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Assessment of Multimodality Imaging for Ablative Irradiation for Isolated Local Recurrence of Pancreatic Cancer

Omer Sager* and Hakan Gamsiz

Department of Radiation Oncology, University of Health Sciences, Gulhane Medical Faculty, Ankara, Turkey

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Corresponding author: Omer Sager, Department of Radiation Oncology, University of Health Sciences, Gulhane Medical Faculty, Ankara, Turkey

Abstract

Objective: This study aimed to assess the contribution of multimodality imaging to target volume definition and treatment planning for ablative irradiation of isolated local recurrence of pancreatic cancer.

Materials and Methods: Our study was conducted at the Department of Radiation Oncology, University of Health Sciences, Gulhane Medical Faculty, a tertiary referral institution with extensive experience in multidisciplinary oncologic management, advanced image-guided radiotherapy, stereotactic irradiation, and adaptive treatment approaches. Patients with pancreatic cancer who developed isolated local recurrence after definitive local treatment were retrospectively evaluated.

Results: Integration of multimodality imaging resulted in clinically relevant modifications of target delineation in a substantial proportion of evaluated cases. Multimodality imaging improved visualization of recurrent tumor boundaries and facilitated differentiation between viable recurrent disease, postoperative fibrosis, soft-tissue changes, and adjacent normal structures. The benefit was particularly evident in recurrences located around the pancreatic bed, surgical anastomoses, mesenteric root, celiac axis, superior mesenteric artery, portal venous structures, and retroperitoneal interfaces. Multimodality imaging also improved assessment of the relationship between recurrent tumor and adjacent stomach, duodenum, small bowel, colon, kidneys, major vessels, and biliary structures.

Conclusion: Multimodality imaging may substantially improve target definition and treatment planning for ablative irradiation of isolated local recurrence of pancreatic cancer. Enhanced visualization of recurrent disease and more reliable discrimination between tumor and postoperative anatomical changes may improve the therapeutic ratio of stereotactic body radiotherapy (SBRT) by facilitating accurate target coverage while limiting radiation exposure to adjacent critical gastrointestinal and vascular structures.

Keywords: Pancreatic cancer; Isolated local recurrence; Stereotactic body radiotherapy; SBRT; Multimodality imaging; Target delineation; Adaptive radiotherapy; Ablative radiotherapy

Abbreviations: PDAC: Pancreatic Ductal Adenocarcinoma; ILR: Isolated Local Recurrence; SBRT: Stereotactic Body Radiotherapy; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; GTV-CT: Gross Tumor Volume CT

Introduction

Pancreatic cancer remains one of the most challenging gastrointestinal malignancies because of its aggressive biological behavior, high propensity for early dissemination, and limited long-term survival despite substantial advances in surgery and systemic therapy [1-3]. Pancreatic ductal adenocarcinoma (PDAC) constitutes the predominant histological subtype and frequently demonstrates both locoregional and distant patterns of treatment failure. Even among patients who undergo potentially curative-intent surgical resection followed by contemporary systemic therapy, disease recurrence remains common. A clinically important subgroup develops isolated local recurrence (ILR) without simultaneous distant metastatic dissemination.

The management of ILR represents a particularly complex clinical problem. Repeat surgical resection may be technically feasible in highly selected patients; however, reoperation is frequently limited by altered postoperative anatomy, vascular involvement, fibrosis, proximity to major vessels and bowel structures, patient comorbidity, and the anatomical location of the recurrence. Systemic therapy remains an important component of management, but local progression may produce substantial morbidity through pain, biliary obstruction, gastrointestinal involvement, vascular compression, or other locoregional complications. Consequently, local ablative treatment has become an increasingly relevant component of multidisciplinary management for appropriately selected patients with isolated recurrent disease [3-5].

Stereotactic body radiotherapy (SBRT) is particularly attractive in this setting because it permits delivery of highly conformal, biologically potent radiation doses over a limited number of treatment fractions. Several retrospective series and systematic reviews have demonstrated the feasibility of SBRT for isolated locally recurrent pancreatic cancer, including patients who have previously undergone pancreatic resection [3-5]. Contemporary prospective evidence remains more limited, but available data support continued investigation of ablative radiotherapy as a local treatment strategy in selected patients.

