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CLINICAL INVESTIGATION

Impact of Short-Course Palliative Radiation Therapy on Pancreatic Cancer-Related Pain: Prospective Phase 2 Nonrandomized PAINPANC Trial

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Purpose: Clinical evidence is limited regarding palliative radiation therapy for relieving pancreatic cancer-related pain. We prospectively investigated pain response after short-course palliative radiation therapy in patients with moderate-to-severe pancreatic cancer-related pain.

Methods and Materials: In this prospective phase 2 single center nonrandomized trial, 30 patients with moderate-to-severe pain (5-10, on a 0-10 scale) of pancreatic cancer refractory to pain medication, were treated with a short-course palliative radiation therapy; 24 Gy in 3 weekly fractions (2015-2018). Primary endpoint was defined as a clinically relevant average decrease of ≥2 points in pain severity, compared with baseline, within 7 weeks after the start of treatment. Secondary endpoint was global quality of life (QoL), with a clinically relevant increase of 5 to 10 points (0-100 scale). Pain severity reduction and QoL were assessed 9 times using the Brief Pain Inventory and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C15-PAL, respectively. Both outcomes were analyzed using joint modeling. In addition, acute toxicity based on clinician reporting and overall survival (OS) were assessed.

Results: Overall, 29 of 30 patients (96.7%) received palliative radiation therapy. At baseline, the median oral morphine equivalent daily dose was 129.5 mg (range, 20.0-540.0 mg), which decreased to 75.0 mg (range, 15.0-360.0 mg) after radiation (P = .021). Pain decreased on average 3.15 points from baseline to 7 weeks (one-sided P = .045). Patients reported a clinically relevant mean pain severity reduction from 5.9 to 3.8 points (P = .011) during the first 3 weeks, which further decreased to 3.2

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until week 11, ending at 3.4 (P = .006) in week 21 after the first radiation therapy fraction. Global QoL significantly improved from 50.5 to 60.8 during the follow-up period (P = .001). Grade 3 acute toxicity occurred in 3 patients and no grade 4 to 5 toxicity was observed. Median OS was 11.8 weeks, with a 13.3% 1-year actuarial OS rate.

Conclusions: Short-course palliative radiation therapy for pancreatic cancer-related pain was associated with rapid, clinically relevant reduction in pain severity, and clinically relevant improvement in global QoL, with mostly mild toxicity.

Introduction

Pancreatic cancer is the seventh leading cause of cancer worldwide, accounting for nearly as many new deaths as new cases due to its poor prognosis.[1] The majority of patients (70%-80%) report pain due to tumor infiltration into the celiac plexus, ductal obstruction or distension, and inflammation in the surrounding tissue during the course of their disease.[2-5] This pain is typically located in the epigastric region or radiates to the back.[2,3,5] The severity of the pain may differ from moderate to severe and is a challenge to manage.[2-4] Overall, along with other symptoms of advanced disease, this leads to reduced performance status and poor overall quality of life (QoL).[2-4]

Different treatment modalities can be used for pain management, such as pharmacologic treatments, chemotherapy or radiation therapy, and celiac plexus block.[3-7] Opioids can be considered to manage moderate-to-severe refractory pancreatic pain.[6-8] However, the use of strong opioids as part of the treatment can cause side effects in many patients which may lead to severely decreased QoL.[9] Using radiation therapy, the cancer-related pain may be reduced, with a possible reduction of the required opioid dose, ultimately resulting in an improvement of QoL.[9]

A number of studies aiming to improve local control and/or overall survival, have suggested that pancreatic cancer pain may decrease after administering high dose radiotherapy.[10-17] Good-quality evidence regarding pain relief using a short-course palliative radiation therapy in patients with pancreatic cancer is limited. Only a few prospective observational studies, with pain as primary outcome, suggested an improvement of pain after a short-course palliative radiotherapy.[18-20] Unfortunately, these studies employed a very limited number of assessments precluding the evaluation of the evolution of pain severity before, during and after palliative radiation therapy. More detailed assessment of the rapidity and extent of radiation therapy-induced pain relief is extremely relevant in view of the often short life expectancy for these patients.

