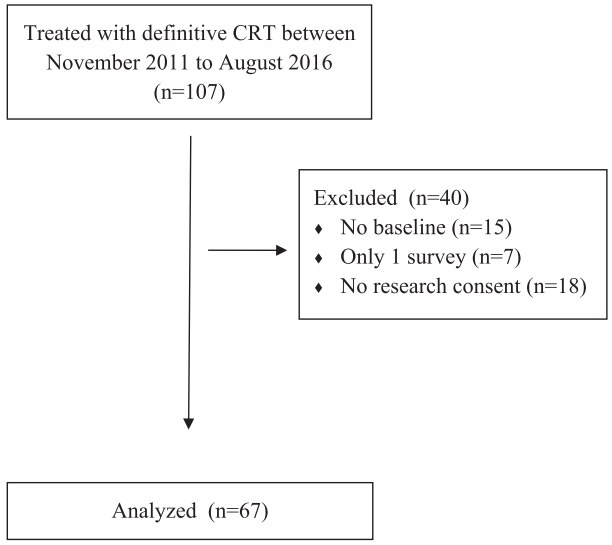


Fig. 1. Consort diagram. CRT = chemoradiation.

Table 1
Baseline patient demographic and treatment characteristics.

Characteristic (n = 67)		
Median follow up time (mos.) (range)		24 (15–45)
Median age at diagnosis (yrs.) (range)		46 (30–77)
Age group at diagnosis, n (%)	<50	41 (61)
	≥50	26 (39)
Median time treatment completion (days) (range)		37 (32–135)
Disease histology, n (%)	Squamous cell carcinoma	50 (75)
	Adenocarcinoma	11 (16)
	Adenosquamous	4 (6)
	Other	2 (3)
FIGO Stage, n (%)	IB	22 (33)
	IIA/B	35 (52)
	IIIA/B	10 (15)
	IVA	0
Nodal involvement, n (%)		31 (46)
EBRT prescribed dose, n (%)	Median (cGy) (range)	4500 (4000–5040)
Lymph node boost		29 (43)
Median brachytherapy prescribed dose (cGy) (range)		2800 (1286–4000)
Brachytherapy dose rate, n (%)	PDR	29 (43)
	HDR	38 (54)
Brachytherapy technique, n (%)	IC	37 (55)
	IC + IS	30 (45)
Mean CTV_{HR} $D_{90\%}$ EQD2, Gy_{10} ± SD		92 ± 7
Mean Rectum D_{2cm3} EQD2; Gy_3 ± SD		63 ± 6.5
Mean Bladder D_{2cm3} EQD2; Gy_3 ± SD		79 ± 10
Mean Sigmoid D_{2cm3} EQD2; Gy_3 ± SD		66 ± 7
Mean Bowel D_{2cm3} EQD2; Gy_3 ± SD		61 ± 10

FIGO = international federation of gynecology and obstetrics, EBRT = external beam radiation therapy; PDR = pulsed dose rate; HDR = high dose rate; IC = intracavitary; IS = interstitial; CTV_{HR} = High-risk clinical target volume; SD = Standard deviation; $D_{90\%}$ = Minimum dose to at least 90% of the volume; D_{2cm3} = Dose to 2 cm^3 volume of the organ at risk (ie: rectum, bladder, sigmoid, bowel).

considered as potential prognostic factors to be adjusted for, but were not statistically significantly associated with longitudinal ESAS measurements (both baseline and follow up) using linear mixed effects model, and therefore were not included in the mixed effects model. Both the linear and logistic mixed models were performed using the *lme4* package. P-values were obtained from likelihood ratio tests by comparing two models, one with the effect in question and the other without. Statistical significance level was set to 5%. All analyses were conducted in R v3.4.1.

