Computer tomography in pre-operative staging of pancreatic cancer
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Chapter 5

Three-dimensional CT angiography in pancreatic head carcinoma: limited value in pre-operative staging

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submitted for publication
Chapter 5

Abstract

Objective
The purpose of the study was to examine whether 3D CT angiography has additional value to axial CT in the pre-operative assessment of porto-mesenteric venous invasion in patients with pancreatic head carcinoma.

Patients and methods
3D CT angiograms were reconstructed from axial CT scans obtained in 32 patients with pancreatic head carcinoma, who underwent explorative laparotomy for attempted resection and in whom the presence or absence of venous invasion by tumor could be established by trial dissection or by resection and histological confirmation. A blinded panel judged the presence of invasion separately for axial CT (tumor concavity towards the vein or > 90 degrees of circumferential involvement of the vein) and for 3D CT (irregularity, clear impression or narrowing). CT findings were correlated with findings at surgery and at histopathology.

Results
At laparotomy 6 of 32 patients were found to have venous encasement that precluded a resection. Twenty-six patients underwent a resection. In eight of these the venous resection margins were tumorpositive. Thus venous invasion was considered to be present in 14 of 32 patients. Axial CT detected 8 cases of venous invasion and 3D CT detected 6. For axial CT the sensitivity and positive predictive value for venous invasion were 57% and 67%, respectively, for 3D CT these were 43% and 75%, respectively. Compared to axial scan, 3D CT detected one additional case of invasion.

Conclusion
3D CT angiography had limited additional value for staging venous invasion in pancreatic head carcinoma, compared to axial CT alone.
Introduction

In pancreatic carcinoma resection is the only chance of cure. A local resection is precluded by vascular invasion, therefore detection of vascular invasion is of major importance in pre-operative staging. Spiral CT with thin sections is the primary imaging modality for staging pancreatic cancer and it has obviated the need for conventional angiography. Still at axial CT scans vascular invasion is underestimated. CT angiography with three-dimensional rendering is capable of showing peripancreatic vessels accurately and the use of 3D CT for staging pancreatic carcinoma has been advocated. Studies on the clinical application of 3D rendering for staging are rare; only one study reports on improved accuracy of CT to detect vascular invasion using 3D CT. In 38 patients that underwent surgery the predictive value of 3D CT for vascular invasion was 96% compared to 70% for axial CT alone. In that study CT findings of invasion were compared with surgical inability to dissect the tumor from the vessel, but not with findings at histopathology. Also the CT criteria used for venous invasion were slightly different. The aim of our study was to examine whether 3D CT angiography can improve detection of venous invasion compared to axial CT alone in patients with potentially resectable carcinoma of the pancreatic head. CT findings were correlated with surgery and histopathology.

Patients and methods

A consecutive series of 108 patients underwent a protocol spiral CT examination for suspected pancreatic carcinoma. Fifty patients (46%) underwent an explorative laparotomy. Metastatic disease, precluding resection, was found in 14 patients. Thirty-six patients with proven carcinoma of the pancreatic head underwent a trial dissection and a resection of the tumor (pylorus preserving pancreatico-duodenectomy) or a surgical dissection of the porto-mesenteric veins. Four of these 36 patients were excluded from analysis (in one CT data were insufficient, in one surgical exploration was prohibited due to severe concomitant pancreatitis, and in another patient delay of surgery was more than 6 weeks. In a fourth patient the tumor was irresectable due to caval vein invasion and the porto-mesenteric system was not explored). The remaining 32 patients were evaluated in this study and findings during resection of the tumor and at pathologic examination were correlated with CT.
The routine pre-operative work-up also consisted of Doppler US and ERCP with endoscopic drainage of the biliary ducts. Diagnostic laparoscopy was performed in selected cases.

CT scanning protocol: all patients underwent a dual slice helical CT (Elscint CT Twin Flash, Haifa), collimation 2 x 2.5 mm, rotation time 1 sec, tablespeed 7.5 mm/sec. One hundred-and-thirty ml of non-ionic contrast material was injected intravenously at a rate of 3.5 ml/sec (Omnipaque 300, Nycomed). Pancreatic phase scanning was performed with a delay of 50 seconds and was used for 3D rendering (A second porto-venous phase scan of the liver was also performed). Images were reconstructed at 1.6-mm interval and were processed at an Omnipro workstation (Elscint, Haifa).

