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Successful Management of Acute SMV occlusion in Pancreatic Conversion Surgery After Carbon Ion Radiotherapy: A rare complication and surgical pitfall

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Case Report

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Successful Management of Acute SMV occlusion in Pancreatic Conversion Surgery After Carbon Ion Radiotherapy: A rare complication and surgical pitfall.

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Abstract

Background:

Pancreatic ductal adenocarcinoma (PDAC) is often locally advanced at diagnosis, and multimodal strategies including conversion therapy are used to increase the chance of margin-negative resection. Carbon-ion radiotherapy (CIRT) enables strong local tumor control. However, the side effect of CIRT toward local vasculature has not yet been fully understood. Literatures regarding the surgical pitfall of vessel reconstruction after CIRT have barely been reported.

Case presentation:

A 45-year-old female initially diagnosed with locally advanced PDAC underwent 14 cycles of systemic chemotherapy followed by CIRT. After conversion, she underwent distal pancreatectomy with common hepatic artery divestment. Superior mesenteric vein (SMV) was partially trimmed due to dense adhesion between pancreas, resulting in a 1.5cm defect. The defect was repaired primarily with 5-0 Prolene suture. On postoperative day2, she developed high fever and rapid deterioration of liver function. Urgent contrast-enhanced computed tomography demonstrated critical narrowing/near-occlusion of portal vein/SMV without definite thrombus. Emergent exploratory laparotomy showed severe intimal fibrosis of SMV causing luminal compromise. The SMV defect was reconstructed using patch augmentation. The patient achieved an R0 resection with final pathological finding revealing residual ductal adenocarcinoma in a fibrotic background (pT1b pN0). Her Liver function rapidly recovered after the venous reconstruction.

Conclusions:

This case shows a rare post-CIRT vascular complication with SMV to portal vein fibrosis causing acute hepatic ischemia after pancreatic cancer conversion surgery, which was successfully rescued with prompt patch augmentation. To avoid such complications in conversion surgery for locally advanced pancreatic cancer (LAPC), it is of crucial importance to take radiation-related vasculopathy into consideration during the manipulation of vasculature nearby to the previously CIRT-radiated area.

Background:

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, with a dismal 5-year overall survival rate of approximately 13% across all stage[1, 2]. At initial diagnosis, nearly 30–35% of patients present with locally advanced pancreatic cancer (LAPC) or borderline resectable disease[3]. Upfront surgery is considered suboptimal in cases with extensive vascular involvement because of the high margin-positive surgery rate [3, 4].

Systemic chemotherapy such as FOLFIRINOX or gemcitabine plus nab-paclitaxel chemotherapy remains the cornerstone of initial management for unresectable or borderline resectable PDAC. Its aim is to both local and systemic control as well as to select suitable candidates for surgery. Nevertheless, treatment failure remains common and is driven by both distant metastasis and uncontrolled local progression[2, 5, 6]. Achieving durable locoregional tumor control and enabling successful conversion to margin-negative (R0) resection are key goals in multimodal treatment strategies[7].

Carbon-ion radiotherapy (CIRT) provides distinct physical and radiobiological advantages that may overcome PDAC treatment resistance[8-11]. Carbon ions have an inverted depth-dose distribution culminating in a sharp Bragg peak, enabling precise high-dose delivery to the target while sharply sparing surrounding luminal organs at risks (OARs)[12]. Clinical series of CIRT in locally-advanced PDAC have demonstrated favorable locoregional control, with reported 2-year local control rates of 76.1%, median OS exceeding 29 months [13].

When applied as neoadjuvant or conversion strategy for advanced PDAC with vascular involvement, CIRT has been associated with substantial pathologic tumor regression. Marked histopathological response (Evans grade III–IV) has been reported in up to 83% of resected cases. By comparison, historical studies of photon-based chemoradiotherapy or total neoadjuvant chemotherapy have reported a response rate of merely 10% to 40%[8]. Favorable surgical and local control outcomes have also been reported, with R0 resection rates approaching 92% among patients undergoing conversion surgery and a low incidence of local recurrence within the irradiated field[14]. Nonetheless, several practical questions remain, including how to best integrate CIRT with systemic chemotherapy, particularly in balancing concurrent treatment intensity against the total duration of chemotherapy; the lack of reliable tools for assessing treatment response after CIRT; and the effects of irradiation on surrounding vasculature [10, 13].

