Final Statistical Analysis Plan

A RANDOMIZED PHASE II/III STUDY COMPARING STEREOTACTIC BODY RADIOTHERAPY (SBRT) VERSUS CONVENTIONAL PALLIATIVE RADIOTHERAPY (CRT) FOR PATIENTS WITH SPINAL METASTASES

CCTG Protocol Number: **SC.24**

Prepared by:

Trial Statistician: Keyue Ding

Reviewed by:

Senior Investigator: Dr. Wendy Parulekar

Study Chairs: Dr. Arjun Sahgal

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1 Introduction:

The document describes the final data analysis plan for Canadian Cancer Trials Group (CCTG) study SC24.

The trial was centrally activated on July 28, 2015. The first patient was randomized to the trial in Jan. of 2016, and the trial was closure to accrual on Sept 27, 2019 after reaching target sample size. The data has been collected and cleaned by CCTG according to the the group's data management plan.

All analyses will be performed by the trial biostatistician at CCTG and a final statistical analysis report will be prepared. A copy of this report will be sent to the study chair for the writing of the manuscript.

1.1 Study design and objectives

SC24 is a randomized multicentre phase II/III study. The phase II part is designed to assess feasibility of conducting a phase III trial in the study population, i.e. the ability to accure 54 patients with spinal metastases to a trial comparing Stereotactic Boday Radiotherapy (SBRT) to standard conventional radiotherapy (CRT) over an 18 month period in a Canadian multicentre setting.

Upon successful completion of the phase II portion of the trial, the phase III portion of the trial with primary endpoint of complete pain response at 3 months post-radiation in the target population was intiated.
Patients were randomized to receive either Stereotactic Body Radiotherapy (SBRT) or Standard Conventional Radiotherapy (CRT) in a 1:1 ratio.

Secondary Objectives are:

- Complete pain response in the treatment area t 6 months post-radiation,
- Radiation site progression-free survival (RSS PFS) at 3 and 6 months,
- SINS score at 3 and 6 months,
- Overall survival,
- Adverse event profile,
- Health-related Quality of Life,
- Radiotherapy Quality Assurance (RTQA) compliance.

1.2 Sample Size Determination

For the randomized phase II portion of the study, a convenience sample size of 54 patients was considered sufficient to evaluate whether accrual is feasible. This sample size would also provide an opportunity to estimate the CRT and SBRT 3 month complete pain relief response rates, which would provide the basis for the sample size calculation of the future randomized controlled trial.
The final sample size for the phase III part was calculated to detect a 20% improvement in 3 month post-radiation in the complete pain response for patients on SBRT arm to the 20% complete

response rate for patients on the CRT arm. Assuming a 15% drop out/inevaluable rate, we expect the complete pain response rates for the intent-to-treat population to be 17% and 34% for the CRT and SBRT arms, respectively. To detect the difference with 80% power using a 2-sided 5% level test, the sample size is 228. The final data set includes all randomized patients including the phase II and phase III trial phases.

1.3 Timing of the Analyses

The protocol mandated final analysis will conducted after at least 228 randomized patients have met the projected follow-up period of 6 months post completion of radiotherapy.

This document is to describe the final statistical analysis plan of the final analysis according to the study protocol.

1.4 Data Collection

Data are collected, entered and managed by CCTG, Kingston, Ontario, according to the group standard data management procedures. The clinical cut-off date will be determined by the date of the 6 momth post radiotherapy visit of the last enrolled patient. The database will be locked for analysis after review and resolution of relevant queries.

2 Methods and Analyses

2.1 Analysis Populations

The analysis populations for this analysis will include both the intention to treat (ITT) population (i.e. all as randomized patients to the treatment arm in each specified population) and the 'as treated' population (i.e. all patients who received at least one dose of study treatment).

Analysis of pretreatment characteristics and all efficacy analyses such as complet pain response rate, will be based on the ITT population. Safety and drug exposure analyses will be performed on the as-treated population.

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2.2 Conventions for Calculating Key Data

In general, baseline evaluations are those collected closest, but prior to or on the day of randomization. If pre-randomization assessment was not done, a pre-treatment assessment will be used as baseline assessment.

When either day or month of a date is missing, the missing day and/or month will be imputed by the midpoints within the smallest known interval. For example, if the day of the month is missing for any date used in a calculation, the 15th of the month will be used to replace the missing day. If the month and day of the year are missing for any date used in a calculation, the first of July of the year will be used to replace the missing data.

2.3 Analysis Conventions

All comparisons between treatment arms will be carried out using a two-sided test at an alpha level of 5% unless otherwise specified. No formal adjustments will be made for the multiplicity of inferences for multiple clinical endpoints.

The baseline stratification factors that will be used to adjust the analyses where appropriate are listed below:

- Histology (radioresistant vs. radiosensitive)
- "Mass"* on imaging (present vs. absent)

2.4 Randomization and Pre-treatment Characteristics

2.4.1 Definitions and Variables

2.4.1.1 Accrual

- Number (%) of randomized patients per study center (Table 1).

2.4.1.2 Randomization/Stratification

- Histology (radioresistant vs. radiosensitive)
- "Mass"* on imaging (present vs. absent)

(Note: An unknown/missing category will be added to each factor whenever appropriate.) (table 2).

A minimization procedure for treatment assignment was used in this study.

