Preoperative downstaging of pancreatic adenocarcinoma: does it affect the accuracy of size measurements at CT?

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Aims and objectives

Pancreatic adenocarcinoma is the most common neoplasm of the pancreas, accounting for approximately 90% of cases.

It is a disease with a very poor prognosis, mainly because of its late clinical presentation. This is why it is usually detected in advanced unresectable stages. The only potentially curative treatment option is resection; chemotherapies and radiotherapies are not very effective.

Treatment options

Unfortunately, only about 5-20% of patients undergo surgery (upfront tumours).

Most patients can only be palliated (unresectable tumours). Exclusion criteria for surgery are:

- Distant metastases (hepatic, visceral, pleural, peritoneal, distant lymph node, …)
- Locally advanced disease (extrapancreatic visceral spread, except for bile duct and duodenum infiltration)

Another group of patients with tumour previously considered unresectable because of a close contact with surrounding vessels may benefit from neoadjuvant therapies (borderline resectable tumours) [1]. Even if pancreatic adenocarcinoma is not very sensitive to chemotherapy, tumour may sometimes downstage and become resectable.

Prognostic factors: T parameter

Many prognostic factors have been identified and used to choose appropriate treatment and predict outcome. TNM staging system is one of the most relevant.

However, according to the 7th edition, most patients were classified as T3 ("tumour that extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery"), because not only large tumours but also the smallest ones often extend beyond the pancreas at the time of detection.

In 2016, AJCC/UICC released the 8th edition, introducing a new definition of the T-parameter based on tumour size (T1 # 2 cm; 2 cm < T2 # 4 cm; T3 > 4 cm) to correlate worsening prognosis with larger lesions and better stratify patient’s risk [2-5].
Measuring T parameter

Pancreatic adenocarcinoma is a fibrous hypovascular tumour with ill-defined borders. At CT the pancreatic or late arterial phase is the most important acquisition phase for detection and staging: the normal surrounding parenchyma shows the highest enhancement and the difference with the hypodense tumour is therefore maximum. Tumour is usually hypodense also in venous phase, except for its peripheral component, less fibrous than the centre, that may become isodense (fig. 1) [6].

![CT images](image)

Fig. 1: A case of cephalo-pancreatic cancer. This CT shows how to measure the longest diameter of the lesion in the axial plane, according to RECIST 1.1. a. late arterial phase b. venous phase

References: Department of Radiology, Policlinico G.B. Rossi Borgo Roma - Verona/IT

The "gold standard" in measuring the T parameter is based on histologic examination.

A more accurate preoperative assessment of tumour diameter could aid in a more precise prognostic definition for the patient even before surgery. Downstaging cytotoxic treatments have been reported to reduce the accuracy in assessing tumour borders, and therefore might also impair an accurate evaluation of tumour size [7-11].

In our study we have compared CT and pathological measurements, both in upfront and downstaged patients. The purpose was to evaluate if the accuracy of CT for measuring the tumour diameter in arterial and venous phase is affected by preoperative downstaging.
Methods and materials

Patient population

Informed consent was waived for this retrospective study that was performed under the regulations of the declaration of Helsinki.

We considered for inclusion patients who underwent resection for pancreatic adenocarcinoma between 2009 and 2015. All patients performed a preoperative multiphasic MDCT within 3 months before surgery. Our final population included 106 patients, 49 males and 57 females, with a mean age of 61.3 years.

85/106 patients had upfront surgery (group A), whereas 21/106 patients underwent preoperative downstaging chemotherapy (group B).

According to pathological measurements, there were 41 T1 tumours, 59 T2 tumours and 6 T3 tumours.

CT scanner and protocol

MDCT examinations were performed on a 64-row scanner.

Patients received a weight-based bolus of iodinated contrast agent (1.5 ml/kg, 370).

A multiphasic protocol was used, including unenhanced, pancreatic arterial and venous phases, acquired respectively 15 and 60 seconds after bolus tracking.

Image analysis

CT images were reviewed by one resident radiologist with 5 years of experience in abdominal imaging.

For each exam, the reader measured the longest axial diameter of the pancreatic lesion, both in arterial and venous phase (Diam-art and Diam-ven respectively) (fig. 1). The diameters from the pathology reports were also logged (Diam-path). We have chosen to measure the lesion in the axial plane in order to obtain more easily reproducible results, according to the widely adopted RECIST 1.1 system [12].

