

Supplemental Table 1. Cross-sectional studies of symptom clusters in samples of patients who received chemotherapy

Author, year, purpose and design	Sample size, patient characteristics, time of symptom assessment	Symptom assessment instrument(s); number of symptoms on instrument; statistical analysis method; symptom dimension(s) used to create symptom clusters; analysis of additional outcomes	Number of symptom clusters, specific symptoms within each cluster Evaluation of additional outcomes	Strengths and Limitations
<p>Chen et al., 2021</p> <p><u>Purpose(s)</u>: Identify the symptom clusters of adult patients with acute leukemia undergoing chemotherapy</p> <p>Analyze the relationship between the symptom clusters and functional performance and QOL</p> <p><u>Design</u>: cross-sectional</p> <p><u>Location</u>: China</p>	<p><i>n</i> = 132</p> <p>Mean age: 39.2 (±13) years Range: NR</p> <p>Female: 58.3%</p> <p>Ethnicity: NR</p> <p>Race: NR</p> <p>Employment status: Working 27.3% Not working 72.7%</p> <p>Inpatients: <i>n</i> = 132 Outpatients: <i>n</i> = 0</p> <p>Diagnosis: AML 53.0% ALL 47.0%</p> <p>Treatment: CTX 100.0%</p>	<p><u>Instrument(s)</u>: Chinese version of the Condensed MSAS: 14 symptoms</p> <p><u>Criteria used to exclude symptoms</u>: Yes</p> <p><u>Analysis</u>: PCA</p> <p><u>Dimension(s)</u>: Distress</p> <p><u>Symptoms allowed to load on more than one factor</u>: No</p> <p><u>Minimum factor loadings required to include symptom within cluster</u>: 0.40</p>	<p>4 symptom clusters identified:</p> <p><u>Psychological cluster</u>: feeling nervous, worrying, feeling sad</p> <p><u>Nutrition-impaired cluster</u>: weight loss, nausea, lack of appetite, shortness of breath, feeling drowsy, difficulty concentrating</p> <p><u>Pain-fatigue-sleep cluster</u>: pain, lack of energy, difficulty sleeping</p> <p><u>Dry mouth-constipation cluster</u>: constipation, dry mouth</p>	<p><u>Strengths</u>:</p> <p>Evaluated for associations between symptom cluster factor scores and other patient reported outcomes</p> <p>Evaluated for symptom clusters in patients with hematologic cancers</p> <p>Used a valid and reliable symptom inventory</p> <p><u>Limitations</u>:</p> <p>Cross-sectional study design</p>

	<p>Time of symptom assessment: Not specified</p>	<p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints:</u> NA</p> <p><u>Analysis of secondary outcomes:</u> Functional performance status assessed with the Barthel ADL Index</p> <p>QOL assessed with the FACT-Leukemia version 4</p>	<p><u>Additional outcomes:</u> ADL score was negatively correlated with the psychological, nutrition-impaired, and pain-fatigue-sleep symptom clusters</p> <p>Total QOL score was negatively correlated with the psychological, nutrition-impaired, and pain-fatigue-sleep symptom clusters</p>	<p>Relatively small sample size</p> <p>Lack of consistent timepoint for symptom assessment</p> <p>Recruited patients from only one hospital clusters</p> <p>Used only a single dimension to evaluate for symptom clusters</p>
<p>Cherwin & Perkhounkova, 2017</p> <p><u>Purpose(s):</u> Describe GI symptom clusters based on symptom distress using a GI comprehensive symptom assessment</p> <p>Explore how distress-based GI symptom clusters impact symptom</p>	<p>$n = 105$</p> <p>Mean age: 56.7 (± 15.3) years Range: 18-86 years</p> <p>Female: 43.8%</p> <p>Ethnicity: Non-Hispanic or Latino 95.2% Hispanic or Latino 1.0% Missing 3.8%</p> <p>Race: White 96.2% Black or African American 1.0% Asian 1.0% America Indian or Alaskan Native</p>	<p><u>Instrument(s):</u> MSAS (modified): 41 symptoms; 30 clinically relevant symptoms used in the analysis</p> <p><u>Criteria used to exclude symptoms:</u> Yes</p> <p><u>Analysis:</u> EFA</p> <p><u>Dimension(s):</u> distress</p> <p><u>Symptoms allowed to load on more than one factor:</u> No</p>	<p>6 symptom clusters identified:</p> <p><u>Image cluster:</u> image change, skin change</p> <p><u>Fatigue cluster:</u> feeling drowsy, lack of energy, shortness of breath, feeling dizzy</p> <p><u>Emotions cluster:</u> difficulty concentrating, feeling nervous, feeling sad,</p>	<p><u>Strengths:</u></p> <p>Used symptom distress to create symptom clusters</p> <p>Evaluated for associations between symptom cluster factor scores and other patient reported outcomes</p> <p>Evaluated symptom clusters in patients with types of hematologic cancers</p>

<p>interference with daily life and QOL</p> <p><u>Design:</u> cross-sectional</p> <p><u>Location:</u> United States</p>	<p>1.0% Missing 1.6%</p> <p>Employment status: NR</p> <p>Inpatients: NR Outpatients: NR</p> <p>Diagnosis: Lymphoma 83.8% Leukemia 10.5% Leukemia & lymphoma 3.8% Myelodysplastic syndrome 1.9%</p> <p>Type of treatment: Standard CTX 88.6% Reduced CTX 11.4%</p> <p>Time of symptom assessment: Day 7 of CTX</p>	<p><u>Minimum factor loadings required to include symptom within cluster:</u> NR</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints:</u> NR</p> <p><u>Analysis of additional outcomes:</u> Symptom Interference Subscale of the MDASI</p> <p>Fox Simple QOL Scale</p>	<p>hair loss, swelling of arms or legs</p> <p><u>Bloating cluster:</u> belching, feeling bloated, diaphoresis</p> <p><u>Worry cluster:</u> worrying, numbness</p> <p><u>Appetite cluster:</u> lack of appetite, nausea, taste changes</p> <p><u>Additional outcomes:</u> Compared to no distress, patients with mild or greater than mild bloating symptom distress scores were significantly more likely to report greater symptom interference</p> <p>Relationship between appetite symptom distress scores and symptom interference was moderated by CTX emetogenicity</p> <p>Compared to no distress, patients with greater than mild</p>	<p>Used a valid and reliable symptom inventory</p> <p><u>Limitations:</u></p> <p>Cross-sectional design</p> <p>Relatively small sample size</p> <p>Primarily a non-Hispanic, Caucasian sample</p> <p>Used only a single dimension to evaluate for symptom clusters</p>
