MDCT determination of resectability in locally advanced pancreatic ductal adenocarcinoma: assessment of survival prognostic factors

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Purpose

Pancreatic carcinoma is the 4th most common cause of cancer related death worldwide and one of the most aggressive human tumors. Despite improved quality of surgery, the prognosis of patients with pancreatic cancer is still dismal. At the moment of diagnosis, in fact, only 10% of neoplasms are confined to the gland, while 40% are locally advanced and 50% show distant metastases. Surgical resection still represents the best therapeutic approach but only 20-25% of patients can benefit from it with a median survival after surgery of 90% at 1 year and of 2-4% at 5 years.

However, the progressive increase in number of reference centres specialized in pancreatic surgery has helped to reduce the perioperative morbidity and mortality. Thanks to these improvements, many efforts have been done in order to extend the indications for curative surgery, trying to obtain the maximum neoplastic removal by applying new surgical techniques such as retroperitoneal tissue cleaning and lymphadenectomy, and vascular resection. Moreover, in order to obtain a pre-operative downstaging in patients with locally advanced disease, chemo-radiotherapeutic protocols can be applied before surgery.

For these reasons, while the presence of distant metastases, peritoneal carcinosis or arterial infiltration is usually considered as absolute criteria of unresectability, suspected porto-mesenteric axis infiltration, lymph nodal metastases or peripancreatic invasion are now generally judged as relative criteria for unresectability [1].

Traditionally, arterial invasion (celiac trunk, hepatic artery, superior mesenteric artery - SMA) has been deemed to be inoperable in patients with pancreatic head cancer because of the high morbidity of arterial reconstruction and the concomitant presence of extensive celiac or mesenteric neural invasion. Moreover, a positive surgical margin, whether gross or microscopic, predicts survival similar to that of patients who have locally advanced disease and who are considered as surgically unresectable.

However, nowadays the indication of treatment in case of arterial infiltration are debated; according to some authors, early arterial invasion is considered resectable in carefully selected cases, like isolated infiltration of celiac trunk or common hepatic artery [2], particularly in cases responding to neoadjuvant chemoradiotherapy.

Instead, the infiltration of mesenteric-portal veins may be present also in absence of an extended retroperitoneal fat tissue infiltration, so that, while only ten years ago a cancer showing sign of infiltration of the portal venous axis was considered as locally advanced and unresectable, this is no longer true. In fact, many studies from reference centres specialized in pancreatic surgery indicate the opportunity of a venous vascular resection as the standard treatment of pancreatic cancer involving the mesenteric-portal veins, demonstrating that survival of patients submitted to pancreatectomy with vascular venous resection is not different or sometimes better than that of patients subjected to standard...
pancreatectomy, in particular when a curative surgery has been obtained (R0) or when microscopic neoplastic residual is present (R1) [2]. This concept has been confirmed in the most recent expert consensus statement published in 2009 by the American Society of Surgeons [3].

Regarding peripancreatic fat tissue infiltration, literature data indicate that about 40% of pancreatic resections are not radical because of the presence of a microscopic residual on one of the surgical margins. In particular, in cases of pancreatic adenocarcinomas of the head/uncinate process, the prognosis after surgery is strongly influenced by the persistence of tumoral involvement at the retroperitoneal resection margin (also called SMA margin, according to the 2009 expert consensus statement), mainly by virtue of the difficulty of obtaining a radical debulking at that site.

Even if it is still only at laparotomy that resectability can be definitely determined, the quality of surgical resection has improved over the last decade thanks to a better preoperative imaging staging. For these reasons, an adequate pre-operative evaluation is mandatory in order to select resectable patients, who may really benefit from surgery in terms of survival.

Aim of our study was to evaluate the predictive value of multidetector CT in assessing resectability in patients affected by locally advanced ductal adenocarcinoma of the pancreas submitted to surgery with vascular resection.

As second goal, the local staging parameters were compared with survival in order to identify possible prognostic factors of survival at preoperative CT.
Methods and Materials

We included 54 patients with locally-advanced pancreatic adenocarcinoma submitted to surgery with vascular resection.

All the exams were performed by a multidetector CT (Light Speed Plus, GE Medical System, Milwaukee USA or Light Speed VCT, GE Medical System, Milwaukee USA); the study was done after gastroduodenal hyperdistension, obtained by oral administration of 750/1000 mL of water and by pharmacological hypotonization (Buscopan® o GlucaGen®), in order to improve the visualization of the relationships between the gastric wall and pancreatic body and between the duodenal wall and the pancreatic head. All the CT studies were performed before and after intravenous administration of high concentrated iodinated contrast medium (Iomeron® 400), at 4mL/s injection flow-rate. Post-contrast scans were performed both in pancreatic (35"delay; slice thickness 2.5-1.25 mm, reconstruction interval 1.25-0.6 mm ) and venous phases (70" delay; slice thickness 1.25-0.6 mm, reconstruction interval 0.6 mm).