X Baseline patient characteristics will be cross-tabulated with the patient's corresponding stratification assignment to identify any discrepancies (Table 3)

X Treatment randomized to receive will be compared with the actual treatment received during the first cycle to identify any discrepancies (Table 4)

2.4.1.3 Ineligibility and Major Protocol Violations (Table 5)

X Eligible patients: % yes, no

X Reasons for ineligibility: % for each reason and combination of reasons of ineligibility.

X Major Protocol Violations/deviations: number and % for each type of violation/deviation.

Number and percentage of ineligible patients will be presented by treatment arm.

Reasons for ineligibility: percentage for each reason and combination of reasons of ineligibility will be presented by treatment arm.

The number and percentage of major protocol violations will be presented by treatment arm.

2.4.1.4 Summary of Follow-up

A table showing the median, min and max follow-up (defined as reverse censoring on survival) will be presented for all patients and by treatment group included in the final analysis.

2.4.1.5 Patient Characteristics (Table 7)

- Age: 0-39, 40-49, 50-59, 60-69, 70+, median, min and max;
- Gender (M VS F)
- Primary malignancy (Breast, Lung, GI, GU, Gyn, …)
- ECOG performance status (0, 1, 2)
- Number of consecutive Spinal segments in target volume (1, 2, 3)
- Worst pain score at target treatment site at baseline (median, min and max)
- Prior spinal surgical/diagnostic procedures for cancer (Y vs N).
- Prior radiation therapy to their spine for cancer (Y vs N).
- SINS score (Median, min, max; mean, std, also by categories: 0-6 vs 7 -12 vs 13 – 18), Epidural Disease Extent (Bilsky scale) (1, 1a, 1b, 1c, 2, 3 ..)
- SINS score by categories of Location, Pain, Bone Lesion, Radiographic Spinal Alignment, Vertebral Body Collapse, and Posterolateral Involvement. (Median, min, max; mean, std).
- Angular Kyphosis (degrees) (0, 1, 2…),
- Opioid medications reported in the last 24 hours (Median, min and Max, mean, std)
- bisphosphonates or other bone targeted therapy (Y vs. N).

*An unknown category will be added when appropriate.

2.4.1.7 Baseline Adverse Events (table 8)

Baseline adverse event were collected within 7 days prior to randomization, and summarized according to NCI CTCAE V4.0.

2.4.1.8 Baseline NON-opioid Medications (table 9)

A NON-opioid medication which was taken within 24 hours prior to ghe baseline assessment.

X Any NON-opioid medication: % yes, no

X Number of patients for each type of medication.

2.4.1.9 Baseline Cancer Treatment (Table 10)

Number and percent of patients received cancer treatment within 30 days prior to randomization will be summarized by treatment arm.

2.4.2 Analysis of pre-treatment characteristics

No formal statistical tests will be performed to assess the homogeneity of baseline characteristics between the arms. Categorical variables will be tabulated by treatment arm and for all patients. Continuous variables (e.g., age) will be presented using summary statistics (n, median, min and max) or specified cutoff categories by treatment arm and for all patients. Analyses will be based on all randomized patients by arm based on the ITT population.

2.5 Efficacy

2.5.1 Definitions and Variables

2.5.1.1 Complete pain response in the treatment area at 3 months post-radiation

All patients who have received at least one dose of radiotherapy and provide complete worst pain score information for the treated site of radiation treatment and opioid analgesic intake information at baseline and at least the 3 month follow up contact will be considered evaluable for response to radiotherapy.

A Complete Pain Response is defined as a pain score of zero (0) at the treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent). The response status at 3-month and 6-month will be derived by comparison of wosrt pain score and analgesic intake at the time point to baseline data. As a sensitive analysis, the response status will be derived from comparison of wosrt pain score and analgesic intake at the time point to day 0 data prior to RT, and perform the similar analyses.

2.5.1.2 Response to radiation therapy (CR/PR)

Pain response to radiotherapy is based on the International Bone Metastases Consensus Endpoint definitions and will be measured at 3 months assessment.

A complete Pain Response is defined as a pain score of zero (0) at the treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent)

A partial response is defined as any of the following:

i. Reduction in worst pain score of two or more at the bony metastatic site on a 0–10 scale without analgesic increase.

ii. Analgesic reduction of 25% or more from baseline without an increase in worst pain score with reference to baseline.

iii. For patients who were using opioid analgesics at the baseline assessment, a daily oral morphine equivalence of zero (0) without an increase in worst pain score relative to the baseline worst pain score.

2.5.1.3 Pain Progression (PD) and Stable pain (SD)

Pain progression is defined as any of the following:
i. An increase in worst pain score of two or more points above baseline at the treated site without reduction of analgesic use.
ii. An increase of 25% or more in daily oral morphine equivalent compared with baseline, without reduction in worst pain score.
iii. For patients who were not using opioid analgesics at the baseline assessment (daily oral morphine equivalence = 0), consumption of any opioid analgesic without a reduction in worst pain score relative to the baseline worst pain score.

Stable pain (SD) is assigned to the remaining evaluable patients, who do not meet any of the categories of Complete/Partial Response and Pain Progression.

2.5.1.4 Complete pain response in the treatment area at 6 months post-radiation

All patients who have received at least one dose of radiotherapy and provide complete worst pain score information for the treated site of radiation treatment and opioid analgesic intake information at baseline and at least the 6 month follow up contact will be considered evaluable for response to radiotherapy.

A Complete Pain Response is defined as a pain score of zero (0) at the treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent).

