Evaluation of diagnostics guidelines for hepatobiliary and pancreatic disease
Tilleman, E.H.B.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Value of CT criteria as prognostic factors for survival in patients with potentially resectable pancreatic carcinoma

S.S.K.S. Phoa¹, E.H.B.M. Tilleman², O.M. van Delden¹, P.M.M. Bossuyt³, D.J. Gouma², J.S. Laméris¹

Departments of Radiology¹, Surgery² and Clinical Epidemiology³ of the Academic Medical Center, Amsterdam

Submitted
Abstract

Objective. To establish the prognostic value of CT data obtained from a preoperative CT scan in patients with potentially resectable pancreatic head carcinoma.

Background. Pancreatic tumors are frequently explored and sometimes resected, in spite of a high risk for unresectability predicted by CT. We correlated CT data with survival in patients with pancreatic head carcinoma, to find criteria that are useful in deciding whether or not to attempt a surgical resection.

Patients and methods. In 71 consecutive patients with potentially resectable pancreatic head carcinoma prognostic factors on CT e.g. tumor size, peripancreatic infiltration, grades of vascular encasement and enlargement of lymph nodes. Criteria for local unresectability were > 180 degrees circumferential vascular encasement, tumor concavity towards a vessel and presence of any infiltration. All patients underwent surgical exploration. CT findings were compared with results of surgery and histopathology. Prognostic factors for resected and unresected tumors were analyzed using single and multivariate analysis.

Results. A resection was performed in 41 of the 71 patients (in 24 the resection was radical). The sensitivity, specificity and positive predictive value of CT with respect to surgical unresectability were 0.67, 0.63 and 0.57, respectively. With respect to a non-radical resection these were 0.62, 0.75 and 0.83, respectively. Median survival was 21 months for resectable and 9.7 months for unresectable tumors. For resected tumors survival was relatively poor for tumor with a diameter >3 cm (relative hazard 3.8) and when CT signs of local unresectability were noted. Median survival of resected tumors < 2 cm was nearly 30 months. Encasement of the superior mesenteric artery had a poor prognosis in all tumors.

Conclusion. CT signs of local unresectability and tumor diameter >3 cm predict a poor survival in resected tumors.
CT criteria as prognostic factors for survival in pancreatic carcinoma

Introduction

Pancreatic carcinoma has a very poor prognosis. Only 10-15% of tumors are resectable at the time of diagnosis and hence are potentially curable. Many techniques are used to determine the resectability including CT, MRI and diagnostic laparoscopy. In the diagnostic work-up of patients CT is predominantly used to determine unresectability of tumors and thus to avoid unnecessary surgery. The accuracy of CT in determining surgical resectability is 77-90%. Prediction of a resectable tumor by CT is relatively poor, due to metastases that are missed or due to unexpected local tumor extension. In patients with signs of local unresectability on CT, resections are often attempted, sometimes successfully. Prediction of unresectability by CT is not 100% accurate. Resectability may also depend on the surgeon's opinion whether a venous resection is done or whether a high risk of tumor-positive resection margins is accepted. Thus surgical resection itself is not a reference standard in the evaluation of CT in the prediction of results of treatment. A better reference standard for CT would be a radical resection confirmed histologically, but even this standard may be influenced by the individual surgeon. Clinically the most important outcome is survival of the patient. Previous studies on survival have examined prognostic factors in patients with tumors, that were already known to be unresectable or in patients after a resection had already been performed. One study demonstrated that the CT finding of venous invasion had prognostic value.

The aim of this study was to examine the chances of survival in a group of patients with pancreatic head carcinoma, who were potential surgical candidates and to determine whether a preoperative CT scan can predict survival. If CT findings can be identified that predict survival, they may be helpful in selecting candidates for surgery or other therapy.

Patients and methods

Between February 1997 and July 1999 approximately 200 patients suspected of having pancreatic carcinoma underwent a spiral CT for staging at the Academic Medical Center, Amsterdam. Of these, 72 consecutive patients with pancreatic head carcinoma eventually underwent surgery for attempted resection with curative intent. The diagnosis was confirmed histologically in all of these patients. Periampullary tumors were included, but distal cholangiocarcinomas, cystic tumors or endocrine tumors were excluded. One patient was excluded from analysis because of lack of follow up. The remaining 71 patients were included in this study.
Patients

There were 33 males and 38 females, their median age was 62 years (range 42-76). Forty-one patients underwent a pylorus preserving pancreatico-duodenectomy (PPPD). In 30 the tumors were proven unresectable at surgery, because of metastases (n=10) or local tumor extension into surrounding blood vessels or the mesocolon. Patients with unresectable tumors usually had a double bypass surgery (hepato-jejunostomy and gastro-enterostomy with cholecystectomy and celiac plexus blockage with alcohol), three patients had a single bypass only.