All native images were sent to a dedicated workstation (Advantage Windows 4.0, GE Medical System, Milwaukee USA) and processed with multiplanar reconstruction (MPR) in order to evaluate in different planes the relationship between the neoplastic lesions and the surrounding structures.

At CT we evaluated the following criteria: vascular involvement (celiac trunk arteries, superior mesenteric artery, portal-mesenteric venous axis), fat tissue infiltration (mesenteric root and transverse mesocolon, retroperitoneal fat corresponding to the SMA margin).

For the evaluation of the vascular involvement, we used the following grading system published by Mazzeo et al. (2007) [4]: no contact between neoplasm and vessel (grade 0); focal contiguity between neoplasm and vessel, without modifications of the vessel caliber (grade I); the neoplasm surrounds partially or completely the vessel, without caliber reduction (grade II); the neoplasm surrounds partially or completely the vessel, with reduction or obstruction of the vessel lumen (grade III). On the basis of the results of this work, we considered as infiltrated vessels with grade II and III (positive predictive values - PPV - of infiltration 80%) and not infiltrated vessels with grade 0 and I (negative predictive value - NPV - of infiltration 82%) [4].
Regarding neoplastic infiltration of fat tissue, it was suspected in the presence of one of the following signs (Fig. 2):

- tissue obliteration, representing a sign of macro-infiltration, according to a study published by Mazzeo at al. in 2010, with a PPV of 94%;

- alteration of the tissue density, classified as suspicion of micro-infiltration with a PPV of 50% [5];

In all patient was evaluated the presence of infiltration at the level of mesenteric and transverse mesocolic root and the fat tissue corresponding to SMA margin identifiable as the fat tissue between the left margin of the head/uncinate process and the right wall of the proximal 3-4 cm of the superior mesenteric artery.
On the basis of both vascular and fat tissue involvement, patients were divided into 3 different groups: resectable (absence of vascular and fat tissue infiltration), borderline resectable (peripancreatic and venous infiltration liable to resection, likely R0) and palliative resectable (arterial or venous infiltration associated to peripancreatic infiltration, liable to resection likely R+).

All CT local staging findings and the overall resectability judgement were compared to histopathological results after resection.

In order to identify possible prognostic factors of survival, Kaplan-Meier survival curves were obtained by considering size and location of the tumor, length of tumor-vessel contact (cut-off 20mm), type of vessel infiltrated (venous, arterial, artero-venous), retroperitoneal fat tissue and mesenteric/mesocolic root infiltration, judgement of resectability at MDCT and histological SMA margin infiltration.
Fig. 0: Vascular infiltration grading system

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**Fig. 0:** Imaging findings of fat tissue infiltration

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Results

All cases were confirmed at histology as ductal adenocarcinoma of the pancreas. Resection margin with microinfiltration (R+) was present in 11 cases (18.5%) of whom 9 localized at the SMA margin and 2 at the pancreatic resection margin.

In 37 patients the lesion was located in the pancreas head/uncinate process and in 8 patient in the pancreatic body, with a lesion dimension ranging between 15mm and 60mm.

CT examination considered 67 vessels (42 veins and 25 artery) as infiltrated and 43 vessels (12 veins and 31 artery) as not infiltrated, with an overall judgement of venous infiltration in 24 patients, arterial in 5 patients and artero-venous in 18 patients. In 7 cases the tumor was classified at CT as not locally advanced, because of the absence of signs of vascular infiltration. Regarding the length of vascular encasement, in 38 cases it was >20mm and in 9 cases it was <20mm.

Sixtyfour vessels were resected (52 venous tract, 12 artery-5 SMA and 7 celiac trunk). Pathological analysis demonstrated the presence of infiltration in 46 out of 64 resected vessel (72%).

Regarding the 67 vessels considered as infiltrated at CT, pathology confirmed the presence of infiltration in 50 vessels (12 artery and 38 veins). Four artery and 38 veins were effectively resected, while 8 non resected SMA were considered infiltrated only indirectly, because histology showed a R+ on the SMA margin.

False positive vessels were 17 (4 veins and 13 artery) of whom 11 had been resected, while in the remaining 6 non resected artery, the absence of infiltration was obtained at intraoperative examination of the perivascular fat tissue (1 case) or indirectly because of an negative (R0) SMA resection margin (5 cases).