3. Results

3.1. Baseline characteristics

Between November 2011 and September 2016, 107 cervical cancer patients with FIGO stages IB to IVA disease treated with definitive CRT and who completed at least one ESAS-r were identified. Of these, 40 were excluded and 67 patients (736 ESAS-r assessments) met inclusion criteria for analysis (Fig. 1). The median follow-up time was 24 months (range: 15–45). Questionnaire completion rates decreased over time; 40 (60%) patients had completed an ESAS-r (188assessments) at ≥ 1 year and 21 (31%) patients (85assessments) at ≥ 2 years post-treatment. The majority (61%) of patients were < 50 years old (mean 46 years; range: 30–77). Six patients (9%) died and 37 patients (55%) experienced a recurrence within the study period: 8 locally, 18 regionally and 11 distantly. Baseline characteristics are displayed in Table 1.

3.2. ESAS-r analysis

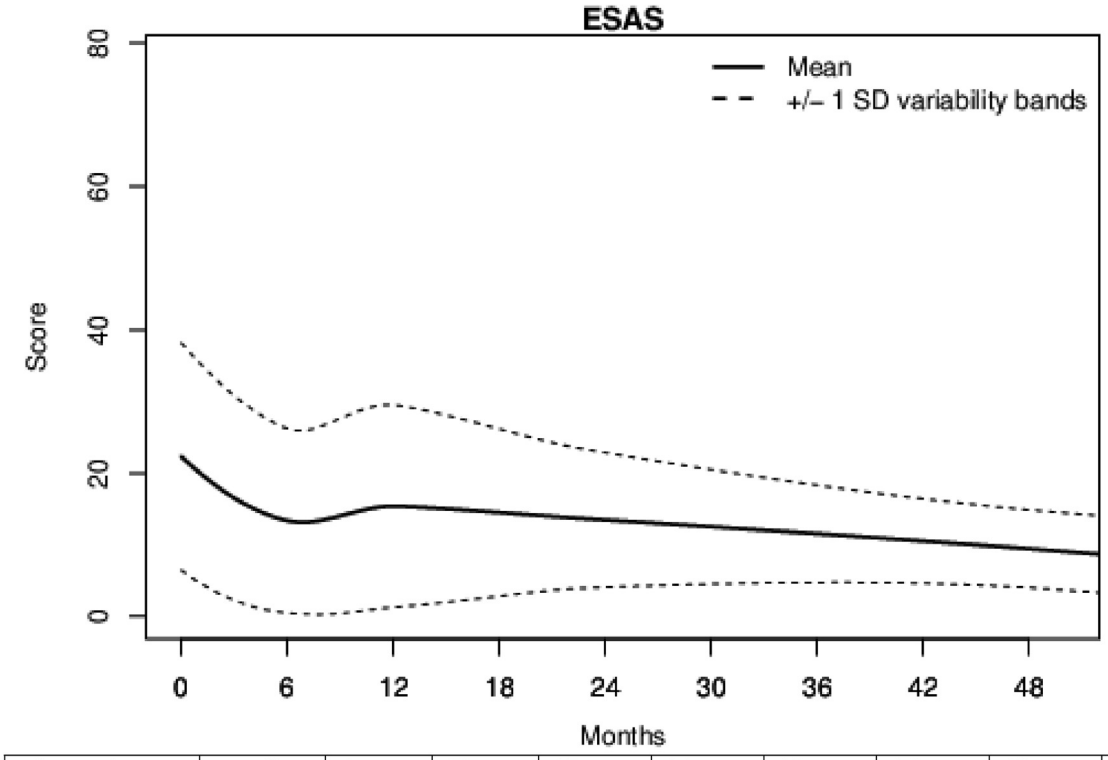
The median (interquartile range, or IQR) total ESAS-r score at baseline was 19 (22.0). Individual median (IQR) ESAS-r scores were: 1 (3.0) for pain, 3 (4.0) for fatigue, 0 (2.0) for nausea, 1 (4.0) for drowsiness, 1 (5.0) for loss of appetite, 3 (4.0) for well-being, 0 (2.0) for shortness of breath, 2 (4.0) for depression, and 3 (4.5) for anxiety. Mean total ESAS-r scores are shown in Fig. 2(a) and individual symptom scores in Fig. 2(b). There was a statistically significant decrease in ESAS over time ($p < 0.001$). The trend was non-linear ($p < 0.001$), most substantial during the first 4 months (from a mean of 20 points at baseline down to mean of 14 points at 4 months) and then plateaued (mean of 9 points at 4 years). In addition, baseline ESAS-r was strongly predictive of ESAS-r at follow up visits, meaning patients reporting higher distress at baseline had similar rates of distress at follow-up ($p < 0.001$). Patients who had a baseline score prior to starting radiation (n = 41) and those who had a baseline after (n = 26) had similar ESAS scores ($p = 0.07$). There were no statistically significant associations identified between baseline ESAS-r and any of the following variables: age, stage, nodal involvement, brachytherapy technique and physician-reported toxicity, all p-values were > 5% (Table 2).

