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ORIGINAL RESEARCH

Investigating the Efficacy and Safety of the CyberKnife System for Treating Primary Pancreatic Cancer with Metastases to the Gastrointestinal Tract

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Objective: This study aimed to investigate the effectiveness and safety of CyberKnife in the treatment of primary pancreatic cancer with metastases to the gastrointestinal tract (ie, primary pancreatic adenocarcinoma metastasizing to gastrointestinal organs).

Methods: A total of 106 patients with primary pancreatic cancer and metastases to the gastrointestinal tract admitted to our hospital received CyberKnife treatment. Recent treatment efficacy (assessed at 3 months post-treatment), median survival period, pain levels, and adverse reactions were analyzed.

Results: Among the 106 patients, 17 cases (16.04%) achieved complete response (CR), 61 cases (57.55%) achieved partial response (PR), 20 cases (18.87%) had stable disease (SD), and 8 cases (7.55%) had progressive disease (PD), resulting in an objective response rate (ORR) of 73.59% and an overall disease control rate (DCR) of 92.45% (98 cases). The one-year and two-year overall survival (OS) rates were 74.53% and 55.66%, respectively, while the local control (LC) rates were 92.45% and 87.74%, respectively. The median OS was 8.17 months (range: 1–25 months). Mean pain scores (Visual Analog Scale) decreased significantly from 5.38±1.37 at baseline to 2.01±0.35 post-treatment ($p<0.001$). Abdominal and lumbar pain significantly improved after 2 weeks of radiotherapy. Among the 68 patients with baseline pain who experienced relief, analgesic medication was discontinued in 25 (36.8%) patients, reduced by ≥50% in 18 patients (26.5%), and by approximately 25% in 5 patients (7.3%). Quality of life improved in 27 patients, remained stable in 52, and declined in 27, yielding an overall improvement or stabilization rate of 74.53% (79 cases).

Conclusion: CyberKnife SBRT appears to be a promising treatment modality for managing primary pancreatic cancer with metastases to the gastrointestinal tract, with minimal adverse reactions.

Keywords: CyberKnife, pancreatic cancer, gastrointestinal metastases, stereotactic body radiotherapy, survival outcomes

Introduction

Gastrointestinal cancers are common malignancies posing a significant health burden in China. Global cancer statistics (2020) show gastric and colorectal cancers account for 5.6% and 10.0% of cases, respectively, with mortality rates ranking fourth and second worldwide.[1,2] Pancreatic cancer, a highly aggressive digestive malignancy, has seen rising incidence rates.[3] In China, it ranks eighth in urban incidence and fifth in mortality.[4] Prognosis remains poor, with a median survival of <6 months and 5-year survival <5% despite advances in surgery, chemotherapy, and radiotherapy.[5] By 2025, pancreatic cancer is projected to become the third leading cause of cancer deaths in Europe.[6]

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This study focuses on patients with primary pancreatic adenocarcinoma that has metastasized to gastrointestinal organs (eg, stomach, colon). These patients typically present with advanced disease, rendering them ineligible for curative surgery. Palliative radiotherapy and chemotherapy are standard but limited by pancreatic anatomy (proximity to radiosensitive organs) and the intrinsic radioresistance of pancreatic adenocarcinoma.[7]

CyberKnife, a robotic stereotactic body radiotherapy (SBRT) system, offers novel advantages for this cohort. It facilitates the delivery of SBRT with high precision. Its real-time image guidance and submillimetric precision enable high-dose tumor targeting while sparing adjacent organs.[8] Compared to conventional radiotherapy, CyberKnife SBRT achieves superior dose conformity, shorter treatment durations, and reduced toxicity—critical for managing metastases to gastrointestinal organs.[9,10] Despite promising applications in localized pancreatic cancer, data on its role in metastatic settings remain scarce. This study is the first to evaluate CyberKnife SBRT specifically for primary pancreatic cancer with metastases to the gastrointestinal tract, addressing a critical gap in precision radiotherapy for advanced disease.