Improvement of pain may have a positive effect on other domains of QoL.[21] Therefore, including the patient perspective is important in clinical studies and incorporating validated suitable patient-reported outcome measures (PROMs) may aid in monitoring the course in pain severity reduction and QoL over time.[21,22] PROMs are particularly important in patients with poor life expectancy, and thus in the palliative setting.[9,21,22]

Despite the necessity of well-timed assessments,[23] no previous studies investigated the effect of radiation therapy on pain and/or QoL at multiple time points during and after radiation therapy in pancreatic cancer patients. The aim of this prospective phase 2 nonrandomized trial was to assess pain severity reduction, the primary outcome, and global QoL, secondary outcome, at multiple frequently repeated time points during short-course palliative radiation therapy and follow-up, using validated PROMs in patients with pancreatic cancer-related pain refractory to pain medication. Furthermore, acute toxicity and OS were also investigated.

Methods and Materials

Study design and population

A prospective phase 2 single center nonrandomized trial was conducted at the Amsterdam UMC (University Medical Centers). The protocol was approved by the ethics committee on August 24, 2015 (NR:191#C20151591). The study was performed in accordance with the declaration of Helsinki and registered in the Netherlands Trial Register as the PAIN-PANC study (NTR5143). The "strengthening the reporting of observational studies in epidemiology" (STROBE) checklist for cohort studies was used to prepare this article.

Eligible patients with painful pancreatic cancer, who gave written informed consent, were treated with a short-course palliative radiation therapy between 2015 and 2018. Included patients received a diagnosis of primary or recurrent, irresectable pancreatic cancer with or without distant metastases, according to the seventh edition of the Union for International Cancer Control's staging guidelines.[24] All patients had a pathologically confirmed adenocarcinoma of the pancreas and a diagnostic computed tomography (CT) scan ≤3 months before study entry; refractory cancer-related pain score ≥5 (0-10 scale), difficult to manage with oral opioids or celiac plexus block; ≥18 years of age; World Health Organization performance status ≤2 and had received their last chemotherapy ≥14 days before the start of radiation therapy. Exclusion criteria were resectable or borderline resectable tumors without distant metastases, neuroendocrine pancreatic cancer, suspicion of metastases from another malignancy in the pancreas, pregnancy, and no previous radiation therapy of the abdomen was allowed.

Treatment

Before the radiation therapy, all patients underwent a planning computed tomography (CT) scan from the thorax to

the groin with a slice thickness of 2.5 mm. Patients were placed in a supine position with their arms raised above the head. No vascular contrast was used, and the diagnostic imaging was fused for target delineation. The planning CT scan was acquired using a GE LightSpeed RT16 scanner (General Electric Co). Because it was a palliative treatment, no motion management was used during simulation, nor during treatment, but generous clinical target volume-planning target volume (PTV) margins of 2 cm in craniocaudal direction were applied. Radiation therapy consisted of short-course radiation therapy of 24 Gy in 3 fractions of 8 Gy, once weekly (on day 1, 8, and 15).[25]

The treating radiation oncologist delineated the target volumes. The gross tumor volume included the tumor and fat infiltration. The clinical target volume included the gross tumor volume with 5 mm margin. PTV was defined by adding 10 mm margin in anteroposterior and lateral directions, and 20 mm in craniocaudal direction. The kidneys, liver, duodenum, and spinal cord were delineated as organs at risks.

The treatment was delivered by intensity modulated radiation therapy or volumetric-modulated arc therapy with 6 to 10 MV photons using a 4- or 5-field technique and 1 or 2 arcs, respectively. According to the International Commission on Radiation Units and Measurements guidelines; at least 95% of the prescribed dose should cover ≥99% of the PTV.[26] The treatment planning was homogenous, with a minimum dose of 95% in the PTV and a maximum dose of 107%. The Quantitative Analyses of Normal Tissue Effects in the Clinic criteria were used to define dose constraints for organs at risks.[27] The dose constraints to the spinal cord, stomach, small bowels, and liver were not met with this prescribed dose, and both kidneys were spared as much as possible. Radiation therapy had to be started within 1 week after inclusion, and patients were seen by the radiation oncologist before the second and third fraction.

During the course of radiation therapy, antiemetics and proton pump inhibitors were prescribed to all patients. In case of any grade 3 or 4 acute toxicity, according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), potential discontinuation of radiation therapy was discussed with the patient.

Study endpoints/assessments

The primary endpoint, pain severity reduction, was measured with the Brief Pain Inventory (BPI) Dutch version.[28] The BPI Dutch version measures pain severity (3 items), the effect of pain on functioning (interference; 7 items), and also the location of pain (that respondents can indicate on a picture; Fig. E1). The response scale ranges from 0 to 10 (no pain −worst possible pain or no interference-complete interference). A pain severity score was calculated from the mean of the 3 pain severity items and a pain interference score from the mean of the 7 pain interference items. An average decrease of ≥2 points, compared with the baseline, within 7 weeks after the start of treatment, was considered clinically significant. This definition was based on literature and Amsterdam UMC experience with palliative radiation.[29,30] Besides, the Dutch federation of medical specialists defined that a decrease of minimally 2 points, on the scale of 0 to 10, is considered clinically relevant for patients with pancreatic cancer.[31] In addition, the proportion of patients who reported pain reduction of at least 2 points until death or last follow-up were collected from patient charts.