CT post-processing: three-dimensional surface-rendered angiographic models of the portal and superior mesenteric veins were reconstructed in a semi-automatic way by an experienced abdominal non-observer radiologist, who was also blinded for surgical and histopathological findings. A region of interest surrounding the veins was drawn manually, while segmentation of the vessels within this region was performed using window settings to highlight a vessel and by point seeding. The complete 3D angiographic model was saved on harddisk for interactive viewing by a panel.

Image evaluation:

Consensus reading was performed at a workstation by a panel consisting of an experienced abdominal radiologist and a pancreatic surgeon, both blinded for outcome. First only the 3D angiography was examined for presence and severity of vessel irregularity or indentation (scored as: normal; slight irregularity; clear impression/narrowing; severe narrowing > 50% of the lumen). If an abnormality was scored, pointing this area would show the correlating axial slices. Then the panel judged on these axial slices, whether the vessel irregularity or narrowing was related to tumor (the software allowed exact correlation of any point of the 3D model with a corresponding point on the axial CT slice). Only the 3D findings regarded as tumor-related were used for further correlation with surgery and pathology. The quality of 3D rendering was judged as good, adequate (sufficient for diagnosis) or poor (limiting diagnostic evaluation). The 3D CT angiography was not used in the decision to operate.

In a separated blinded session the panel reviewed only axial CT scans. Criteria for venous invasion at axial scans were circumferential involvement of the vein, scored in three categories (0-90 degrees, 90-180 degrees, >180 degrees) and tumor contact towards the vein judged as convex or concave, modified after Loyer. The assumption
Three-dimensional CT angiography

was that tumor concavity and/or > 90 degrees circumferential involvement would signify venous invasion. A convex contour with less than 90 degrees involvement was regarded as absence of invasion \(^3,11,12,20^\).

CT findings were correlated with surgical findings in non-resected tumors and with the reports of histopathology in resected specimen. Venous invasion was considered present if tumor adherence to the vessel was found at surgical dissection precluding a resection (with tumor confirmed in frozen section biopsy) or if vascular margins were positive for tumor at histopathologic examination of the resected tumors.

Results

There were 14 males and 18 females included in the study, with a mean age of 64 years (37-76 yrs). The mean size of the tumors at CT was 2.4 cm (range of 1.4 - 4.5 cm). The mean size of resected tumors was 2.8 cm at pathologic examination (range 1 - 5 cm).

A resection was performed in 26 of the 32 patients. In six patients the tumor was locally unresectable due to venous invasion. In eight of the 26 resected tumors (31%) the vascular margin was tumor-positive at histopathologic examination. Overall venous invasion was present in 14 patients.

Table 1 CT criteria correlated with venous invasion at surgery and histopathology

<table>
<thead>
<tr>
<th>CT criteria for invasion</th>
<th>n</th>
<th>surgery and histopathology</th>
<th>invasion present</th>
<th>invasion absent</th>
<th>sens</th>
<th>spec</th>
<th>ppv</th>
<th>acc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>invasion present</td>
<td>12</td>
<td></td>
<td>8</td>
<td>4</td>
<td>57%</td>
<td>78%</td>
<td>67%</td>
<td>69%</td>
</tr>
<tr>
<td>(&gt; 90 degrees or concavity)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>invasion absent</td>
<td>20</td>
<td></td>
<td>6</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt; 90 degrees and convexity)</td>
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<tr>
<td>3D CT</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe narrowing</td>
<td>1</td>
<td></td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clear indentation</td>
<td>6</td>
<td></td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>slight irregularity</td>
<td>1</td>
<td></td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D abnormal overall</td>
<td>8</td>
<td></td>
<td>6</td>
<td>2</td>
<td>43%</td>
<td>89%</td>
<td>75%</td>
<td>69%</td>
</tr>
<tr>
<td>3D normal</td>
<td>24</td>
<td></td>
<td>8</td>
<td>16</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

55
Correlation of CT findings and presence of venous invasion at surgery or histopathology of resected specimen are given in Table 1. At axial CT eight of fourteen patients with venous invasion were identified correctly as well as 14 of the 18 cases without invasion. This yielded a sensitivity of 57%, a specificity of 78%, and a positive predictive value for invasion 67%. Overall accuracy was 69%.

Three-dimensional angiographic images could be reconstructed in all patients. Image quality was judged as good in 20, adequate in 11 and poor in one patient. At 3D CT severe narrowing was seen in one patient (invasion proven), a clear indentation was seen in six (four with invasion), and slight irregularity was seen in one (invasion proven).

Table 2 Combined 3D and Axial CT correlated with venous invasion at surgery and histopathology.