CT technique

All patients were prospectively included to undergo a pre-operative CT according to protocol, using a dual slice technique (CT Twin Flash, Elscint, Haifa). Collimation was 2 x 2.5 mm, 120 kVp, 199 mAs, table speed 7.5 mm/s. Intravenous contrast injection was given at a rate of 3.5 ml/s (130 ml Omnipaque 300, Nycomed, Oslo). A dual phase scan was performed, the pancreatic phase of the scan had a delay of 50 seconds.

The CT scans were retrieved after surgery and reviewed on a workstation by two experienced abdominal radiologists, separately. The only information given to the radiologist was that patients had been explored for suspected pancreatic cancer. If there was disagreement between readers, a third consensus reading was held.

CT variables used for survival analysis were (i) tumor size (if tumors were visible at CT); (ii) infiltration of peripancreatic fat planes, the hepatoduodenal ligament and the mesentery, scored as present or absent (regardless whether this infiltration was presumed to be due to tumor infiltration or to inflammatory infiltration); (iii) encasement of the portal or superior mesenteric vein, measured in three degrees of circumferential involvement (< 90 degrees, between 90-180 degrees, > 180 degrees). (iv) tumor convexity grade A-E. (according to Loyer7: grade A: fat plane visible between tumor and vessel; grade B: normal pancreatic tissue between tumor and vessel; grade C: tumor adjacent to vessel with a contour convex towards the vessel; grade D: tumor adjacent to vessel with a contour concave towards the vessel, grade E: circumferential involvement of vessel; grade F: thrombosis or occlusion of vessel. (v) encasement of the hepatic artery and the superior mesenteric artery, regarded as present if involvement was >180 degrees. (vi) suspected liver metastases (vii) distant lymph nodes larger than 1 cm. Also an overall CT variable local resectability was scored. Local resectability combined several CT criteria: a tumor was regarded as locally not resectable if any infiltration was present, or if any vessel showed involvement of > 180 degrees or if tumor convexity was scored as grade D or E.

The CT variable local resectability was also compared to whether surgical resection was done and the histopathology of resected tumors. Completeness of the resection (whether resection margins were tumor negative) was established by reviewing histopathology reports.
Survival

In February 2001, 12 of the patients were known to be alive. In these patients the average follow up time after surgery was 34 months (range 23-41). This was used as survival time (censored cases). The time of death was known in 57 patients, survival was calculated from the date of surgery. In 2 patients known to have died, the exact date of death could not be determined. The last visit to the outpatient clinic was used as endpoint for survival in these patients. We compared the survival for patient groups defined according to CT criteria, using separate variables and a multivariable model. All CT variables, as well as the clinical variables age and sex, were used for survival analysis. For univariable analysis Kaplan Meier survival curves were determined, using the logrank for significance. The median age of 62 years was used as the cut-off level for age. For tumor size several cut-off levels were analyzed. Multivariable analysis was performed for all tumors and for surgically resectable and unresectable tumors separately. A Cox regression analysis was performed for factors that had significant prognostic value to determine the relative risk for death.

Results

CT scans of 36 of the 71 patients were scored as locally resectable and of 35 as locally unresectable. A surgical resection could be performed in 26 and 15 patients respectively. The overall resection rate was 57 percent. The sensitivity of CT for surgical unresectability was 0.67 (20/30) and the predictive value for unresectability was 0.57 (20/35), (Table 1a). In the 26 and 15 patients that underwent a resection, the resection margins were tumor-negative at pathology in 18 and 6 patients respectively. Accordingly the rate of a radical resection was 59 percent (24/41). The sensitivity of CT for a non-radical resection was 0.62 (29/47) with a predictive value of 0.83 (29/35), (Table 1b,c).