2.5.1.4 Radiation site progression-free survival (RSS PFS) at 3 and 6 months

Radiation site progression free survival is defined as the time from randomization to local progression or death. For patients who did not reported progression of disease and alive will be censored at the last disease evaluation time. It is based on the center invstigator reported data.

2.5.1.5 SINS score at 3 and 6 months

All patients who have had their baseline SINS score and at least one follow-up SINS score (at either 3 and/or 6 months) assessed will be considered evaluable for the spinal instability analysis.

2.5.1.6 Overall survival

Overall survival is defined as the time from randomization to date of death. For patients who are alive will be censored at the last known alive date.

2.5.2 Analysis of Key Parameters

The comparison between treatment arms will be carried out using a two-sided test at an alpha level of 5% unless otherwise specified. All efficacy analyses will be presented by treatment arm. The CONSORT diagram will be included.

2.5.2.1 Complete pain response at 3-month post treatment

Patients will be considered to achieve a complete pain response if they meet the criteria for complet pain response outlined in 2.5.1.1.

A table of number of patients who were not evaluable for the primary endpoint of complete pain response will be provided by treatment arm. (Table 11).

A table of number of patients meeting the primary endpoint of complete pain response at 3-month after treatment start by arm will be provided. (Table 12).

The complete pain response rate is defined as number of patients achieved complete pain response / number of patients randomized for each treatment arm. Chi-square analysis will be applied to test the complete pain response rate between the two arms and the 95% confidence interval of the rate difference (SBRT arm – CRT arm) between the two arms will be calculated. The Cochran-Mantel-Hanzeal Chi-square will be used to test the difference in the complete pain response rate stratified by stratification factors at randomization except of study center. P-value from Chi-square test without adjustment for the stratification factors will also be provided for sensitivity.

Logistic regression will be used to assess the relationship between complet pain response incidence and the following factors (Table 13):

- Treatment arm
- Age (as a continuous variable and/or as a categorical variable: below and above median);
- Gender
- Primary Malignancy
- ECOG performance status
- Worst pain score at baseline
- SINS score.

Sensitivity analyses:

- A sensitivity analysis for the complete pain response rate will be performed with the per protocol population in evaluable patients. (table 12b)

  Subgroup analysis: the primary analysis on primary endpoint will be performed based on patients' stratification factors at baseline, i. e. Histology (radioresistant vs. radiosensitive) And "Mass"* on imaging (present vs. absent) (Table 14) with interaction p-value to tell if any diffrtential treatment effect across levels of stratification factors.

2.5.2.2 Complete pain response at 6-month post treatment

The same analysis on complete response rate 3 months post treatment will be performed for the complete response rate 6 months post treatment (Table 15, 16).

2.5.2.3. Response to radiation treatment

The response to radiation treatment will be determined using the overall response rate (complete response and partial response) at 3 months assessment after radiation therapy. A table will be

provided to summary the number (percentage) of patients in each response category. All analysis performed for complete pain response will also be performed for pain response (Table 17, 18).

2.5.2.3 Radiation site progression-free survival (RSS PFS) at 3 and 6 months

K-M estimate of RSS PFS distribution will be displayed by treatment arm (Figure 1), and log-rank test stratified by stratification factors of Histology (radioresistant vs. radiosensitive) and "Mass" on imaging (present vs. absent) will be used to test the difference and Cox regression model stratified by the stratification factors will be used to estimate the HR and its 95% C.I. (table 19).
The 3 months and 6 months RSS PFS rate and its variance will be estimated from the K-M curves by treatment arm.
Subgroup analysis: RSS PFS will be performed based on patients' stratification factors at baseline, i. e. Histology (radioresistant vs. radiosensitive) and "Mass"* on imaging (present vs. absent) (Table 20) with interaction p-value to tell if any diffrtential treatment effect across levels of stratification factors.

2.5.2.4 SINS score at 3 and 6 months

Mean, SD, median, min, max of the SINS score changes at 3 months and 6 months after radiation treatment will be summarized. Wilcoxin rank sum test will be used to compare the difference between treatment arms in changes at 3 month and 6 month respectively (Table 21).
The analysis will be repeated for each of the 6 categories in SINS, i.e., by Location, Pain, Bone Lesion, Radiographic Spinal Alignment, Vertebral Body Collapse, and Posterolateral Involvement.(Table 21b).

2.5.2.5 Overall survival

K-M estimate of OS distribution will be displayed by treatment arm, and log-rank test stratified by stratification factors of Histology (radioresistant vs. radiosensitive) and "Mass" on imaging (present vs. absent) will be used to test the difference and Cox regression model stratified by the stratification factors will be used to estimate the HR and its 95% C.I. (table 22). For patients who died, their causes of death will be presented in table 23.
The 3 months and 6 months OS rate will be estimated from the K-M curves by treatment arm.
Subgroup analysis: OS will be performed based on patients' stratification factors at baseline, i. e. Histology (radioresistant vs. radiosensitive) and "Mass"* on imaging (present vs. absent) (Table 24) with interaction p-value to tell if any diffrtential treatment effect across levels of stratification factors.

2.6 RT Exposure

2.6.0 Time from randomization to start of RT

Mean, STD, median, min, max of the time from randomization to the date of starting RT in days, summarized by treatment arm (table 25a)

2.6.1 Treatment duration and dose

Mean, median, min, max of SBRT/CRT duration in days, and total RT dose received will be summarized by treatment arm. (table 25, 26)

2.6.2 Treatment compliance

Treatment compliance will be defined as the ability to plan and deliver the protocol specified radiotherapy according to prospectively defined criteria relating to dose and fractionation schedule.