<table>
<thead>
<tr>
<th>combined Axial and 3D CT criteria</th>
<th>invasion present</th>
<th>invasion absent</th>
<th>sensitivity for invasion</th>
<th>pos predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial and 3D both abnormal</td>
<td>n = 7</td>
<td>5</td>
<td>2</td>
<td>36%</td>
</tr>
<tr>
<td>Either abnormal</td>
<td>n = 6</td>
<td>4</td>
<td>2</td>
<td>64%</td>
</tr>
<tr>
<td>One or both abnormal (subtotal)</td>
<td>n = 13</td>
<td>9</td>
<td>4</td>
<td>66%</td>
</tr>
<tr>
<td>Both normal</td>
<td>n = 19</td>
<td>5</td>
<td>14</td>
<td>67%</td>
</tr>
</tbody>
</table>
Overall 3D CT correctly detected invasion in six of 14 patients with a sensitivity and positive predictive value of 43% and 75%, respectively. The specificity of 3D CT was 89% and overall accuracy was 69%. This was not significantly different from axial CT. If axial CT was combined with 3D CT, one additional case of invasion could be detected. If both axial and 3D CT were abnormal, the predictive value for invasion was slightly higher (80%) (Table 2). Subjectively the panel agreed that 3D CT had added little new information to axial scans. Only in three patients the panel found 3D helpful: in two patients 3D showed vascular irregularity or indentation that was not suspected at axial scans. This finding would have changed tumor staging in one patient compared to the axial scans. Both lesions were resected and in both a tumor-positive vascular margins was found at pathology (Fig 1,2). In a third patient 3D CT appeared normal, while axial scans showed the tumor as concave with circumferential involvement between 90 and 180 degrees. This tumor was resectable without evidence of invasion at pathology. Marked vascular indentations that were not related to tumor were seen four times at 3D imaging, e.g. impressions caused by a dilated pancreatic or biliary duct (Fig 3).
**Fig 3a** Axial CT: large pancreatic head carcinoma (T) with stent in the common bile duct. Severe tumor indentation of SMV (arrow).

**Fig 3b** Axial scan cranial plane: severe dilatation of the pancreatic duct and common bile duct with stent. Impression on SMV by the dilated pancreatic duct (arrows). (SV splenic vein)

**Fig 3c** 3D CT angiography anterior view: Clear tumor impression (T) on SMV with irregularity of vessel wall (arrows). Marked smooth impressions by dilated pancreatic duct (pd). At surgery the tumor proved to be unresectable due to venous invasion.

**Discussion**

In local staging of pancreatic head carcinoma CT criteria for unresectability due to vascular invasion have received much attention.\(^{1,3,5,6,10,13,20-22}\). Detection of vascular invasion by CT has major implications as this precludes a potentially curative resection of the tumor. However, axial CT alone still underestimates the presence of vascular invasion.\(^{8,11-13,19}\). Three-dimensional CT angiography has been used to image splanchnic vessels and is capable of depicting peripancreatic vessel anatomy accurately.\(^{15-18}\). The
use of 3D CT in clinical practice has become more widespread as reconstruction times of 3D images have decreased from several hours to a couple of minutes. A potential advantage of 3D CT angiography is that it may show subtle changes in vessel contour. Also some advantage of 3D CT may be expected, if tumor extension is not in the transverse plane and axial scan direction would be sub-optimal (e.g. for a pancreatic head tumor extending cranially towards the caudal surface of the portal vein). The clinical impact of 3D imaging on staging pancreatic carcinoma has not been studied widely. One problem in evaluating the additional value of 3D is in reading the images truly independent from axial CT scans. As the 3D volume is segmented from the axial scans these images cannot be ignored. For this reason the 3D images were prepared by a non-observer radiologist. After reading the 3D volume as abnormal the panel also looked at the correlating axial scans. This procedure was meant to exclude the cases of marked impressions on a vessel that were clearly non tumorous e.g. caused by a dilated biliary duct. From the 3D images alone it is not possible to know at what location the tumor is, therefore correlation with the axial scans at this point was allowed. This may also have had some influence on interpretation of 3D findings at the level of the tumor, with potential exclusion of false positive 3D findings, however, we think that this procedure was valid to demonstrate the additional abnormalities that 3D CT might have over axial CT.

