# Celiac plexus radiosurgery for pain management in advanced cancer: a multicentre, single-arm, phase 2 trial

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## Summary

**Background** Refractory upper abdominal pain or lower back pain (retroperitoneal pain syndrome) related to celiac plexus involvement characterises pancreatic and other upper gastrointestinal malignancies and is an unmet need. We hypothesised that ablative radiation delivered to the celiac plexus would decrease pain.

**Methods** This multicentre, single-arm, phase 2 study was done at eight hospitals in five countries (Israel, Poland, Canada, the USA, and Portugal). Eligible patients aged 18 years or older with an average pain level of 5–10 on the Brief Pain Inventory short form (BPI-SF), an Eastern Cooperative Oncology Group performance status score of 0–2, and either pancreatic cancer or other tumours involving the celiac axis, received a single fraction of 25 Gy of external-beam photons to the celiac plexus. The primary endpoint was complete or partial pain response based on a reduction of the BPI-SF average pain score of 2 points or more from baseline to 3 weeks after treatment. All evaluable patients with stable pain scores were included in response assessment. The trial is registered with ClinicalTrials.gov, NCT03323489, and is complete.

**Findings** Between Jan 3, 2018, and Dec 28, 2021, 125 patients were treated, 90 of whom were evaluable. Patients were followed up until death. Median age was 65·5 years (IQR 58·3–71·8), 50 (56%) were female and 40 (44%) were male, 83 (92%) had pancreatic cancer, and 77 (86%) had metastatic disease. Median baseline BPI-SF average pain score was 6 (IQR 5–7). Of the 90 evaluable patients at 3 weeks, 48 (53%; 95% CI 42–64) had at least a partial pain response. The most common grade 3–4 adverse events, irrespective of attribution, were abdominal pain (35 [28%] of 125) and fatigue (23 [18%]). 11 serious adverse events of grade 3 or worse were recorded. Two grade 3 serious adverse events were probably attributed to treatment by the local investigators (abdominal pain [n=1] and nausea [n=1]), and nine were possibly attributed to treatment (seven were grade 3: blood bilirubin increased [n=1], duodenal haemorrhage [n=2], abdominal pain [n=2], and progressive disease [n=2]; and two were grade 5: gastrointestinal bleed from suspected varices 24 days after treatment [n=1] and progressive disease [advanced pancreatic cancer] 89 days after treatment [n=1]).

**Interpretation** Celiac plexus radiosurgery could potentially be a non-invasive palliative option for patients with retroperitoneal pain syndrome. Further investigation by means of a randomised comparison with conventional celiac block or neurolysis is warranted.

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## Introduction

Retroperitoneal pain syndrome characterises pancreatic cancer and other tumours that invade the celiac axis, and is frequently severe, debilitating, and refractory to treatment. This pain radiates from the lower back to the upper abdomen in a belt-like distribution; this is thought to be due to the invasion or compression of the celiac nerve plexus. The celiac nerve plexus lies posteriorly to the pancreas between the levels of the twelfth thoracic and second lumbar vertebrae, inclusive; visceral afferent fibres within the celiac plexus convey pain from proximal abdominal viscera including the pancreas.[1,2] Celiac plexus block or neurolysis, in which local anaesthetic or a sclerosing agent are injected around the plexus, respectively, are commonly proposed interventions. However, results from clinical trials of these invasive procedures have been disappointing.[3,4]

Retrospective reports suggest some palliative effect of low-dose tumour-directed radiotherapy in pancreatic cancer.[5–8] A 2022 systematic review reported a temporary improvement in pain following tumour-targeting stereotactic body radiotherapy in locally advanced pancreatic adenocarcinoma.[9] The studies reviewed were retrospective case series that used heterogeneous endpoints and excluded metastatic patients.[9] We hypothesised that the palliative impact might be enhanced by targeting the nerve. Consequently, we developed a novel intervention targeting the celiac plexus

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## Research in context

### Evidence before this study

Retroperitoneal pain syndrome is primarily observed in patients with advanced pancreatic cancer. The condition is often unresponsive to standard-of-care therapies, and hence is an area of unmet need. Invasive celiac plexus block or neurolysis can be used; however, accessibility remains a major concern, and recent evidence shows inadequate palliative efficacy. Retrospective studies suggest some palliative effect of low-dose radiotherapy. A 2022 systematic review examined the palliative efficacy of conventional stereotactic body radiotherapy targeting the tumour, delivered in three to six fractions, in locally advanced pancreatic cancer. Pain appeared to be improved by stereotactic body radiotherapy; the maximum pain palliation effect was reached at approximately 1 month after treatment. Subsequently, pain levels appeared to increase. The studies reviewed used heterogeneous methods of measuring pain and opioid usage. There remains a substantial knowledge gap regarding stereotactic body radiotherapy delivered to novel anatomical targets for palliative intent in patients with retroperitoneal pain syndrome with either locally advanced or metastatic cancer.

A single-institution pilot study by our group targeted the celiac plexus with high-dose stereotactic radiosurgery, showing little toxicity and promising results in relieving retroperitoneal pain; these positive results were the impetus for our study. We searched PubMed for relevant published studies from database inception until Oct 1, 2023, with no language restrictions. The search terms used were "celiac plexus" and "radiotherapy". We found no additional research on the use of radiotherapy targeting the celiac plexus to reduce pain in patients with retroperitoneal pain syndrome.

