Original Article

Gender differences in pain and patient reported outcomes: a secondary analysis of the NCIC CTG SC. 23 randomized trial

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Background: Gender differences may contribute to variations in disease presentations and health outcomes. To explore the gender difference in pain and patient reported outcomes in cancer patients with bone metastases undergoing palliative radiotherapy on the National Cancer Institute of Canada (NCIC) SC. 23 randomized trial.

Methods: Patients completed the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life (QOL) bone metastases module (QLQ-BM22) and EORTC QOL Core-15-Palliative (QLQ-C15-PAL) before treatment and at days 10 and 42 after a single 8 Gy radiation treatment. Patient demographics, performance status, analgesic consumption, BM22 and C15 were compared between males and females using the 2-sample t-test for continuous variables or the Chi-squared test for categorical variables. Multiple linear regression models were used to check the difference between gender groups adjusting for the baseline demographics and primary disease sites.

Results: There were 298 patients (170 male, 128 female) with median age of 69 years. The most common primary cancer sites were lung, prostate and breast. At baseline, there were no differences in BM22 and C15 scores, except a worse nausea and vomiting score (P=0.03) in females on the C15. In patients with moderate baseline worst pain scores (WPS), females reported worse scores in painful sites of BM22. At day 42, there was no significant difference in response to radiotherapy. Among the responders, females reported better improvement in emotional aspect.

Conclusions: In cancer patients with bone metastases undergoing palliative radiotherapy, the majority of symptom presentations, patient reported outcomes, and response to radiation was not significantly different between genders. Trial registration: NCT01248585.

Keywords: Gender; bone metastases; palliative radiation treatment

Submitted Jul 17, 2017. Accepted for publication Aug 11, 2017.
doi: 10.21037/apm.2017.08.12
View this article at: http://dx.doi.org/10.21037/apm.2017.08.12

Introduction

Due to the differences in physiology and psychology, as well as economic and social circumstances, men and women may differ in their health risks and outcomes (1). This includes the experience of pain, where experimental studies have found gender differences in pain thresholds, tolerance, and responses to both pharmacological and non-pharmacological pain interventions (2-6). Contributing factors include biological differences, such the menstrual cycle in females and the influence from the complex interaction of sex-specific hormones that lead to differences in pain perception (4). On top of this, different social expectations of masculinity and femininity may also lead to gender-specific differences in the reporting of pain. Identification of the areas in which males and females differ is required in order to guide clinical practice to understand and better help patients.

Pain is one of the most common and distressing symptoms experienced by patients with advanced cancer (5). Unrelieved pain can disrupt and interfere with many activities of daily living, quality of life (QOL), and mood (6). In cancer patients with painful bone metastases, palliative radiotherapy is an effective treatment option in improving pain and QOL. However, there are few studies that assess potential differences in responses between males and females.

In the conclusion of the NCIC Clinical Trials Group (NCIC CTG) Symptom Control SC.23 study in cancer patients with painful bone metastases, treatment with dexamethasone significantly reduced pain flare incidence in comparison to placebo (7). The present study is a secondary analysis based on the SC. 23 trial, with the objectives of exploring differences in pain between men and women, including differences in response to palliative radiotherapy, and its effect on other patient reported QOL outcomes.

Methods

Patients were enrolled in the double-blind, placebo controlled study conducted across 23 Canadian cancer centres (7). Patients were eligible if they were at least 18 years of age, receiving a single 8 Gy dose of radiation for bone metastases at one or two locations, and had pain severity of at least 2 out of 10 in the Brief Pain Inventory (BPI) at the treatment site(s) (8,9). Ineligibility criteria included Karnofsky Performance Status (KPS) below 40, use of corticosteroids concurrently or within 7 days of study initiation, evidence of pathological or impending fracture, or spinal cord compression. Written consent was obtained for all patients enrolled and approvals from the research ethics boards of the 23 cancer centers involved in this study were obtained. The study was approved by provincial Ontario Cancer Research Ethics Board (OCREB) (No. 10-094).

Demographic information including patient gender, age, KPS, primary malignancy site, and treatment site was collected. Patients were randomly assigned to 1 of 2 arms. The treatment arm consisted of two tablets of 4 mg of dexamethasone or placebo taken at least 1 h before start of radiotherapy then every day for 4 days after radiotherapy. Patients kept a pain diary in which they recorded worst pain scores (WPS) on the BPI from a scale of 0 to 10, analgesic intake before treatment and daily for 10 days after radiotherapy. WPS was classified as mild [1–5], moderate [6] and severe [7–10] (10). Analgesic intake was converted into an oral morphine equivalent (OME) daily.

