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FULL PAPER

Diagnostic evaluation of simulation CT images for adjuvant radiotherapy in pancreatic adenocarcinoma

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Objective: The purpose of this study is to review simulation CT scans and evaluate their diagnostic value in patients treated with adjuvant radiotherapy for pancreatic adenocarcinoma.

Methods: 73 patients who had undergone simulation CT scans for adjuvant radiotherapy in pancreatic adenocarcinoma were reviewed. All simulation CT scans were reviewed by professional abdominal radiologists, who compared the images with corresponding prior CT scans to identify new lesions. Newly detected cancer-related lesions were classified into one of three categories: distant metastasis, locoregional recurrence and indeterminate lesions. Indeterminate lesions were reviewed for malignancy during follow-up imaging work-ups.

Results: Of 73 patients, distant metastasis, locoregional recurrence and indeterminate lesions were found in 4 (5.5%), 5 (6.8%) and 32 patients (43.8%), respectively. Among 32 indeterminate lesions, 24 (75.0%) were soft

tissue lesions neighbouring the superior mesenteric vessels. Follow-up PET-CT and diagnostic CT scans revealed that 43.7% of indeterminate lesions were malignant presenting local failures. The 3-year overall survival was significantly higher among patients who had no cancer-related lesions than among who did have such findings (44.8% vs 10.8%, $p = 0.002$).

Conclusion: Professional review of simulation CT scans have ample diagnostic value as they help detect early progressions or potential failures in patients treated with adjuvant radiotherapy for pancreatic adenocarcinoma. Simulation CT scans should be carefully reviewed before the delivery of adjuvant radiotherapy.

Advances in knowledge: Generally, simulation CT scan has been known to provide limited diagnostic values and clinical impact. However, the results of this study showed a high detection rate of cancer-related lesions, which could potentially affect subsequent treatment strategies in patients with pancreatic adenocarcinoma.

INTRODUCTION

As the fourth leading cause of all cancer deaths, pancreatic adenocarcinoma is a devastating disease with a 5-year survival rate of only 7%.^{1,2} Although surgical resection with multidisciplinary supports remains the only curative treatment, less than 20% of patients have resectable disease at the time of diagnosis.³ Given that recurrence occurs in as much as 90% of patients, adjuvant therapies such as radiotherapy, chemotherapy and combined approaches have been recommended even after successful curative resection.⁴ To decrease the rate of locoregional failure, adjuvant radiotherapy has been implemented in certain cases, although its survival benefit has been questioned in several randomised trials.⁵⁻⁷

Given the aggressive nature of pancreatic adenocarcinoma, early treatment failure is often found even within several weeks after surgery. According to our institutional treatment protocol for pancreatic cancer, adjuvant radiotherapy is delivered concurrently with adjuvant chemotherapy within 4–8 weeks after surgery. Therefore, CT simulation scans can serve as an early follow-up imaging work-up. Although general diagnostic reviews are performed by a radiation oncologist, CT simulation scans may further show newly developed or undetected metastatic or progressed lesions. Such simulation scans had not been routinely reviewed by radiologists in our institution. Therefore, by having experienced radiologists review these images, we aimed to

evaluate the diagnostic value of CT simulation scans in identifying newly developed lesions and their significance in modifying overall therapeutic plans.

METHODS AND MATERIALS

This study was approved by our institutional review board, and the requirement for informed consent was waived. From January 2001 to February 2016, 104 patients were referred for adjuvant radiotherapy after curative surgery for pancreatic cancer. Among them, 75 patients consented to receive adjuvant radiotherapy and underwent simulation CT scans. Except for 2 patients (incidental liver metastasis in 1 and decline in performance status in 1), 73 patients treated with adjuvant radiotherapy with/without concurrent chemotherapy were analysed.

Radiotherapy began within 4–8 weeks after surgery, and three-dimensional conformal radiotherapy was implemented with a dose of 45–54 Gy, targeting to the tumour bed and surrounding regional lymphatics. Simulation CT scans from the lower chest to lower abdomen were obtained with a 16-channel multidetector CT scanner (Brilliance Big Bore; Philips Healthcare, Amsterdam, The Netherlands). Transverse images were acquired by using 1.5 mm detector collimation, 120 kVp, tube-current modulation (160–230 mAs) and 5 mm slice thickness. All patients were administered intravenous contrast agents and scanned 70 s after the injection in a fixed time-delay manner to obtain portal venous phase images. Diagnostic reporting of simulation CT scans has not been established as a routine radiotherapy planning process.