To date, literatures regarding vascular complications after RT or CIRT for PDAC remain limited. Even less are those which received conversion surgery following CIRT. When it comes to vascular reconstruction after CIRT, the optimal approach and surgical pitfall for vascular reconstruction have not yet been fully elucidated. Herein, we report a rare case of severe venous fibrosis and early postoperative venous obstruction shortly after distal pancreatectomy with SMV injury and repair. Considering the promising application of CIRT in the treatment of pancreatic cancer, it is important to have more awareness about the potential vascular-related complications. This experience highlights the need for heightened perioperative vigilance and careful consideration of radiation-induced venous fibrosis and compromised vessel healing when performing vascular reconstruction on patients previously treated with CIRT for pancreatic cancer.

Case presentation:

A 45-year-old woman without systemic underlying presented with dull epigastric pain for approximately 2 months. Abdominal computed tomography (CT) revealed a 4.6cm, hypodense lesion at pancreatic body with encasement of common hepatic artery, portal vein, SMV and splenic vein. Biopsy confirmed the diagnosis of pancreatic ductal adenocarcinoma. Initial clinical stage was T4N0. With the impression of locally advanced PDAC, she received SLOG regimen chemotherapy (oxaliplatin/gemcitabine/tegafur–gimeracil–oteracil) for 14 cycles, followed by carbon ion radiotherapy (CIRT). The prescribed radiation doses were as follows: 6000 cGy (or GyE) to the FDG-avid tumor, 5520 cGy to the gross tumor, 5040 cGy to the lymph nodes and blood vessels adjacent to the tumor, and 3960 cGy to the subclinical regions. CT imaging after combined chemotherapy and carbon-ion radiotherapy revealed fibrotic change around pancreas body adjacent to portal vein with remarkable tumor regression. Tumor marker CA199 had dropped significantly from 979 (U/mL) at diagnosis to 21.7 (U/mL) before surgery. Therefore, she underwent conversion surgery with distal pancreatectomy and common hepatic artery (CHA) divestment. Dense adhesion between SMV and pancreas was encountered during dissection. Part of SMV had to be trimmed, leaving a 1.5cm venous defect. The venous defect was then managed by primary repair using 5-0 Prolene (Figure 1).

On postoperative day 1 (POD1), the elevated AST and ALT levels (909 and 740 U/L, respectively) were initially suspected to be due to liver injury caused by portal vein clamping during venous repair. However, on POD2, she developed worsening abdominal pain, tachycardia and remarkably elevated AST/ALT (2101/1738 U/L). Abdominal CT revealed severe narrowing to near-complete occlusion at portal vein/SMV with hypoperfusion of live (Figure 2). Notably, no definite thrombus was identified, and other portal venous branches remained opacified.

Emergent exploratory laparotomy was performed for presumed postoperative vascular compromise involving the SMV–portal system. The SMA, SMV, and portal vein were explored. (Figure 3A) Venotomy of the SMV was then performed, and thickened venous intima was observed (Figure 3B). No thrombus was found within the SMV, and strong backflow was noted. The SMV was subsequently reconstructed using patch augmentation with a bovine pericardial patch (approximately 3 × 2 cm). (Figure 3C)
After the second operation, continuous heparin infusion was maintained postoperatively to support patency of the reconstructed portal venous/SMV flow. Her liver function improved rapidly back to normal (trend of liver enzyme level is shown in Figure 4), indicating successful restoration of venous flow. The remainder of the postoperative course was uneventful. Follow-up of abdominal CT on postoperative day 11 showed fair liver perfusion without signs of portal hypertension, despite the foreseenable occlusion of the reconstructed portal vein–superior mesenteric vein (SMV). (Figure 5).

Final pathology showed ductal adenocarcinoma with residual disease in a fibrotic background (Figure 6A). Tumor was confined to the pancreas with pT1b pN0 (Stage IA), with R0 resection status and tumor regression grade 1. The closest invasive margin was over 1.5 mm. Lymphovascular invasion and perineural invasion were not identified, and the spleen was free of tumor. Notably, the pathological finding also revealed significant venous fibrosis, compatible with our clinical finding of thickened venous intima (Figure6B). The patient was discharged on POD30 after a prolonged stay due to delayed gastric emptying and postoperative ileus. Her hemodynamic status and liver function had returned to normal by discharge.