Response to radiotherapy was defined according to the International Bone Metastases Consensus Endpoint definitions (11). In brief, complete response (CR) refers to no pain at treatment site with no increase in analgesic intake; partial response (PR) refers to WPS reduction of at two or more without increase in analgesic intake, or no increase in WPS but reduction in 25% or more of analgesic intake when compared to baseline. Pain progression (PP) refers to at least a 2-point increase in the WPS without decrease in analgesic intake, or an increase of 25% or more of analgesic intake but no change in WPS. Remaining patients were characterised as having stable pain.

Within 7 days before treatment, and at 10 and 42 days after treatment, patients completed the European Organisation for Research and Treatment of Cancer (EORTC) QOL bone metastases module (QLQ-BM22) (12,13) and the EORTC QOL Core-15-Palliative (QLQ-C15-PAL) (14,15) questionnaires. The QLQ-BM22 is a questionnaire validated specifically for patients with bone metastases (12,13). It assesses two symptomatic (painful characteristics and painful sites) and two functional (functional interference and psychosocial aspects) scales. The QLQ-C15-PAL is the short form of the QLQ-C30 and was designed specifically in the palliative population (14,15). It contains single and multi-item scales that assess symptoms and functioning. All items in both scales, except for the global QOL item in the QLQ-C-15-PAL were scored on a Likert scale from 1 (not at all) to 4 (very much). Higher values indicate worse symptoms, but better functioning. All scores were linearly converted into a scale of 0–100 according to EORTC guidelines (16). A score change of 10 or more on this scale represented a clinically significant difference (17).

Descriptive statistics including mean and standard deviation were used to describe the patient baseline characteristics, scores, and score changes in the QLQ-BM22 and QLQ-C15-PAL at baseline and 42-day follow-up. Comparisons of patient demographics, performance status, analgesic consumption, BM22 and C15 were compared between gender groups with the 2-sample *t*-test for continuous variables and the Chi-squared test for categorical variables. Multiple linear regression models were used to check the difference in changes in QOL scores between gender groups adjusting for the baseline demographics and primary disease sites. P values <0.05 were considered statistically significant. All analyses were done with SAS, version 9.2.

Results

There were 298 patients (170 male, 128 female) with a median age of 69 years. Baseline demographics are presented in *Table 1*. The most common primary cancer sites were lung, prostate and breast. Most patients had a baseline WPS of 7–10, and KPS of 70 or 80. At baseline, there were no significant differences between males and females in WPS, KPS, or first palliative radiotherapy treatment site. As would be expected, male and female patients differed significantly in the common primary cancer sites of prostate and breast.

At baseline, there were no differences between males and females in the scores of the four QLQ-BM22 domains (*Table 2*). However, on the QLQ-C15-PAL, males and females differed significantly in the domain of nausea and vomiting, with females scoring higher than males (P=0.03).

To investigate whether severity of baseline pain influenced gender-specific outcomes after radiotherapy, males and females were also compared across the QLQ-BM22 and QLQ-C15-PAL domains after being stratified by severity of their baseline WPS (*Table 3*). In patients with moderate pain, the only significant difference between males and females was in the domain of painful sites of the QLQ-BM22, where females reported worse score than males (P=0.01). In patients with severe pain, females reported worse nausea and vomiting scores (P=0.03).

There were no differences between males and females in response to radiotherapy when evaluated at day 42 (female: 41.2% *vs.* male: 35.9%, P=0.36, *Table 4*). Males and females had similar overall rates of CR, PR, and non-response. When stratified according to pain severity categories at baseline, no significant differences in radiotherapy response were identified.

Males and females were evaluated for changes in QOL domains from baseline to day 42 after radiotherapy (*Table 5*). No differences existed between males and females except in the item of psychosocial aspect in the QLQ-BM22 questionnaire, in which a higher proportion of males reported either improvement or worsening of this domain (P=0.002).