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			appetite symptom distress scores were significantly more likely to report lower QOL	
<p>Chongkham-ang, et al., 2018</p> <p><u>Purpose(s):</u> Evaluate the occurrence, frequency, severity, and distress of multiple symptoms in Thai women with breast cancer receiving CTX</p> <p>Evaluate for similarities in symptom clusters that were identified based on ratings of severity and distress</p> <p><u>Design:</u> cross-sectional</p> <p><u>Location:</u> Thailand</p>	<p>$n = 322$</p> <p>Mean age: 52.0 (± 9.2) years Range: 41-60 years</p> <p>Female: 100.0%</p> <p>Ethnicity: Thai 100.0%</p> <p>Race: NR</p> <p>Employment status: Farmers 28.9%</p> <p>Inpatients: $n = 0$ Outpatients: $n = 322$</p> <p>Diagnosis: Breast cancer = 100.0%</p> <p>Type of treatment: CTX 100.0%</p> <p>Time of symptom assessment: Day 7 after CTX</p>	<p><u>Instrument(s):</u> Thai-MSAS: 32 symptoms</p> <p><u>Criteria used to exclude symptoms:</u> Yes</p> <p><u>Analysis:</u> PCA</p> <p><u>Dimension(s):</u> severity, distress</p> <p><u>Symptoms allowed to load on more than one factor:</u> No</p> <p><u>Minimum factor loadings required to include symptom within cluster:</u> 0.40</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints:</u> Yes</p> <p><u>Analysis of additional outcomes:</u> N/A</p>	<p>4 symptom clusters identified using severity:</p> <p><u>Emotion-related cluster:</u> worrying, feeling sad, feeling nervous, feeling irritable, difficulty sleeping, difficulty concentrating, feeling drowsy, sweats</p> <p><u>GI and energy related cluster:</u> nausea, vomiting, difficulty swallowing, feeling bloated, dizziness, lack of energy, shortness of breath, lack of appetite</p> <p><u>Image and nutrition related cluster:</u> changes in skin, hair loss, "I don't look like myself," mouth sores, change in the way food tastes, weight</p>	<p><u>Strengths:</u></p> <p>Recruited patients from eight different hospitals</p> <p>Relatively large sample size</p> <p>Utilized a valid and reliable symptom assessment instrument</p> <p>Symptom clusters were created using two dimensions of the symptom experience</p> <p><u>Limitations:</u></p> <p>Cross-sectional design</p> <p>Recruited outpatients from only one region (Northern Thailand)</p>

			<p>loss, constipation, dry mouth</p> <p><u>Pain and discomfort related cluster:</u> pain, numbness/tingling in hands/feet, itching, problems with urination, cough</p> <p>4 symptom clusters identified using symptom distress:</p> <p><u>Emotion, energy, and pain related cluster:</u> worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, difficulty concentrating, lack of energy, feeling drowsy, pain, numbness/tingling in hands/feet, shortness of breath, sweats</p> <p><u>GI related cluster:</u> nausea, vomiting, difficulty swallowing, lack of appetite, dizziness</p> <p><u>Image related cluster:</u> "I don't look like</p>	
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			<p>myself,” changes in skin, hair loss</p> <p><u>Discomfort, nutrition, and elimination related cluster:</u> itching, mouth sores, constipation, dry mouth, problems with urination, weight loss, cough, feeling bloated, change in the way food tastes</p> <p><u>Evaluation of additional outcomes:</u> N/A</p>	
<p>Han et al., 2019</p> <p><u>Purpose(s):</u> Describe the occurrence, severity, and distress of 38 symptoms</p> <p>Identify whether the number and types of symptom clusters differed based on the symptom dimensions used to create the clusters</p> <p><u>Design:</u> cross-sectional</p>	<p>$n = 339$</p> <p>Mean age: 57.9 (± 11.8) years Range: NR</p> <p>Female: 45.1%</p> <p>Ethnicity and Race: White 68.7% Black 9.0% Asian or Pacific Islander 11.5% Hispanic, Mixed, or other 10.8%</p> <p>Employment status: Working 33.3% Not working 66.7%</p> <p>Inpatients: $n = 0$ Outpatients: $n = 399$</p>	<p><u>Instrument(s):</u> MSAS (modified): 38 symptoms</p> <p><u>Criteria used to exclude symptoms:</u> Yes</p> <p><u>Analysis:</u> EFA</p> <p><u>Dimension(s):</u> occurrence, severity, distress</p> <p><u>Symptoms allowed to load on more than one factor:</u> Yes</p>	<p>4 symptom clusters identified across each symptom dimension:</p> <p><i>Occurrence symptom clusters</i></p> <p><u>Psychological cluster:</u> lack of energy, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad, worrying, feeling irritable, changes in skin</p> <p><u>CTX-related cluster:</u> dry mouth, nausea,</p>	<p><u>Strengths:</u></p> <p>Symptom clusters were created using multiple dimensions of the symptom experience</p> <p>Evaluated symptom clusters in patients with types of gastrointestinal cancers</p> <p>Utilized a valid and reliable symptom inventory</p> <p><u>Limitations:</u></p>