Materials and Methods

Clinical Data

A total of 106 patients with histologically confirmed pancreatic ductal adenocarcinoma and radiologically verified metastases to gastrointestinal organs (eg, gastric or colonic lesions) admitted to our hospital from February 2020 to July 2021 were enrolled. The study included patients with de novo metastatic pancreatic cancer to GI organs as well as those who developed GI metastases after initial diagnosis of pancreatic cancer, provided they met other eligibility criteria. This prospective observational study was approved by the Ethics Committee of The First Hospital of Hebei Medical University (NO. 19-B056), and informed consent was obtained from all participants.

Inclusion and Exclusion Criteria

Inclusion criteria required an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2,[11] at least one measurable pancreatic primary lesion and at least one measurable metastasis to a gastrointestinal organ, and adequate blood, liver, and kidney function (hemoglobin ≥90 g/L, neutrophil count $\geq 2.0\times10^9$/L, platelet count $\geq 90\times10^9$/L, total bilirubin ≤1.2× upper limit of normal [ULN], aspartate aminotransferase/alanine aminotransferase ≤2.5×ULN, serum creatinine ≤1.25×ULN). Patients with prior treatments (eg, surgery, chemotherapy) were eligible if therapies were discontinued ≥4 weeks before CyberKnife. Exclusion criteria included concomitant malignancies other than the primary pancreatic cancer and its GI metastases, pregnancy/lactation, significant bleeding tendencies (prothrombin time <40% or platelet count $<50\times10^9$/L), presence of uncontrolled metastatic disease in other non-GI organs that would preclude benefit from localized treatment to GI metastases, and elevated bilirubin (>51 μmol/L) or liver enzymes without biliary obstruction.

CT Simulation and Localization

Fiducial markers were implanted at least one week prior to localization near the pancreatic tumor and/or GI metastases as deemed necessary for tracking. Patients were positioned using a Philips large-aperture CT simulation machine in supine or prone positions based on tumor location. For tumors affected by respiratory motion, a respiratory motion management (RPM) system was employed, and four-dimensional CT (4D-CT) scans were acquired to assess tumor motion. Patients underwent breath-hold training if consistent breath-hold was achievable; otherwise, free-breathing scans with motion-encompassing techniques (generating an internal target volume from the 4D-CT) were used. Scanning parameters included a tube current of 400 mAs and slice thickness/spacing of 1.5 mm. Localization images were transferred to the CyberKnife planning system for target delineation.

Target Delineation

Gross tumor volume (GTV) encompassed all radiologically confirmed lesions: primary pancreatic tumor, metastatic lymph nodes if targeted, and gastrointestinal metastases (≤5 cm in diameter; larger lesions required multidisciplinary approval). No clinical target volume (CTV) was routinely added for microscopic disease. For tumors exhibiting

significant respiratory motion as identified on 4D-CT, an Internal Target Volume (ITV) was created to encompass the GTV across all phases of respiration. The Planning target volume (PTV) expanded GTV or ITV by 2–5 mm to account for organ motion and setup errors, following International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62 guidelines.

Treatment Planning

Treatment plans were developed using 6 MV X-rays for SBRT delivery via the CyberKnife MultiPlan® Treatment Planning System. A median prescription dose of 45 Gy (range: 35–50 Gy) in 5 fractions was delivered to the primary pancreatic lesions and involved regional lymph nodes, if treated. Metastases to gastrointestinal organs received a median dose of 35 Gy (range: 30–40 Gy) in 3–5 fractions. Dose constraints included a maximum point dose (Dmax) of ≤25 Gy for stomach/small bowel and ≤18 Gy for duodenum, aiming to keep V20Gy of the stomach/duodenum/bowel to <10cc.[12] Representative planning CT images are shown in Figure 1.

Treatment Implementation

The CyberKnife system tracked tumor positions using fiducial markers and its Synchrony® Respiratory Tracking System for tumors affected by respiratory motion. This system correlates external optical markers with internal fiducial positions based on a periodically updated model. For lesions without significant motion or where fiducials were directly visualized, Xsight® Spine or Skull Tracking was used if applicable, or fiducial tracking alone. All targeted lesions (primary pancreatic, gastrointestinal metastases, and involved lymph nodes if planned) were irradiated. Treatment was administered after verifying six-dimensional positional accuracy.