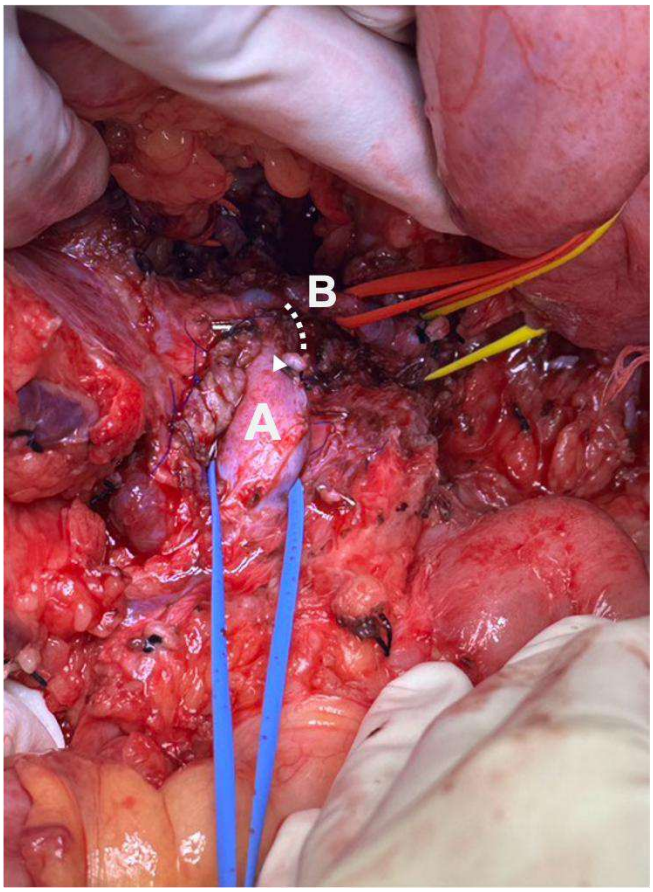


Figure 1. Primary repair with 5-0 Prolene for the superior mesenteric vein (SMV) defect. A: SMV; B: common hepatic artery; white triangle: ligated splenic vein; dash line: running suture with 5-0 Prolene.



Figure 2. Venous stenosis (yellow arrow) from SMV (white arrowhead) to portal vein (yellow arrowhead) with liver ischemia (white arrow).

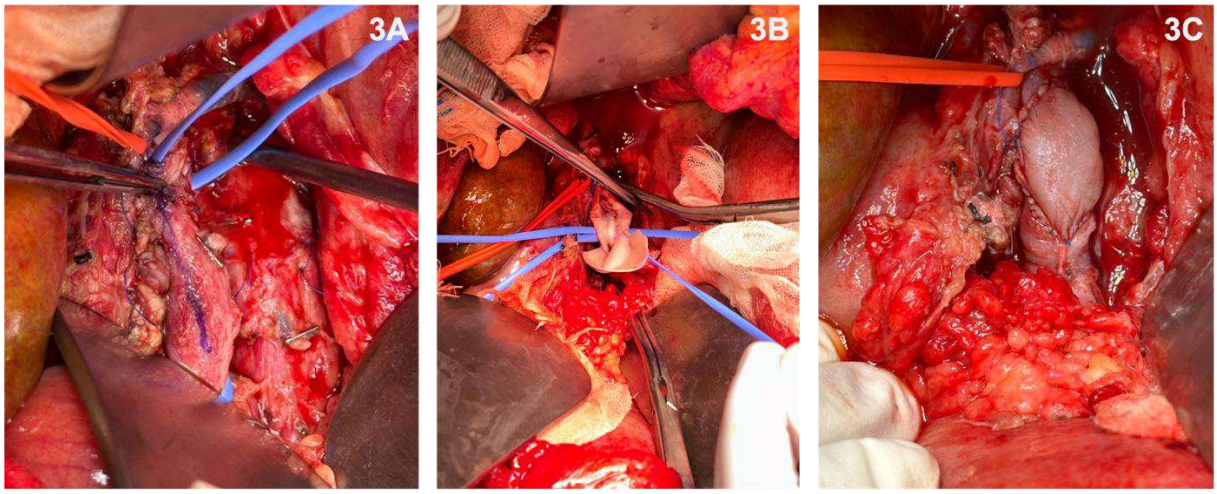


Figure 3. Intraoperative finding of the second operation.
(A) Stenosis and fibrosis of SMV to portal vein. The SMV (looped with blue vessel loop) showed long and narrowed segment with fibrotic change. (B) Thickened intima of SMV, and repaired with bovine patch (C) Reconstructed SMV with patch augmentation