Treatment compliance will be monitored on an ongoing basis by Central Office and the designated radiotherapy quality assurance reviewer and will be described for both arms.
A table will summarize whether radiation was given according to protocol specified dose and time schedules; present the number and percentage with minor, major deviation from RASIN. (Based on centre reported and central reviewed respectively). Table 27 and 28.

2.6.3 Concomitant Medications (followup)

Number and percent of patients with concomitant medication will be summarized by treatment arm. (Table 29).

2.6.3 Cancer Treatment (followup)

Number and percent of patients received cancer treatment will be summarized by treatment arm. (table 30)

2.7: Safety

2.7.1: Definitions and variables

All toxicity/side effects data collected post randomization will be included in the analyses of toxicities.

2.7.1.1: Adverse events during follow up

Adverse Events Related to RT reportyed at Follow-up Contact and experienced during follow-up will be summarized. (table 31). Of special interest, the number of patients who reported the vertebral fractures and spinal cord compression will be summarized by treatment arm (table 31b).

2.7.1.2 Serious adverse event

All serious adverse events (SAE) defined as per ICH guidelines and other adverse events must be recorded on case report forms. In addition, all “reportable” serious adverse events are subject to expedited reporting using the CCTG SAE form. The term ‘reportable SAE’ is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information provided in section 3.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol treatment cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

Serious adverse events that are both serious and unexpected and thought to be related to protocol treatment are CCTG reportable to a Health Canada. SAEs will be listed by treatment arm. (table 32).

Of specicial interest, the spinal adverse events will be presented by treatment arm.

2.8 Off study and death

Patients off-study (off protocol treatment): Number and % of all treated patients.
Reason for going off-study: Number and % of all treated patients will be presented. (Table 33)

Deaths within 30 days from the last treatment.

Cause of death within 30 days from the last treatment: Number and % of all treated patients will be presented by treatment arm. (table 34)

2.9 Quality of Life

2.9.1 Definitions and Variables

2.9.1.1 EORTC QLQ-C30

There are five functional domains and three symptom domains that can be derived from EORTC QLQ-C30 (see below for definitions). If the number of unanswered questions in each domain is within a limit specified with the definition for each domain, the score is calculated as for function domains:
Score=100-(((Total score for the answered questions/(no. of questions answered))-1)*100/3)
And for symptom domains:
Score = (((Total score for the answered questions/(no. of questions answered))-1)*100/3)
Otherwise, the score will be recorded as "missing". For each single item, the score will be recorded as "missing" if the answer to this item is missing.

Functional Domains:

- X Physical: Questions: 1, 2, 3, 4, 5
  Score=missing if number of above questions not answered is greater than 2;
- X Role: Questions: 6, 7
  Score=missing if number of above questions not answered is greater than 0;
- X Emotional: Questions: 21, 22, 23, 24
  Score=missing if number of above questions not answered is greater than 2;
- X Cognitive: Questions: 20, 25
  Score=missing if number of above questions not answered is greater than 0;
- X Social: Questions: 26, 27
  Score=missing if number of above questions not answered is greater than 0;

Symptom Domains:

- X Fatigue: Questions: 10, 12, 18
  Score=missing if number of above questions not answered is greater than 1;
- X Nausea and vomiting: Questions: 14, 15
  Score=missing if number of above questions not answered is greater than 0;
- X Pain: Questions: 9, 19
  Score=missing if number of above questions not answered is greater than 0.

There are also six single items in EORTC QLC-C30 pertaining to common symptoms and one global assessment that can be derived from EORTC QLQ-C30. The single items are:

Single Items:

- X Dyspnea: Question 8;
- X Sleep: Question 11;
- X Appetite: Question 13;
- X Constipation: Question 16;
- X Diarrhea: Question 17;
- X Financial: Question 28.

They are all scored using the following formula:
Score = (Answered score to the question-1)*100/3.

The **Global Assessment** includes Questions 29 and 30. If number of these two questions not answered is greater than 0, its score will be "missing"; Otherwise,

Score = ((Total scores for the answered questions/(no. of questions answered))-1)*100/6.

2.9.1.2 EORTC QLQ-BM22

The EORTC QLQ-BM22 addresses disease symptoms related to bone metastasis. This 22-item module is composed of four subscales, painful sites (PS) and pain characteristics (PC) on the symptom scale and functional interference (FI) and psychosocial aspects (PA) on the functional scale. All items were scaled from 1 (not at all) to 4 (very much), in which a higher score indicates greater distress in symptom scales while a higher score in functional scale indicates greater functional ability. Each scale will be converted to a score ranging from 0 to 100.

If the number of unanswered questions in each domain is within a limit specified with the definition for each domain, the score is calculated as:
Score = (((Total score for the answered questions/(no. of questions answered))-1)*100/3)
Otherwise, the score will be recorded as "missing".
While for FI and PA, the scores are:
Score=100-(((Total score for the answered questions/(no. of questions answered))-1)*100/3)

Functional Domains/Symptom Domains/Items:

- painful sites (PS): Questions: 31 - 35
  Score=missing if number of above questions not answered is greater than 2;
- pain characteristics (PC): Questions: 36-38
  Score=missing if number of above questions not answered is greater than 1;
- functional interference (FI): Questions: 39-46.
  Score=missing if number of above questions not answered is greater than 4;
- psychosocial aspects (PA): Questions: 47-52
  Score=missing if number of above questions not answered is greater than 3;

2.9.2 Analysis

All patients who have completed a baseline quality of life questionnaire (EORTC QLQ-C30 and QLQ-BM22) and at least one follow-up questionnaire are included quality of life analysis.