Data Collection

Radiographic films were placed in phantoms to validate positional accuracy. After correcting six-dimensional errors, verification plans were compared to treatment plans using gamma analysis (1 mm/1%, 2 mm/2%, 3 mm/3%) and

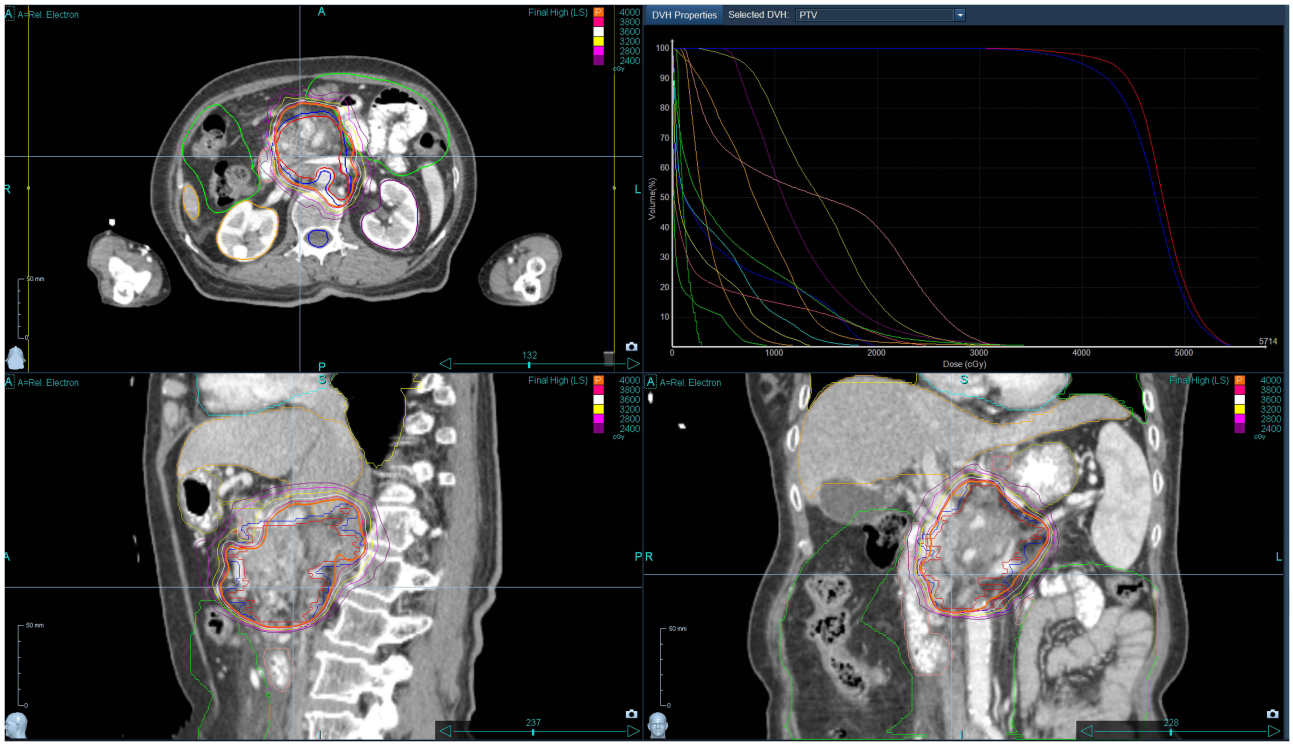

Figure 1 Representative planning CT images and dose distributions for patients with primary pancreatic cancer and metastases to the gastrointestinal tract.
Notes: Axial, sagittal, and coronal images are shown for the representative patient.

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distance-to-agreement (DTA, 2 mm) within the 50% maximum dose curve range. Data on PTV size, plan complexity (eg, beam numbers), and pass rates were analyzed.