<p><u>Location:</u> United States</p>	<p>Diagnosis: Colon 46.4% Rectal 20.1% Pancreatic 18.5% Esophageal 5.3% Gastric 4.8% Gallbladder/bile duct 2.5% Liver 1.5% Small intestine 1.5% Anal 1.3% Other 6.3%</p> <p>Treatment: Adjuvant CTX 91.5% Neoadjuvant CTX 8.5%</p> <p>Time of symptom assessment: Within 7 days prior to start of 2nd or 3rd cycle of CTX</p>	<p><u>Minimum factor loadings required to include symptom within cluster:</u> 0.40</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints:</u> Yes</p> <p><u>Analysis of additional outcomes:</u> N/A</p>	<p>itching, lack of appetite, weight loss, change in the way food tastes, changes in skin, dizziness</p> <p><u>GI cluster:</u> feeling bloated, abdominal cramps, constipation</p> <p><u>Weight change cluster:</u> Increased appetite, weight gain</p> <p><i>Severity symptom clusters</i> <u>Psychological cluster:</u> lack of energy, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad, worrying, feeling irritable, problems with sexual interest or activity</p> <p><u>CTX-related cluster:</u> dizziness, weight loss, lack of appetite, itching, hair loss, change in the way food tastes, "I don't look like myself," changes in skin</p>	<p>Cross-sectional design</p> <p>Heterogeneity in types of GI cancers</p>
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			<p><u>GI cluster</u>: nausea, feeling bloated, diarrhea, abdominal cramps</p> <p><u>Weight change cluster</u>: increased appetite, weight gain</p> <p><i>Distress symptom clusters</i></p> <p><u>Psychological cluster</u>: difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, lack of energy, feeling drowsy, difficulty sleeping, pain, sweats</p> <p><u>CTX-related cluster</u>: dizziness, change in the way food tastes, lack of appetite, weight loss, itching, "I don't look like myself," changes in skin, hair loss</p> <p><u>Weight change cluster</u>: increased appetite, weight gain</p>	
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			<p><u>GI cluster</u>: diarrhea, abdominal cramps</p> <p><u>Additional outcomes</u>: N/A</p>	
<p>Li et al., 2019</p> <p><u>Purpose(s)</u>: Examine and compare the differences in symptoms and symptom clusters between postmenopausal women with early stage breast cancer who did and did not receive chemotherapy prior to aromatase inhibitor therapy</p> <p><u>Design</u>: cross-sectional</p> <p><u>Location</u>: United States</p>	<p>Total sample: $n = 339$ CTX Group: $n = 111$ No CTX Group: $n = 228$</p> <p>Mean age: Total sample: 61.2 (± 6.2) years CTX Group: 59.3 (± 5.5) years No CTX Group: 62.1 (6.3) years Range: NR</p> <p>Female: 100.0%</p> <p>Ethnicity: NR</p> <p>Race: White 96.5% Black 3.5%</p> <p>Employment status: Working 70.4% Not working 29.6%</p> <p>Inpatients: NR Outpatients: NR</p> <p>Diagnosis: Breast cancer 100.0%</p> <p>Treatment: CTX 32.7% No CTX 67.3</p>	<p><u>Instrument(s)</u>: Breast Cancer Prevention Trial Symptom Checklist: 42 symptoms Profile of Mood States: 2 symptoms (i.e., fatigue, anxiety) Brief Pain Inventory: 1 symptom Beck Depression Inventory-II: 2 symptoms (i.e., depression, changes in sleep pattern) Patient's Assessment of Own Functioning: 1 symptom</p> <p><u>Criteria used to exclude symptoms</u>: Yes</p> <p><u>Analysis</u>: EFA</p> <p><u>Dimension(s)</u>: severity</p> <p><u>Symptoms allowed to load on more than one factor</u>: No</p>	<p>8 symptom clusters identified within the CTX Group:</p> <p><u>Cognitive cluster</u>: difficulty concentrating, easily distracted, forgetfulness, perceived cognitive</p> <p><u>Musculoskeletal cluster</u>: joint pain, general aches, muscle stiffness, general pain</p> <p><u>Psychological cluster</u>: depression, anxiety, fatigue, avoidance of social affairs</p> <p><u>Urinary cluster</u>: difficulty with bladder control when laughing or crying, difficulty with bladder control at other times</p>	<p><u>Strengths</u>:</p> <p>Utilized valid and reliable symptom inventories</p> <p>Compared differences in the severity of symptom clusters between women who did or did not receive CTX prior to aromatase inhibitor therapy</p> <p><u>Limitations</u>:</p> <p>Cross-sectional design</p> <p>Primarily a Caucasian sample</p> <p>Used a single dimension to evaluate for symptom clusters</p> <p>Relatively small sample size for the group that received CTX (Group 1)</p>

	<p>Time of symptom assessment: After completion of CTX but prior to start of aromatase inhibitory therapy</p>	<p><u>Minimum factor loadings required to include symptom within cluster:</u> 0.40</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints:</u> N/A</p> <p><u>Analysis of additional outcomes:</u> N/A</p>	<p><u>Vasomotor cluster:</u> hot flashes, night sweats</p> <p><u>Sexual cluster:</u> pain with intercourse, vaginal dryness</p> <p><u>GI cluster:</u> diarrhea, nausea</p> <p><u>Weight cluster:</u> weight loss, decreased appetite</p> <p>7 symptom clusters identified within the No CTX Group:</p> <p><u>Cognitive cluster:</u> difficulty concentrating, easily distracted, forgetfulness, perceived cognitive</p> <p><u>Musculoskeletal cluster:</u> joint pain, general aches, muscle stiffness, general pain, swelling of hands or feet</p> <p><u>Psychological cluster:</u> depression, anxiety, fatigue, avoidance of</p>	
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			<p>social affairs, change in sleep pattern</p> <p><u>Urinary cluster:</u> difficulty with bladder control when laughing or crying, difficulty with bladder control at other times</p> <p><u>Vasomotor cluster:</u> hot flashes, night sweats</p> <p><u>Sexual cluster:</u> pain with intercourse, vaginal dryness</p> <p><u>Weight cluster:</u> weight loss, decreased appetite</p> <p><u>Additional outcomes:</u> N/A</p>	