### Added value of this study

We present the results of a phase 2 trial investigating the use celiac plexus radiosurgery, a new non-invasive treatment modality, for the management of pain in patients with retroperitoneal pain syndrome. Our findings show that in the setting of an international multi-institutional study, the treatment can be safely delivered and appears to be a promising approach to alleviate pain in the majority of patients, suggesting that the treatment might help to address an unmet medical need.

### Implications of all the available evidence

To date, radiotherapy has not been widely used for retroperitoneal pain in metastatic pancreatic cancer and other cancers invading the celiac axis. Our study provides support for a new approach, targeting peripheral nerves with high-dose radiation, that warrants further investigation and might lead to a paradigm shift in retroperitoneal pain syndrome, and is potentially applicable to other cancer pain syndromes.

by means of single-fraction radiosurgery. The dose of 25 Gy was chosen based on experience in the single-fraction treatment of pancreatic cancer,[10] and a pilot study of celiac plexus radiosurgery that produced promising results.[11] We aimed to assess the effect of celiac plexus radiosurgery on pain and interference with daily living, to assess toxicity, and to determine the effect on analgesic use. The celiac plexus radiation target is shown in the appendix (p 37).

## Methods

### Study design and participants

This was a multicentre, international, single-arm, phase 2 trial. Patient were recruited from eight hospitals across five countries (Israel, Poland, Canada, the USA, and Portugal; appendix p 7). The clinical protocol has previously been published[12] and is in the appendix. The key eligibility criteria were typical retroperitoneal pain syndrome, uncontrolled despite analgesia, with an average pain intensity of at least 5 on the BPI-SF 0–10 pain score in patients aged 18 years or older[8] with a metastatic or unresectable malignancy. To meet the criteria of anatomical involvement of the celiac plexus, it was necessary to have either pancreatic cancer (regardless of celiac axis involvement) or in the case of other cancers, either clear evidence of involvement of the celiac blood vessels or haziness around them. Additional criteria were an Eastern Cooperative Oncology Group performance status score of 0–2, written informed consent, and willingness to attend post-treatment assessments. Patients with a life expectancy of less than 8 weeks, confusion, leptomeningeal spread, spinal cord compression, clinically significant comorbidities, conditions associated with increased side-effects to radiotherapy, and patients with acute adverse effects of previous anticancer therapy were excluded. Previous radiotherapy to the upper abdomen was an exclusion criterion. Previous celiac plexus block or neurolysis were neither inclusion or exclusion criteria. Sex and ethnicity were self-defined.

The trial was approved by the Sheba Medical Center's ethics committee (SMC-17-4292), and by each subsite's ethics committee. A data safety monitoring committee monitored the trial data at regular intervals. Study data were collected and managed by the Israeli Center for Cardiovascular Research using REDCap hosted at the Sheba Medical Center.[13] Selective distant monitoring was done. The amendments detailed in the protocol were approved by each subsite's ethics committee.

See Online for appendix

### Procedures

The intervention was a single fraction of 25 Gy of external-beam photons delivered to the celiac plexus. The technique has been previously described,[11,12] and further details are in the appendix (pp 3–6) and in a series of educational videos.[14–17] Briefly, patients were simulated in

the supine position with arms above the head, use of oral and intravenous contrast was required unless contraindicated, and likewise motion management was required to account for small bowel movement. Special care was required to correctly contour the third part of the duodenum, which is adjacent to the celiac plexus, yet can be difficult to identify. The celiac plexus is not visible on conventional imaging; hence, the lateral and anterior aspects of the abdominal aorta, from levels of the 12th thoracic to the second lumbar vertebrae inclusive, were used as a surrogate structure based upon anatomical descriptions (appendix pp 3–4).[1,2] The planning target volume (PTV) consisted of a 0·5 cm uniform expansion of the celiac plexus. The decisions as to whether or not to include the infiltrating tumour mass within the target volumes, and to what dose to irradiate the tumour, were left to physician discretion; in cases of locally advanced disease, it was suggested that the tumour be irradiated to 15 Gy. Of note, even when excluded, tumour located nearby would have received a substantial dose of radiation (appendix pp 38–42). A dose-painting technique involving four planning target volumes (PTV10 Gy, PTV15 Gy, PTV20 Gy, and PTV25 Gy) was applied to respect normal tissue constraints. Although we aimed for comparatively homogeneous target dose distributions within each PTV, the celiac plexus itself generally received a heterogenous dose: parts of the celiac plexus located at least 1 cm from bowel were prescribed a 25 Gy dose, whereas areas closer to bowel were prescribed lower doses.

Participating centres were required to undergo a comprehensive educational and quality assurance process that included detailed written instructions, educational videos,[14–17] an online assessment, a standardised benchmark case, and rapid central review of the first three cases from each site. Beyond these initial cases, real-time central review of inclusion criteria and treatment plans was not done.

Treatment delivery within 10 days of consent was strongly recommended. Concurrent chemotherapy or biological treatment was prohibited from 6 days before until 6 days following radiotherapy. Effective prophylactic antiemetic medication was required before radiotherapy on the day of treatment, typically a combination of steroids, a 5-HT3 receptor antagonist, with or without a neurokinin 1 receptor antagonist administered before treatment. A daily proton-pump inhibitor was recommended for 1 month after radiotherapy. Image guidance at time of treatment was required. No limitations were placed upon the use of pain medications before or after treatment. Weekly telephone contact with a palliative nurse practitioner was required to aid with analgesic dose adjustment. Patients underwent a brief assessment at time of accrual, and a more detailed assessment immediately before treatment, and 3 weeks and 6 weeks following treatment. The 3-week and 6-week visits were intended to be in-person visits; however, due to the COVID-19 pandemic, telemedicine visits were allowed (amendment made on Sept 1, 2020); consequently, functional outcomes (hand grip test and 6-min walk) could not be tested in these patients. Telephone follow-up was maintained for up to 2 years. Patients were requested to keep a daily pain diary commencing at enrolment and continuing until 6 weeks after treatment.