Table 6 presents the analysis of the change in QOL among males and females separated according to radiotherapy responders and non-responders. Among the responders, higher proportions of males reported either improvement or deterioration in psychosocial aspect from the QLQ-BM22 (P=0.04), while more females reported improvement in emotional aspect of the QLQ-C15-PAL (P=0.03). Among the non-responders, there were significant differences in psychosocial aspect of the QLQ-BM22, again with higher proportion of males reporting either improvement or worsening in this domain when compared to females (P=0.04). On the other hand, higher proportion of females reported either improvement or worsening of the dyspnea item in the QLQ-C15-PAL (P=0.02).

Discussion

Our study identified limited differences between men and women in baseline characteristics and QOL domains and

Table 1 Patient demographics and baseline characteristics

Patient demographic/characteristic	Males	Females	Total
Baseline worst pain score (WPS), n (%)			
WPS 1–5	61 (35.9)	47 (36.7)	108 (36.2)
WPS 6	18 (10.6)	14 (10.9)	32 (10.7)
WPS 7–10	91 (53.5)	67 (52.3)	158 (53.0)
Karnofsky performance status, n (%)			
40–60	44 (25.9)	24 (18.8)	68 (22.8)
70–80	86 (50.6)	79 (61.7)	165 (55.4)
90–100	40 (23.5)	25 (19.5)	65 (21.8)
First palliative radiotherapy treatment site, n (%)			
Vertebrae	57 (33.5)	46 (35.9)	103 (34.6)
Pelvis/Hips	49 (28.8)	43 (33.6)	92 (30.9)
Others	64 (37.6)	39 (30.5)	103 (34.6)
Primary cancer site*, n (%)			
Lung	45 (26.5)	39 (30.5)	84 (28.2)
Prostate	74 (43.5)	0 (0.0)	74 (24.8)
Breast	1 (0.6)	65 (50.8)	66 (22.1)
Other	50 (29.4)	24 (18.8)	74 (24.8)
Baseline total daily OME (oral morphine equivalent) (mg)			
n	165 (56.9%)	125 (43.1%)	290
Mean	91.2	37.9	83.8
Standard deviation	311.7	185.1	264.4
Median	20	20	20
Range	0–3,750	0–1,740	0–3,750

*, statistically significant difference between males and females using the Chi-squared test.

pain levels, as well as in response to palliative radiotherapy in terms of pain reduction and QOL domains. This finding held after stratification of patients according to severity of symptom presentation at baseline.

Existing literature on gender differences in pain presentation and QOL in cancer patients have been inconclusive. The patient population in Wong *et al.* was similar to the present study (18). The authors investigated 396 patients with advanced cancer who underwent palliative radiotherapy for painful bone metastases. They found that female gender was associated with better baseline functional interference and painful characteristics domains on the QLQ-BM22. However, males and females did not significantly differ in QOL changes from baseline to follow-up. Our study yielded similar results in that there were no differences between males and females in all QLQ-BM22 domains except for psychosocial aspect. Since the baseline WPS and KPS were not significantly different between males and females, a plausible explanation may be that males were more responsive to changes in pain in terms of psychosocial aspects. However, unlike the results from Wong *et al.*, we also did not identify any differences in

Table 2 Baseline BM22 and QLQ-C15-PAL scores

Domain	Males			Females			P value*
	n	Mean	SD	n	Mean	SD	
QLQ-BM22							
Painful sites	161	34.3	16.9	121	36.8	19.1	0.25
Painful characteristics	161	44.5	21.8	121	47.5	22.5	0.25
Functional interference	161	51	22.3	121	47.9	23.4	0.26
Psychosocial aspect	161	51	19.1	121	49.2	20.5	0.45
QLQ-C15-PAL							
Physical	161	75	24.9	121	70.9	25.4	0.17
Emotional	160	69.5	27.6	121	68.3	25.5	0.72
Global QOL	158	47.6	23.3	121	49.2	23.3	0.57
Pain	159	62.4	26.9	120	65.3	25.3	0.36
Fatigue	160	46.9	27.4	120	46.3	28	0.85
Nausea and vomiting	*160*	*15.4*	*26.1*	*121*	*22.9*	*30.4*	*0.03*
Dyspnea	161	25.5	28.8	120	22.2	28.5	0.35
Insomnia	161	36.7	31	121	37.5	34.3	0.83
Appetite	161	31.5	34.8	121	38	37.1	0.13
Constipation	160	31.3	33.6	120	36.1	36.8	0.25

*, the 2-sample *t*-test was used to calculate P values. Statistically significant differences are in italic form. QOL, quality of life.

patient-reported QOL domains at baseline.