<p>Matzka et al., 2018</p> <p><u>Purpose(s):</u> Identify symptom clusters in patients with cancer undergoing treatment</p> <p>Investigated which of the symptom clusters explained</p>	<p><i>n</i> = 304</p> <p>Mean age: 57.4 (±14.5) years Range: 18-88 years</p> <p>Female: 59.0%</p> <p>Ethnicity: NR</p> <p>Race: NR</p> <p>Employment status: NR</p>	<p><u>Instrument(s):</u> German – Rotterdam Symptom Checklist: 30 symptoms</p> <p><u>Criteria used to exclude symptoms:</u> NR</p> <p><u>Analysis:</u> EFA</p> <p><u>Dimension(s):</u> distress</p>	<p>4 symptom clusters identified:</p> <p><u>Fatigue and pain cluster:</u> tiredness, lack of energy, low back pain, sore muscles, shortness of breath, depressed mood</p>	<p><u>Strengths:</u></p> <p>Used symptom distress to create symptom clusters</p> <p>Evaluated for associations between mean summated symptom scores for each symptom cluster</p>

<p>most of the variation in QOL in patients with cancer undergoing treatment while accounting for psychosocial resources</p> <p><u>Design</u>: cross-sectional</p> <p><u>Location</u>: Austria</p>	<p>Inpatients: NR Outpatients: NR</p> <p><u>Diagnosis</u>: Lymphoid, hematopoietic, and related tissue 26.0% Breast 21.1% Digestive organs 17.8% Female genital organs 9.0% Respiratory and intrathoracic organs 6.0% Others 20.1%</p> <p><u>Type of treatment</u>: CTX 75.0% Chemo-radiation 25.0%</p> <p><u>Time of symptom assessment</u>: NR</p>	<p><u>Symptoms allowed to load on more than one factor</u>: Yes</p> <p><u>Minimum factor loadings required to include symptom within cluster</u>: NR</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints</u>: N/A</p> <p><u>Analysis of additional outcomes</u>: German – Connor-Davidson Resilience Scale</p> <p>Multidimensional Scale of Perceived Social Support</p> <p>TSO</p>	<p><u>Anxiety and depression cluster</u>: despairing about the future, anxiety, worrying, nervousness, tension, depressed mood, irritability</p> <p><u>Nausea and vomiting cluster</u>: nausea, vomiting, lack of appetite</p> <p><u>Cancer therapy-related toxicity cluster</u>: Sore mouth/pain when swallowing, tingling hands or feet, loss of hair, burning/sore eyes, difficulty concentrating, dry mouth</p> <p><u>Additional outcomes</u>: The fatigue and pain, nausea and vomiting, and cancer therapy-related symptom clusters were each negatively associated with overall QOL</p> <p>Among patients with low TSO scores, the</p>	<p>and other patient reported outcomes</p> <p>Utilized a valid and reliable symptom inventory</p> <p><u>Limitations</u>:</p> <p>Cross-sectional design</p> <p>Recruited patients from a single medical center</p> <p>Symptom clusters were created using a single dimension of the symptom experience</p> <p>Timing of symptom assessments were not specified</p> <p>Heterogeneity in the types of cancer diagnoses included in analysis</p> <p>Used only a single dimension to evaluate for symptom clusters</p>
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			<p>nausea and vomiting and cancer therapy-related toxicity clusters were negatively associated with overall QOL</p> <p>Among patients with medium TSO scores, the anxiety and depression and nausea and vomiting clusters were negatively associated with overall QOL</p> <p>Among patients with high TSO scores, the fatigue and pain and cancer therapy-related toxicity clusters were negatively associated with overall QOL</p>	
<p>Papachristou et al., 2019</p> <p><u>Purpose(s):</u> Evaluate the relationships among 38 symptoms using Network Analysis</p> <p>Explore if network structures for occurrence,</p>	<p><i>n</i> = 1328</p> <p>Mean age: 57.2 (±12.4) years Range: NR</p> <p>Female: 77.7%</p> <p>Race or Ethnicity: White 69.5% Non-white 30.5%</p> <p>Employment status:</p>	<p><u>Instrument(s):</u> MSAS (modified): 38 symptoms</p> <p><u>Criteria used to exclude symptoms:</u> Yes</p> <p><u>Analysis:</u> Network analysis</p>	<p>6 symptom clusters identified using symptom occurrence:</p> <p><u>Psychological cluster:</u> difficulty sleeping, worrying, feeling sad, feeling irritable, feeling nervous, difficulty concentrating, lack of</p>	<p><u>Strengths:</u></p> <p>Symptom clusters were created using multiple dimensions of the symptom experience</p> <p>Utilized a valid and reliable symptom inventory</p>

<p>severity, and distress have different properties</p> <p><u>Design</u>: cross-sectional</p> <p><u>Location</u>: United States</p>	<p>Working 35.1% Not working 64.9%</p> <p>Inpatients: <i>n</i> = 0 Outpatients: <i>n</i> = 1328</p> <p>Diagnosis: Breast 40.2% Gastrointestinal 30.7% Gynecological 17.3% Lung 11.8%</p> <p>Treatment: CTX 100.0%</p> <p>Time of symptom assessment: Within 7 days prior to start of 2nd or 3rd cycle of CTX</p>	<p><u>Dimension(s)</u>: occurrence, severity, distress</p> <p><u>Symptoms allowed to load on more than one factor</u>: N/A</p> <p><u>Minimum factor loadings required to include symptom within cluster</u>: N/A</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints</u>: Yes</p> <p><u>Analysis of additional outcomes</u>: N/A</p>	<p>energy, feeling drowsy</p> <p><u>Hormonal cluster</u>: sweats, hot flashes, problems with sexual interest/activity</p> <p><u>Respiratory cluster</u>: shortness of breath, difficulty breathing, cough, chest tightness</p> <p><u>Nutritional cluster</u>: weight gain, weight loss, increased appetite</p> <p><u>CTX-related cluster</u>: itching, hair loss, changes in skin, I don't look like myself, change in the way food tastes, lack of appetite, mouth sores, difficulty swallowing, dry mouth, vomiting, nausea, dizziness, constipation</p> <p><u>Pain and abdominal cluster</u>: diarrhea, abdominal cramps, feeling bloated,</p>	<p>Evaluated for symptom clusters using a new analytic method</p> <p><u>Limitations</u>:</p> <p>Cross-sectional design</p> <p>Heterogeneity in types of cancers</p>