Regarding individual ESAS-r items, there seemed to be a decrease in reported pain, drowsiness, lack of appetite, depression and anxiety and an increase in reported tiredness and well-being over time. Tiredness and well-being were reported as the most distressing symptoms, both at baseline and during follow-up. Age and stage were identified as potential predictors of distress; however, there was no association between age or stage and baseline ESAS-r score.

3.3. MCID analysis

The proportion of patients with a clinically meaningful improvement, deterioration or stability of total and individual symptom scores over time relative to baseline are shown in Fig. 3(a) and 3(b). The proportion of patients who reported an improvement in total ESAS-r (i.e. reduction in distress) from baseline significantly increased over time ($p < 0.001$) whereas the proportion of who deteriorated also significantly decreased over time

A:



Time point:	Baseline	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Patients:	67	54	40	25	21	16	12	7	2
Questionnaires:	67	438	548	610	651	687	707	721	733

Fig. 2. Mean total (2A) and individual scores (2B) over time.

($p < 0.001$). The proportion with symptom stability did not change over time ($p = 0.26$). Baseline distress scores were predictive of improvement ($p < 0.001$) and deterioration ($p = 0.019$), but not stability ($p = 0.259$).

Regarding individual ESAS-r items, there seemed to be an increase in the proportion of patients with an MCID for improvement for anxiety, depression and lack of appetite and an increase in the proportion of patients with an MCID for stability for pain, drowsiness, nausea and well-being over time. The proportion of patients with MCID's for tiredness did not seem to change much over time.

3.4. Physician-reported late adverse events

Eight (12%) patients experienced at least a grade 3 gastrointestinal (GI), genitourinary (GU), vaginal or musculoskeletal (MSK) late toxicity. The crude rates of GU toxicity were 10%, 5%, 2% and 2% for grades 1, 2, 3 and 4 toxicities respectively. The grade 4 toxicity was a vesico-vaginal fistula. The crude rate of GI toxicity were 12%, 8%, 9% and 2% for grades 1, 2, 3 and 4 toxicities respectively. The grade 4 toxicity was a small bowel obstruction. Vaginal toxicity rates were 8% and 13% for grades 1 and 2 toxicities respectively. The rate of MSK toxicity (insufficiency fractures) was 5% and 2% for grades 2 and 3 toxicities respectively. There were no associations identified between any physician-associated toxicity and the change in ESAS-r over time.

4. Discussion

This study evaluated longitudinal patient-reported distress, using the validated ESAS-r, in locally advanced cervical cancer patients treated with definitive CRT with a baseline assessment. A significant reduction in distress was found in long-term cervical cancer survivors; importantly, this reduction was to an extent in which patients would detect and notice the change. Tiredness and well-being were correlated and reported as the most distressing symptoms, both at baseline and during follow-up. Distress at diagnosis was predictive of distress in follow-up, but no additional variables were found to be predictive for distress. Unfortunately, in this study there was attrition of questionnaire completion over time.