The technical challenge of ablative irradiation for recurrent pancreatic cancer, however, differs substantially from that encountered in the treatment of an intact primary pancreatic tumor. Surgical resection produces major anatomical alterations, including pancreatic jejunostomy, hepaticojejunostomy, gastrojejunostomy, vascular reconstruction, displacement of bowel loops, postoperative fibrosis, and changes in the normal relationships between the pancreas, stomach, duodenum, liver, spleen, and major abdominal vessels. Consequently, recurrent tumor may develop within or adjacent to complex postoperative anatomical planes where distinction between viable malignancy and benign postoperative tissue can be difficult.

Accurate target delineation is therefore fundamental to safe and effective ablative radiotherapy. In SBRT, steep dose gradients are intentionally created around the target to deliver a high biological dose while limiting exposure to surrounding normal structures. Even relatively small contouring uncertainties may consequently have clinically meaningful effects on tumor coverage or organ-at-risk exposure. This is especially important in pancreatic recurrence because the target may be directly adjacent to the stomach, duodenum, jejunal loops, colon, kidneys, liver, spinal cord, biliary structures, and major vascular structures [6-8]. Computed tomography (CT) remains the fundamental imaging modality for radiotherapy simulation because of its geometric reliability, compatibility with treatment planning systems, and ability to provide electron-density information for dose calculation.

Contrast-enhanced CT scan additionally provides valuable information concerning tumor enhancement, vascular involvement, and postoperative anatomy. Nevertheless, CT may have limited soft tissue contrast when recurrent tumor is embedded within postoperative fibrosis or when the recurrence is closely associated with vascular and gastrointestinal structures. Magnetic Resonance Imaging (MRI) provides complementary anatomical and tissue-characterization information. High soft-tissue contrast, multiplanar imaging, diffusion-weighted imaging, and contrast-enhanced sequences can facilitate visualization of recurrent pancreatic malignancy and improve differentiation between tumor and surrounding postoperative tissue. MRI-based contouring recommendations have specifically been developed for pancreatic radiotherapy because of its potential value in improving gross tumor volume and organ-at-risk delineation.

The potential role of MRI is particularly relevant after pancreatic surgery. Postoperative fibrosis and inflammatory changes may produce nonspecific soft-tissue abnormalities on CT, whereas recurrent tumors may appear as an infiltrative soft-tissue process around vascular structures or within the surgical bed. MRI may provide additional information regarding tissue composition, tumor conspicuity, diffusion characteristics, and the relationship between recurrent disease and adjacent organs. Functional imaging may provide further complementary information. In selected patients, positron emission tomography/computed tomography (PET/CT) can contribute to assessment of metabolic activity and detection of occult distant disease, thereby assisting patient selection for a potentially definitive local treatment approach.

However, functional imaging should generally be interpreted in conjunction with anatomical imaging because inflammatory and postoperative changes may demonstrate increased metabolic activity. Multimodality imaging may therefore be particularly valuable when the treatment objective is ablative local control rather than conventional palliative irradiation. In a curative-intent or potentially disease-controlling SBRT strategy, the treatment volume must encompass all clinically relevant recurrent diseases while avoiding unnecessary expansion into normal tissues. This balance is especially important in previously operated patients, in whom the recurrent lesion may be difficult to distinguish from fibrosis and in whom critical gastrointestinal structures may lie immediately adjacent to the target. Target definition also interacts directly with respiratory motion management.

Although pancreatic tumors may exhibit less motion than lesions in the upper abdomen, respiratory-induced displacement and deformation can still affect the position of recurrent disease and adjacent organs. Four-dimensional CT, respiratory-correlated imaging, breath-hold techniques, abdominal compression, fiducial-based image guidance, and MRI-based motion assessment may therefore contribute to reducing geometric uncertainty. Re-

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cent advances in MRI-guided radiotherapy have further expanded the potential role of multimodality imaging. Online MRI-guided treatment permits improved soft-tissue visualization immediately before and during treatment and may facilitate adaptive replanning according to daily changes in tumor position and gastrointestinal anatomy. Early clinical experience with MR-guided SBRT for recurrent pancreatic cancer suggests that this approach may enable ablative treatment while maintaining attention to the narrow therapeutic window imposed by adjacent gastrointestinal organs.

Current expert recommendations also emphasize the importance of appropriate target delineation, motion management, image guidance, and careful consideration of adjacent organs in pancreatic radiotherapy. Despite these advances, the specific contribution of multimodality imaging to target volume definition for ablative irradiation of isolated local pancreatic recurrence remains insufficiently characterized. There is a need to better understand how MRI integration modifies CT-based contours, whether imaging integration improves identification of postoperative recurrent disease, and whether more precise target definition translates into improved dosimetric characteristics. Accordingly, the present study aimed to assess the role of multimodality imaging in target definition and treatment planning for ablative irradiation of ILR of pancreatic cancer.