Adverse events were classified with the National Cancer Institute's revised Common Terminology Criteria for Adverse Events version 4.03, and collected at fixed timepoints: 48 h after treatment, 1 week after treatment, at 3 weeks, 6 weeks, and 3 months, and every 3 months thereafter. Since we suspected that many of the adverse events being recorded during the study were manifestations of the underlying disease process, the protocol was amended on Sept 1, 2020, to additionally record adverse events recorded at baseline. Serious adverse events (SAEs) were defined as an adverse event resulting in either death, a life-threatening adverse event, an inpatient hospitalisation or prolongation of existing hospitalisation for at least 24 h, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. SAEs were categorised by the local investigator as definitely, probably, possibly, unlikely, or unrelated to treatment. Adverse events and SAEs were collected separately.

### Outcomes

The primary endpoint was complete or partial pain response, based on the average pain scale (0–10) reported in the BPI-SF 3 weeks after treatment. A partial response was defined as a decrease of two points or more between the score immediately before treatment and 3 weeks after treatment,[18] which had to also be at least two points greater than any decrease in score between registration and immediately before treatment. A complete pain response was defined as an average pain score of 0 on the BPI-SF. The BPI-SF includes four measures of pain (average pain, current pain [right now], least pain in the last 24 h, and worst pain in the last 24 h) and seven measures of pain interference with daily living, which are similarly reported here. Secondary endpoints included 3-week and 6-week changes in BPI-SF average pain over the previous 24 h compared with immediately before treatment, 3-week and 6-week changes in opioid use (measured in mg of intravenous morphine equivalents), relationship between changes in opioid usage between responders and non-responders, changes in BPI average pain score, and changes in other endpoints (eg, opioid use, functionality, and health-related quality of life), and 3-week and 6-week changes in BPI worst pain over the previous 24 h compared with immediately before treatment. An additional secondary endpoint was combined pain response and change in opioid dose (yes or no), with yes defined as having a pain response at 3 weeks while the opioid use did not increase

by more than 25% over the pretreatment dose. If the pain response or opioid dose was missing, this was defined as no combined response. Health-related quality-of-life data (secondary endpoints: 3-week change in overall quality of life [FACT-Hep], 3-week and 6-week changes in Hepatobiliary Cancer quality-of-life subscale, a measure of gastrointestinal toxicity) were collected, and will be reported separately as the analysis is not yet complete.

Additional secondary endpoints that included 3-week and 6-week changes in functionality (eg, hand grip and walking ability) and 3-week and 6-week changes in the use of short-acting opioids for breakthrough pain measured both in morphine-equivalent dose per day and number of times taken per day, averaged over the previous 3 days, are not reported here, due to missing data (as a result of the COVID-19 pandemic) and unclear missing data (the case report forms did not clearly differentiate between no use of short-acting opioids and their use not being reported—ie, missing data), respectively.

### Statistical analysis

In the previous pilot trial,[11] approximately 60% of patients had a complete or partial pain response. Assuming that the true response rate was 60%, a trial with 90 evaluable patients had 97% statistical power to show that the response rate was higher than 40% using a two-sided test at the 5% significance level. It was expected that approximately 10% of patients would be non-evaluable; however, the number of evaluable patients was monitored during the trial and recruitment continued until a minimum of 90 evaluable patients were entered into the trial.

An evaluable patient was defined as a patient eligible for enrolment per the defined criteria who received the therapy per protocol and remained alive until the 3-week post-treatment pain and quality-of-life assessments. A further evaluability criterion was that BPI-SF average pain score was 4 or higher at the assessment immediately before the first treatment (the eligibility level cutoff at recruitment was 5). A further criterion was that any reduction between the screening BPI-SF and the BPI-SF immediately before treatment was not more than 2. This was required to ensure that all patients had pretreatment pain at a sufficient level to allow detection of pain relief following treatment. Toxicity was assessed in all patients, even those who did not complete an assessment 3 weeks after treatment. The statistical analysis was done in accordance with a formal predefined statistical analysis plan (appendix).

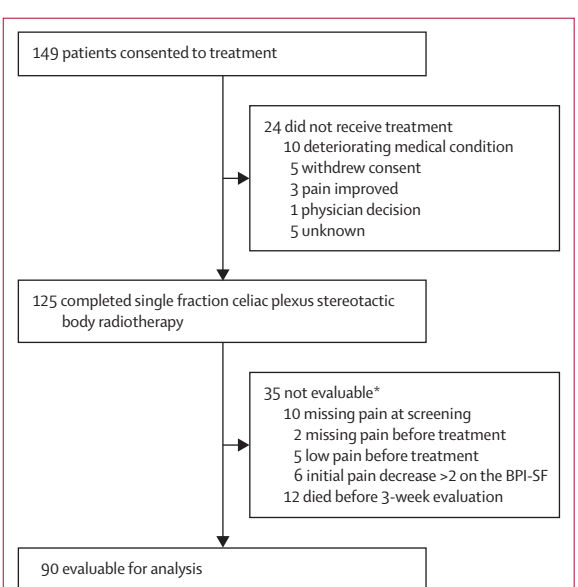


***Figure 1:*** **Trial profile**
BPI-SF=Brief Pain Inventory short form. *Evaluability criteria were predefined in the protocol.