Outcome Measures

Short-term efficacy was evaluated at 3 months post-treatment using Response Evaluation Criteria in Solid Tumors (RECIST 1.1),[13] categorizing responses as complete response (CR),[14] partial response (PR),[15] stable disease (SD), or progressive disease (PD). Pain severity was assessed via visual analog scale (VAS, 0–10) at baseline and 2 weeks post-treatment. Quality of life was measured using changes in Karnofsky Performance Status (KPS)[16] and the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30). The EORTC QLQ-C30 was administered at baseline and 3 months post-CyberKnife treatment to assess global health status/QoL and various functional and symptom scales. Adverse reactions were graded using WHO criteria (0–4)[17] and Radiation Therapy Oncology Group (RTOG) acute toxicity scales.

Statistics

Survival outcomes (overall survival [OS] and local control (LC)) were calculated from CyberKnife initiation to death or last follow-up (censored July 31, 2022), with censoring applied for non-cancer-related deaths or loss to follow-up. LC was defined as the absence of progression (increase in size by >20% or appearance of new features of progression) of the treated lesions based on RECIST 1.1 criteria. Pain scores (VAS) before and after treatment were compared using a paired *t*-test. Data were analyzed using SPSS 26.0, with $p<0.05$ considered statistically significant.

Results

Patient Characteristics

A total of 106 patients with primary pancreatic cancer and metastases to the gastrointestinal tract were included in this study. The baseline patient, tumor, and treatment information of the patients are summarized in Table 1.

Table 1 Patient, Tumor, and Treatment Characteristics of 106 Patients with Primary Pancreatic Cancer and Gastrointestinal Metastases Treated with CyberKnife SBRT

Item	Value
Gender (n)	
Male	77
Female	29
Age (years), mean ± SD	59.81±13.28
ECOG Performance Status (n)	
0	30
1	60
2	16
Site of Gastrointestinal Metastasis (n)	
Stomach	43
Rectum	27
Colon	26
Small Intestine	10
Number of GI Metastases (n)	
1	70
2	25
>2	11
Location of Primary Pancreatic Lesion (n)	
Head of Pancreas	80
Body and Tail of Pancreas	23

(*Continued*)

Table 1 (Continued).

Item	Value
Pathological Results (n)	
Adenocarcinoma	89
Adenosquamous Carcinoma	8
Mucinous Carcinoma	7
Acinar Cell Carcinoma	2
Clinical Stage of Primary Pancreatic Cancer (AJCC 8th ed.) (n)*	
Stage I	36
Stage II	42
Stage III	22
Stage IV (M1 at diagnosis, prior to current GI mets focus)	6
Differentiation Grade (Primary Pancreatic Tumor) (n)	
Poorly Differentiated	34
Moderately Differentiated	69
Well Differentiated	3
Tumor Volume (Primary Pancreatic Tumor, cm^3), mean ± SD	26.37±6.29
Prior Chemotherapy (n)	
Yes	60
No	46
Smoking (n)	13
Alcohol Consumption (n)	38
Complications	
Diabetes	19
Hypertension	13
Peripancreatic Invasion (Primary Pancreatic Tumor) (n)	18
Vascular Tumor Emboli (Primary Pancreatic Tumor) (n)	23
CA19-9 (U/mL), mean ± SD	254.76±13.29
Positive CA19-9 (>37 U/mL) (n)	39
TNM Stage (Primary Pancreatic Tumor, AJCC 8th ed.) (n)	
T3 (Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery)	92
T4 (Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor))	14
N0 (No regional lymph node metastasis)	91
N1 (1–3 region lymph node metastasis)	15

Notes: *Staging refers to initial TNM classification prior to development of GI metastases; all patients with GI metastases were classified as stage IV (M1) at study enrollment.

Treatment Efficacy

Among the 106 patients with primary pancreatic cancer with metastases to the gastrointestinal tract, 17 cases (16.04%) achieved CR, 61 cases (57.55%) achieved PR, 20 cases (18.87%) had SD, and 8 cases (7.55%) had PD. The overall objective response rate (ORR; CR+PR) was 73.59% (78 cases), and the DCR (CR+PR+SD) was 98 cases (92.45%), as shown in Figure 2.