A second study that utilized the QLQ-BM22, in addition to the QLQ-C30-PAL, was conducted by Püsküllüoğlu *et al.* (19). They found that in 110 Polish patients with cancer, men reported higher pain, worse fatigue, and worse nausea and vomiting compared to women. Moreover, at the 2-week follow-up, men also reported worse outcomes in the BM22 functional interference domain, and the QLQ-C30 social, emotional, and cognitive functioning domains. On the other hand, a study by Montague *et al.* of 96 cancer patients identified no differences between males or females in any of the QLQ-C30 subscales (20). Moreover, there were no gender differences in the duration and quality of breakthrough pain, or in the efficacy of pain medications.

While several studies on gender differences have been conducted using the QLQ-C30 questionnaire, this present study is the first to use the abbreviated QLQ-C15-PAL questionnaire. We identified that males and females report similar scores in the symptomatic and functional domains at baseline. In all but the psychosocial aspect domain, males and females report similar changes from baseline to follow-up. However, our finding that males report more improvement and deterioration in psychosocial aspect may be limited in its clinical implication, and will require further investigation to assess any potential significance. Overall, inconsistent findings in this area warrant further research to establish whether gender affects pain and QOL in cancer patients. This will help inform the interpretation of patient-reported symptoms and health outcomes, as well as guide improvements in health care practice that reflect the potentially different needs of each gender.

Conclusions

In cancer patients with bone metastases undergoing palliative radiotherapy, there appears no significant difference in general between genders in symptom presentations, patient reported outcomes and response to

Table 3 Baseline BM22 and C15 scores in patients with moderate or severe pain

Domain	Males			Females			P value*
	n	Mean	SD	n	Mean	SD	
Moderate pain, QLQ-BM22							
Painful sites	*16*	*31.3*	*12.4*	*14*	*47.6*	*19.9*	*0.01*
Painful characteristics	16	43.1	21.4	14	57.9	23.9	0.08
Functional interference	16	58.1	16.6	14	45.8	22.6	0.10
Psychosocial aspect	16	56.6	14.9	14	44.4	17.7	0.05
Moderate pain, QLQ-C15-PAL							
Physical	16	72.2	22.6	14	69.8	25.2	0.79
Emotional	*16*	*83.3*	*19.3*	*14*	*67.9*	*32.3*	*0.12*
Global QOL	16	41.7	21.1	14	53.6	19.8	0.12
Pain	15	63.3	22	14	67.9	26.5	0.62
Fatigue	16	40.6	23.6	14	46.4	29.4	0.55
Nausea and vomiting	15	13.3	16.9	14	19.1	36.3	0.59
Dyspnea	16	18.8	32.1	14	19.1	21.5	0.98
Insomnia	16	31.3	19.1	14	54.8	40.5	0.05
Appetite	16	37.5	34.2	14	40.5	41.7	0.83
Constipation	16	31.3	35.4	14	45.2	36.1	0.29
Severe pain, QLQ-BM22							
Painful sites	87	38.5	16.6	63	41	18.8	0.41
Painful characteristics	87	51.5	21.3	63	54.9	20.6	0.32
Functional interference	87	43.2	21.3	63	39	*21.5*	*0.24*
Psychosocial aspect	87	45.8	18.1	63	45.3	19.7	0.88
Severe pain, QLQ-C15-PAL							
Physical	87	70.4	26.2	63	63.3	26.7	0.11
Emotional	87	63.2	27.6	63	65.3	25.3	0.63
Global QOL	86	42.3	21.8	63	41.5	22.2	0.84
Pain	86	73.1	23.7	63	73.8	22.5	0.85
Fatigue	87	52.9	27.5	63	51.3	27.5	0.73
Nausea and vomiting	*87*	*19.5*	*29*	*63*	*30.7*	*33*	*0.03*
Dyspnea	87	30.3	30.3	62	27.4	31.7	0.58
Insomnia	87	39.9	32.9	63	39.2	34.7	0.90
Appetite	87	37.9	37.4	63	42.9	37.1	0.43
Constipation	86	40.3	35.8	62	43.6	37.5	0.60

*, the 2-sample *t*-test was used to calculate P values. Statistically significant differences are in italic form.