Eleven vessels (1 artery and 10 veins), considered as not infiltrated at CT, were otherwise resected: histology confirmed the absence of infiltration in 7 vessels (1 artery e 6 vein), while 4 veins resulted to be infiltrated.

In the evaluation of vascular infiltration, CT showed overall sensitivity of 93% (in particular, 100% for venous and 90% for arterial infiltration), specificity of 70% (71% for venous and 67% for arterial infiltration) and diagnostic accuracy of 81% (77% for venous and 85% for arterial infiltration), positive predictive value 75% (48% for venous and 90% for arterial infiltration), negative predictive value 91% (100% for venous and 67% for arterial infiltration) (Fig 1).
At CT, the suspicion of retroperitoneal fat corresponding to the SMA margin infiltration was posed in 31/54 cases, judging 22 cases as macroinfiltrated and 9 cases as microinfiltrated.

Histology demonstrated the presence of infiltration of the fat tissue (T3) in 29 cases, in particular in 27 out of 31 case (87%) suspected at MDCT; more in detail, infiltration was confirmed in 21/22 (95%) cases judged as macroinfiltrated at CT and in 6/9 (76%) microinfiltrated cases.

Infiltration of the mesenteric/mesocolic root was suspected at CT in 23 cases and was confirmed by histology in 20 cases (the false positive CT diagnoses were due to chronic inflammation of the fat tissue). Overall, in the evaluation of the peripancreatic fat tissue infiltration, CT showed a sensitivity and a specificity of 96% and 91% respectively and a diagnostic accuracy of 91%. The positive and negative predictive values resulted to be 85% and 97%, respectively. (Fig.2)
Results: SMA margin and mesenteric/mesocolic root infiltration

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At CT, 7 patients resulted to be resectable, 23 borderline resectable and 24 palliative resectable and at pathology 7, 30 and 17 respectively, with concordance in 39/54 cases (72%).

In judging resectability CT showed sensibility of 85%, specificity of 60%, PPV of 68% NPV of 80% and diagnostic accuracy of 72%. The corresponding dates in judging unresectability was 94%, 78%, 67%, 97% e 83% (Fig. 3).
Regarding statistical analysis, 6 patients (11%) were excluded, because they died in the perioperative period because of complication.

Of the remaining 48 patients, 16 were still alive at the moment of the study (with a follow-up ranging between 5 and 113 months) and 32 were died (with a follow-up between 1 and 100 months). Survival was 84% and 57% at 6 month and 1 year respectively, and particularly 1 year survival was 100% for patients identified as resectable, 75% for borderline resectable and 28% for palliative resectable.

No statistical correlation with survival existed by considering location of the tumor on page (p=0.5), size of the tumor at CT on page (p=0.16) and length of tumor-vessel contact on page (p=0.75).

A statistically significant correlation with survival was obtained by considering type of vessel infiltrated on page (p=0.03), retroperitoneal fat corresponding to the SMA margin on page (p=0.03), mesenteric/mesocolic root on page (p=0.02) and histological SMA margin on page (p=0.03) infiltration.
Finally judgement of resectability at MDCT resulted to be strongly related to survival ($p=0.0008$) (Fig. 4).

**Fig.** Kaplan-Meier survival curves, up to 113 months, based on the judgement of resectability at MDCT ($p=0.0008$)

**References:** oncology transplants and advanced technologies in medicine, university hospital pisa - pisa/IT
### Results: vascular infiltration

- **Venous infiltration**: 24 pz
- **Arterial infiltration**: 5 pz
- **Arterio-venous**: 18 pz

**Diagnostic Accuracy 81%**
- Sensitivity: 93%
- Specificity: 70%
- PPV: 75%
- NPV: 91%

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**Fig. 0**: Results: vascular infiltration

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**Fig. 0:** Results: SMA margin and mesenteric/mesocolic root infiltration

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**Fig. 0:** Results: resectability judgement

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**Fig. 0:** Kaplan-Meier survival curves, up to 113 months, based on the judgement of resectability at MDCT (p=0.0008)

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Conclusion

The high mortality rate from cancer recurrence makes difficult the intraoperative distinction between curative and palliative resection. Nonetheless, some patients do benefit from resection, especially if a margin negative resection can be accomplished. Particularly, vascular resection is justified on the basis of the intrinsic difficulty in differentiating preoperatively between inflammatory and tumoral adhesions.

MDCT represents an accurate technique that can help in identifying borderline resectable patients that can benefit from therapeutic surgery or patients that need neo-adjuvant chemotherapy.

Moreover each parameter of local staging and the overall judgement of resectability can be related to survival, so confirming the strong contribution of MDCT in the therapeutic planning.
References

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