Materials and Methods

This retrospective study was conducted at the Department of Radiation Oncology, University of Health Sciences, Gulhane Medical Faculty, a tertiary referral institution with extensive experience in multidisciplinary management of gastrointestinal malignancies, stereotactic radiotherapy, image-guided treatment, and advanced treatment planning. Patients with histologically confirmed pancreatic cancer who subsequently developed ILR following definitive local treatment were retrospectively evaluated. The study population included patients in whom recurrent disease was considered suitable for definitive or ablative local irradiation following multidisciplinary assessment.

ILR was defined as radiologically or pathologically documented recurrent disease confined to the pancreatic surgical bed or regional locoregional compartment without evidence of distant metastatic disease requiring treatment of disseminated systemic disease at the time of radiotherapy planning. Patient eligibility for ablative irradiation was determined through multidisciplinary evaluation involving radiation oncology, medical oncology, surgical oncology, gastroenterology, diagnostic radiology, and other relevant specialties.

Selection criteria included:

- Isolated or predominantly isolated locoregional recurrence;
- Absence of uncontrolled distant metastatic disease;
- Adequate performance status;
- Clinically acceptable hepatic, renal, and hematological function;
- Appropriate interval from previous definitive treatment;
- Adequate recovery from surgery;
- Absence of uncontrolled gastrointestinal obstruction or active gastrointestinal bleeding;
- Anatomical feasibility of stereotactic irradiation;
- Availability of appropriate diagnostic imaging; and
- Consideration of previous radiotherapy exposure when applicable.

Patients with widespread metastatic disease or lesions judged unsuitable for safe ablative treatment because of extensive gastrointestinal or vascular involvement were excluded from the present analysis. All patients underwent multidisciplinary evaluation before treatment. Previous operative reports, pathology findings, systemic treatment history, radiation treatment records where applicable, serial imaging studies, and clinical status were reviewed. Attention was given to the temporal evolution of the recurrent lesion. New or enlarging soft-tissue abnormalities were assessed in conjunction with serial imaging, serum tumor markers when available, and clinical findings. The diagnostic evaluation generally included contrast-enhanced thoracoabdominal CT. Dedicated pancreatic imaging and MRI were obtained according to clinical availability and institutional practice.

In selected patients, PET/CT was additionally reviewed to assess metabolic activity and exclude unsuspected distant disease. The combination of serial imaging and multimodality assessment was considered particularly important because postoperative anatomical distortion and fibrosis may mimic recurrent malignancy. Patients underwent CT simulation in the supine position using individualized immobilization systems designed to minimize inter- and intrafraction setup variation. Simulation procedures were standardized as far as clinically feasible. Reproducible positioning of the thorax and upper abdomen was emphasized because of the proximity of the recurrent target to the stomach, small bowel, abdominal wall, and major vascular structures. Patients received respiratory and dietary preparation according to institutional practice.

When clinically appropriate, fasting and controlled gastrointestinal filling were used to reduce variability in stomach and bowel position. Thin-slice CT simulation images were acquired using a dedicated radiotherapy CT simulator. Intravenous contrast was administered when clinically appropriate to improve visualization of recurrent disease, vascular anatomy, and adjacent organs. Respiratory motion assessment was performed using available motion-management techniques. The planning CT served as

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the geometric reference dataset for treatment planning and dose calculation. MRI examinations were performed using dedicated abdominal or pancreatic imaging protocols.

MRI was reviewed with particular attention to:

- Recurrent Tumor Margins;
- Tumor–Vessel Relationships;
- Postoperative Fibrosis;
- Pancreatic Bed Anatomy;
- Surgical Anastomoses;
- Perivascular Tumor Extension;
- Diffusion Characteristics;
- Necrotic Or Heterogeneous Tumor Components; and
- Interfaces with the Stomach, Duodenum, Jejunum, Colon, Kidneys, And Biliary Structures.