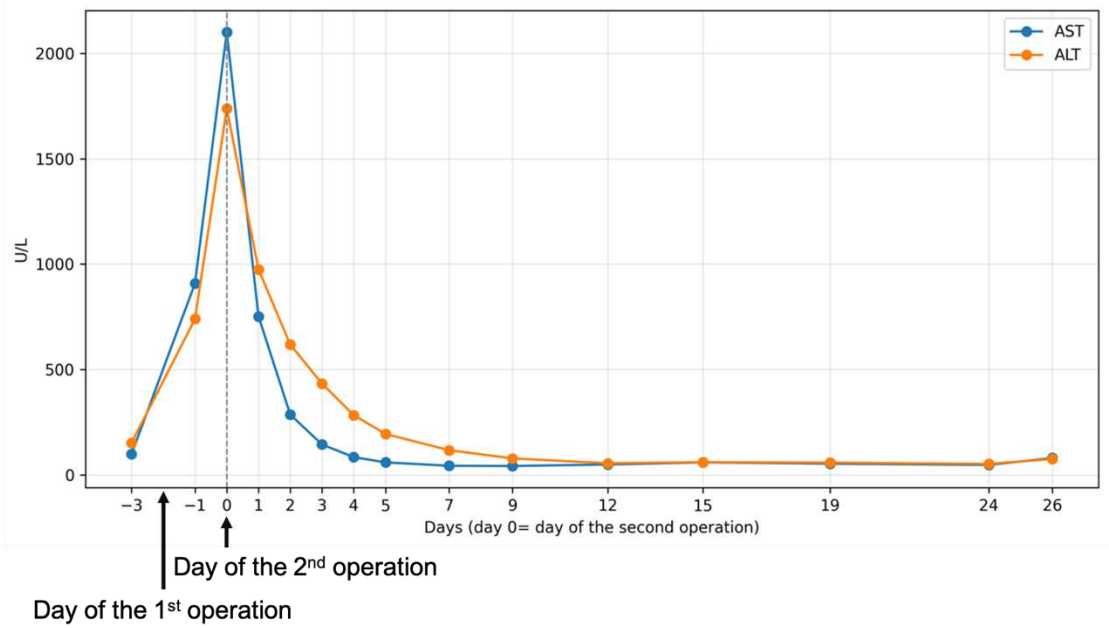


Figure 4. Trend of the liver enzyme after the second operation.
AST=Aspartate aminotransferase; ALT= Alanine aminotransferase.



Figure 5. Portal vein/SMV occlusion with flow interruption (yellow arrow). Fair liver perfusion after patch augmentation of SMV.

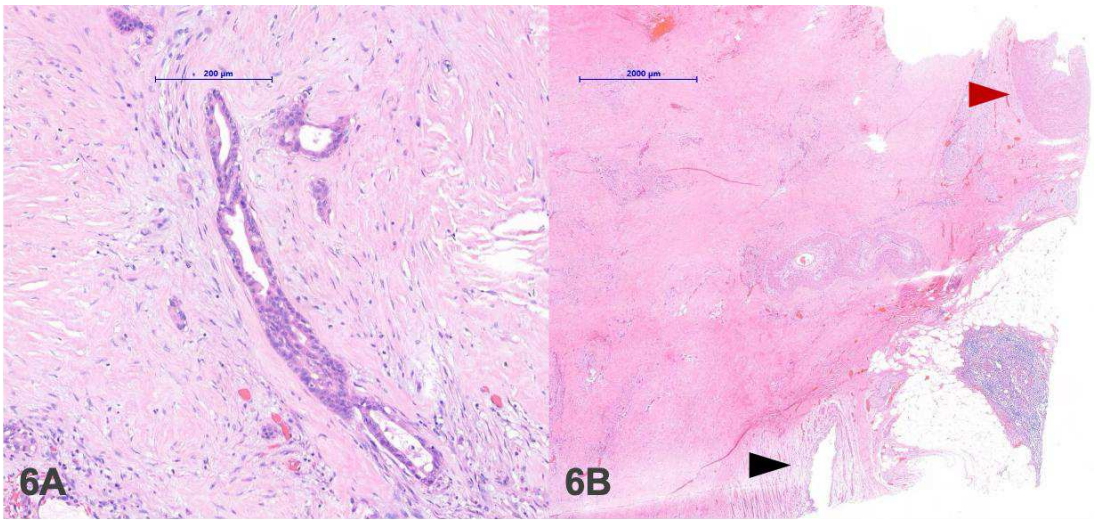


Figure 6. Pathological finding of the first operation showing residual of pancreatic ductal adenocarcinoma (A) and vascular fibrosis (B). The red arrowhead marked the fibrosis of splenic artery, while the black arrowhead marked the fibrosis of SMV.