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			<p>swelling of arms or legs, pain, numbness/tingling in hands/feet, problems with urination</p> <p>5 symptom clusters identified using symptom severity:</p> <p><u>Psychological cluster:</u> difficulty sleeping, worrying, feeling sad, feeling irritable, feeling nervous, difficulty concentrating, lack of energy, feeling drowsy, problems with sexual interest/activity</p> <p><u>Hormonal cluster:</u> sweats, hot flashes</p> <p><u>Respiratory cluster:</u> shortness of breath, difficulty breathing, cough, chest tightness</p> <p><u>Nutritional cluster:</u> weight gain, weight loss, increased appetite, nausea,</p>	
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			<p>vomiting, lack of appetite</p> <p><u>CTX-related cluster:</u> itching, hair loss, changes in skin, I don't look like myself, change in the way food tastes, mouth sores, difficulty swallowing, dry mouth, dizziness, constipation, swelling of arms or legs, problems with urination, diarrhea, abdominal cramps, numbness/tingling in hands/feet, pain, feeling bloated</p> <p>7 symptom clusters identified using symptom distress:</p> <p><u>Psychological cluster:</u> difficulty sleeping, worrying, feeling sad, feeling irritable, feeling nervous, difficulty concentrating, problems with sexual interest/activity</p>	
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			<p><u>Hormonal cluster:</u> sweats, hot flashes</p> <p><u>Respiratory cluster:</u> shortness of breath, difficulty breathing, cough, chest tightness</p> <p><u>Nutritional cluster:</u> weight gain, weight loss, increased appetite, nausea, vomiting, lack of appetite, change in way food tastes</p> <p><u>CTX-related cluster:</u> mouth sores, difficulty swallowing, dry mouth, dizziness, constipation, swelling of arms or legs, problems with urination, numbness/tingling in hands/feet, pain, lack of energy, feeling drowsy</p> <p><u>GI cluster:</u> diarrhea, abdominal cramps, constipation, feeling bloated</p>	
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			<p><u>Epithelial cluster</u>: hair loss, I don't look like myself, itching, skin changes</p> <p><u>Additional outcomes</u>: N/A</p>	
<p>Pozzar et al., 2021</p> <p><u>Purpose(s)</u>: Describe ratings of symptom occurrence, severity, and distress for 38 symptoms in a sample of patients with gynecological cancer receiving CTX</p> <p>Identify and compare the number and types of symptom clusters identified using these ratings</p> <p><u>Design</u>: cross-sectional</p> <p><u>Location</u>: United States</p>	<p>$n = 232$</p> <p>Mean age: 59.6 (± 12.7) years Range: NR</p> <p>Female: 100.0%</p> <p>Ethnicity and Race: White 77.1% Black 3.5% Asian or Pacific Islander 8.8% Hispanic, Mixed, or other 10.6%</p> <p>Employment status: Working 31.0% Not working 69.0%</p> <p>Inpatients: $n = 0$ Outpatients: $n = 232$</p> <p>Diagnosis: Ovarian/fallopian tube/primary peritoneal 65.4% Uterine (including endometrial) 32.9% Other 5.7%</p> <p>Treatment: Adjuvant CTX 100.0%</p>	<p><u>Instrument(s)</u>: MSAS (modified): 38 symptoms</p> <p><u>Criteria used to exclude symptoms</u>: Yes</p> <p><u>Analysis</u>: EFA</p> <p><u>Dimension(s)</u>: occurrence, severity, distress</p> <p><u>Symptoms allowed to load on more than one factor</u>: Yes</p> <p><u>Minimum factor loadings required to include symptom within cluster</u>: 0.30</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints</u>:</p>	<p>5 symptom clusters identified across each symptom dimension:</p> <p><i>Occurrence symptom clusters</i></p> <p><u>Hormonal cluster</u>: sweats, hot flashes, problems with sexual interest or activity, abdominal cramps, difficulty concentrating, feeling irritable, feeling drowsy, pain, feeling bloated</p> <p><u>Respiratory cluster</u>: difficulty breathing, shortness of breath, pain, cough, dry mouth, numbness/tingling in hands/feet, feeling bloated, dizziness, difficulty sleeping</p>	<p><u>Strengths</u>:</p> <p>Symptom clusters were created using multiple dimensions of the symptom experience</p> <p>Evaluated symptom clusters in patients with gynecological cancers</p> <p>Utilized a valid and reliable symptom inventory</p> <p><u>Limitations</u>:</p> <p>Cross-sectional design</p> <p>Heterogeneity in types of gynecological cancers</p>

	<p>Time of symptom assessment: Within 7 days prior to start of 2nd or 3rd cycle of CTX</p>	<p>Kirkova and Walsh, 2007</p> <p><u>Analysis of additional outcomes:</u> N/A</p>	<p><u>Psychological cluster:</u> worrying, hair loss, feeling sad, "I don't look like myself", changes in skin, weight loss, change in the way food tastes, itching, lack of appetite, dizziness, feeling irritable, feeling nervous</p> <p><u>GI cluster:</u> diarrhea, abdominal cramps, constipation, sweats, itching, hot flashes</p> <p><u>Weight change cluster:</u> weight gain, increased appetite, lack of appetite, weight loss</p> <p><i>Severity symptom clusters</i></p> <p><u>Hormonal cluster:</u> sweats, hot flashes, problems with sexual interest or activity, difficulty concentrating, pain</p> <p><u>Respiratory cluster:</u> difficulty breathing, shortness of breath, pain, cough</p>	