The response rate was defined as the proportion of evaluable patients who has a complete or partial pain response at 3 weeks after treatment. The 95% CIs were calculated based on the binomial distribution. Trial success was defined in the protocol as demonstration that the response rate was 40% (the rate that would be considered high enough to justify the adoption of the treatment assuming acceptable toxicity) or higher. A statistical test of the null hypothesis that the response rate was 40% was conducted at the two-sided 5% level, based on the binomial distribution. Patients who were still alive but did not provide a 3-week pain assessment were included as failures. Additionally, a sensitivity analysis was planned in which patients with no 3-week pain assessment were excluded from the analysis. A similar sensitivity analysis was done for the combined pain response and change in opioid dose endpoint. The sensitivity analysis of 3-week and 6-week changes in BPI average pain endpoint assumed that patients with a missing pain assessment at the post-treatment timepoint had zero change from immediate pre-treatment pain level. In a post-hoc analysis, diary self-reported pain levels in 27 patients were analysed over time using a linear mixed model.

All changes between baseline and 3 or 6 weeks in secondary outcomes were tested using the *t* test, including post-hoc analyses of pain interference. Correlations between baseline variables and the 3-week change in BPI-SF were estimated using the Pearson correlation coefficient. A prespecified exploratory analysis to determine who benefits from the intervention was planned based on baseline demographic and pain characteristics. Adverse events were analysed as total events and per patient as cumulative incidence. A post-hoc analysis of serious adverse events was done, stratifying the events by both time and centrally assigned attribution based on expected radiation toxicity. A further post-hoc analysis examined the cumulative incidence of serious adverse events after treatment, regarding death as a competing risk. Since all patients in the trial were followed until

| | Patients (n=90) |
|---|---|
| Sex | |
| Female | 50 (56%) |
| Male | 40 (44%) |
| Ethnicity | |
| White | 85 (94%) |
| Asian | 3 (3%) |
| Hispanic | 1 (1%) |
| Not declared | 1 (1%) |
| Marital status | |
| Single | 19 (21%) |
| Together | 65 (72%) |
| Other | 6 (7%) |
| Geographical region | |
| Middle East | 59 (66%) |
| Europe | 16 (18%) |
| North America | 15 (17%) |
| Age, years | 65·5 (58·3–71·8) |
| BMI* | 22·8 (20·4–25·2) |
| <18·5 | 12 (13%) |
| 18·5–24 | 50 (56%) |
| 25–29 | 25 (28%) |
| ≥30 | 2 (2%) |
| Current weight, kg | 64·0 (54·0–72·4) |
| Weight 2 months before enrolment, kg | 68·0 (58·5–76·0) |
| Primary tumour | |
| Pancreas | 83 (92%) |
| Cholangiocarcinoma | 3 (3%) |
| Gastric | 1 (1%) |
| Colon | 1 (1%) |
| Retroperitoneal leiomyosarcoma | 1 (1%) |
| Primary unknown, head and neck | 1 (1%) |
| Metastatic disease | |
| Any metastases | 77 (86%) |
| Liver metastases | 58 (64%) |
| Peritoneal metastases | 19 (21%) |
| Ascites approximately >100 mL | 10 (11%) |
| Months from diagnosis | 9·5 (3·5–16·8) |
| Previous abdominal surgery of relevance to current cancer | 31 (34%) |
| Partial or total pancreatectomy | 19 (21%) |
| Small bowel resection | 2 (2%) |
| Large bowel resection | 0 |
| Unsuccessful tumour resection | 6 (7%) |
| Other | 6 (7%) |
| (Table 1 continues on next column) | |
| (Continued from previous column) | |
| Previous use of chemotherapy | |
| Yes | 72 (80%) |
| No | 18 (20%) |
| Days since last chemotherapy | 27 (13–64)† |
| Number of systemic treatment lines | |
| None | 18 (20%) |
| 1 | 33 (37%) |
| 2 | 26 (29%) |
| 3 | 9 (10%) |
| 4 | 1 (1%) |
| 5 | 3 (3%) |
| ECOG performance status | |
| 0 | 6 (7%) |
| 1 | 58 (64%) |
| 2 | 26 (29%) |
| Invasion of celiac plexus‡ | |
| Invasion of the celiac plexus by the primary tumour | 59 (66%) |
| Invasion of the celiac plexus by metastasis or lymph-node metastasis | 8 (9%) |
| Invasion of the celiac plexus by recurrent tumour following resection | 10 (11%) |
| Pancreatic cancer without further comment | 13 (14%) |
| No invasion of the celiac plexus | 0 |
| Pain level at baseline | 6 (5–7) |
| Use of opioids at baseline | 84 (93%) |
| Opioid use, intravenous morphine equivalent, mg | 30·9 (12·5–66·7) |
| Celiac block or neurolysis previously performed | |
| Yes | 2 (2%)§ |
| No | 88 (98%) |

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *Data missing for one patient. †Data missing for two patients. ‡For details see the appendix (p 48). §Celiac block done 1 month before radiation and neurolysis done 18 months before radiation.

***Table 1:*** **Baseline characteristics of evaluable patients**

death, median survival was calculated as the sample median of the survival times measured from the day of radiotherapy. All p values are two-sided. All adverse events were followed through day 30. All SAEs and adverse events of special interest were recorded through day 90. Statistical analyses were carried out using R version 4.2.2. The trial is registered with ClinicalTrials.gov, NCT03323489.


## Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.