Approximately 30% of gynecological cancer patients experience distress, which may impact on QoL [17,27]. Distress and QoL are poorer amongst long-term cervical cancer survivors treated with radiation than healthy controls or surgical cohorts [15–16,19–20]. Longitudinal assessment of distress in locally advanced cervical cancer patients managed with definitive CRT is lacking, in particular, studies comparing to baseline functioning. PRO studies have primarily included those with early stage disease, single modality treatments and/or lacked a baseline assessment [2,17–21]. Baseline evaluation permits individualized comparisons and in one study, the baseline PRO FACT-CX score had prognostic value [28]. Mantegna et al. published one of the few studies evaluating QoL

B:

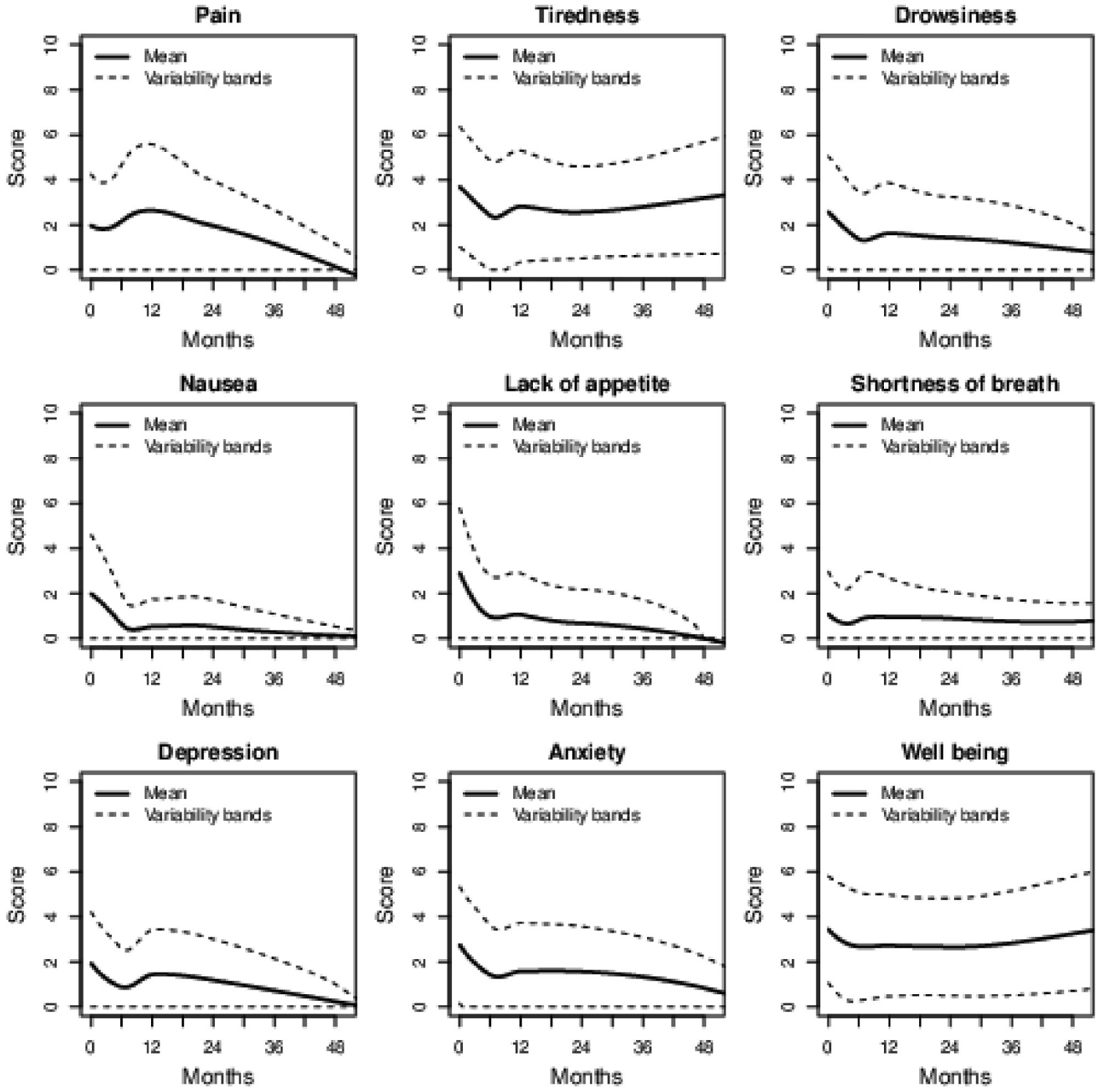


Fig. 2 (*continued*)