To identify new abnormal findings, two board-certified radiologists with expertise in interpreting abdominopelvic CT studies reviewed all the simulation CT scans by comparing them with the corresponding past diagnostic CT images of patients scanned preoperatively/postoperatively. The radiologists were blinded to the clinical outcomes. The cancer-related findings were classified into one of the three categories: (1) distant metastasis, (2) locoregional recurrence and (3) indeterminate lesions warranting further evaluations or follow-ups. Additionally, benign yet clinically significant lesions were evaluated in all patients. Distant metastasis was defined as single or multiple, well-defined hypovascular nodules in the intra-abdominal solid organs or distant metastatic lymph nodes that were either newly detected or growing more than 50% on the simulation CT scans compared with the prior CT.⁸ Locoregional failure was defined as new necrotic soft tissue or growing soft tissue in the pancreatic/peripancreatic and regional lymphatic areas absent in corresponding postoperative CT scans. Indeterminate lesions were defined as either new non-necrotic soft tissue or new focal lesions that were too small to characterise in the solid organ. To define whether the indeterminate findings were benign or malignant, follow-up evaluations (CT or PET-CT) were reviewed. All new lesions on simulation CT scans were identified and classified by achieving consensus.

The overall survival time was defined as the interval between the date of surgery and date of the last follow-up visit or death. The Kaplan-Meier method with long-rank test was used for the calculation and statistical comparison of the overall survivals. Two-sided

p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using R statistical packages.⁹

RESULTS

The characteristics of the study population are summarised in Table 1. Patient age ranged from 35 to 76 years (median, 60), and 47 patients (64.4%) were male. The resection margin was positive in 18 patients (24.7%), and nodal metastasis was found in 48 patients (65.8%). Administered radiation doses ranged from 45.0 to 59.4 Gy (median, 50.4 Gy) and 57 patients (78.1%) received adjuvant chemotherapy concurrently with adjuvant radiotherapy. Adjuvant chemotherapy was withheld in patients with combined comorbidities (5 patients) and those who refused (11 patients).

Diagnostic review of CT simulation scans revealed 4 cases of distant metastasis (5.5%), 5 cases of locoregional failure (6.8%),

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Age (y)	
Median (range)	60 (35–76)
Gender	
Male	47 (64.4)
Female	26 (35.6)
Preoperative CA 19-9 (U ml ⁻¹)	
Mean (range)	73.2 (0.6–2745)
Resection margin status	
Positive	18 (24.7)
Negative	55 (75.3)
*Pathologic T stage	
T1	2 (2.7)
T2	1 (1.4)
T3	67 (91.8)
T4	3 (4.1)
*Pathologic N stage	
N0	25 (34.2)
N1	48 (65.8)
Types of surgery, <i>n</i> (%)	
PPPD	56 (76.7)
DP	17 (23.3)
Radiation dose (Gy)	
Median (range)	50.4 (45.0–59.4)
Concurrent chemotherapy	
Yes	57 (78.1)
No	16 (21.9)

CA 19-9, carbohydrate antigen 19-9; DP, distal pancreatectomy; PPPD, pylorus-preserving pancreaticoduodenectomy.

*According to American Joint Committee on Cancer seventh edition.

32 cases of indeterminate lesions (43.8%) and 21 cases of benign lesions (28.8%) (Table 2). Of the four patients with distant metastases, three patients had liver metastases manifested as a single nodule. The other patient had a single lung metastasis that appeared on the scanned basal lung. Locoregional failure manifested mostly as a growing soft tissue mass compared with prior CT scans or as necrotic soft tissue located either posterior to the superior mesenteric vessels or at the resection margin (Figure 1a). A total of 32 indeterminate lesions were noted, including 24 soft tissue lesions (75.0%) that were predominantly located posterior to the superior mesentery vessels (Table 3). Additionally, three lesions in the liver (9.4%) were irregularly margined nodules ranging from 1 to 2 cm. Of these indeterminate findings, 18 lesions (56.3%) were later found to be benign (Figure 1b), whereas the other 14 lesions (43.8%) were local recurrences at the posterior area to superior mesenteric vessels (Figure 1c). Of the 14 cases found to be local recurrences, 9 cases were confirmed on follow-up PET-CT scans, whereas the remaining were confirmed on follow-up CT scans. The median time for confirming local recurrences ranged from 0.2 to 13.3 months (mean, 5.8 months). No differences of CA 19-9 levels were noted between groups with benign/intermediate and malignant/intermediate lesions (preoperative median level, 113.7 U ml⁻¹ vs. 97.0 U ml⁻¹, $p = 0.648$; postoperative median level, 13.0 U ml⁻¹ vs. 12.0 U ml⁻¹, $p = 1.000$).

Potentially significant benign findings on simulation CT were identified in 21 (28.8%) patients. The most common lesion was pseudocysts at the pancreatic resection sites (52.4%), followed by venous thrombus, intra-abdominal abscess, and ascites (Table 4).