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			<p><u>Psychological cluster:</u> worrying, feeling sad, feeling irritable, feeling nervous, abdominal cramps</p> <p><u>GI/epithelial cluster:</u> lack of appetite, change in the way food tastes, weight loss, changes in skin, constipation, nausea, dizziness, itching, "I don't look like myself", hair loss</p> <p><u>Weight change cluster:</u> weight gain, increased appetite, weight loss</p> <p><i>Distress symptom clusters</i></p> <p><u>Hormonal cluster:</u> sweats, hot flashes, problems with sexual interest or activity, pain</p> <p><u>Respiratory cluster:</u> difficulty breathing, shortness of breath, cough</p>	
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			<p><u>Psychological/GI cluster:</u> abdominal cramps, feeling sad, feeling bloated, worrying, feeling nervous, diarrhea, problems with sexual interest or activity, difficulty concentrating, feeling drowsy, constipation, feeling irritable, itching</p> <p><u>GI/epithelial cluster:</u> lack of appetite, change in the way food tastes, changes in skin, nausea, dizziness, itching, "I don't look like myself", hair loss, dry mouth, feeling irritable</p> <p><u>Weight change cluster:</u> weight gain, increased appetite, lack of appetite, weight loss, feeling bloated</p> <p><u>Additional outcomes:</u> N/A</p>	
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<p>Ren et al., 2017</p> <p><u>Purpose(s)</u>: Describe symptom experiences and explore whether symptoms were clustered</p> <p>Explore the potential predictors of each symptom cluster</p> <p>Analyze the correlations between symptom clusters and QOL in bladder cancer patients three months after radical cystectomy with an ileal conduit or orthotopic neobladder reconstruction</p> <p><u>Design</u>: cross-sectional</p> <p><u>Location</u>: China</p>	<p>$n = 99$</p> <p>Mean age: 61.9 (± 9.6). Range: NR</p> <p>Female: 6.1%</p> <p>Ethnicity: NR</p> <p>Race: NR</p> <p>Employment status: NR</p> <p>Inpatients: NR Outpatients: NR</p> <p>Diagnosis: Histologically confirmed bladder cancer 100%</p> <p>Treatment: Adjuvant CTX 45.5%</p> <p>Time of symptom assessment: 3 months post radical cystectomy with an ileal conduit or orthotopic neobladder reconstruction</p>	<p><u>Instrument(s)</u>: Chinese - MDASI (modified): 15 symptoms</p> <p><u>Criteria used to exclude symptoms</u>: No</p> <p><u>Analysis</u>: EFA</p> <p><u>Dimension(s)</u>: severity</p> <p><u>Symptoms allowed to load on more than one factor</u>: NR</p> <p><u>Minimum factor loadings required to include symptom within cluster</u>: NR</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints</u>: N/A</p> <p><u>Analysis of secondary outcomes</u>: Accordion Severity Grading System of surgical complications</p> <p>ASA score</p> <p>FACT-General</p>	<p>3 symptom clusters identified:</p> <p><u>Fatigue-malaise cluster</u>: fatigue, drowsiness, pain, memory problems, loss of appetite</p> <p><u>GI cluster</u>: Nausea, vomiting</p> <p><u>Psycho-urinary cluster</u>: sleep disturbance, body image impairment, urinary dysfunction, sadness, distress</p> <p><u>Additional outcomes</u>: Age, complication severity, plasma albumin level, orthotopic neobladder reconstruction, adjuvant CTX and ASA score significantly predicted fatigue-malaise distress</p> <p>CTX, orthotopic neobladder reconstruction, female gender, ASA</p>	<p><u>Strengths</u>:</p> <p>Evaluated symptom clusters in patients with bladder cancer</p> <p>Utilized a valid and reliable symptom inventory</p> <p>Correlated symptom cluster factor scores with other patient outcomes</p> <p><u>Limitations</u>:</p> <p>Cross-sectional design</p> <p>Small sample size</p> <p>Recruited patients from a single medical center</p> <p>Used only a single dimension to evaluate for symptom clusters</p>
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			<p>score and albumin significantly predicted gastrointestinal distress</p> <p>Being unmarried, having a higher level of education, and higher complication severity level significantly predicted psycho-urinary distress</p> <p>Negative correlations were found between QOL and each symptom cluster factor score</p>	
<p>Sezgin & Bektas, 2020</p> <p><u>Purpose(s)</u>: Determine the symptoms experienced by lymphoma patients</p> <p>Determine the symptom clusters of lymphoma patients</p> <p>Determine the functional status of lymphoma patients</p>	<p><i>n</i> = 109</p> <p>Mean age: NR Range: 19-84 years</p> <p>Female: 41.3%</p> <p>Ethnicity: NR</p> <p>Race: NR</p> <p>Employment status: Unemployed 74.3% Employed part-time 14.7% Employed full-time 11.0%</p> <p>Inpatients: <i>n</i> = 0</p>	<p><u>Instrument(s)</u>: Turkish MSAS: 32 symptoms</p> <p><u>Criteria used to exclude symptoms</u>: No</p> <p><u>Analysis</u>: HCA</p> <p><u>Dimension(s)</u>: frequency, severity, distress</p> <p><u>Symptoms allowed to load on more than one factor</u>: No</p>	<p>3 symptom clusters identified across each symptom dimension:</p> <p><i>Frequency symptom clusters</i></p> <p><u>Main cluster I</u>: nausea, vomiting, loss of appetite, dry mouth, fatigue or energy loss, pain</p> <p><u>Main cluster II</u>: diarrhea, being/feeling sensitive, dizziness,</p>	<p><u>Strengths</u>:</p> <p>Symptom clusters were created using multiple dimensions of the symptom experience</p> <p>Utilized a valid and reliable symptom inventory</p> <p>Evaluated symptom clusters in patients with lymphoma</p> <p><u>Limitations</u>:</p>