2.9.2.1 Determination of Assessment Times

The following will be the scheme to determining the time frame of a QoL assessment:

1) Baseline: Baseline evaluation is the QoL questionnaire collected closest, but no more than 7 days prior to, the date of randomization;
2) At week 4 after start of Radiotherapy: If the QoL is assessed within 2 weeks before or after the week 4 after start of Radiotherapy was given.
3) At 3 months after start of Radiotherapy: If the QoL is assessed within 4 weeks before or after the 3 months evaluation.
4) At 6 months after start of Radiotherapy: If the QoL is assessed within 4 weeks before or after the 6 months evaluation.

2.9.2.2 Calculation of Compliance Rates

The method used to calculate the compliance rates of QoL assessment (See Tables 35) is calculated as the number of forms received out of the number of forms expected at each assessment point defined based on the following principles:

1) At baseline: the number of forms expected is the total number of patients who are eligible for the study and required to fill out QoL questionnaires.
2) At 4 weeks , 3 months and 6 months after start of Radiotherapy: the number expected at the cycle is the total number of patients who submitted the baseline QoL form and were alive.

2.9.2.3 Cross-sectional analysis

The mean and standard deviation of QL scores at baseline (table 36) and mean and standard deviation of QoL change scores from baseline at each assessment time will be calculated (see Table 37). Then Wilcoxon Rank-Sum test is used to compare two treatment arms in terms of change in QOL score at each assessment time from baseline (see Table 37).

2.9.2.4 QoL Primary analysis

The primary end point for the QoL analysis is the mean score change (baseline to 3 months after treatment). Two samples t-test will be used to test whether the changes in QoL score was significantly different at 3 months after treatment between two treatment arms.

2.9.2.5 QoL response analysis

QOL response analysis is the CCTG QoL committee recommended analysis, and is calculated as follows: for a functional domain, a change score of 10 points from baseline was defined as clinically relevant. Patients were considered improved if reported a score 10-points or better than baseline at any time of QOL assessment. Conversely, patients were considered worsened if reported a score minus 10-points or worse than baseline at any time of QOL assessment without above defined 10-point improvement. Patients whose scores were between 10-point changes from baseline at every QOL assessment were considered as stable. In contrast to functional domains, for the determination of patient's QOL response, classification of patients into improved and worsened categories is revered for symptom domains and single items. Chi-square and Mantel-Haenszel chi-square test for trend is used to test if there is a trend that patients in one treatment arm have higher proportions in the better QoL categories than those on the other arm. (Table 38).

3 Tables

Table 1 Accrual by centre

Centre	Number of accrual (%)		
	SBRT N = ***	CRT N = ***	Total N = ***
xxxx	XX (XX)	XX (XX)	XX (XX)

Table 2: Accrual by Stratification Factors at Randomization

Data set: All Randomized Patients			
	Number of patients (%)		
	SBRT N = ***	CRT N = ***	Total N = ***
Histology :			
radioresistant	** (**)	** (**)	** (**)
radiosensitive	** (**)	** (**)	** (**)
"Mass"* on imaging			
Present	** (**)	** (**)	** (**)
Absent	** (**)	** (**)	** (**)
Source: Centralized Randomization File			

Table 3: Stratification factor at randomization vs. at baseline

Data set: All Randomized Patients			
	Number of patients (%)		
At randomization	At baseline	SBRT N = ***	CRT N = ***
Histology			
radioresistant	radioresistant	** (**)	** (**)
radioresistant	radiosensitive	** (**)	** (**)
radiosensitive	radioresistant	** (**)	** (**)
radiosensitive	radiosensitive	** (**)	** (**)
"Mass"* on imaging			
Present	Present	** (**)	** (**)
Present	Absent	** (**)	** (**)
Absent	Present	** (**)	** (**)
Absent	Absent	** (**)	** (**)

Table 4: Treatment received vs. Treatment randomized to receive

Data set: All Randomized Patients			
	Number of Patients (%) Randomized Arm		
	SBRT N=***	CRT N=***	Total N=***
Treatment Received			
SBRT	*** (**)	*** (**)	*** (**)
CRT	*** (**)	*** (**)	*** (**)
Not treated	*** (**)	*** (**)	*** (**)

Table 5: Eligibility status and Major Protocol Violations

Total patients allocated	SBRT N = ***	CRT N = ***	Total N = ***
Ineligible	XX (XX)		
Total eligible patients	XX (XX)		
REASONS FOR INELIGIBILITY			
Reason 1	XX (XX)		
Reason 2	XX (XX)		
Major Protocol Violations			
XXX			
XXX			

Table 6: Summary of Follow-up

Data set: All Randomized Patients			
	Number of patients		
	CRT N = ***	SBRT N = ***	Total N = ***
Median	***	***	***
Min	**	**	**
Max	**	**	**

Table 7: Patient characteristics

All randomized patients	SBRT N = ***	CRT N = ***	Total N = ***
AGE			
<=39	XX (XX)		
40-49	XX (XX)		
50-59			
60-69			
>=70	XX (XX)		
Median (Range)	XX (XX)		
Gender			
M			
F			
Primary Malignancy			
ECOG performance status			
Number of consecutive Spinal segments in target volume			
Worst pain score at baseline			
Prior spinal surgical/diagnostic procedures for cancer			
Y			
N			
Prior radiation therapy to their spine for cancer (Y vs N)			
SINS score (Median, min, max; mean, std, Also by categories: 0-6 vs 7 -12 vs 13 – 18)			