in locally advanced cervical cancer patients treated with definitive radiation that included a baseline assessment. An improvement in emotional distress and QoL was found in the year following diagnosis [29]. However, in this study, 94% of patients also underwent surgery and therefore, it is challenging to generalize the severity and trajectory of side effects of these patients to our patient population. In the prospective, multi-center EMBRACE study fatigue, a subcomponent of distress, was identified at baseline and minor fluctuations were observed over time [30]. In our study a longitudinal, clinically meaningful reduction in distress in comparison to baseline was found in long-term cervical cancer survivors. Although it appears this reduction is most pronounced during the first 4 months before plateauing suggesting that patients who do not have a reduction in distress at this time point may continue to have increased distress. This information can be used to counsel patients that distress is likely to improve with time in comparison to pre-treatment levels.

With improvements in cervical cancer outcomes, accurately identifying and addressing morbidity is important. Incorporation of PROs into clinical practice can engage patients and facilitate identification of impairments, while respecting and recognizing diversity amongst patients' experiences and priorities. A strength of the ESAS-r is a defined threshold for a MCID to help distinguish results that are statistically significant and clinically meaningful to patients. Identification of distressing symptoms, such as lack of appetite or fatigue, permits early interventions and targeted resource allocation, such as dieticians or psychosocial clinics. Kim et al. evaluated ESAS in palliative cervical cancer patients. The total baseline ESAS score in this study was higher (35) than our own study [22]; however, this is expected given the difference in

Table 2
ESAS association with patient and treatment variables.

Variable	p-value
Age at diagnosis	0.55
Stage	0.25
Nodal involvement	1.00
Brachytherapy technique	0.17
Physician-assessed GI toxicity	0.79
Physician-assessed GU toxicity	0.10
Physician-assessed sexual toxicity	0.13

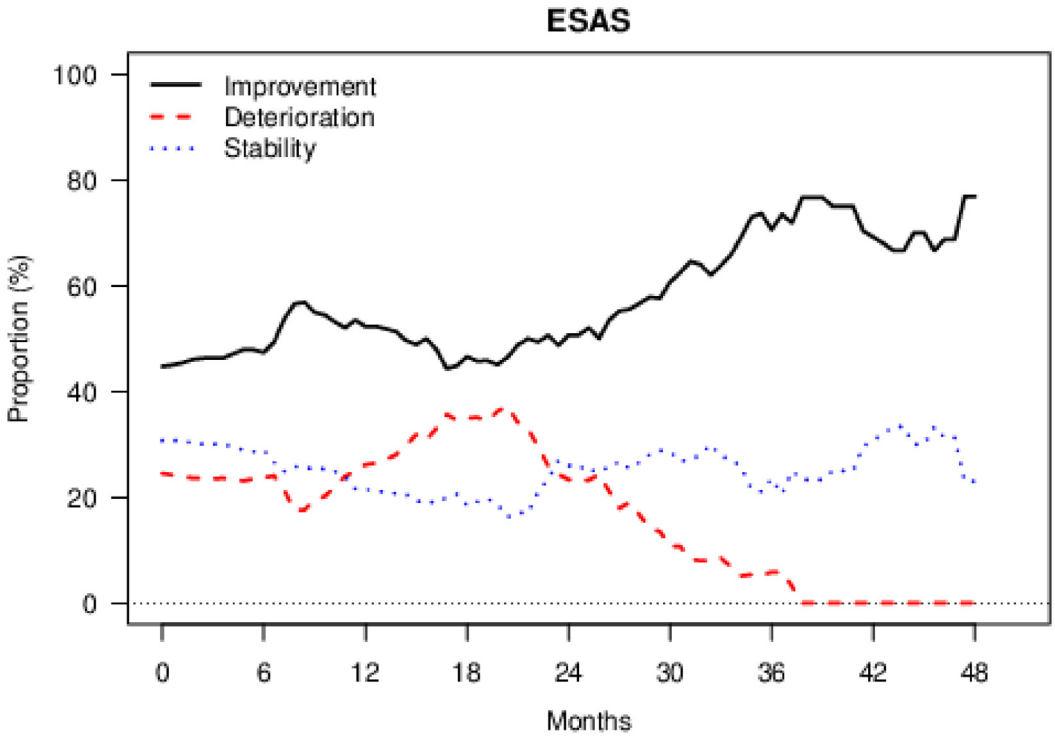
GI = gastrointestinal, GU = genitourinary.