MRI datasets were subsequently registered to the planning CT. Registration quality was evaluated by comparison of stable anatomical landmarks and major vascular structures. Potential uncertainties arising from differences in patient positioning, bowel filling, respiratory phase, and postoperative anatomical deformation were considered during the fusion process. Initial gross tumor volume (GTV-CT) was delineated using the planning CT dataset and conventional diagnostic imaging available at the time of treatment planning. The initial contour was subsequently reviewed following incorporation of MRI information. A second target volume, designated GTV-MRI, was generated or modified according to the additional anatomical and tissue-characterization information provided by MRI.

Attention was directed toward distinguishing recurrent tumor from:

- Postoperative Fibrosis;
- Inflammatory Changes;
- Vascular Structures;
- Surgical Clips;
- Anastomotic Changes;
- Adjacent Bowel Loops;
- Normal Pancreatic or Retroperitoneal Tissue; and
- Nonspecific Postoperative Soft-Tissue Thickening.

The final target volume represented the multidisciplinary consensus interpretation of all available imaging modalities. Clinical target volume expansion was individualized according to institutional practice, recurrence pattern, prior treatment, and perceived risk of microscopic extension. Planning target volume margins accounted for residual setup uncertainty, image-guidance accuracy, motion-management strategy, and treatment delivery technique. Given the proximity of recurrent pancreatic disease to radiosensitive gastrointestinal organs, margin selection was carefully balanced against the requirement for adequate tumor coverage.

Attention was directed toward delineation of the following organs and structures:

- Stomach;
- Duodenum;
- Small Bowel;
- Colon;
- Liver;
- Kidneys;
- Spinal Cord;
- Abdominal Wall;
- Major Vascular Structures;
- Biliary Structures; And
- Other Clinically Relevant Postoperative Anatomical Structures.

For previously irradiated patients, cumulative dose considerations were incorporated into treatment planning whenever prior radiation plans were available. Treatment plans were generated using advanced conformal radiotherapy techniques, including intensity-modulated radiotherapy and/or volumetric modulated arc therapy according to institutional practice. Ablative treatment plans were optimized to provide appropriate target coverage while maintaining dose constraints for critical organs.

Comparative planning was performed using:

1. CT-based target delineation; and
2. multimodality imaging-guided target delineation.

The two planning approaches were compared while maintaining the same treatment technique and prescription framework whenever technically feasible. Comparative dosimetric evaluation was performed between CT-only and multimodality imaging-guided plans. Dose-volume histogram analysis was used to quantify differences between treatment plans.

Results

Patients with ILR of pancreatic cancer following definitive local treatment were included in the analysis. The recurrent lesions demonstrated heterogeneous anatomical characteristics and were located within or adjacent to the pancreatic surgical bed, retroperitoneum, mesenteric root, perivascular regions, or postoperative anastomotic areas. The majority of patients had under-

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gone previous pancreatic surgery and systemic therapy. Previous treatment history was carefully reviewed because prior surgery and, in selected patients, previous radiation therapy substantially influenced both anatomical interpretation and treatment planning. Integration of MRI into the radiotherapy planning workflow resulted in clinically meaningful modifications of target volumes in a substantial proportion of evaluated cases.

The benefit of MRI was particularly apparent in lesions demonstrating:

- infiltrative morphology;
- indistinct CT margins;
- perivascular extension;
- proximity to surgical anastomoses;
- retroperitoneal localization;
- close contact with the stomach or duodenum;
- postoperative fibrosis; and
- heterogeneous contrast enhancement.

In several cases, CT-only imaging resulted in relatively broad contours because of uncertainty regarding the extent of recurrent disease. MRI allowed more selective delineation of the abnormal tissue and facilitated exclusion of adjacent postoperative changes. Conversely, MRI identified areas of suspected tumor extension that were poorly conspicuous on CT, resulting in expansion of the target in selected cases. Thus, multimodality imaging did not uniformly decrease target volume. Rather, it resulted in more anatomically individualized target definition, with both expansion and contraction of CT-derived contours depending on the imaging characteristics of each recurrence.

Discussion

Isolated local recurrence remains a clinically important pattern of failure following treatment of pancreatic cancer. Although distant metastatic progression is common, a subgroup of patients develops recurrence confined to the pancreatic bed or regional locoregional compartment. For these patients, aggressive local treatment may provide an opportunity for meaningful disease control, particularly when recurrence occurs after a prolonged disease-free interval and systemic disease remains controlled. Previous systematic reviews and retrospective series suggest that local treatment, including SBRT, can be feasible in carefully selected patients with isolated recurrence [3-5]. The present study focuses on a component of recurrent pancreatic cancer management that is sometimes underestimated: the accuracy of target definition itself.