The secondary endpoint, global QoL, was measured with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C15-PAL (EORTC QLQ-C15-PAL).[32] The QLQ-C15-PAL, developed for patients with cancer in palliative care, consists of 15 questions, including 2 multi-item functional scales (physical and emotional functioning), 2 multi-item symptom scales (fatigue and pain), 5 single symptom items (nausea/vomiting, dyspnea, insomnia, appetite loss, and constipation), and a question regarding overall QoL (global health status). All scales were transformed to range from 0 to 100 according to the QLQ-PAL-15 scoring manual.[33] Higher scores for functional scales or global QoL indicate better functioning/global QoL, whereas for symptom scales, higher scores indicate more symptoms. Significant increase over time of minimally 5 to 10 points were considered clinically important.[34]

The BPI and EORTC QLQ-C15-PAL were administered at 9 time points: at baseline (defined as before the start of the radiation therapy), before the second and third radiation therapy fraction, and at 4, 5, 7, 11, and 19 weeks after the first radiation therapy fraction, and every 3 months thereafter if the patient was still alive.

OS was calculated from the date of inclusion until death, with death from any cause as an event. Patients alive were censored at the last follow-up. Acute toxicity based on clinician reporting was defined according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) and considered acute when occurring within 3 months.[35]

Sample size and statistical analysis

The primary endpoint was defined as a clinically relevant average decrease of ≥2 points in pain severity, compared with baseline, within 7 weeks after the start of treatment. Assuming a large effect size (standardized mean difference) of 0.8, an alpha level of 0.05 and power equal to 0.80, we had calculated that 12 patients were required to identify a mean change between baseline and 7 weeks pain severity reduction based on a one-sided paired t test.[29] We assumed that half of the patients would be lost by seventh week, meaning that 24 patients were required, and increased the sample size by 25% to account for potential loss to follow-up, and ultimately 30 patients were recruited (Fig. 1). We performed a power calculation to support an extension to the primary outcome analysis based on a joint model, assuming a small to medium association between the survival and longitudinal outcome effect, a sample size of 30 patients, similar death and loss to follow-up rates and an α of 0.05, the calculated power of a joint model equals to 0.96.[36] Furthermore, to check the

robustness of our analysis a sensitivity analysis assuming a worst-case scenario was performed, assuming that all patients lost to follow-up had an increase of 20% to 40% in BPI pain severity at their following time point.[37-39]

Patient and clinical characteristics are presented with means and standard deviations, or count-percentages. PROMs and acute toxicity are presented by descriptive statistics. The actuarial Kaplan-Meier method was used for assessing OS.

Inherent to the nature of locally advanced or recurrent pancreatic cancer, many patients deteriorated and died within several months, leading to many missing data points. Although it is difficult to formally test the pattern of missingness, it may very well be assumed that the missing is missing-not-at-random (MNAR), and the missing data mechanism could be associated with the main outcomes. More specifically, we assumed that missing (censored or deceased) patients would have had increased pain severity and poorer QoL in comparison to patients who provided data at follow-up. As a result, traditional mixed models were deemed not appropriate, and this informative missingness is the main reason why joint modeling was used. This technique allows integration of longitudinal data, which includes repeated measurements of patients and the MNAR patterns over time, and time-to-event data, that represent the expected time before death occurs.[40-42] By using joint modeling, it allows correction for possible biases due to informed missingness and to investigate the association between PROMs and survival. Two covariates were included in the model that are clinically known to influence the outcomes: the radiation therapy scheme (<24 Gy/24 Gy) and an increase of ≥25% in the prescription of opioids medication. The joint model produced a traditional output of a Cox regression and a mixed model, that can be interpreted as such. All analyses were performed based on intention-to-treat. The joint modeling analyses of QoL were kept similar to that of the pain severity for more clarity.

We performed all the analysis using R (version 4.2.1) with packages JM and JMbayes2, and JMdesign (version 1.5-2; 0.3-0; 1.3), survival, and survminer (version 3.4-0; 0.4.9). The primary endpoint analysis was based on a 1-sided t test, and the joint model-based tests are 2-sided. All tests were considered statistically significant at $P < .05$.