treatment intents and expected symptomatology. Similar to our study, these authors reported all clinically significant ESAS symptoms improved with follow-up [31]. A population-based study, with just over 10% of patients with a gynecological malignancy, examined the trajectory of ESAS-r, and reported an improvement in moderate-to-severe ESAS-r individual scores with time [32].

To aid in survivorship planning, it is imperative to identify patients at risk for persistent distress. Although there was a longitudinal reduction in distress and baseline distress scores were predictive of distress scores in follow-up, no high-risk population could be identified, such as age or stage. The impact of stage on distress has variable reported associations, whereas age appears to be associated with higher distress [18,21,32]. The lack of disease-specific associations and distress in our study may be related to the interplay of additional factors associated with distress such as sexual and vaginal symptoms, comorbidities, social support and self-esteem [2,21,33]. One study in a heterogenous gynecological cancer population reported that physical and mental QoL, total needs and post-traumatic stress disorder were independent predictors of distress, with poorer a QoL being associated with higher distress [17]. PRO tools, such as the ESAS-r, may screen patients most in need of supportive care interventions and disease-specific questionnaires may be more appropriate to address patients' needs.

The main limitation of this study includes the retrospective nature and attrition of ESAS-r questionnaire completion rates over time; reasons for non-completion could not be evaluated. There is the potential for bias, such that survivors experiencing more toxicity or recurrences may be more or less likely to complete the ESAS-r. Factors, such as advanced age, are associated with lower rates of ESAS reporting, which could impact differential participation rates [32]. There was heterogeneity in our population, reflective of routine clinical practice, and treatment practices, which evolved over time in sync with technological advantages. Furthermore, distress is multi-factorial and several components of distress

A:



Time point:	Baseline	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Patients:	67	54	40	25	21	16	12	7	2
Questionnaires:	67	438	548	610	651	687	707	721	733

Fig. 3. Proportion of patients with a clinically meaningful stability, worsening, or improvement or stability in total and symptom scores over time relative to baseline for total ESAS-r score (3A) and individual ESAS-r items (3B).

3B:

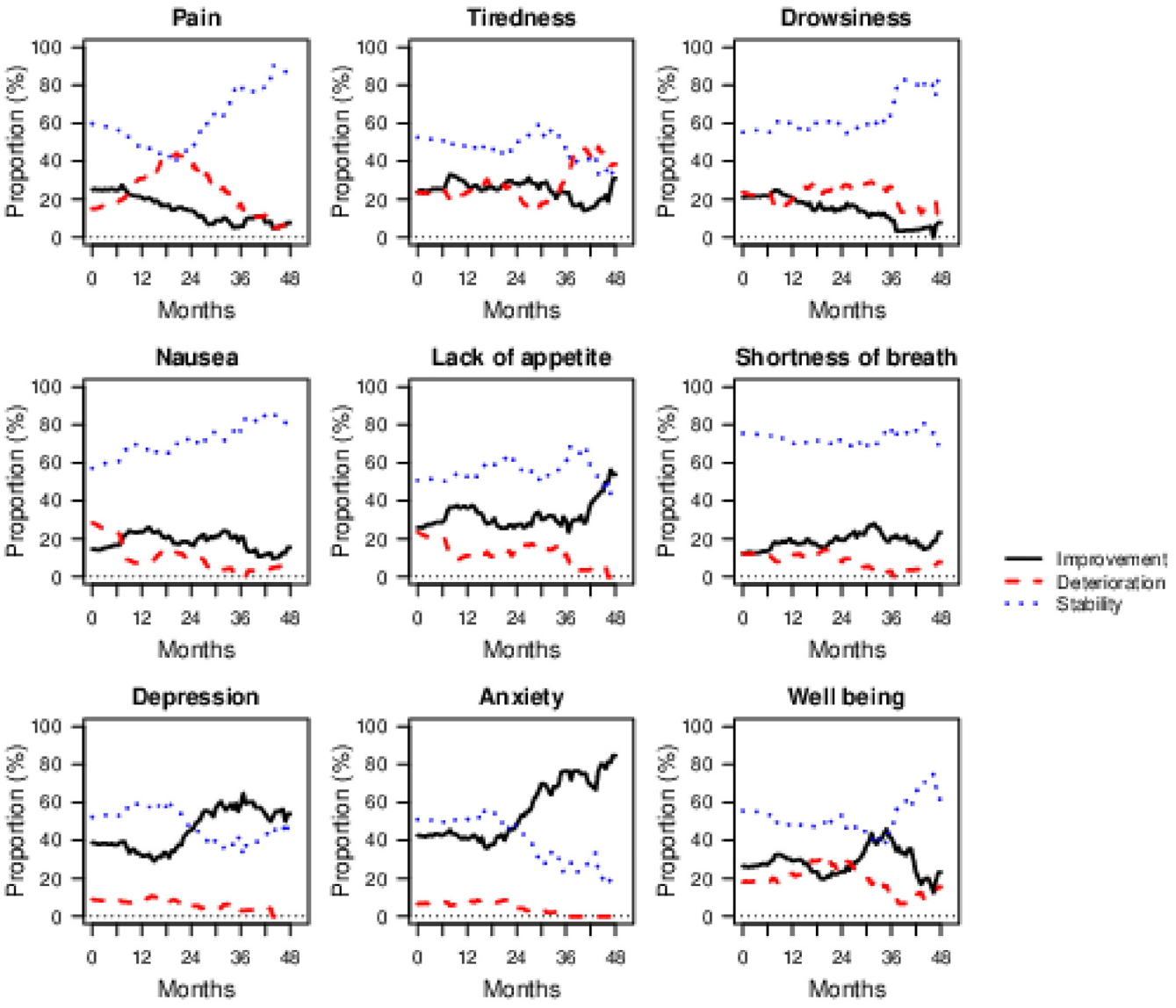


Fig. 3 (*continued*)

are not assessed by the ESAS-r whereas some domains are not relevant to this patient population.

Cervical cancer patients should be informed that distress at diagnosis is expected and normal. In most cases, distress will decline after completing treatment. This information can be used to inform health professionals and patients about the difficulties patients may encounter and the evolution. A patient-centered approach must be endorsed, and the use of symptom response pathways can facilitate early interventions. Our results found that distress at baseline was predictive for distress in follow-up. Therefore, we recommend that women with high levels of distress at consultation be targeted for early interventions, such as psychosocial oncology/social work referrals. Furthermore, women with cervical cancer experience unique disease- and treatment-related symptoms that are not necessarily captured with a generic PRO, such as the ESAS-r. Therefore, prospective collection of PROs using a cervical-cancer specific questionnaire may be more appropriate for this patient population to identify impairments associated with diagnosis and treatment. A multi-institutional feasibility study, including our institution, has been recently completed and results pending.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2020.04.005.

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