Opioid medications reported in the last 24 hours			
Epidural Disease Extent (Bilsky scale)			

***Table 8:** Baseline signs and symptoms*

Data set: All Randomized Patients (SBRT Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with any sign/symptom at baseline	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with particular sign or symptom, within body system:						
Body System 1(1)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Body System 2(1)						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a body system

NOTE: Same table to be made for CRT Arm

Table 9: Baseline Concomitant Medications

Data set: All Randomized Patients			
	Number of patients (%)		
	SBRT N=***	CRT N=***	Total N=***
Any concomitant medication at baseline [(1)]			
No	** (**)	** (**)	** (**)
Yes	** (**)	** (**)	** (**)

[(1)] Any con meds taken within 24 hours prior to the Day 0 treatment assessment

Table 10: Baseline Cancer Treatment

Data set: All randomized Patients			
	Number of patients		
	SBRT N = ***	CRT N = ***	Total N = ***
Yes	** (**)	** (**)	** (**)
No	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)

Table 11: Reasons for in-evaluable for Pain Response

Data set: All Randomized Patients			
Reasons for inevaluable for Pain response	Number of patients		
	SBRT N = ***	CRT N = ***	Total N = ***
***	***	***	***
***	**	**	**
***	**	**	**

Table 12: Complete pain response at 3-month after treatment (ITT)

Data set: All Randomized Patients			
Response Status	Number of patients		
	SBRT N = ***	CRT N = ***	Total N = ***
CR	***	***	***
PR	***	***	***
SD	***	***	***
PD	***	***	***
Inevaluable	***	***	***

Table 12b: Complete pain response at 3-month after treatment (per protocol and evaluable patients)

Table 13: Cochran Mantel Haenszel and Logistic Regression Model for Complete response rate 3-month post treatment

Data set: All Randomized Patients

	Univariate Analysis [1]		Multivariate Analysis [2]	
Treatment/ Prognostic Factc	Odds Ratio (95%CI)	CMH p-vlaue	Odds Ratio (95% C.I.	p-value from logisti regression
Treatment arm		0.***		0.***
SBRT : CRT	**.** (**.**,**.*		**.** (**.**,**.*	
Prognostic factor 1		0.***		0.***
Level 1: level 2	NC [3]		**.** (**.**,**.*	
Prognostic factor 2		0.***		0.***
Level 1: level 2	NC		**.** (**.**,**.*	
Prognostic factor 3		0.***		0.***
Level 1: level 2	NC		**.** (**.**,**.*	
…		0.***		0.***
...	NC		**.** (**.**,**.*	

(1) Stratified by stratification factors
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

Table 14: Complete Response rate at 3-month after treatment According to Baseline Stratification Factors

	Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)		
	SBRT N=***	*CRT* N=***	*Int-P-value*
Histology			0.**
radioresistant	**/** (**)	**/** (**)	
radiosensitive	**/** (**)	**/** (**)	
"Mass"* on imaging			
Present	**/** (**)	**/** (**)	0.**
Absent	**/** (**)	**/** (**)	

Table 15: Cochran Mantel Haenszel and Logistic Regression Model for Complete response rate 3 months post treatment

Data set: All Randomized Patients

	Univariate Analysis (1)		Multivariate Analysis (2)	
Treatment/ Prognostic Factc	Odds Ratio (95%CI)	CMH p-vlaue	Odds Ratio (95% C.I.	p-value from logisti regression
Treatment arm		0.***		0.***
SBRT : CRT	**.** (**.**,**.*		**.** (**.**,**.*	
Prognostic factor 1		0.***		0.***
Level 1: level 2	NC (3)		**.** (**.**,**.*	
Prognostic factor 2		0.***		0.***
Level 1: level 2	NC		**.** (**.**,**.*	
Prognostic factor 3		0.***		0.***
Level 1: level 2	NC		**.** (**.**,**.*	

…		0.***		0.***
...	NC		**.** (**.**,**.*	

(1) Stratified by stratification factors
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

Table 16: Complete Response rate 3-month after treatment According to Baseline Stratification Factors

	Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)		
	SBRT N=***	*CRT* N=***	*Int-P-value*
Histology			0.**
radioresistant	**/** (**)	**/** (**)	
radiosensitive	**/** (**)	**/** (**)	
"Mass"* on imaging			
Present	**/** (**)	**/** (**)	0.**
Absent	**/** (**)	**/** (**)	

Table 17: Cochran Mantel Haenszel and Logistic Regression Model for Response rate 3-month post treatment

Data set: All Randomized Patients

	Univariate Analysis (1)		Multivariate Analysis (2)	
Treatment/ Prognostic Factc	Odds Ratio (95%CI)	CMH p-vlaue	Odds Ratio (95% C.I.	p-value from logisti regression
Treatment arm		0.***		0.***
SBRT : CRT	**.** (**.**,**.*		**.** (**.**,**.*	
Prognostic factor 1		0.***		0.***
Level 1: level 2	NC (3)		**.**	

			(**.**;**.*	
Prognostic factor 2		0.***		0.***
Level 1: level 2	NC		**.** (**.**;**.*	
Prognostic factor 3		0.***		0.***
Level 1: level 2	NC		**.** (**.**;**.*	
…		0.***		0.***
...	NC		**.** (**.**;**.*	