The fundamental challenge in ablative irradiation of recurrent pancreatic cancer is that the target is frequently surrounded by anatomy that has been profoundly altered by previous surgery. Unlike treatment of an intact primary tumor, where recognizable pancreatic anatomy may assist target delineation, the postoperative setting may contain fibrosis, anastomotic changes, vascular reconstruction, clips, displaced bowel, inflammatory tissue, and altered organ relationships. Consequently, the recurrent lesion may not have a clearly identifiable anatomical boundary on CT. Our findings indicate that multimodality imaging, particularly CT-MRI fusion, can substantially improve the characterization of these complex recurrent lesions. MRI has several characteristics that make it particularly attractive for recurrent pancreatic cancer.

First, MRI provides superior soft-tissue contrast compared with CT. This may facilitate identification of recurrent tumor embedded within fibrotic postoperative tissue. Second, multiparametric MRI provides information beyond simple anatomical morphology. T1-weighted, T2-weighted, diffusion-weighted, and contrast-enhanced sequences may provide complementary information regarding tumor cellularity, tissue composition, enhancement, and anatomical extension. Third, MRI provides multiplanar visualization that may be particularly useful when recurrent disease extends along complex vascular or retroperitoneal planes. Published MRI-based contouring recommendations for pancreatic radiotherapy emphasize the potential value of MRI for improving delineation of both tumor and organs at risk [7].

Our findings extend this concept to the particularly challenging setting of ILR, where anatomical distortion makes CT-only contouring especially vulnerable to uncertainty. The therapeutic ratio is particularly important in pancreatic SBRT. Pancreatic recurrence is often located immediately adjacent to highly radiosensitive gastrointestinal organs. The stomach and duodenum may be separated from the recurrent lesion by only a few millimeters, and jejunal loops may occupy variable positions within the surgical bed. This anatomical proximity creates a narrow margin between effective tumor ablation and clinically significant toxicity. A contouring uncertainty of only a few millimeters may therefore determine whether an ablative dose can be safely delivered.

More precise target definition can potentially improve the therapeutic ratio in two complementary ways:

1. by reducing geographic miss through improved identification of recurrent tumor; and

2. by reducing unnecessary irradiation of normal tissues through exclusion of nonmalignant postoperative changes.

This concept is particularly relevant to dose-escalated SBRT and MRI-guided adaptive radiotherapy. Another important implication of our findings is the potential integration of multimodality imaging with adaptive radiotherapy. Pancreatic and upper abdominal anatomy can change substantially between treatment fractions because of differences in stomach filling, bowel position, respiratory motion, weight loss, tumor regression, or changes in postoperative anatomy. A treatment plan generated from a single simulation CT may therefore not optimally represent the anatomy present on every treatment day. MRI-guided radiotherapy offers

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the possibility of evaluating these anatomical changes immediately before treatment and adapting the treatment plan accordingly.

The clinical feasibility of SBRT for isolated local recurrence has been reported in multiple retrospective studies [3-5]. For patients with previously irradiated recurrent or locally progressive pancreatic cancer, SBRT reirradiation has also been investigated, with retrospective data supporting feasibility but emphasizing the importance of careful toxicity assessment. The practical implication of the present study is that multimodality imaging should be considered an integral component of treatment planning for selected patients with isolated local pancreatic recurrence rather than simply an optional diagnostic supplement. In conclusion, the present study demonstrates the potential value of multimodality imaging for ablative irradiation of ILR of pancreatic cancer.

Integration of MRI with planning CT improves visualization of recurrent disease, facilitates differentiation between recurrent tumor and postoperative fibrosis, and provides additional information regarding tumor relationships with major vessels and adjacent gastrointestinal structures. In the technically demanding setting of recurrent pancreatic cancer, where ablative treatment is frequently limited by the proximity of the stomach, duodenum, small bowel, and other critical structures, accurate target definition is essential for achieving an appropriate therapeutic ratio. CT-MRI fusion may therefore improve the precision of target delineation and facilitate more conformal stereotactic treatment planning while reducing unnecessary irradiation of uninvolved tissues. The potential integration of multimodality imaging with four-dimensional imaging, MRI-guided treatment, and online adaptive radiotherapy represents a promising direction for further improving the management of isolated local pancreatic recurrence.

Conflicts of Interest

There are no conflicts of interest and no acknowledgement.

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