Results

Study population

A total of 30 eligible patients gave informed consent and were enrolled in the study (Fig. 1). Of these, 29 patients received palliative radiation therapy as one patient died before the start of radiation therapy. Baseline patient, tumor, and treatment characteristics are summarized in Table 1. At baseline, the average BPI pain severity score was 6 (scale 0-10). The vast majority of the patients had a World Health Organization performance status ≥1 (n = 27, 90%), 56.7% (n = 17) had metastatic disease, and in 63.3% (n = 19) the tumor was located in the head of the pancreas. Eight patients (26.7%) did not receive the total dose of 24 Gy due to clinical deterioration or tumor progression.

Pain management

Of all patients receiving radiation therapy, a reduction in pain medication was possible in 16 patients (55.2%) during

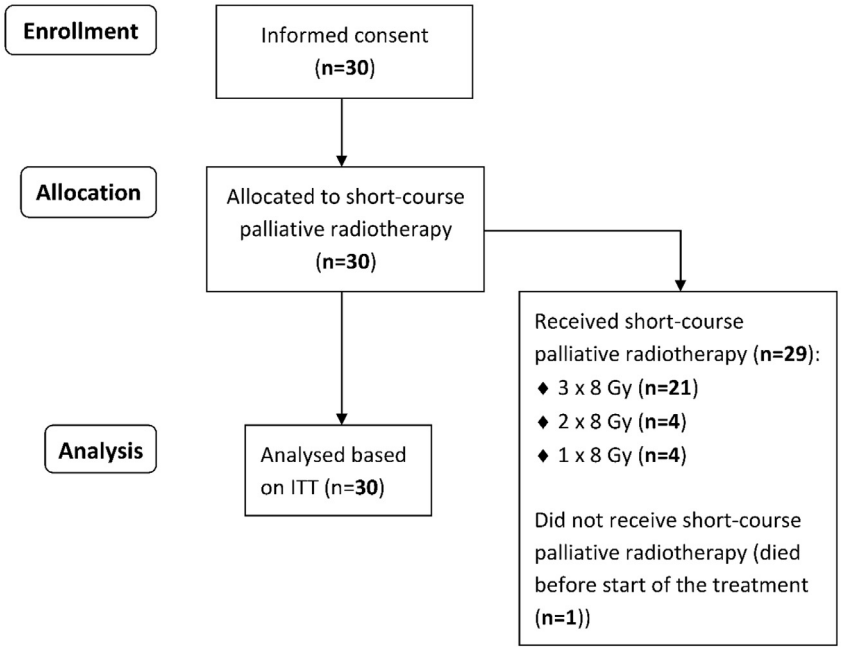

Fig. 1. PAINPANC flowchart. *Abbreviation:* ITT = intention-to-treat.

Table 1 Baseline characteristics

Characteristic	n = 30
Age, y	61.5 (45.0-84.0)
Sex	
Male	17 (56.7%)
Female	13 (43.3%)
WHO performance status	
0	3 (10.0%)
1	14 (46.7%)
2	13 (43.3%)
Pain severity BPI*	5.9 (5.1-6.7)†
Tumor location	
Head	19 (63.3%)
Body	6 (20.0%)
Tail	5 (16.7%)
Distant metastases	
Yes	17 (56.7%)
No	13 (43.3%)
Chemotherapy‡	
Yes	16 (53.3%)
No	14 (46.7%)
Radiation therapy technique	
IMRT	6 (20.0%)
VMAT	24 (80.0%)
Planning target volume	472 cc (215.0-1305.0)
Total Radiation therapy dose§	
1 × 8 Gy	4 (14.4%)
2 × 8 Gy	4 (14.4%)
3 × 8 Gy	21 (71.2%)
Nonopioid medication	
PCM	18 (60.0%)
NSAID	2 (6.7%)
Both	7 (23.3%)
None	3 (10.0%)
Opioids‖	
Yes	28 (93.3%)
No	2 (6.7%)
OMED, mg	129.5 (20.0-540.0)

Values are presented as the mean (95% confidence interval)*; median (range) or number of patients (%).