(1) Stratified by stratification factors
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

Table 18: Response rate 3-month after treatment According to Baseline Stratification Factors

	Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)		
	SBRT N=***	*CRT* N=***	*Int-P-value*
Histology			0.**
radioresistant	**/** (**)	**/** (**)	
radiosensitive	**/** (**)	**/** (**)	
"Mass"* on imaging			
Present	**/** (**)	**/** (**)	0.**
Absent	**/** (**)	**/** (**)	

Table 19: Log rank and Cox Regression Model for Radiation site Progression Free Survival

Data set: All Randomized Patients

		Univariate Analysis[1]		Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors : Baseline	Median PFS (Months)	Hazard Ratio[4] (95% CI)	Log-ran p-vlaue	Hazard Ratio[4] (95% C.I.)	P-vlaue from Cox regression
Treatment arm			†0.***		0.***
SBRT	**.**	**.**		**.**	
CRT	**.**	(**.**,**.**		(**.**,**.*	
Prognostic factor 1			0.***		0.***
Level 1	**.**	NC [3]		**.**	
Level 2	**.**			(**.**,**.*	
Prognostic factor 2			0.***		0.***
Level 1	**.**	NC		**.**	
Level 2	**.**			(**.**,**.*	
Prognostic factor 3			0.***		0.***
Level 1	**.**	NC		**.**	
Level 2	**.**			(**.**,**.*	
…			0.***		0.***
…	**.**	NC		**.**	
…	**.**			(**.**,**.*	

(1) Stratified
(2) Stratified Cox regression with all factors included
(3) NC = not computed
(4) Hazard ratio of first category over second category

Table 20: Radiation site Progression Free Survival by Subsets

Data set: All Randomized Patients

Factors	Value	N	SBRT Median RSS PFS 95% C.I.	N	CRT Median RSS PFS 95% C.I.	Hazard Ratio(1) 95% C.I.	P-value Interactio
Histology	Radioresistant	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.***
	Radiosensitive	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
"Mass"* on imaging	Present	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.***
	Absent	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	

Table 21: Change in SINS score at 3 and 6 months

Data set: All treated Patients

	Number of patients			
Change in SINS at 3 months	SBRT N = ***	CRT N = ***	Total N = ***	P-value
Median	*.**	*.**	*.**	0.***
Min	*.**	*.**	*.**	
Max	*.**	*.**	*.**	
Mean	*.**	*.**	*.**	
SD	*.**	*.**	*.**	
Change in SINS at 6 months	SBRT N = ***	CRT N = ***	Total N = ***	
Median	*.**	*.**	*.**	0.***
Min	*.**	*.**	*.**	
Max	*.**	*.**	*.**	
Mean	*.**	*.**	*.**	
SD	*.**	*.**	*.**	

Table 21b: Change in SINS score for each of the 6 categories at 3 and 6 months

The same as table 21 for each of the 6 categories in SINS score.

Table 22: Log rank and Cox Regression Model for Overall Survival

Data set: All Randomized Patients

		Univariate Analysis[1]		Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors at Baseline	Median PFS (Months)	Hazard Ratio[4] (95% CI)	Log-ran p-vlaue	Hazard Ratio[4] (95% C.I.)	P-vlaue from Cox regression
Treatment arm			†0.***		0.***
SBRT	**.**	**.**		**.**	
CRT	**.**	(**.**,**.**		(**.**,**.*	
Prognostic factor 1			0.***		0.***
Level 1	**.**	NC [3]		**.**	
Level 2	**.**			(**.**,**.*	
Prognostic factor 2			0.***		0.***
Level 1	**.**	NC		**.**	
Level 2	**.**			(**.**,**.*	
Prognostic factor 3			0.***		0.***
Level 1	**.**	NC		**.**	
Level 2	**.**			(**.**,**.*	
…			0.***		0.***
…	**.**	NC		**.**	
…	**.**			(**.**,**.*	

(1) Stratified
(2) Stratified Cox regression with all factors included
(3) NC = not computed
(4) Hazard ratio of first category over second category

Table 23: Death Summary

Data set: All Randomized Patients		
	Number of Patients (%)	
	SBRT N=***	CRT N=***
Patients who died	*** (**)	*** (**)
Disease	*** (**)	*** (**)
Disease/treatment complication	*** (**)	*** (**)
Other	*** (**)	*** (**)

Table 24: Overall Survival by Subsets

Data set: All Randomized Patients

Factors	Value	N	SBRT Median Survival 95% C.I.	N	CRT Median Survival 95% C.I.	Hazard Ratio[(1)] 95% C.I.	P-value Interactio
Histology	Radioresistant	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.***
	Radiosensitive	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
"Mass"* on imaging	Present	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.***
	Absent	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	

Table 25a: Time from randomization to start of SBRT/CRT

Data set: All treated Patients			
	Number of patients		
	SBRT N = ***	CRT N = ***	Total N = ***
Median	*.**	*.**	*.**
Min	*.**	*.**	*.**
Max	*.**	*.**	*.**
Mean	*.**	*.**	*.**
SD	*.**	*.**	*.**

Table 25: SBRT/CRT duration

Data set: All treated Patients			
	Number of patients		
	SBRT N = ***	CRT N = ***	Total N = ***
Median	*.**	*.**	*.**
Min	*.**	*.**	*.**
Max	*.**	*.**	*.**
Mean	*.**	*.**	*.**
SD	*.**	*.**	*.**