## Results

Between Jan 3, 2018, and Dec 28, 2021, 149 patients were recruited and 125 patients received treatment, 90 of whom were evaluable and included in the analysis (figure 1). 50 (56%) were female and 40 (44%) were male, 85 (94%) were White, and median age was 65·5 years (IQR 58·3–71·8; table 1). 83 (92%) had pancreatic cancer, and the other seven cases with non-pancreatic cancer anatomically involving the celiac axis are shown in the appendix (p 48). Median baseline average pain score was 6 (IQR 5–7), and median daily opioid usage was 30·9 mg (IQR 12·5–66·7) of intravenous morphine equivalents.

All patients were followed up until death. Median survival of evaluable patients from day of enrolment was 120 days (IQR 77–186); all evaluable patients were alive at the 3-week timepoint, 78 evaluable patients were alive at the 6-week timepoint, and all patients had died by time of study closure (appendix p 8). No patients were lost to follow-up; however, not all patients were fully compliant with the scheduled evaluations (data not shown).

Of the 90 evaluable patients, 76 (84%) were simulated with oral contrast, 59 (66%) were simulated with intravenous contrast, 47 (52%) underwent abdominal compression, and 71 (79%) underwent four-dimensional CT; 89 (99%) patients were treated using an intensity-modulated radiotherapy or volumetric modulated arc therapy technique (appendix p 9).

For the 90 evaluable patients, the median volume of the celiac plexus was 31·3 mL (IQR 26·6–36·5), which was irradiated to a median dose of 22·7 Gy (IQR 21·1–23·6, mean dose to the structure). The adjacent tumour was excluded in 19 (21%) cases, partially included in 32 (36%) cases, and fully included within target volumes in 38 cases (42%), with a median prescription dose to the adjacent targeted tumour of 15 Gy (IQR 10–15 Gy). For participants in whom the tumour was partially included, the median tumour target volume was 31·2 mL (IQR 21·2–40·8), and in those in which the tumour was fully included, the median tumour target volume was 56·9 mL (33·6–88·0). In patients in whom the tumour was not included within the planning volumes, it most likely also received a low dose of irradiation (representative treatment plans are in the appendix pp 38–42).

Median total planning target volume was 157·3 mL (IQR 112·1–211·6) across 90 evaluable patients; 111·0 mL (IQR 90·0–122·0) when no tumour was irradiated and 179·5 mL (IQR 136·3–237·9) when the tumour was partially or fully included. In 86 (96%) of 90 participants, all dosimetric target coverage goals were met (including acceptable deviation), and in 85 (94%) of 90 participants, all organ-at-risk constraints were met (appendix pp 10–12). Additional dosimetric and volumetric details are presented in the appendix (p 13). The complete radiation treatment was delivered successfully in all 125 treated patients; two patients complained of pain during treatment. Among the 90 evaluable patients, treatment was delivered a median of 9 days after accrual (range 1–28).

The distribution of pretreatment and post-treatment pain scores are shown in figure 2 and the appendix (p 43). Of the 90 evaluable patients at 3 weeks, 48 (53%; 95% CI 42–64; p=0·013 for test of primary endpoint) had a complete or partial pain response. In the preplanned sensitivity analysis in which four non-reporting patients were removed, 48 (56%) of 86 patients had a response (95% CI 45–66; p=0·004 for test of primary endpoint).

Pain levels at 3 and 6 weeks were all significantly decreased from baseline (p<0·001 in all four pain indices recorded by the BPI-SF). The absolute mean average pain score, which was 6·0 (IQR 5·0 to 7·0) at baseline, decreased by 2·5 points at 3 weeks and 3·2 points at 6 weeks. In a prespecified sensitivity analysis in which an imputed value of zero (ie, no change) was assumed for missing follow-up pain scores (four patients at 3 weeks and 23 patients at 6 weeks), there was a mean decrease in pain level of 2·4 points at 3 weeks and 2·3 points at 6 weeks. Regarding worst pain, there was a meaningful mean change (ie, improvement) at both 3 weeks, with a mean change of –2·5 (95% CI –3·2 to –1·9), and at 6 weeks, with a mean change of –3·4 (95% CI –4·3 to –2·6). A post-hoc analysis of diary self-reported pain levels over time in 27 patients is shown in the appendix (p 44).

Changes in median daily opioid are presented in table 2. In a prespecified secondary analysis, responding and non-responding participants (at the 3-week timepoint) were analysed separately; at 3 weeks, responding participants had a mean decrease in daily opioid intake of 5·3 mg (SD 23·0) and non-responding participants had a mean increase of 5·4 mg (SD 39·4). Pain interference scores were reported for all domains at baseline (in 78 [87%] of 90 patients), 3 weeks (87 [97%]),

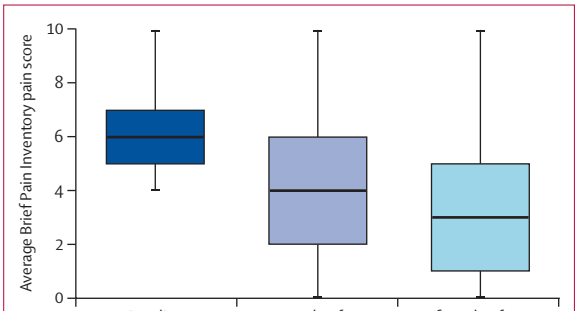


***Figure 2:*** **Levels of average pain before treatment, and 3 weeks and 6 weeks after treatment**

Average pain refers to the descriptive text of the question within the Brief Pain Inventory short form questionnaire, "Please rate your pain by marking the box beside the number that best describes your pain on the average." The distribution of pain scores reported by evaluable patients before treatment, and 3 and 6 weeks after treatment. The whiskers denote $Q_{25}$–1·5($Q_{75}$–$Q_{25}$) and $Q_{75}$+1·5($Q_{75}$–$Q_{25}$) in which $Q_{25}$ and $Q_{75}$ are the first and third quartiles.