Survival Outcomes

The overall survival rates at 1 year and 2 years for the 106 patients with primary Pancreatic Cancer with metastases to the gastrointestinal tract were 74.53% and 55.66%, respectively. The local control (LC) rates were 92.45% at 1 year and 87.74% at 2 years. The median overall survival was 8.17 months (range: 1–25 months), as shown in Figure 3.

Pain Relief Rate

Among the 106 patients, 68 (64.15%) experienced significant tumor-related pain prior to CyberKnife treatment. Of these 68 patients, pain locations included abdominal pain (n=45, 66.2%), lower back pain (n=23, 33.8%), or both. Pain was

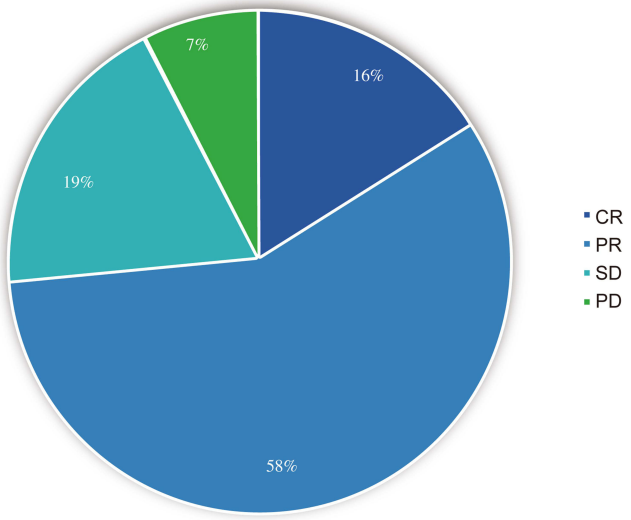

Figure 2 Short-term treatment efficacy in patients with primary pancreatic cancer with metastases to the gastrointestinal tract after CyberKnife therapy.
Notes: Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) are depicted.

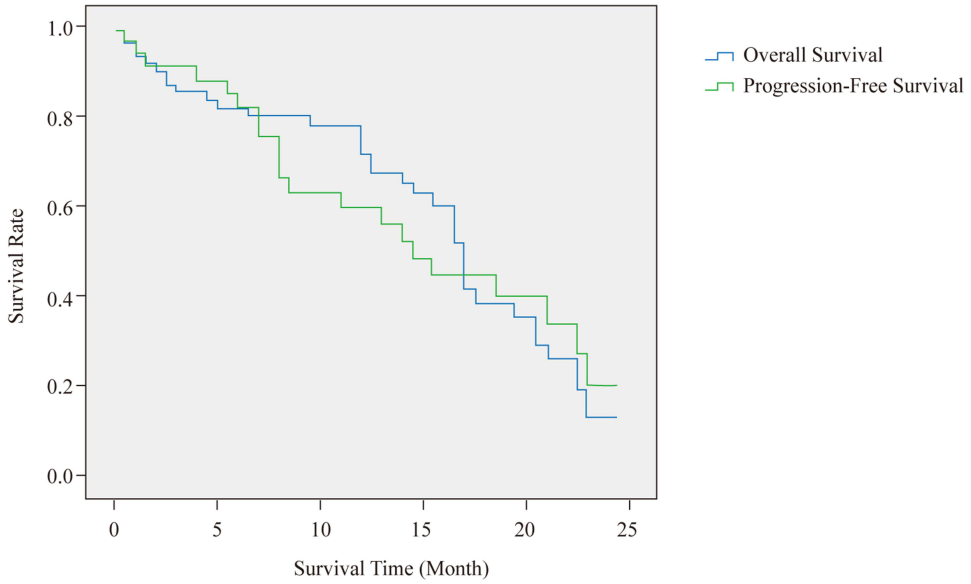

Figure 3 Overall survival and local control curves at 2 years in patients with primary pancreatic cancer with metastases to the gastrointestinal tract.