† Pain score before the first radiation therapy fraction.
‡ ≥14 days before the start of radiation therapy.
§ Data missing for one patient.
‖ Prescribed opioids = fentanyl 25-150 mcg, morphine 60-480 mg, and oxycodone 5-130 mg.
Abbreviations: BPI = brief pain inventory; IMRT = intensity-modulated radiation therapy; OMED = oral morphine equivalent dose; PCM = paracetamol; VMAT = volumetric-modulated arc therapy; WHO = world health organization.

the treatment and follow-up. In 6 patients (20.7%), the pain medication remained unchanged, and 5 patients (17.2%) required ≥25% increase in the prescription of opioids medication, of whom 3 patients reported a decrease of pain medication during the follow-up. The adjustment of pain medication was unknown in 2 patients (6.9%), both received only one radiation therapy fraction. The location of the pain varied (Fig. E1) and was most often felt in the back. Twenty-eight patients (93.3%) used strong opioids with a median oral morphine equivalent daily dose of 129.5 mg (range, 20.0-540.0 mg) at baseline. After radiation, the median oral morphine equivalent dose was 75.0 mg (range, 15.0-360.0 mg; $P = .021$).

Based on the patient charts, a total of 24 patients (80.0%) reported pain reduction of ≥2 points, 21 (70.0%) until death or last follow-up. In 3 patients, the pain reduction was temporary. The pain increased again after 3, 4, and 5 weeks, respectively. Three patients (10.0%) had an increase in pain severity, and in 2 patients (6.7%) the pain remained unchanged. The mean change from baseline to 7 weeks showed a decrease of 3.15 points in pain on average ($P = .045$).

Pain severity reduction

The baseline and follow-up pain severity scores are presented for each assessment per patient as well as the median scores per time point in Figure E2. Additionally, the raw data for pain severity are presented in Figure E4.

The joint model showed a clinically relevant decrease in pain severity score from 5.9 to 3.8 (Table 2; $P = .011$) between baseline and 3 weeks after the first radiation therapy fraction, that continued to decrease to 3.2 until week 11. From week 12 up to week 21, pain severity slightly increased to 3.4 ($P = .006$) and continued to increase to 4.7 up in week 31 ($P = .971$). The joint model predicted average clinical pain severity over time and is illustrated in Figure 2A.

The sensitivity analysis assuming a 20% to 40% increase in BPI pain severity showed that the adjusted joint model retained a similar shape, and the one-sided paired t test remained marginally significant ($P = .047$).

Global quality of life

The baseline and follow-up global QoL scores are presented for each assessment per patient as well as the median scores per time point in Figure E3. Additionally, the raw data for pain severity are presented in Figure E4.

Between baseline and 5 weeks after the first fraction of radiation therapy, the joint model showed a clinically relevant improvement of global QoL from 50.5 to 55.5 (Table 2; $P = .035$). At week 21, the mean global QoL increased by 10 points up to 60.8 ($P = .001$). Figure 2B illustrates the predicted average clinical global QoL over time. The joint model showed that patients treated with 3 radiation therapy fractions reported better global QoL compared with patients

Table 2 Pain severity and quality of life scores at several time points

		BPI		EORTC QLQ-C15-PAL	
		Severity*		Global QoL†	
Assessment time points	n	Mean	95% CI	Mean	95% CI
Baseline	30	5.9	5.1-6.7	50.5	45.8-54.5
1 wk	28	4.9	4.3-5.6	52.1	48.3-56.1
2 wk	27	4.2	3.6-4.9	53.4	49.2-58.0
4 wk	25	3.6‡	2.9-4.4	54.9	50.6-59.7
5 wk	25	3.5‡	2.8-4.3	55.5‡	51.2-60.0
7 wk	24	3.3‡	2.5-4.3	56.3‡	52.2-60.4
11 wk	17	3.2‡	2.1-4.4	57.8‡	53.4-62.0
19 wk	11	3.4‡	2.0-5.4	60.0‡	54.9-64.6
31 wk	7	4.7	2.2-8.1	62.0‡	55.9-70.4

* Scores range from 0-10. Lower scores indicate less pain severity.
† Scores range from 0-100. Higher scores indicate better global quality of life.
‡ Clinically relevant. Values from joint model are reported as means and 95% CI.
Joint model results after adjusting for radiation therapy scheme
(<24 Gy/24 Gy) and increase of ≥25% of opioids. For pain severity and global QoL an individual model was performed.
Abbreviations: BPI = Brief Pain Inventory; CI = confidence interval; EORTC QLQ-C15-PAL = European organization for research and treatment of cancer quality of life questionnaire-C15-PAL; QoL = quality of life.

treated with less than 3 fractions during the follow-up ($P = .028$).

Other quality of life outcomes

For exploratory reasons, we also analyzed the other QoL outcomes, which can be found in Table E1-E4.