Discussion

To our knowledge, there has been limited literatures emphasizing the vascular complications after conversion surgery on previously CIRT-treated PDAC. We presented a rare case of initially unresectable PDAC which had been previously treated by CIRT, and developed acute portal vein/SMV occlusion following conversion surgery with venous reconstruction. With timely recognition and prompt management, we were able to successfully salvage the complication, resulting in rapid restoration of liver perfusion and favorable clinical recovery. Our experience showcased the need of high clinical vigilance and cautious approach while performing venous reconstruction on patient previously treated with CIRT because of radiation-induced venous fibrosis.

In the last few decades, several approaches tried to improve the oncological outcome of patients with locally advanced pancreatic cancer (LAPC). One important concept is downstaging to potential conversion surgery. With the promising local effects of radiotherapy, studies have shown potential benefit of chemoradiation over chemotherapy alone. Comparing with traditional radiotherapy, carbon ion therapy on pancreatic cancer has just been recently introduced over the past few years. Although the therapeutic benefit of CIRT on PDAC still lack the supports of solid evidence, some preliminary studies on CIRT in locally-advanced PDAC have demonstrated favorable locoregional control, with reported 2-year local control rates of 76.1%, median overall survival exceeding 29 months.[13] Lai et al reported estimated 1-year LC, OS, and DFS rates of 91%, 82.3%, and 43.5%, respectively. The conversion surgery rate was reported to be 22% for initially unresectable tumors[11]. However, the promising outcome of CIRT does not come without its side effect.

Ionizing radiation causes progressive vascular dysfunction via a dual process involving DNA double-strand breaks (DSBs) and excessive reactive oxygen species (ROS) production[15]. Radiation-induced DSBs activate ataxia-telangiectasia mutated kinase and promote the activation of NF-κB signaling, while ROS from water radiolysis and mitochondrial dysfunction activates redox-sensitive transcription factors including NF-κB, activator protein (AP)-1, and nuclear factor erythroid 2–related factor (NRF) 2. This amplifies inflammatory mediators and disrupts endothelial barrier integrity, increasing adhesion molecules that recruit inflammatory cells and fibrocytes, which further drives endothelial senescence, leading to excessive collagen deposition,

extracellular matrix accumulation, and ultimately vessel stenosis and fibrotic occlusion [16-21].

Multiple studies have targeted radiation-induced vascular disease (RIVD) and related tissue toxicities. Thoracic irradiation for breast cancer or Hodgkin lymphoma commonly leads to radiation-induced coronary artery disease (RICAD), which often affects the coronary arteries with adventitial fibrosis, medial destruction, and vulnerable intraplaque hemorrhage[20, 22-24]. Thoracic radiotherapy for pulmonary, mediastinal, or esophageal cancers can trigger acute radiation pneumonitis from endothelial barrier disruption and inflammatory cytokines, which leads to organizing alveolitis and late pulmonary fibrosis. Head and neck radiotherapy increases carotid stenosis and ischemic cerebrovascular events, while pelvic and abdominal irradiation can cause severe peripheral arterial disease [24-27].

Carbon-ion radiotherapy activates pathways similar to other forms of radiotherapy, producing endothelial dysfunction and fibroproliferative signaling, but it shows a higher RBE for intercellular adhesion molecule (ICAM)-1 induction than low- linear energy transfer (LET) X-rays. High-LET heavy ions also cause direct, complex and often irreparable DNA DSBs, leading to strong endothelial cytotoxic and pro-inflammatory effects[18]. Despite this cellular potency, carbon-ion therapy is associated with a lower incidence of severe late vascular and parenchymal toxicity[28]. However, high-dose CIRT near major vessels can still cause localized late focal complications, including vascular occlusion. In hepatocellular carcinoma (HCC), perihilar-type tumors treated with CIRT have a higher risk of late biliary strictures, leading to recurrent obstructive jaundice, refractory cholangitis, and death, with increased incidence when lesions involve the portal vein trunk branch region[29]. The relatively low incidence of related complications across other disease spectrums, such as pancreatic cancer in our case, is likely due to its only recent introduction into clinical management.