Table 1a Local resectability at CT correlated with surgical resection

<table>
<thead>
<tr>
<th>Surgery</th>
<th>resected</th>
<th>not resected</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Local resectable</td>
<td>26</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>Local unresectable</td>
<td>15</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>30</td>
<td>71</td>
</tr>
</tbody>
</table>
Table 1b Local resectability at CT correlated with surgical resection

<table>
<thead>
<tr>
<th>Histology</th>
<th>resection margins tumor-CT</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>negative</td>
<td>positive</td>
<td>total</td>
<td></td>
</tr>
<tr>
<td>Local resectable</td>
<td>178</td>
<td>18</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Local unresectable</td>
<td>6</td>
<td>29</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>47</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

Table 1c Predictive value of CT scan for unresectability and non-radical resection

<table>
<thead>
<tr>
<th></th>
<th>unresectability</th>
<th>non-radical resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.67 (20/30)</td>
<td>0.62 (29/47)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.63 (26/41)</td>
<td>0.75 (18/24)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.57 (20/35)</td>
<td>0.83 (29/35)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.72 (26/36)</td>
<td>0.50 (18/36)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.65 (46/71)</td>
<td>0.66 (47/71)</td>
</tr>
</tbody>
</table>

The estimated mean survival of the group (n=71) was 16 months (median 10.8 months) with a probability of survival at 6, 12, 24 months of 82%, 43%, 20% respectively. Median survival time was 21 months for patients with resected tumors (n=41), compared to 9.7 months after a bypass procedure (n=30), (Fig 1).

Factors that were used in univariable analysis for resected and unresected tumors are listed in Table 2a and 2b. In non-resected tumors the only significant survival factor was encasement of the mesenteric artery, which implied a median survival time of 4 months. The mortality increased by a factor of 5 if encasement was present.

For resected tumors size was a significant prognostic factor. Median survival time was 19.3 months for tumors with a diameter smaller than 3 cm, and 9.9 months for tumors with a diameter larger than 3 cm. Ten of the 28 tumors with diameters larger than 3 cm could be resected, but the resection margins were tumor-negative in only three. All patients that were alive had tumors smaller than 3 cm. Further analysis showed a difference in survival between tumors with a diameter of 2 -3 cm and those with a diameter smaller than 2 cm. Seventeen patients, who had a tumor with diameters of 2-3 cm, had a median survival time of 16.6 months (Fig 2).
CT criteria as prognostic factors for survival in pancreatic carcinoma

Infiltration of the hepatoduodenal ligament and infiltration of the peripancreatic fat had prognostic value. All patients that survived had no evidence of infiltration on CT.

Venous encasement of > 90 degrees had prognostic value. The prognostic value of involvement of > 180 degrees was statistically not significant. The median survival of patients that had > 180 degrees tumors was 8.7 months, for patients with < 180 degrees tumors this was 17.6 months. Tumor concavity had significant prognostic value. For patients with grade DE tumors the relative risk of death was a factor 5 greater than for patients with grade ABC tumors. Patients with grade A tumors showed a significantly longer survival time of almost 30 months.

Age and sex did not have a significant influence on survival. The factor local resectability had significant prognostic value with median survival time of 8.5 months if tumors were considered as being locally unresectable (Fig 3).
Chapter 3

**Figure 2a. Survival for tumor size in unresected tumors (n=29)**

*Multivariable analysis*

The CT factors with statistically significant prognostic value in the univariate analysis were included in a stepwise Cox regression model. For analysis of all patients the factors included were: presence of peripancreatic fat infiltration, encasement of the superior mesenteric artery, tumor diameter of >3 cm, tumor convexity > grade A, venous involvement of >90 degrees and presence of infiltration of the hepatoduodenal ligament. Of these factors the model showed that independent factors for survival were encasement of the SM artery, tumor convexity grade B or higher and tumor diameter larger than 3cm. Corrected for age and sex the Relative Risk for death increased by a factor of 4.7 for SMA involvement, by a factor of 2.1 for tumors larger than 3 cm and by a factor of 3.2 for tumor convexity grade B or higher (Table 3a).

For resected tumors the analysis showed two independent factors: tumor convexity grade DE and tumor size larger than 2 cm (Table 3b). The RR for death increased by a factor of 4.9 and 3.2 respectively.
The variable *local resectability at CT* was compared separately. There was an increased risk of death, that was independent of the factor tumor diameter of > 2 cm. The Relative Risk for death increased by a factor of 3.2 if tumors were considered to be unresectable according to the CT (p-value 0.008).