The follow-up time of all patients ranged from 2.5 to 61.3 months (median, 19), and the 3-year OS was 24.5%. The OS of patients without cancer-related lesions on simulation CT scans was significantly higher than that of patients who manifested these findings (3-year survival, 44.8% vs 10.8%, $p = 0.002$) (Figure 2). Out of the 73 patients, 59 experienced recurrences. Among the patients with recurrences, 39 (66.1%) received subsequent systemic chemotherapy.

DISCUSSION

In this study, we reviewed the diagnostic value of simulation CT scans in patients treated with adjuvant radiotherapy for pancreatic adenocarcinoma, and the results showed that 56.2% of patients developed cancer-related lesions after definitive surgery (Table 2). Moreover, 43.7% of indeterminate lesions were malignant as determined through PET-CT or follow-up diagnostic CT scans. This high rate of newly developed cancer-related lesions suggests that simulation CT scans have diagnostic value in detecting early metastatic and progressed lesions, which also implies their impact on the choice of subsequent therapies.

Since CT simulations have introduced three-dimensional conformal radiotherapy, their diagnostic value has been the subject of several studies.¹⁰⁻¹⁵ These investigations have reported that cancer-related lesions were found in 8-12% of patients and that only a small portion of these lesions affected the subsequent treatment. By contrast, our study results showed a remarkably high

detection rate of cancer-related lesions, which is mainly due to our study population showing a rapid progressive nature of pancreatic adenocarcinoma. Discrimination between abnormal findings and general postoperative changes is difficult because pancreatic surgery is a complex procedure requiring pancreatic resection and creating several anastomoses that are not uncommonly associated with leakage.^{8,16-18} Of the 75 patients in our study, only 1 case of liver metastasis (1.3%), which was later treated using systemic chemotherapy only, was detected without an official radiologist review. However, our retrospective diagnostic review revealed additional metastases in four patients (5.5%) (Table 2). If these metastases had been found before delivering radiotherapy, then the treatment method for these patients would have been significantly altered. Therefore, the results of our study suggest that simulation CT images in pancreatic adenocarcinoma must be meticulously evaluated by experienced radiologists.

In this study, the diagnostic review of simulation CT scans resulted in the detection of definite locoregional recurrence in 5 patients (6.8%) and indeterminate locoregional lesions in 32 patients (43.8%). Among the 32 patients with indeterminate lesions, 14 (43.8%) were found to have malignant lesions upon follow-up evaluation. Although these locoregional lesions may have been detected at the time of radiotherapy planning, they did not appear to have been considered in planned treatments. These lesions were likely considered as normal postoperative changes. Moreover, even if they were malignant lesions, they could have been treated with conventional radiation fields. However, most of these locoregional lesions eventually developed further despite adjuvant radiotherapy with/without combined chemotherapy. These findings imply that new locoregional failure or indeterminate lesions found on simulation CT scans may be one of the risk factors predicting poor clinical outcomes, warranting the diagnostic review of simulation CT images. A meticulous diagnostic review of simulation CT would aid in determining the necessity of adjuvant radiotherapy. In this study, the survival of patients without cancer-related lesions on simulation CT scans was significantly higher than that of patients with cancer-related lesions (3-year OS; 44.8% vs 10.8%, $p = 0.002$) (Figure 1). Reviewing simulation CT may also help adjust the radiation fields and doses in patients with locoregional cancer-related lesions. Intensified chemotherapy may be considered to overcome the poor clinical outcomes of these patients.

Simulation CT scans can serve as an early follow-up imaging work-up to detect early progression in pancreatic adenocarcinoma. Early recurrence within 6 months after surgical resection

Table 2. Summary of new lesions on simulation CT scans

Category	No. of patients (%)
Distant metastasis	4 (5.5)
Locoregional failure	5 (6.8)
Indeterminate finding	
Later found to be benign	18 (24.7)
Later found to be malignant	14 (19.2)
Benign lesions	21 (28.8)

Figure 1. Representative cancer-related lesions on simulation CT scan. (a) Definite locoregional recurrence on simulation CT scan. (b) Indeterminate lesion found to be benign: simulation CT scan (left) and follow-up diagnostic CT scan (right). (c) Indeterminate lesion found to be malignant: simulation CT scan (left) and follow-up diagnostic CT scan (right). All arrows indicates cancer-related lesions.

was associated with several clinical factors, such as preoperative CA 19-9 and preoperative tumour size, and resulted in poor prognosis.¹⁹ In our study, the value of preoperative CA 19-9 and tumour size was not statistically different between the groups with and without cancer-related lesions (Supplementary Table 1, supplementary material available online). Although our study did not show the associations between cancer-related lesions and CA 19-9 or tumour size, simulation CT scans should be thoroughly checked

for distant metastasis and local failure in patients who have potential risk factors for early recurrence.