| | Mean (SD) | Median (IQR) | p value |
|---|---|---|---|
| Opioid use on day of treatment, intravenous morphine equivalent, mg*† | 54·0 (68·9); n=90 | 30·0 (11·6 to 65·4) | .. |
| Opioid change at 3 weeks compared with baseline | 0·15 (31·98); 95% CI –6·74 to 7·05; n=86 | 0·00 (–10·38 to 8·85) | 0·965 |
| Opioid change at 6 weeks compared with baseline | –16·67 (48·69); 95% CI –28·45 to –4·89; n=69 | –5·00 (–22·30 to 5·00) | 0·006 |

Missing values removed. Significance tested by means of *t* test. *For opioid use on day of treatment. †95% CI and p value data are for mean opioid changes from baseline, and whether the mean change is different from zero.

***Table 2:*** **Change in daily opioid use at 3 and 6 weeks**

and 6 weeks (67 [74%]); post-hoc analyses of pain interference are shown in the appendix (p 45).

In a prespecified exploratory univariate analysis, we assessed the correlation of baseline variables with the 3-week change in average pain (appendix pp 14–18).

Among the 90 evaluable patients, 35 (40%) had a combined response at 3 weeks—ie, decreased pain without increased opioid dose (95% CI 28·8–49·7; p=0·91 for probability of response rate >40%; appendix p 19). The prespecified sensitivity analysis of combined change in pain and opioid use at 3 weeks removing four patients with incomplete data is shown in the appendix (p 20).

At 6 weeks after treatment, among the 90 evaluable patients, 38 (42%) had a combined response (95% CI 31·9–53·1; p=0·67 for probability of response rate >40%; appendix p 21). The prespecified sensitivity analysis of combined change in pain and opioid use at 6 weeks removing four patients with incomplete data is shown in the appendix (p 22).

The most common grade 3–4 adverse events within the first 30 days after treatment were abdominal pain (35 [28%] of 125), fatigue (23 [18%]), and nausea (five [4%]; table 3; appendix pp 23–24). Adverse events recorded at baseline are shown in the appendix (pp 25–27, 47), although these symptoms worsened immediately following treatment, they mostly resolved by 3 weeks (appendix p 47).

149 SAEs were recorded in 94 participants during the trial. The most common SAEs were abdominal or tumour pain (eight [6%] of 125), biliary tract infection (five [4%]), and vomiting (five [4%]). Among the SAEs, 0, 2, 12, 77, and 58 were categorised locally as definitely, probably, possibly, unlikely, or unrelated to treatment, respectively; an additional ten SAEs occurred before treatment delivery (appendix pp 28–30). 11 SAEs of grade 3 or worse that were classified by the local investigator as definitely, probably, or possibly related to treatment are detailed in the appendix (pp 31–32). Two grade 3 SAEs were classified as probably related to treatment (abdominal pain [n=1] and nausea [n=1]). Of the nine SAEs possibly related to treatment, seven were grade 3 (blood bilirubin increased [n=1], duodenal hemorrhage [n=2], abdominal pain [n=2], progressive disease [n=2]) and two were grade 5 (gastrointestinal bleed from suspected varices 24 days after treatment [n=1] and progressive disease [advanced pancreatic cancer] 89 days after treatment [n=1]). A cumulative graph of combined adverse events and SAEs grade 3 or worse is shown in the appendix (p 46); in a post-hoc analysis, the estimated cumulative incidence of grade 3–5 adverse events that were judged to be possibly, probably, or definitely related to treatment (local investigator attribution) was 8% (95% CI 3–13) after 30 days, 14% (8–21) after 91 days, 22% (15–30) after 182 days, and 28% (20–36) after 365 days. 13 SAEs within the first 4 weeks after treatment were centrally attributed as at least possibly related to treatment based upon expected toxicities of the intervention (appendix pp 33–34).

| | Grades 1–2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|
| **Adverse events, up to 30 days after treatment** | | | | |
| Fatigue | 99 (79%) | 23 (18%) | 0 | 0 |
| Abdominal pain | 79 (63%) | 35 (28%) | 0 | 0 |
| Nausea | 77 (62%) | 5 (4%) | 0 | 0 |
| Vomiting | 45 (36%) | 1 (1%) | 0 | 0 |
| Diarrhoea | 34 (27%) | 4 (3%) | 0 | 0 |
| Constipation | 10 (8%) | 1 (1%) | 0 | 0 |
| Anaemia | 0 | 2 (2%) | 0 | 0 |
| Blood bilirubin increase | 0 | 2 (2%) | 0 | 0 |
| Bile duct stenosis | 0 | 2 (2%) | 0 | 0 |
| Duodenal haemorrhage | 0 | 2 (2%) | 0 | 0 |
| Confusion | 0 | 0 | 1 (1%) | 0 |
| Pleural effusion, ascites | 0 | 0 | 0 | 1 (1%) |
| Dizziness and vertigo | 0 | 1 (1%) | 0 | 0 |
| Stroke | 0 | 1 (1%) | 0 | 0 |
| Ileal obstruction | 0 | 1 (1%) | 0 | 0 |
| Bowel sub-occlusion | 0 | 0 | 0 | 1 (1%) |
| Back pain | 0 | 1 (1%) | 0 | 0 |
| Hyponatraemia | 0 | 1 (1%) | 0 | 0 |
| Ascites | 0 | 1 (1%) | 1 (1%) | 0 |
| Thromboembolic event | 0 | 1 (1%) | 0 | 0 |
| **Adverse events of special interest, defined as bowel haemorrhage and obstruction, 31–90 days after treatment** | | | | |
| Anal haemorrhage | 1 (1%) | 0 | 0 | 0 |
| Colitis | 1 (1%) | 0 | 0 | 0 |
| Duodenal haemorrhage | 0 | 1 (1%) | 0 | 0 |
| Upper gastrointestinal haemorrhage | 1 (1%) | 0 | 0 | 0 |