Acute toxicity

During the study, 22 patients (73.3%) developed at least one acute toxicity. The most clinician-reported acute toxicities consisted of grade 1 to 2 fatigue (n = 12) and grade 1 to 2 nausea (n = 10; Table 3). Besides, these symptoms were reported in the EORTC QLQ-C15-PAL (Table E3.4). Three patients required 1 or 2 day(s) of hospitalization due to a grade 3 transient flare-up of pain combined with grade 3 nausea or vomiting after the first radiation therapy fraction. No grade 4 toxicity or radiation therapy-related death was reported.

Overall survival

The median OS for the total group was 11.8 weeks (range, 0.9-251.7 weeks; Fig. 3), with 1-year OS rate of 13.3%. There was a significant difference in OS between patients with metastasized disease (median, 9.3 weeks, range, 1.4-32.2 weeks) and nonmetastasized disease (median, 28.8 weeks; range, 0.9-251.7 weeks; hazard ratio, 0.3; 95% CI 0.1-0.7; $P = .007$).

Discussion

This prospective phase 2 nonrandomized trial is the first to investigate pain response and QoL at frequently repeated multiple time points in patients with pancreatic cancer-related pain undergoing short-course palliative radiation therapy. We found a rapid clinically relevant and consistently reduced pain severity within weeks, lasting for 11 weeks and longer, along with an increase in global QoL, accompanied by mostly mild acute toxicities.

Our results indicate that a short course of palliative radiation therapy is an effective treatment for patients with painful pancreatic cancer. This palliative effect was present in 80.0% of patients during and after the treatment. A similar effect was found in retrospective observational studies.[43,44] Observational studies focusing on reducing pain severity after a short course of palliative radiation therapy for pancreatic cancer showed a decrease in pain of 0.3 to 5.3 points (scale 0-10), 4 weeks after the radiation therapy treatment.[19,20,29] However, these studies had far fewer observation time points during and after the treatment, compared with our study. Additionally, a large percentage of patients included in these studies had a relatively favorable performance status, less advanced disease or the disease stage was not clearly reported, and the time interval between the last chemotherapy and radiation therapy was unclear, which makes it difficult to compare the results.[19,20,29]

The reduction in pain severity was also reflected by the clinically relevant improvement in global QoL throughout the follow-up. In the conducted observational studies where patients received a short course of palliative