Table 4 Radiation response in males and females evaluated at 42 days post treatment

Pain	Males, n (%)		Females, n (%)		P value*
	Responders	Non-responders	Responders	Non-responders	
All patients	70 (41.2)	100 (58.8)	46 (35.9)	82 (64.1)	0.36
Mild pain	26 (42.6)	35 (57.4)	23 (48.9)	24 (51.1)	0.51
Moderate pain	8 (44.4)	10 (55.6)	4 (28.6)	10 (71.4)	0.36
Severe pain	36 (39.6)	55 (60.4)	19 (28.4)	48 (71.6)	0.14

*, the Chi-squared test was used to calculate P values.

Table 5 Change in quality of life evaluated at 42-days post treatment

Domain	Male, n (%)			Female, n (%)			P value*
	Improved	Stable	Worsened	Improved	Stable	Worsened	
QLQ-BM22							
Painful sites	48 (43.6)	42 (38.2)	20 (18.2)	47 (50.0)	32 (34.0)	15 (16.0)	0.662
Pain characteristics	70 (63.6)	20 (18.2)	20 (18).2	55 (58.5)	21 (22.3)	18 (19.1)	0.712
Functional interference	63 (57.3)	33 (30.0)	14 (12.7)	49 (52.1)	34 (36.2)	11 (11.7)	0.646
Psychosocial aspect	*46 (41.8)*	*27 (24.5)*	*37 (33.6)*	*30 (31.9)*	*45 (47.6)*	*19 (20.2)*	*0.002*
QLQ-C15-PAL							
Physical	31 (28.4)	39 (35.8)	39 (35.8)	35 (37.2)	25 (26.6)	34 (36.2)	0.279
Emotional	42 (38.2)	34 (30.9)	34 (30.9)	40 (42.6)	33 (35.1)	21 (22.3)	0.388
Global	39 (36.1)	37 (34.3)	32 (29.6)	45 (47.9)	27 (28.7)	22 (23.4)	0.236
Pain	59 (55.1)	28 (26.2)	20 (18.7)	62 (66.7)	18 (19.4)	13 (14.0)	0.251
Fatigue	35 (32.4)	35 (32.4)	38 (35.2)	30 (31.9)	26 (27.7)	38 (40.4)	0.689
Nausea and vomiting	17 (15.5)	71 (64.5)	22 (20.0)	23 (24.5)	45 (47.9)	26 (27.7)	0.054
Dyspnea	17 (15.5)	74 (67.3)	19 (17.3)	18 (19.4)	55 (59.1)	20 (21.5)	0.487
Insomnia	35 (32.1)	51 (47.8)	23 (21.1)	24 (25.5)	54 (57.4)	16 (17.0)	0.317
Appetite	19 (17.3)	58 (52.7)	33 (30.0)	26 (27.7)	41 (43.6)	27 (28.7)	0.185
Constipation	27 (24.8)	56 (51.4)	26 (23.9)	26 (28.0)	50 (53.8)	17 (18.3)	0.612

*, the Chi-squared test was used to calculate P values. Statistically significant differences are in italic form.