**Figure 2b.** Survival for tumor size in resected tumors (n=36)

- \( p = 0.02 \) for \( T < 2 \text{ cm} \) versus \( T > 2 \text{ cm} \)
- \( p = 0.001 \) for \( T < 3 \text{ cm} \) versus \( T < 3 \text{ cm} \)
Figure 3a. Survival in resected tumors (n=41)

Figure 3b. Survival for unresectable tumors at laparotomy (n=30)
Table 3a Relative hazard of independent factors in Multivariate Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative hazard for survival</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM Artery encased</td>
<td>4.7</td>
<td>0.027</td>
</tr>
<tr>
<td>Tumor convexity B or larger</td>
<td>3.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Tumor &gt; 3 cm</td>
<td>2.1</td>
<td>0.022</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.5</td>
<td>0.164</td>
</tr>
<tr>
<td>Age &lt; 62 years</td>
<td>1.5</td>
<td>0.142</td>
</tr>
</tbody>
</table>

Table 3b Relative hazard of independent factors in Multivariate Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative hazard for survival</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor convexity D or E</td>
<td>4.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Tumor &gt; 2 cm</td>
<td>3.2</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Discussion

Prognostic factors for survival have been described in patients in whom a surgical resection has been performed and in patients with advanced pancreatic cancer. In the group of pre-operative patients data on prognosis are lacking. We examined CT findings and assessed the prognostic factors in this selected group of patients. The results show that a tumor diameter larger than 2 cm, tumor convexity grade DE, and ‘local resectability’ predicted by CT have important prognostic value. Ideally one would like to analyze CT criteria in a group of patients with pancreatic cancer that are surgical candidates. However, to compensate for the effects of a surgical resection, the predictive values of CT factors had to be analyzed separately for resected and unresected tumors. If a significant CT factor is found in either subgroup, potentially therapeutic strategy would be changed. If no significant factor can be identified, this would imply no change in surgical strategy. However, if a CT factor predicts a poor survival in all patients, it may merely predict the resectability of the tumor. Most CT factors relate to unresectability of the tumor, but their predictive value varies. This can be quantified by comparing the relative numbers of patients for each factor in resected and unresected patients (Table 2 bc). For example: in unresectable tumors 18 of 29 had
a diameter larger than 3 cm and in resected tumors 10 of 36 had diameters larger than 3 cm. The relative risk of a tumor diameter >3 cm to be unresectable was 0.64 (18/28) compared to the risk of 0.30 (11/37) for tumors with diameters <3 cm.

If a factor has a high risk for unresectability the number of patients with this factor in the resected group will be relatively low e.g. for venous encasement of >180 degrees. The prognostic value for survival may not reach statistical significance for these factors, but an important effect on prognosis may be suggested if large differences in survival exist.

For unresected tumors CT factors had little predictive value. A poor effect on survival was seen for mesenteric artery encasement, although the number of patients was low. Tumors completely separate from the vessels (grade A convexity) seem to have a slightly better (but not significant) survival. Probably unresectability is the major factor that determines survival.

Several CT factors predict survival after a resection has been performed (Table 2b). In the multivariate analysis 2 factors remained: tumor diameter >2 cm and tumor convexity >grade C. Nearly all tumors with diameters smaller than 2 cm were resected and median survival time of patients with these tumors was nearly 30 months after resection. Tumor size is a well known prognostic factor in patients with resected tumors as well as in those with advanced carcinoma. A comparable prognosis for patients with small tumors was found previously in patients after a resection: for patients with tumors <2cm at pathology the median survival was 29.7 months compared to 10.7 months for patients with tumors >2 cm. The present study also showed that patients with resected tumors with diameters of 2-3 cm have a better prognosis than patients with resected tumors larger than 3 cm. Furthermore no patient that survived had a tumor resected with a diameter larger than 3 cm.

SMA involvement and tumor convexity grade D are CT signs of local unresectability. SMA involvement indicated a poor prognosis. Survival was also relatively poor in patients with non-resected tumors. The number of patients with arterial involvement was very limited. It is probable that surgery had already been avoided in most patients with arterial involvement.

The overall CT variable for local unresectability, takes into account the risk of both arterial and venous invasion. Median survival after resection was 8.5 months for tumors considered to be locally unresectable and 23.1 months if considered to be locally resectable. The number of survivors in both groups were one and eleven, respectively. For the variable local unresectability venous involvement of >180 degrees was regarded as an indicator of an unresectable tumor. This was based on a previous study. Portal vein involvement of >90 degrees also has a high predictive value for invasion and Furukawa showed that portal vein involvement of >90 degrees is associated with a poor survival (33% 1 year survival). Indeed in the present study involvement of >90 degrees had significant prognostic value. There
were four tumors resected with involvement between 90-180 degrees. Median survival of these patients was 8.6 months, which is comparable to the survival of those regarded as locally unresectable by CT.