This case provides a rare but clinically critical mechanism of early postoperative venous obstruction after primary repair of SMV previously treated with carbon ion radiotherapy. The patient achieved tumor regression grade 1 after receiving chemotherapy and carbon ion radiotherapy (CIRT), and underwent conversion surgery for pancreatic cancer. After the first operation, she rapidly developed severe SMV–main portal vein occlusion with hypoperfusion of liver. Emergent reintervention revealed marked SMV intimal thickening without evidence of thrombus with strong backflow. This finding supported the concept that CIRT-associated vascular remodeling may have produced a fibrotic/stenotic venous segment which leads to

higher risk of luminal compromise compare to normal venous intima while performing primary repair on portal vein/SMV. Although follow-up of CT imaging on POD 11 still showed portal vein/SMV occlusion, the liver perfusion was in fair state, and there was no bowel congestion. This finding supports our hypothesis that the venous stricture of our patient is less likely due to technical failure of the previous primary repair, but rather a result of precipitated vascular fibrosis around the targeted area by preoperative CIRT. Furthermore, this finding further emphasizes the importance of preventing immediate portal vein/SMV occlusion after surgery. Although chronic venous occlusion seems inevitable as our case had demonstrated, this allows liver to build up collateral venous return and prevents acute liver failure.

From a surgical standpoint, this experience suggests that radiation-related fibrosis should be taken into account while performing venous reconstruction on previous CIRT-treated cases. If preoperative imaging and intraoperative assessment raise suspicion of poor venous wall quality or severe intimal thickening, simple primary repair or tension-prone anastomosis may be insufficient because the reconstructed segment can be prone to early occlusion due to fibrosis and inflammatory change around the targeted area receiving preoperative CIRT. Therefore, the choice of reconstruction technique should prioritize on the establishment of adequate lumen caliber and durable vascular wall reconstruction such as patch augmentation or graft interposition with resection of fibrotic segments.

Finally, this case highlights the need for heightened vigilance and rapid management when patient presents with postoperative liver hypoperfusion after CIRT-treated pancreatic cancer. Early recognition of portal vein/SMV occlusion and prompt surgical management can convert a potentially catastrophic event into a favorable outcome. Future prospective investigations are needed to clarify the incidence, imaging predictors, and optimal reconstructive techniques for radiation-associated venous fibrosis; nonetheless, our case provides a valuable clinical experience that carbon-ion radiotherapy may induce venous wall fibrosis leading to stenotic obstruction.

Conclusions:

This case shows post-CIRT SMV to portal vein fibrosis after conversion surgery causing acute hepatic ischemia, which was successfully rescued with prompt patch augmentation. Taking radiation-related vasculopathy into consideration during the manipulation of vasculature nearby previous radiated area is of crucial importance while performing conversion surgery on pancreatic cancer patient with prior CIRT.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of National Cheng Kung University Hospital (A-EC-115-031).

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The consent form is retained by the authors and is available for review by the journal if requested.

Availability of data and materials

All the data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

A performed the literature review and drafted the manuscript. B supervised manuscript preparation and critically revised the manuscript. CDEF contributed to patient management, interpretation of clinical findings, and manuscript revision. All the authors read and approved the final manuscript.

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Abbreviations

AP: activator protein
CIRT: Carbon-ion radiotherapy
CT: computed tomography
DSBs: double-strand breaks
DNA: deoxyribonucleic acid
HCC: hepatocellular carcinoma
ICAM: intercellular adhesion molecule
LET: linear energy transfer
NF-κB: unclear factor kappa B
OARs: organs at risks
PDAC: Pancreatic ductal adenocarcinoma
POD: postoperative day
RBE: relative biological effectiveness
RICAD: radiation-induced coronary artery disease
RIVD: radiation-induced vascular disease

ROS: reactive oxygen species
NRF: nuclear factor erythroid 2-related factor
SMA: superior mesenteric artery
SMV: superior mesenteric vein
TNF-α: tumor necrosis factor-alpha
TGF-β: transforming growth factor-β

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