<p>Determine the effect of symptoms on the functional status of lymphoma patients</p> <p><u>Design</u>: cross-sectional</p> <p><u>Location</u>: Turkey</p>	<p>Outpatients: $n = 109$</p> <p>Diagnosis: Non-Hodgkin's lymphoma 73.4% Hodgkin's lymphoma 26.6%</p> <p>Treatment: CTX 100.0%</p> <p>Time of symptom assessment: NR</p>	<p><u>Minimum factor loadings required to include symptom within cluster</u>: NR</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints</u>: NR</p> <p><u>Analysis of additional outcomes</u>: N/A</p>	<p>difficulty in swallowing, difficulty in concentrating, difficulty in urinating, feeling swelled, feeling angry, problems with sexual desire and activity</p> <p><u>Main cluster III</u>: feeling sad, worrying difficulty in sleeping, cough, shortness of breath, feeling sleepy or dizzy, sweating, numbness/tingling in hands or feet, itching</p> <p><i>Severity symptom clusters</i> <u>Main cluster I</u>: mouth sores, changes in tasting foods, nausea, vomiting, weight loss, pain, fatigue or energy loss, sweating</p> <p><u>Main cluster II</u>: constipation, swelling of arms or legs, changes in skin, dry mouth, feeling sad, worrying, feeling sleepy or dizzy,</p>	<p>Cross-sectional design</p> <p>Timing of symptom assessment was not reported</p> <p>Clusters were not named</p> <p>Did not use a method to assess for stability of symptom clusters across symptom dimensions</p>
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			<p>difficulty in sleeping, itching</p> <p><u>Main cluster III:</u> cough, shortness of breath, numbness/tingling in the hands or feet, difficulty in swallowing, swelling of arms or legs, dizziness, swelling feeling, difficulty in urinating, difficulty in concentrating, feeling angry, diarrhea, I don't like myself, feeling/being sensitive, problems with sexual desire and activity</p> <p><i>Distress symptom clusters</i></p> <p><u>Main cluster I:</u> dizziness, difficulty in swallowing, feeling sleepy or dizzy, cough</p> <p><u>Main cluster II:</u> shortness of breath, swelling of arms or legs, changes on skin, itching, difficulty in concentrating,</p>	
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			<p>feeling angry, feeling swelled, difficulty in urinating, diarrhea, feeling/being sensitive, I don't like myself, numbness/tingling in hands or feet, problems with sexual desire and activity</p> <p><u>Main cluster III:</u> feeling sad, worrying, difficulty in sleeping, sweating, nausea, loss of appetite, mouth sores, change in taste of food, weight loss, pain, fatigue or energy loss, dry mouth, vomiting, hair loss, constipation</p> <p><u>Additional outcomes:</u> N/A</p>	
<p>Sullivan et al., 2017</p> <p><u>Purpose(s):</u> Identify whether the number and types of symptom clusters differed based on symptom occurrence rates or severity ratings were</p>	<p><i>n</i> = 515</p> <p>Mean age: 53.3 (±11.6) years Range: 21-90 years</p> <p>Female: 99.2%</p> <p>Ethnicity and Race: White 66.9% Black 6.9%</p>	<p><u>Instrument(s):</u> MSAS (modified): 38 symptoms</p> <p><u>Criteria used to exclude symptoms:</u> Yes</p> <p><u>Analysis:</u> EFA</p>	<p>5 symptom clusters identified using symptom occurrence:</p> <p><u>Psychological cluster:</u> feeling nervous, feeling sad, worrying, feeling irritable, "I don't look like myself"</p>	<p><u>Strengths:</u></p> <p>Symptom clusters were created using two dimensions of the symptom experience</p> <p>Utilized a valid and reliable symptom inventory</p>

<p>used to create the symptom clusters</p> <p><u>Design:</u> cross-sectional</p> <p><u>Location:</u> United States</p>	<p>Asian or Pacific Islander 15.3% Hispanic, Mixed, or other 10.9%</p> <p>Employment status: Working 41.0% Not working 59.0%</p> <p>Inpatients: <i>n</i> = 0 Outpatients: <i>n</i> = 515</p> <p>Diagnosis: Breast Cancer 100.0%</p> <p>Treatment: Adjuvant CTX 74.0% Neoadjuvant CTX 26.0%</p> <p>Time of symptom assessment: 7 days after the administration of the 2nd or 3rd cycle of CTX</p>	<p><u>Dimension(s):</u> occurrence, severity</p> <p><u>Symptoms allowed to load on more than one factor:</u> Yes</p> <p><u>Minimum factor loadings required to include symptom within cluster:</u> 0.40</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints:</u> Kirkova and Walsh, 2007</p> <p><u>Analysis of additional outcomes:</u> N/A</p>	<p><u>Hormonal cluster:</u> hot flashes, difficulty sleeping, sweats, problems with sexual interest or activity</p> <p><u>Nutritional cluster:</u> dry mouth, nausea, lack of appetite, change in the way food tastes, weight loss, abdominal cramps, diarrhea</p> <p><u>GI cluster:</u> weight loss, feeling bloated, weight gain</p> <p><u>Epithelial cluster:</u> “I don’t look like myself”, change in the way food tastes, hair loss, mouth sores</p> <p>6 symptom clusters identified using symptom severity:</p> <p><u>Hormonal cluster:</u> hot flashes, sweats</p> <p><u>Psychological cluster:</u> feeling sad, feeling nervous, worrying, feeling irritable</p>	<p><u>Limitations:</u> Cross-sectional design</p>
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			<p><u>CTX neuropathy cluster</u>: feeling drowsy, numbness or tingling in hands/feet, pain</p> <p><u>GI cluster</u>: feeling bloated, abdominal cramps, weight gain</p> <p><u>Nutritional cluster</u>: weight gain, weight loss, nausea, lack of appetite</p> <p><u>Epithelial cluster</u>: hair loss, changes in the way food tastes, “I don’t look like myself”, changes in skin, mouth sores</p> <p><u>Additional outcomes</u>: N/A</p>	