Most indeterminate lesions were in the soft tissue neighbouring the superior mesenteric vessels, and 58.3% of them were determined as malignant on succeeding PET-CT or CT scans (Table 3). All indeterminate lesions at other sites were found benign. Indeterminate lesions that later found to be malignant were all located

Table 3. Sites and incidence of indeterminate lesions with its follow-up findings

Sites	No. of patients (%)	Follow-up findings	
		Benign	Malignant
Posterior to SMA/SMV	24 (75.0)	10	14
Liver	3 (9.4)	3	0
Portacaval space	2 (6.3)	2	0
Along the CHA	2 (6.3)	2	0
Left para-aortic space	1 (3.1)	1	0

CHA, common hepatic artery; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

around the superior mesenteric vessels. These findings suggest that superior mesenteric area should be reviewed carefully in evaluating simulation CT scans. Moreover, such simulation CT scans may later be used as reference images for comparison with future diagnostic CT scans.

Indeterminate lesions were determined to be benign or malignant through follow-up diagnostic CT or PET-CT. FDG PET-CT have superior sensitivity to contrast-enhanced abdominal CT scans in detecting local recurrences of pancreatic adenocarcinoma.²⁰ Several studies demonstrated that PET-CT was more sensitive in detecting recurrences in patients who have equivocal CT findings, which further helps differentiate postoperative inflammatory changes from local recurrences.^{18,21} These studies suggest the potential usefulness of PET-CT scanning with trends of CA 19-9 levels as a tool in assessing indeterminate findings of simulation CT. However, consensus on the appropriate imaging modality and timing when confirming indeterminate lesions is unclear. Further studies are warranted to find the proper method of confirming indeterminate lesions detected in simulation CT scan.

The high percentage of intermediate lesions may be due to the limited imaging quality of CT simulation scans compared with that of diagnostic CT scans. The CT simulation scans only consider the venous phase, thus possibly decreasing the sensitivity of detecting local disease. The scanning level of simulation CT scans can also affect the detected rate of cancer-related lesions, particularly in lung metastases.

Table 4. Detailed descriptions for potentially significant benign findings

Lesions	No. of patients (%)
Pseudocyst	11 (52.4)
Venous thrombus	2 (9.5)
Intra-abdominal abscess	2 (9.5)
Ascites	2 (9.5)
SMA pseudoaneurysm	1 (4.8)
Pancreatitis	1 (4.8)
Incisional hernia	1 (4.8)
Incision site hematoma	1 (4.8)

SMA, superior mesenteric artery.

The usefulness of our study evaluating diagnostic value of CT simulation scans may be superseded by the patterns in clinical practices. Upfront use of adjuvant chemotherapy is routinely administered regardless of margin status. Adjuvant chemoradiotherapy is delayed and sometimes omitted after adjuvant chemotherapy. Restaging using diagnostic CT prior to adjuvant therapies also limits the value of CT simulation scan as an early follow-up imaging. However, even in delayed adjuvant radiotherapy with restaging imaging work-up, CT simulation scans may provide additional diagnostic information considering the aggressive nature of pancreatic adenocarcinoma. Further studies are needed to investigate the diagnostic value of CT simulation scans in these clinical settings.

This study is limited by its retrospective design and small sample size. That simulation CT scans were reviewed by consensus reading may also implicate variability in interpretations. However, all prior diagnostic CT scans were officially reviewed by expert abdominal radiologists from our institution and re-examined by the current CT professional in consensus. In addition, the interpretation of simulation CT scans relied on relatively objective criteria, such as the growth rate of lesions, presence or absence of necrosis in lesions, and whether the lesion appeared abruptly. To the best of

Figure 2. Kaplan-Meier overall survival curves between the groups with/without cancer-related lesion on simulation CT scan.

our knowledge, this is the first study to evaluate the diagnostic value of simulation CT scans specifically for adjuvant radiotherapy in pancreatic adenocarcinoma.

CONCLUSIONS

Simulation CT scans performed for adjuvant radiotherapy in patients with pancreatic adenocarcinoma have significant diagnostic values in detecting early distant metastasis and

local failure, which could also potentially affect subsequent treatment strategies. Furthermore, detecting indeterminate soft tissue lesions along the superior mesenteric vessels requires additional studies or sequential follow-up CT scans to differentiate between postoperative change and recurrent tumour. Therefore, simulation CT images should be carefully reviewed before beginning adjuvant radiotherapy for pancreatic adenocarcinoma.

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