Data are n (%). Events were defined using Common Terminology Criteria for Adverse Events version 4.03. Adverse events of grades 1–2 occurring in at least 10% of patients or grades 3–5 occurring in any patient are reported.

***Table 3:*** **Acute adverse events, regardless of attribution, in the entire study population**

Overall, within 4 weeks of treatment, there were two episodes of duodenal grade 3 bleeding, one report of small-bowel obstruction (grade 3), and five events related to the biliary tract (two hyperbilirubinemia, two binary tract stenosis, and one infection). An exploratory post-hoc analysis of SAEs stratified by time and type of event did not suggest a temporal pattern related to treatment delivery (appendix pp 33–34). The use of a subsequent traditional celiac block was not formally collected, investigators reported post hoc that this occurred in two patients. There were two deaths that local investigators classified as possibly related to treatment: the first case occurred 89 days after treatment in the context of progressive pancreatic cancer; the second case occurred 24 days after treatment in a patient with hepatocellular carcinoma who died of a gastrointestinal bleed from suspected varices (appendix p 32). On central review, neither was considered to be treatment related.

## Discussion

To our knowledge, this is the first multicentre, prospective clinical trial investigating celiac plexus radiosurgery as a

novel palliative treatment. Within the limitations discussed below, the treatment appears to be safe and shows promising activity in relieving retroperitoneal pain.

The positive outcome of the study gives strength to our hypothesis that targeting radiotherapy to the nerve plexus, as opposed to the tumour, could be effective. In this study, physicians were given flexibility regarding whether or not to irradiate the adjacent tumour; however, this did not appear to influence outcomes. Nevertheless, it should be appreciated that, even when not included within the planning treatment volumes, the primary tumour might well have received low-dose irradiation. It is unclear whether the treatment's mechanism of action is related to the destruction of infiltrating tumour cells or ablation of the nerve itself. The only comparable treatment, stereotactic radiosurgery for trigeminal neuralgia, involves a substantially higher radiation dose leading to axonal degeneration.[19]

In any trial of cancer pain, use of analgesics is a confounding factor. Of note, in our trial, the daily baseline use of opioid analgesics was substantial (31 mg of intravenous morphine equivalent) and opioid use during the trial was not restricted. We noted a modest decrease in opioid consumption after treatment, which appeared to lag 3 weeks behind the improvement in pain. The lack of an early decrease in opioid usage, even in those with significant pain relief, might reflect other non-celiac plexus pain syndromes (eg, liver and bone metastases), or could represent a lag in the time for treating physicians to respond to the reduction in pain and advise a reduction in dose of opioid, which would then be carefully tapered over time to avoid withdrawal. Future studies could consider a protocol-specified down-titration of opioid after a pain response. Pain relief for patients with incurable cancer, even in the presence of opioid consumption, should be viewed as a success.

Analysis of the adverse events was difficult due to several reasons: (1) this is a single-arm trial that did not have a comparator group; (2) many patients received additional aggressive treatment modalities (eg, chemotherapy) before or following treatment; (3) local side-effects of radiation are often indistinguishable from symptoms of the tumour itself; for instance, a duodenal bleed (recorded in three patients) is a frequent event in pancreatic cancer, but, equally, might be a side-effect of radiation, since the duodenum is adjacent to the celiac plexus; and (4) all trial participants had advanced cancer, with the majority being in the final third of their disease trajectory. The typical patient had metastatic pancreatic cancer, having previously received one or two lines of systemic therapy, with a median time from diagnosis of over 300 days, and a median survival from enrolment of just 3 months (for reference, median survival for newly diagnosed metastatic pancreatic cancer in the USA is just 2 months).[20] Hence, many adverse events related to the cancer itself would be expected, including bleeds, bowel obstruction, cholangitis, and death. Indeed, all SAEs that were classified by the local investigator as possibly or probably related to treatment are common manifestations of the disease itself. Based on both the local and central review of the reported adverse events, analyses based on the time interval between treatment and the event, and analyses of adverse events before treatment delivery, we conclude that the trial intervention appears to be safe with minimal side-effects.