predominantly dull in nature. Pain intensity was assessed using the VAS, with scores ranging from 3 to 8, and the average score was (5.38±1.37). Prior to the procedure, oral hydrocodone hydrochloride was administered for pain relief, with doses ranging from 10 to 40 mg, taken every 12 hours based on pain severity. Significant pain relief in both the abdomen and lower back was observed after 2 weeks of radiation therapy. Among the 68 patients with baseline pain, 48 (70.6%) reported a clinically significant improvement. Specifically, analgesic medication was discontinued in 25 (36.8%) patients, reduced by ≥50% in 18 patients (26.5%), and by approximately 25% in 5 patients (7.3%). After treatment, the mean VAS score among these 68 patients significantly decreased from a baseline of (5.38±1.37) to (2.01±0.35) ($p<0.001$).

Quality of Life

The average EORTC QLQ-C30 global health status/QoL score at 3-months follow-up was 65.43±12.31 (Range from 45 to 78). Among the 106 patients with primary pancreatic cancer with metastases to the gastrointestinal tract, changes in

Table 2 Adverse Reactions in Patients with Primary Pancreatic Cancer and Gastrointestinal Metastases

Adverse Reactions	Number of Patients (n=106)
Grade I (n)	
Nausea	17
Vomiting	12
Abdominal Pain	15
Diarrhea	13
Grade II (n)	
Nausea	6
Vomiting	5
Abdominal Pain	6
Diarrhea	18
Grade III (n)	
Late-stage Gastrointestinal Reaction (Duodenal Ulcer Bleeding)	1

KPS scores from baseline to 3 months post-treatment showed that 27 cases (25.5%) showed improvement in quality of life (KPS score increased by ≥10 points), 52 cases (49.0%) remained stable (KPS change <10 points), and 27 cases (25.5%) experienced a decline (KPS score decreased by ≥10 points). The overall improvement or stabilization rate in quality of life based on KPS was 79 cases (74.53%).

Adverse Reactions

There were no serious complications, such as pancreatic fistula, intestinal injury, abdominal infection, or abdominal bleeding, during the baseline fiducial marker implantation. In the later stage of treatment, the total incidence of acute grade I–II nausea, vomiting, abdominal pain, and diarrhea was observed in varying degrees among patients, with specific counts detailed in Table 2. Overall, 73 patients (68.9%) experienced at least one grade I or II GI adverse event. One patient developed a grade III late gastrointestinal reaction, characterized by bleeding from a duodenal ulcer at 7 months post-treatment, which was managed conservatively. These findings are summarized in Table 2.

Discussion

Patients with pancreatic ductal adenocarcinoma (PDAC) and metastases to the gastrointestinal tract have a poor prognosis, with median survival historically ranging from 6 to 10 months.[18] Compared to conventional radiotherapy studies (median OS 6–8 months),[19] our results demonstrate comparable if not slightly improved survival (median OS 8.17 months) and promising local control (92.45% DCR, with an LC rate of 92.45% at 1 year), aligning with the advantages of stereotactic body radiotherapy (SBRT) in dose escalation.[20] Even with targeted therapies, survival gains remain modest (2–4 months).[19] Conventional radiotherapy is often limited to <50 Gy due to toxicity concerns, resulting in high local failure rates.[21] CyberKnife's ability to deliver ablative doses while sparing organs at risk addresses this critical gap for both the primary tumor and metastatic sites.[22–25]

CyberKnife's robotic precision enables six-dimensional spatial targeting without immobilization frames, achieving superior accuracy compared to frame-based systems.[26,27] Koong et al[28] reported 100% local control in stage I PDAC with 25 Gy single-fraction SBRT, while Schellenberg et al[29] observed 19% local progression in stage II disease. Our study extends these findings to PDAC with GI metastases, showing comparable local control (92.45% DCR, with an LC rate of 92.45% at 1 year) despite advanced disease, suggesting SBRT's applicability across stages. The 7.55% PD rate underscores CyberKnife SBRT's efficacy in delaying progression at treated sites.