The present study did not show an additional value of 3D for staging vessel invasion. In a study of Raptopoulos et al. 3D CT angiography was shown to be more accurate than axial CT in predicting vascular involvement. Reported accuracy was 96% for 3D CT compared to 70% for axial scans. Some differences between the studies exist: vascular invasion at CT in their study was correlated with surgical resection and 29% of the patients (11/38) had an irresectable tumor at surgery. In our study only 6 of 32 tumors were irresectable (19%). Secondly, as resection is performed with an intention to cure we chose to correlate invasion at 3D CT angiography with a positive venous resection margin at histopathology and not only with surgical resectability. The rate of vascular invasion found was high (44% overall and 31% in resected tumors), in spite of the relatively high surgical resection rate. This is probably due to the fact that microscopic involvement was considered as venous invasion. This also explains the low sensitivity for invasion that was found for both axial and 3D CT. Raptopoulos et al. found a difference in vessel encasement grading for 3D CT and axial CT, in general with lower grades of venous invasion for axial CT scans. The grading system they used for axial scans was slightly different than ours. For example circumferential involvement of 2/3
of the vessel perimeter was regarded as invasion in their study, where we regarded involvement of >90 degrees as invasion. Circumferential involvement of >180 degrees and tumor concavity towards the vein have been recommended as signs for vascular invasion and surgical unresectability \textsuperscript{11,12}. The criterion of >180 degrees involvement or concavity would have yielded a sensitivity of 43% with a predictive value of 67% in the present study. In a previous study we correlated CT findings of invasion with findings at pathology. In that study the best combination of criteria to judge venous invasion were involvement of >90 degrees and presence of tumor concavity (with a sensitivity for invasion of 60% and a positive predictive value of 90\% \textsuperscript{20}). Vessel irregularity and vessel narrowing were also important signs of invasion, but these findings did not have additional value over the combined criteria \textsuperscript{20}.

In the present study axial CT had an accuracy of 69\% for venous invasion, while reported accuracies of CT for resectability and invasion are often much higher, up to 91\% \textsuperscript{23}. Partly this may be explained by the histologic criteria we used for invasion. Invasion was present in a high number of patients, but in many this was microscopic invasion diagnosed at the resection specimen, and it would not be detectable by CT (Fig 4).

Fig 4a Axial scan: pancreatic cancer, scored as no vascular invasion.

Fig 4b 3D CT: posterior view of normal SMV at the level of the tumor (arrow). After resection a tumor positive venous margin was found.

Another factor that may have lowered accuracy is patient selection. If a large proportion of patients with unresectable tumors will have surgical exploration the expected sensitivity for unresectability and accuracy of CT will be higher. The patients in the present study were highly selected as indicated by the resectability rate: at surgery 19\% had an irresectable tumor. For example in the study of Diehl 72\% of patients had
Three-dimensional CT angiography

irresectable tumors at surgery. Sensitivity for vascular invasion was 88% in that study. In the present study there were three patients with >180 degrees of venous involvement. Reviewing the original reports showed there had been doubt in two of these cases, whether this finding was partly due to co-existing pancreatitis, which may have added in the decision not to refrain from surgery. In one of these two patients invasion at axial CT indeed proved to be due to pancreatitis.

A limitation of the study is the relative number of patients with exploration of the veins. Patients with severe encasement or narrowing were excluded from surgery on the basis of axial CT alone and thus the true sensitivity of 3D for invasion cannot be established in this selected group. We expect that 3D CT in these excluded patients would not have yielded additional clinical value.

Another limitation may be that other post-processing techniques such as Multi Planar Reformatting (MPR), Maximum Intensity Projection (MIP) and Volume Rendering were not evaluated. MPR may be of value when interpreting axial scans e.g. if tumor is lying close to the undersurface of the portal vein. Volume rendering may have had advantages over surface shaded 3D, because both the vessel and the tumor can be evaluated in one image. Furthermore, surface rendering only gives information about the vessel contour (lumen contour) and not of the intraluminal structure of the vessels and generally it is more difficult to segment smaller vessels. However, in this study we evaluated large vessels and the area of contact between tumor and vessel could well be evaluated with 3D surface rendering. Interactive viewing can easily be performed on predefined 3D tissues, but Volume Rendering would have required time-consuming editing. An advantage of 3D surface rendering is that during segmentation the correctness of the rendered volume can be verified: when a threshold is chosen, the pixels included in the 3D volume are highlighted on the axial scans allowing visual verification. Such a verification was not possible for the available volume rendering software. The 3D CT angiography was well feasible showing a good image quality and little extra time was needed for segmentation. Multislice CT technique has evolved further and using a slice thickness of 1 mm or less is feasible and may improve the quality of 3D imaging.

In conclusion, 3D CT angiography is capable of showing anatomic relations between tumor and vessels and can suggest a high risk of vascular invasion, but the additional value of 3D CT angiography for staging pancreatic head carcinoma is limited.
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