<p>Vuttanon et al., 2019</p> <p><u>Purpose(s)</u>: Identify symptom clusters in Thai patients with breast cancer who are undergoing CTX</p>	<p><i>n</i> = 96</p> <p>Mean age: Experimental group: 50.7 (±9.1) years Control group: 52.4 (±10.0)</p> <p>Female: NR</p> <p>Ethnicity: Thai 100.0%</p>	<p><u>Instrument(s)</u>: ESAS – Thai version: 9 symptoms</p> <p><u>Criteria used to exclude symptoms</u>: No</p> <p><u>Analysis</u>: EFA</p> <p><u>Dimension(s)</u>: severity</p>	<p>4 symptom clusters identified:</p> <p><u>Cluster 1</u>: anxiety, emotional distress</p> <p><u>Cluster 2</u>: nausea, pain</p> <p><u>Cluster 3</u>: drowsiness, fatigue</p>	<p><u>Strengths</u>:</p> <p>Utilized a valid and reliable symptom inventory</p> <p><u>Limitations</u>:</p> <p>Cross-sectional design</p>

<p>Examine the effect of PMR on symptom clusters</p> <p><u>Design</u>: cross-sectional</p> <p><u>Location</u>: Thailand</p>	<p>Race: NR</p> <p>Employment status: NR</p> <p>Inpatients: NR Outpatients: NR</p> <p>Diagnosis: Breast cancer 100.0%</p> <p>Treatment: Taxane 87.5% Herceptin 12.5%</p> <p>Time of symptom assessment: After completion of CTX</p>	<p><u>Symptoms allowed to load on more than one factor</u>: No</p> <p><u>Minimum cluster value required to include symptom within cluster</u>: NR</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints</u>: N/A</p> <p><u>Analysis of secondary outcomes</u>: N/A</p>	<p><u>Cluster4</u>: depression, lack of appetite</p> <p><u>Additional outcomes</u>: N/A</p>	<p>Small sample size</p> <p>Used 9 symptoms to evaluate for symptom clusters</p> <p>Unclear when the symptoms were assessed in relation to the completion of CTX</p> <p>Used only a single dimension to evaluate for symptom clusters</p> <p>Symptom clusters were not named</p>
<p>Wong et al., 2017</p> <p><u>Purpose(s)</u>: Compare the number and types of symptom clusters identified using ratings of symptom occurrence vs. severity in a homogeneous sample of lung cancer patients one week after CTX administration</p> <p><u>Design</u>: cross-sectional</p>	<p><i>n</i> = 157</p> <p>Mean age: 64.0 (±11.1) years Range: NR</p> <p>Female: 56.6%</p> <p>Ethnicity and Race: White 71.8% Black 9.9% Asian or Pacific Islander 9.9% Hispanic, Mixed, or other 8.5%</p> <p>Employment status: Working 24.8% Not working 75.2%</p> <p>Inpatients: <i>n</i> = 0</p>	<p><u>Instrument(s)</u>: MSAS (modified): 38 symptoms</p> <p><u>Criteria used to exclude symptoms</u>: Yes</p> <p><u>Analysis</u>: EFA</p> <p><u>Dimension(s)</u>: occurrence, severity</p> <p><u>Symptoms allowed to load on more than one factor</u>: Yes</p>	<p>5 symptom clusters identified across each symptom dimension:</p> <p><i>Occurrence symptom clusters</i> <u>Sickness behavior cluster</u>: abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting</p> <p><u>Lung cancer-specific cluster</u>: chest</p>	<p><u>Strengths</u>:</p> <p>Symptom clusters were created using two dimensions of the symptom experience</p> <p>Evaluated symptom clusters in patients with lung cancers</p> <p>Used a valid and reliable symptom inventory</p> <p><u>Limitations</u>:</p>

<p><u>Location:</u> United States</p>	<p>Outpatients: $n = 157$</p> <p>Diagnosis: Non-small cell lung cancer 88.1% Small cell lung cancer 11.9%</p> <p>Treatment: Platinum-doublet CTX 77.9% Single agent CTX 20.0% Monoclonal antibody alone 2.1%</p> <p>Time of symptom assessment: 7 days after the administration of the 2nd or 3rd cycle of CTX</p>	<p><u>Minimum factor loadings required to include symptom within cluster:</u> 0.40</p> <p><u>Method of evaluating for stability of symptoms across symptom dimensions and/or timepoints:</u> Kirkova and Walsh, 2007</p> <p><u>Analysis of additional outcomes:</u> N/A</p>	<p>tightness, cough, difficulty breathing, shortness of breath</p> <p><u>Psychological cluster:</u> difficulty concentrating, feeling bloated, feeling irritable, feeling nervous, feeling sad, problems with sexual interest or activity, worrying</p> <p><u>Nutritional cluster:</u> increased appetite, lack of appetite, weight gain, weight loss</p> <p><u>Epithelial cluster:</u> changes in skin, hair loss, "I don't look like myself," mouth sores</p> <p><i>Severity symptom clusters</i></p> <p><u>Sickness behavior cluster:</u> abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting, feeling bloated,</p>	<p>Cross-sectional design</p>
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			<p>feeling nervous, feeling sad, problems with sexual interest or activity, worrying, dizziness, dry mouth, pain, swelling of arms or legs</p> <p><u>Lung cancer-specific cluster:</u> chest tightness, cough, difficulty breathing, shortness of breath, swelling of arms or legs</p> <p><u>Nutritional cluster:</u> increased appetite, lack of appetite, weight gain, weight loss</p> <p><u>Psychological cluster:</u> feeling irritable, feeling nervous, feeling sad, worrying</p> <p><u>Epithelial cluster:</u> changes in skin, “I don’t look like myself,” mouth sores, swelling of arms or legs</p> <p><u>Additional outcomes:</u> N/A</p>	
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Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ASA = American Society of Anesthesiologists; CTX = chemotherapy; CIPN = chemotherapy-induced peripheral neuropathy; EFA = exploratory factor analysis; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FACT = Functional Assessment of Cancer Therapy; FSIS = Female Sexual Function Index; GI = gastrointestinal; HADS = Hospital Anxiety and Depression Scale; MDASI = M.D. Anderson Symptom Instrument; MSAS = Memorial Symptom Assessment Scale; NA = not applicable; NR = not reported; NRS = Numeric Rating Scale; PCA = principle component analysis; PSQI = Pittsburgh Sleep Quality Index; QOL = quality of life; TSO = Treatment-Specific Optimism