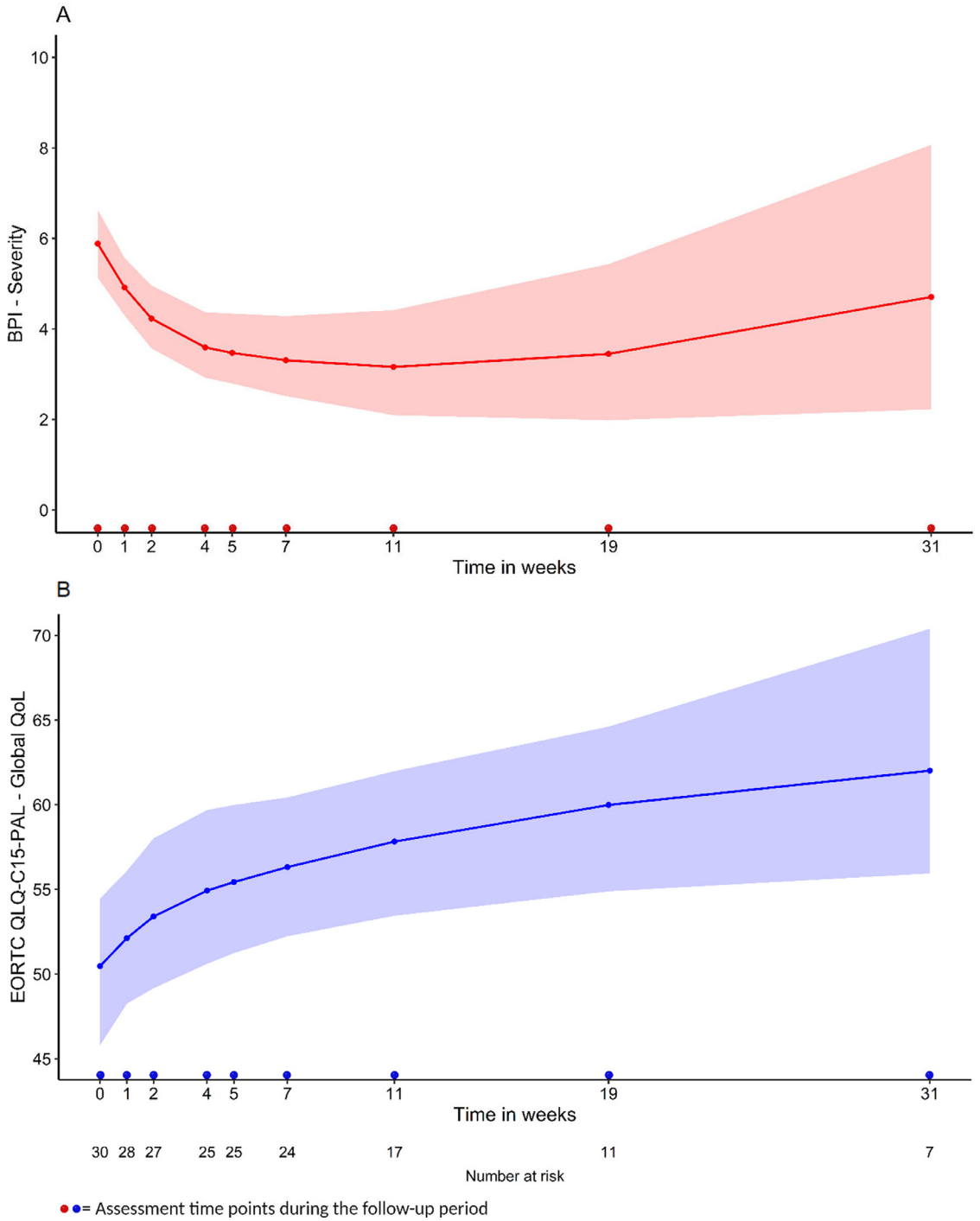

Fig. 2. Predicted average scores for A) pain severity and B) global quality of life over time. Shaded area represents the 95% confidence intervals. Assessment time points: at baseline (0 = before the start of the radiation therapy) and during the follow-up period (before the second and third radiation therapy fraction, at 4, 5, 7, 11, 19, and 31 weeks after the first radiation therapy fraction). *Abbreviations:* BPI = brief pain inventory; EORTC QLQ-C15-PAL = European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire-C15-PAL; QoL = quality of life.

radiotherapy,[18-20,29,43,44] global QoL was only assessed in 2 studies using the QLQ-C30 or SF-36 (Short Form-36).[19,20] The results showed no significant differences between baseline and 3 months after radiation therapy. However, it was not clear when patients received the last chemotherapy before starting with radiation therapy, which may have influenced the results.[19] The other study suggested an improvement in global QoL 4 weeks after the treatment but had not measured global QoL during a more extended period.[20] Our goal was not only to measure the decrease in

Table 3 Number and type of acute toxicities based on clinician reporting defined according to CTCAE v4.0 (n = 30)

CTCAE score	Toxicity	n (%)
1	Nausea	8 (26.7%)
	Vomiting	6 (20.0%)
	Diarrhea	2 (6.7%)
	Fatigue	5 (16.7%)
	Flare-up	6 (20.0%)
2	Nausea	2 (6.7%)
	Vomiting	1 (3.3%)
	Fatigue	7 (23.3%)
	Flare-up	1 (3.3%)
3	Nausea	2 (6.7%)
	Vomiting	1 (3.3%)
	Flare-up	3 (10.0%)
4-5	-	-

73.3% of the patients (n = 22) developed one or more types of toxicity.

Abbreviations: CTCAE v4.0 = Common Terminology Criteria Of Adverse Events version 4.0.

pain severity and global QoL in patients with refractory pancreatic cancer-related pain, but also to investigate the durability of potential improvements.

Applying stereotactic body radiation therapy (SBRT) may prove helpful in achieving pain relief in patients with longer life expectancy. In recent studies/trials SBRT has been applied to achieve pain relief while sparing organs at risk.[45,46] Hammer et al[46] applied a dose painting technique to deliver 25 Gy to the celiac plexus, while respecting dose constraints to the bowel. However, we should consider that SBRT in palliative patients with pain of pancreatic cancer might not be feasible (extensive preparation, long treatment times).[46]