Suspected metastases and enlarged lymph nodes at CT did not have prognostic value. This is probably due to selection; most patients with metastases had already been excluded. Depending on localization, metastases in enlarged lymph nodes on CT can be confirmed with fine needle aspiration and if confirmed surgery will not be performed. When there is doubt about metastases, laparoscopy with laparoscopic ultrasonography may confirm metastases and preclude a resection. Absence of liver metastasis was shown to be the most important prognostic factor in unresectable carcinoma. Microscopic lymph node status after resection is known to correlate with survival. CT is not able to indicate lymph node status in non-enlarged nodes.

For staging pancreatic carcinoma, CT is regarded as the primary modality and it may demonstrate unresectable disease in the majority of patients. The reported accuracy of CT in determining surgical resectability is 77-90%, but accuracy is generally high in patient groups that have a low resection rate, sometimes less than 30%. In the present study fifteen of 35 patients regarded as unresectable by CT underwent a resection. This meant that CT had a predictive value for surgical unresectability of 57%, prediction of a resectable tumor by CT was correct in 72%. The predictive power of CT was therefore only moderate in excluding patients from surgical exploration. This may be partly explained by selection bias as only patients that underwent surgical exploration were selected for this study. Patients with tumors that were regarded as clearly unresectable on CT e.g. by demonstration of extensive invasion or metastases, would not have been selected for surgery.

A major problem is the detection of local tumor extension and vascular invasion, which is present in about 50% of surgical patients. Depending on the criteria used, CT can predict vascular invasion with 100% predictive value, but with a low sensitivity. Therefore a large proportion of patients cannot be excluded from surgical exploration. Extensive surgery is often performed and venous resection is sometimes advocated, even if tumor invasion is demonstrated on CT.

Whether a resection is of therapeutic value is partly dependent on the histopathological findings in resected tumors. Presence of tumor positive resection margins are an important prognostic factor for survival. In the present study, CT had a predictive value for positive margins of 83%. There were 6 patients with radically resected tumors, that were regarded as being locally unresectable on CT. CT underestimated tumor positive microscopic margins: in 50% of tumors predicted as locally resectable by CT, resection margins were shown to be tumor positive. These findings are similar to a previous study comparing CT findings and tumor invasion of vessels: a high risk for invasion can be demonstrated, but in many patients
microscopic invasion is underestimated by CT. It is questionable whether the predictive value of 83% for a positive margin will be sufficient to influence the decision on surgical exploration. These findings support the aim of this study: to find CT criteria that predict a poor survival and thus to refrain from surgery.

A limitation of the present study is that mainly CT parameters were evaluated. Other parameters that may be obtained pre-operatively like baseline clinical performance or serum CA 19-9 are known to have an influence on survival. Furthermore, all patients had a pancreatic head adenocarcinoma with histological confirmation. Caution should be taken to implement these data on patients with a pancreatic mass suspected for tumor. Tumors with a different histology e.g. an endocrine tumor, may have a better prognosis. Post-operative treatment was also not taken into account. Adjuvant therapy however is known to have a limited effect on survival.

In summary, our findings suggest that prognostic factors can be identified at the pre-operative CT scans. Most important are factors that predict survival for resected tumors. Survival is longest in tumors smaller than 2cm. A poor survival is seen in resected tumors that are larger than 3cm and in tumors that showed CT signs of local unresectability: tumor convexity grade D, vascular encasement >180 degrees or infiltration surrounding the pancreas. This parameter might be extended with portal venous encasement >90 degrees. Encasement of the mesenteric artery had an extremely poor prognosis for both resected and unresected tumors. These findings may add to the value of CT for staging pancreatic cancer and may guide the choice of therapy.

References

CT criteria as prognostic factors for survival in pancreatic carcinoma


Chapter 3


30. Raptopoulos V, Steer ML, Sheiman RG, Vrachliotis TG, Gougoutas CA, Movson JS. The use of helical CT and CT angiography to predict vascular involvement from pancreatic cancer: correlation with findings at surgery. AJR 1997;168: 971-7