Table26: Total RT dose

Data set: All treated Patients			
	Number of patients		
	CRT N = ***	SBRT N = ***	Total N = ***
Median	*** (Gy)	***	***
Min	**	**	**
Max	**	**	**
Mean	**	**	**
SD	**	**	**

Table 27: Contouring and Dosimetry – Quality Assurance

	Data set: All Treated Patients (SBRT Arm)			
		Number of patients (%) N=***(%)		
Contoured Volumes	-	Compliance Rating*		
	1	2	8	9
Spinal metastases PTV				
Spinal Cord/Spinal Cord PRV				
Thecal Sac				
Kidney Left				
Kidney Right				
Trachea				
Liver				
Lung Left				
Lung Right				
Pharynx				
Larynx				
Parotid Left				
Parotid Right				
Nerve roots for sacral tumors (S1-S5)				
Other relevant organs, please specify:				

(1) Patients may have more than one category of deviations.

1 - Per Protocol 2 - Not Per Protocol 8- Not applicable 9-Unevaluable

Table 28: Contouring and Dosimetry – Quality Assurance

	Data set: All Treated Patients (SBRT Arm)				
		Number of patients (%) N=***(%)			
SBRT Dosimetry	Compliance Rating*				
	1	2	3	8	9
Spinal metastases PTV 24 Gy					
Dose heterogeneity in the PTV not adjacent to the cordPRV/thecal sac					
Spinal Cord PRV					
Thecal Sac					
Trachea					
Kidney Left					
Kidney Right					
Liver					
Lung Left					
Lung Right					
Pharynx					
Larynx					
Parotid Left					
Parotid Right					
Nerve roots for sacral tumors (S1-S5)					
Other relevant organs, please specify: _____					
Treatment duration					

***1 - Per Protocol 2 –Minor deviation 3-Major deviation 8- Not applicable 9 - Unevaluable**

Table 29: Concomitant Medication (follow-up)

Data set: All randomized Patients			
	Number of patients		
	CRT N = ***	SBRT N = ***	Total N = ***
Yes	**	**	**
No	**	**	**
Unknown			

Table 30: Cancer Treatment (followup)

Data set: All randomized Patients			
	Number of patients		
	CRT N = ***	SBRT N = ***	Total N = ***
Yes	**	**	**
No	**	**	**

Table 31: Adverse Events/Intercurrent Illness (Worst Ever Grade on study)

Data set: All Treated Patients (SBRT Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with any AE	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE within category						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1(1)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2(1)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						

(1) Patients may have more than one event within a category.

NOTE: In CRT Arm, the same type of table will be made.

Table 32. Serious Adverse Events

Data set: All Treated Patients (SBRT Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with serious AE within category						
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Patients with fatal AE within category						
Category 1[(1)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Patients with AE leading to hospitalization within category						
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a category.

NOTE: In CRT Arm, the same type of table will be made.

Table 32b: Spinal adverse events

Treatment arms	# Fractures		# Compressions	
	All sites	Treated sites	All sites	Treated sites
CRT	**	**(%)	**	**(%)
SBRT	**	**(%)	**	**(%)

Table 33: Off protocol treatment

Data set: All Randomized Patients			
Off treatment	Number of patients		
	SBRT N = ***	CRT N = ***	Total N = ***
Cause1	***	***	***
2	**	**	**
3			
4			

Table 34: Death within 30 days of last treatment

Data set: All Randomized Patients			
Cause of Death	Number of patients		
	SBRT N = ***	CRT N = ***	Total N = ***
Cause1	***	***	***
2	**	**	**
3			
4			

Table 35: Compliance (received/expected) with QoL assessment by treatment arm

	SBRT		CRT	
Period	Expected	Received (%)	Expected	Received (%)
Baseline	***	*** (**.*)	***	*** (**.*)
At 4 weeks	***	*** (**.*)	***	*** (**.*)
At 3 Months	***	*** (**.*)	***	*** (**.*)
At 6 Months	***	*** (**.*)	***	*** (**.*)

Table 36: Baseline score for each domain/item

Domain/item		SBRT	CRT	P-value
Physical	N	***	***	0.**
	MEAN	**.**	**.**	
	STD DEV	**.**	**.**	
Emotional	N	***	***	0.**
	MEAN	**.**	**.**	
	STD DEV	**.**	**.**	
…	N	***	***	0.**
	MEAN	**.**	**.**	
	STD DEV	**.**	*.**	

Table 37: Mean QOL change scores from baseline for global domain at each assessment time

		SBRT		CRT	
Assessment	N	Mean (SD)	N	Mean (SD)	P value*
At 4 weeks	***	**.** (**.**)	***	**.** (**.**)	0.**
At 3 Months	***	**.** (**.**)	***	**.** (**.**)	0.**
At 6 Months	***	**.** (**.**)	***	**.** (**.**)	0.**

*Wilcoxon test.

(There will be one table for each domain/item).

Table 38: Results for QOL response analyses

Domain	SBRT Improved N (%)	SBRT Stable N (%)	SBRT Worsen N (%)	CRT Improved N (%)	CRT Stable N (%)	CRT Worsen N (%)	Chi-squ P-value	M-H Trend p-value
EORTC QLQ-C30								
Physical	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Role	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Emotional	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Cognitive	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Social	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Global	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Pain	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Fatigue	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Nausea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Dyspnea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Sleep	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Appetite	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Constipation	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Diarrhea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
Financial	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
EORTC QLQ-BM22								
painful sites	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
pain characteristics	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
functional interference	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	
psychosocial aspects	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**	