Fatigue and nausea/vomiting were the main patient-reported symptoms during therapy, and the main clinician-reported treatment-related acute toxicities. These toxicities were generally mild, and in agreement with previous studies.[18-20,29,43,44,47] In addition, these toxicities were temporary and consistently decreased until week 19 and 31. With the combination of the chosen delivered weekly dose of 8 Gy, the prophylactic antiemetics given before the second and third fraction, and the frequent monitoring of patients, it was possible to considerably reduce acute toxicity. This shows that the use of this regimen could be safely incorporated in clinical practice. Besides, proton pump inhibitors are given as part of the standard (palliative) treatment of patients with pancreatic tumors to protect and prevent the stomach from radiation ulcers. Additionally, dexamethasone is prescribed (3-8 mg per day) as a standard steroid and is used as an antiemetic. By incorporating dexamethasone as part of the treatment, radiation-induced pain flare can be reduced.[48] In our study, the use of dexamethasone resulted in reduction in nausea and improvement in functional activity and appetite, without serious adverse effects. Grade 3 toxicity developed in only 3 patients, in 2 of which patients was due to nausea or vomiting. Since the radiation therapy was delivered weekly, we assumed that the equivalent dose of the duodenum (in fractions of 2 Gy) would not exceed 51 Gy. In the literature, the V55 <1 cc is reported as an important predictor of toxicity, which was not met in this study with this fractionation scheme.[49]

The median OS of 3 months in our study was lower than the median OS of 5 to 7.5 months reported previously.[18-20,43] This difference reflects the selection of patients with an advanced tumor stage and poor performance status. Nevertheless, also for this group of pancreatic cancer patients, short-course palliative radiation therapy proves an important intervention for pain relief and improvement of QoL, many of them for the remainder of their (short) life.

Incorporating PROMs in the palliative phase is presently found essential to monitor pain, symptom burden and QoL.[22] Because pancreatic cancer is known for its poor prognosis, it can be challenging to deal with the type of missing data.[1] MNAR data will often occur in this patient group. By using

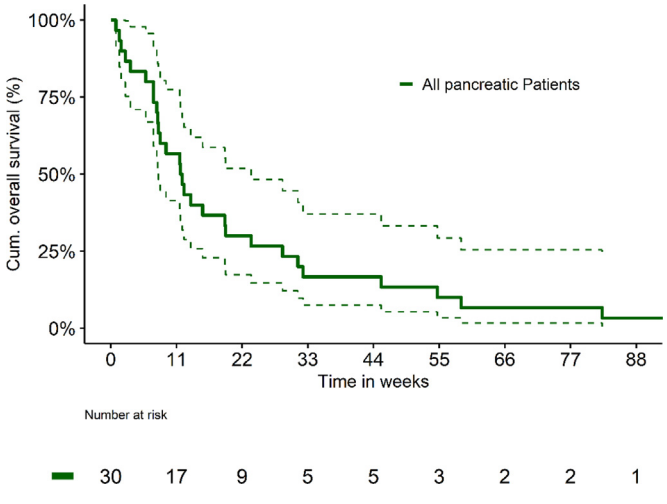

Fig. 3. Kaplan-Meier survival analysis for overall survival. Dashed area represents the 95% confidence intervals.

joint modeling, results allowed valid inferences pertaining to the evolution of pain and QoL over time.

The results of this study should be interpreted in light of several limitations. First, a control group was lacking against which to measure the effect of short-course palliative radiation therapy on pain relief. However, the results of this study may set a standard for future randomized controlled trials for assessing the benefit of palliative short-course radiation therapy compared with other treatments. Second, the sample size of our study can be questioned in light of the many statistical tests performed and the study size could affect the performance of the joint model, mostly because it does not aid an extensive model exploration. However, the similar outcome of our "worst case scenario" analysis suggests the outcome to be robust, despite the small sample size. Yet, larger prospective studies are required to confirm our results and strengthen the evidence. Because the study was powered for pain severity only, the reported results of the other outcomes need to be viewed as exploratory. We therefore have defined a priori criteria for clinically relevant change for pain and overall QoL.

The strength of this study is that we were able to prospectively examine the significant improvements in pain and in QoL by administering suitable PROMs at many repeated time points before, during and after treatment.[22,50] Moreover, we applied the joint modeling framework as one of its advantages is its ability to reduce bias resulting from incomplete data, enabling meaningful use of all available information. Comparison of the pain score (severity) between baseline and a fixed time point using a single test would ignore possibly informative dropouts (death/loss to follow-up), thereby potentially underestimating the severity at week 7 and overestimating the standardized mean change between baseline and week 7.[51]

Conclusion

This prospective phase 2 nonrandomized trial of a short course of palliative radiation therapy for pancreatic cancer-related pain showed a rapid and clinically relevant reduction of pain severity for the majority of patients and an increase in global QoL lasting until death or last follow-up, at the cost of mild, temporary acute toxicities. The positive outcome and feasibility established in the present study should be used for securing reimbursement for palliative radiation for this patient group. Also, confirmation of the role for standard palliative radiation in larger studies is required to further strengthen the evidence.

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