Table 6 Change in quality of life among responders and non-responders

Domain	Male, n (%)			Female, n (%)			P value*
	Improved	Stable	Worsened	Improved	Stable	Worsened	
Responders, QLQ-BM22							
Painful sites	33 (54.1)	23 (37.1)	5 (8.2)	26 (63.4)	13 (31.7)	2 (4.9)	0.60
Pain characteristics	43 (70.5)	10 (16.4)	8 (13.1)	31 (75.6)	7 (17.1)	3 (7.3)	0.65
Functional interference	40 (65.6)	16 (26.2)	5 (8.2)	26 (63.4)	14 (34.1)	1 (2.4)	0.38
Psychosocial aspect	*29 (47.5)*	*15 (24.6)*	*17 (27.9)*	*14 (34.1)*	*20 (48.8)*	*7 (17.1)*	*0.04*
Responders, QLQ-CP15-PAL							
Physical	23 (38.3)	25 (41.7)	12 (20.0)	18 (43.9)	12 (29.3)	11 (26.8)	0.43
Emotional	*28 (45.9)*	*18 (29.5)*	*15 (24.6)*	*23 (56.1)*	*16 (39.0)*	*2 (4.9)*	*0.03*
Global QOL	29 (49.2)	17 (28.8)	13 (22.0)	27 (65.9)	8 (19.5)	6 (14.3)	0.25
Pain	38 (65.5)	13 (22.4)	7 (12.1)	33 (80.5)	5 (12.2)	3 (7.3)	0.26
Fatigue	26 (42.6)	22 (36.1)	13 (21.3)	17 (41.5)	13 (31.7)	11 (26.8)	0.79
Nausea and vomiting	10 (16.4)	39 (63.9)	12 (19.7)	10 (24.4)	23 (56.1)	8 (19.5)	0.59
Dyspnea	15 (24.6)	36 (59.0)	10 (16.4)	7 (17.1)	27 (65.9)	7 (17.1)	0.66
Insomnia	22 (36.1)	30 (49.2)	9 (14.8)	14 (34.1)	20 (48.8)	7 (17.1)	0.95
Appetite	11 (18.0)	37 (60.7)	13 (21.3)	12 (29.3)	22 (53.7)	7 (17.1)	0.41
Constipation	21 (34.4)	31 (50.8)	9 (14.8)	13 (31.7)	23 (56.1)	5 (12.2)	0.86
Non-responders, QLQ-BM22							
Painful sites	15 (30.6)	19 (38.8)	15 (30.6)	21 (39.6)	19 (35.8)	13 (24.8)	0.61
Pain characteristics	27 (55.1)	10 (20.4)	12 (24.5)	24 (45.3)	14 (26.4)	15 (28.3)	0.60
Functional interference	23 (46.9)	17 (34.7)	9 (18.4)	23 (43.4)	20 (37.7)	10 (18.9)	0.93
Psychosocial aspect	*17 (34.7)*	*12 (24.5)*	*20 (40.8)*	*16 (30.2)*	*25 (47.2)*	*12 (22.6)*	*0.04*
Non-responders, QLQ-C15-PAL							
Physical	8 (16.3)	14 (28.6)	27 (55.1)	17 (32.1)	13 (24.5)	23 (43.4)	0.18
Emotional	14 (28.6)	16 (32.7)	19 (38.8)	17 (32.1)	17 (32.1)	19 (35.8)	0.92
Global QOL	10 (20.4)	20 (40.8)	19 (38.8)	18 (34.0)	19 (35.8)	16 (30.2)	0.30
Pain	21 (42.9)	15 (30.6)	13 (26.5)	29 (55.8)	13 (25.0)	10 (19.2)	0.42
Fatigue	9 (19.1)	13 (27.7)	25 (53.2)	13 (24.5)	13 (24.5)	27 (50.9)	0.80
Nausea and vomiting	7 (14.3)	32 (65.3)	10 (20.4)	13 (24.5)	22 (41.5)	18 (34.0)	0.06
Dyspnea	*2 (4.1)*	*38 (77.6)*	*9 (18.4)*	*11 (21.2)*	*28 (53.8)*	*13 (25.0)*	*0.02*
Insomnia	13 (27.1)	21 (43.8)	14 (29.2)	10 (18.9)	34 (64.2)	9 (17.0)	0.12
Appetite	8 (16.3)	21 (42.9)	20 (40.8)	14 (26.4)	19 (35.8)	20 (37.7)	0.45
Constipation	6 (12.5)	25 (52.1)	17 (35.4)	13 (25.0)	27 (51.9)	12 (23.1)	0.19

*, the Chi-squared test was used to calculate P values. Statistically significant differences are in italic form.

radiation. Therefore, men and women should be considered equally in consideration for palliative radiotherapy for painful bone metastases.

Acknowledgements

This study was supported by the NCIC CTG's programmatic grant from the Canadian Cancer Society Research Institute. We thank all the patients who participated, and the research teams.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by provincial Ontario Cancer Research Ethics Board (OCREB) (No. 10-094). Written consent was obtained for all patients enrolled and approvals from the research ethics boards of the 23 cancer centers involved in this study were obtained.

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Cite this article as: Chow S, Ding K, Wan BA, Brundage M, Meyer RM, Nabid A, Chabot P, Coulombe G, Ahmed S, Kuk J, Dar AR, Mahmud A, Fairchild A, Wilson CF, Wu JS, Dennis K, DeAngelis C, Wong RK, Zhu L, Chow E. Gender differences in pain and patient reported outcomes: a secondary analysis of the NCIC CTG SC. 23 randomized trial. Ann Palliat Med 2017;6(Suppl 2):S185-S194. doi: 10.21037/apm.2017.08.12