Notably, patients whose primary pancreatic tumor was initially stage I/II (AJCC 8th ed) but subsequently developed GI metastases (stage IV disease) still exhibited poor survival (median OS 8.17 months), likely due to the aggressive nature of metastatic pancreatic cancer, potentially including occult metastases undetected at diagnosis or aggressive

tumor biology. Su et al[30] and Song et al[31] reported median OS of 9.0–12.5 months in mixed cohorts of unresectable or metastatic pancreatic cancer treated with CyberKnife, while AiMin et al[32] observed 8.5 months in stage IV disease. Our survival outcomes (1-year OS 74.53%, 2-year OS 55.66%) are encouraging within this context and surpass historical data,[19] possibly reflecting patient selection for oligometastatic disease amenable to SBRT or improved supportive care.

Pain relief was significant (VAS reduction from 5.38±1.37 to 2.01±0.35, $p<0.001$), reducing opioid dependence in a substantial proportion of patients (eg, discontinuation in 36.8% of those with baseline pain). Quality of life improved/stabilized in 74.53% based on KPS changes, and the mean EORTC QLQ-C30 global health score was maintained at 65.4 ±12.3 at 3 months, consistent with SBRT's symptom palliation benefits.[33,34] Steinmann et al[35] reported similar gains in brain metastases, though our study is one of the few to quantify this in PDAC with metastases to the gastrointestinal tract.

Adverse events were predominantly mild (most commonly grade I–II nausea/vomiting, abdominal pain, and diarrhea, with 68.9% experiencing at least one such event), with one grade III late duodenal ulcer. This safety profile aligns with Sun et al[36] attributable to CyberKnife's sharp dose gradient and motion tracking. By limiting PTV margins and fractionating doses (eg, 45 Gy/5 fractions to the pancreas), we minimized gastrointestinal toxicity to organs at risk, while delivering ablative doses to the metastatic GI lesions (eg, 30–40 Gy in 3–5 fractions).

There are several limitations in this study. Firstly, the sample size was relatively small, including only 106 patients with primary pancreatic cancer with metastases to the gastrointestinal tract. The limited sample size may affect the stability and generalizability of the research results. Secondly, this study adopted an observational study design without a control group, which means that it is unable to exclude the influence of other confounding factors on the treatment effects. Thirdly, the follow-up period of this study was relatively short, ranging from 1 to 25 months, thus limiting the evaluation of long-term treatment effects and survival rates. Fourthly, the sample selection process lacked randomness, and patients with an expected survival of less than 12 weeks were excluded, which may have introduced a selection bias towards patients with a potentially better prognosis. Lastly, this study mainly focused on the Chinese population, and the results may be influenced by race and geographic limitations, requiring further validation in larger and more diverse cohorts.

In conclusion, SBRT delivered via the CyberKnife system appears to be a promising treatment modality for managing primary pancreatic cancer with metastases to the gastrointestinal tract by potentially prolonging patients' survival, alleviating pain, improving quality of life, achieving good local tumor control, and mitigating related gastrointestinal adverse reactions. The treatment was generally well-tolerated, with severe adverse reactions being minimal. In future research, we recommend larger, prospective, and ideally randomized controlled trials to expand the sample size and optimize sampling methods to enhance the reliability and validity of the research findings, thereby more comprehensively and accurately revealing the benefits and limitations of this approach. This will assist patients with this challenging presentation of advanced-stage pancreatic cancer in selecting more targeted treatment options.

Abbreviations

CR, complete response; SD, stable disease; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; ICRU, International Commission on Radiation Units; OARs, organs at risk; GTV, gross tumor volume; PTV, planning target volume; DTA, distance to agreement; RTOG, Radiation Therapy Oncology Group; VAS, visual analog scale; KPS, Karnofsky Performance Status; PR, partial response; PD, progressive disease; LC, local control; OS, overall survival; SBRT, stereotactic body radiotherapy; RPM, respiratory motion management; ITV, internal target volume; 4D-CT, four-dimensional computed tomography; GI, gastrointestinal; ORR, objective response rate.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The current study was conducted in accordance with the Helsinki Declaration of the World Medical Association and approved by the Ethics Committee of The First Hospital of Hebei Medical University. Informed consent was obtained from all the study subjects before enrollment.

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Disclosure

The authors declare that they have no competing interests in this work.

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