The principal alternative treatments for retroperitoneal pain syndrome are either a traditional celiac plexus block, or celiac neurolysis, in which local anaesthetic, or ethanol, respectively, are injected around the celiac plexus. The reported efficacy of these procedures is variable[3,4,21–24] and difficult to compare due to different populations, endpoints, and use of analgesia (appendix pp 35–36); side-effects include hypotension, acute diarrhoea, local tissue damage, pneumothorax, and pain intensification.[22,24] Many of the published series are small, and include a patient population in better health than that included here; for example, the majority of patients in a randomised trial were newly diagnosed and not using opioids at baseline.[3] Some trials of celiac block or neurolysis have reported improved pain control, concurrent with increased opioid consumption.[3,4,25,26] A 2020 randomised trial from Japan comparing modern synthetic opioids with and without neurolysis showed no difference in pain levels or opioid consumption between the study groups.[4] Compared with celiac plexus block or neurolysis, celiac plexus radiosurgery is less invasive, requiring neither hospitalisation or anaesthesia. It is likely that the two interventions have a different time course, whereas celiac neurolysis might have an immediate effect; in celiac radiosurgery, pain reduction appears to begin at approximately 7–8 days following radiotherapy, continues for up to about 3 weeks, and thereafter stabilises (appendix p 44). Ideally, a future randomised trial will compare a traditional celiac block with celiac radiosurgery regarding both efficacy and side-effects. Other radiation techniques (eg, radiosurgery targeting the tumour itself) also show promise.[27]

The response rate for pain relief reported in this study was 53%. Could this be further improved? One likely obstacle is non-celiac plexus sources of pain (eg, liver and bone metastases). In a prespecified exploratory multivariable analysis, older age was predictive of a positive response. There appear to be age-related changes in nociceptive pain perception[28] with older patients (above age 40 years) having reduced offset analgesia,[29] a form of endogenous pain inhibition. Furthermore, some published literature suggests that older patients react better than younger patients to opioids[30] and palliative radiotherapy.[31]

Some strengths of this trial include its international, multi-institutional nature, the rigorous quality assurance measures employed, and the mandated inclusion of a palliative care nurse practitioner in follow-up. A limitation of this study is the absence of a control

group. Pain is a challenging endpoint, being subjective and labile; we attempted to partially overcome these challenges by removing from analysis those with unstable pain levels before treatment. Results at the 6-week timepoint, a secondary endpoint, should be interpreted in the context of substantial patient dropout, since only 67 evaluable patients reported pain level at 6-weeks and 69 reported opioid use (12 evaluable patients had died by this point). Likewise, compliance with the pain diary was low, preventing a comprehensive analysis of daily pain scores. Potentially, this could have been improved with better monitoring. Nonetheless, the decreases in pain interference on daily living scores adds credibility that the intervention did indeed decrease pain intensity. Similarly, the decrease in opioid usage in those with a pain improvement, and conversely an increase in those whose pain did not improve, suggests a true treatment effect. Pharmacological pain management might have been suboptimal at enrolment, hence the protocol was amended in July, 2018, to include a palliative nurse assessment before treatment; however, in practice, this occurred in just 38 of 90 evaluable patients. A wash-in period to optimise analgesia was not included. An additional limitation is the use of high-technology radiotherapy, which might not be universally available. We would not recommend that this technique be used at centres that do not have CT-based or MRI-based image-guided radiotherapy, or by clinicians who do not have experience in abdominal stereotactic body radiotherapy. The trial's physician choice approach to inclusion of the primary tumour within the target volume provides a degree of uncertainty regarding optimal target volume definition. In a wider context, we are unable to comment on the longer-term efficacy of this intervention beyond 6 weeks; we are also not able to compare the palliative efficacy of celiac plexus radiosurgery with more conventional radiation approaches targeting the primary tumours.

In conclusion, celiac plexus radiosurgery could potentially be a new treatment option for retroperitoneal pain syndrome. Our findings should be compared with other options (eg, a traditional celiac block) in a randomised, larger-scale trial that would also allow a more accurate assessment of toxicity. Future studies should more comprehensively assess the contribution of radiation to the primary tumour.

#### Contributors

Study design: YRL, LSF, TG, MB-A, LAD, ZS, APD, TM, CZ, DH, OMo, TG, SD, and LAD. Enrolment and clinical care: YRL, MM, JW, SD, ASB, DADP, AA, DL, RMP, MB, SD, OMa, TM, DH, OMo, GJ, TG, and LAD. Local lead investigators: YRL, JW, ASB, DADP, AA, DL, RMP, MB, and LAD. Statistics: LSF and RF. Data interpretation: LSF, RF, YRL, CZ, TG, and LAD. Manuscript writing and editing: YRL, LSF, RF, SD, MM, ASB, DADP, AA, DL, RMP, MB, SD, APD, OMa, TM, CZ, DH, OMo, GJ, TG, and LAD. All authors had access to all the data reported in the study. LSF, RF, and YRL accessed and verified the data.

#### Declaration of interests

YRL reports receiving grant funding for this study from Gateway for Cancer Research and the Israel Cancer Association; has received research funding for other studies from Karyopharm Therapeutics, Checkmate Pharmaceuticals (purchased by Regeneron Pharmaceuticals), and Bristol-Myers Squibb; and has received honoraria from Roche Genetech, and has stock ownership in Protean Biodiagnostics. LAD reported being past president and chair of the American Society for Radiation Oncology; had a licensing agreement with Raysearch during the accrual for the present study; and has accepted honoraria from AstraZeneca. LSF reported his institution receiving payment from Gateway for Cancer Research; has clarified that he was at first chairman of the data and safety monitoring board for this trial, and later switched to be the statistician of the data and safety monitoring board; no separate payments were made to him or to his institution for this work. ASB reported having received an honorarium from Eisai. DADP reported having received payment or honoraria from the American Society of Clinical Oncology and travel support from the American Society for Radiation Oncology. All other authors declare no competing interests.

#### Data sharing

The study protocol is available in the appendix. The informed consent form has been previously published.[12] Specific data requests by academic researchers who provide a methodologically sound proposal will be considered by the principal investigator (YRL) for 5 years after publication. A data sharing plan was not included in the trial protocol and hence data sharing will be conditional upon receiving the approval of the Institutional Review Board of the Sheba Medical Center. A data access agreement will be required for access.

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