Statistical analysis included t-test, Bland-Altman's and Fisher's tests.
**Fig. 1:** A case of cephalo-pancreatic cancer. This CT shows how to measure the longest diameter of the lesion in the axial plane, according to RECIST 1.1. 

- a. late arterial phase
- b. venous phase

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Results

The mean difference between Diam-art and Diam-ven was +1 mm in group A (p < 0.0001) (95% limits of agreement: -1.8 mm and 3.9 mm) and +2 mm in group B (p=0.0006) (95% limits of agreement: -2.4 mm and 6.4 mm) (fig. 2).

In group A, the mean difference between Diam-art and Diam-path was -0.9 mm (p=ns) (95% limits of agreement: -12.6 mm and 10.7 mm); the mean difference between Diam-ven and Diam-path was -2 mm (p=0.0020) (95% limits of agreement: -13 mm and 9.1 mm) (fig. 3 and 4).

In group B, the mean difference between Diam-art and Diam-path was +2.1 mm (p=ns) (95% limits of agreement: -12.3 mm and 16.4 mm); the mean difference between Diam-ven and Diam-path was +0.1 mm (p=ns) (95% limits of agreement: -14.6 mm and 14.8 mm) (fig. 3 and 4).

These small differences led to a change in T-category based on tumour size in the arterial phase in 25/85 upfront tumours and in 7/23 downstaged tumours (p=ns); based on the tumour size in the venous phase in 25/85 upfront tumours and in 4/23 downstaged tumours (p=ns) (tab. 1).

DISCUSSION

In our study, we have first used a paired t-test to evaluate if there were significant differences between pathological measurement and CT measurements, both in arterial and venous phase.

We found that these differences were not statistically significant in patients who received preoperative chemotherapy. One could interpret that non-significant results mean no differences between CT and pathological measurements, thus concluding that there is agreement. However, t-test does not evaluate agreement, but only shows the quantitative mean difference between the two measurements, which is influenced by extremely large and extremely small values. Poor agreement between CT and pathology can be hidden in the distribution of differences, and thus the two methods can appear to agree even if it's not true.

For this reason we used Bland Altman test, defining "a priori" the limit of maximum acceptable differences, based on clinical/prognostic necessities (that is changing T-category). We judged qualitatively the scattering in the Bland Altman plot (fig. 3 and 4). The wide range of the confidence interval (Diam-art vs Diam-path: between -12.25
and +16.44 mm; Diam-ven vs Diam-path: between -14.56 and +14.75 mm) reflects the variability of our measurements: in a minority of cases, the difference between measurements was higher than 10 mm and in some cases higher than 15 mm.

**Fig. 3**: This graph shows Bland Altman test assessing the agreement of measurements between CT late arterial phase and pathology, both in downstaged and upfront tumours

**References**: Department of Radiology, Policlinico G.B. Rossi Borgo Roma - Verona/IT

**Fig. 4**: This graph shows Bland Altman test assessing the agreement of measurements between CT venous phase and pathology, both in downstaged and upfront tumours

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Than we used a **Fisher test** to evaluate if preoperative chemotherapy had induced an increase in the percentage change of T-category, if compared with patients who undergo upfront surgery. We observed that 7/23 downstaged tumours were classified with a wrong
T-category by the radiologist reading the arterial phase (vs 25/85 upfront tumours) and 4/23 when reading the venous phase (vs 25/85 tumours) (p=ns) (tab. 1).

**Table 1**: This table shows Fisher test evaluating if the accuracy of CT for measuring the tumour diameter is affected by preoperative downstaging.

**References**: Department of Radiology, Policlinico G.B. Rossi Borgo Roma - Verona/IT

<table>
<thead>
<tr>
<th>Change in T-category</th>
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<th>Diam-ven vs Diam-path</th>
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<tr>
<td></td>
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<td>Upfront (A)</td>
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<table>
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<th>Diam-ven vs Diam-path</th>
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<tbody>
<tr>
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<td>Downstaged (B)</td>
<td>Upfront (A)</td>
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<td>25 (29.4%)</td>
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<tr>
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</tr>
</tbody>
</table>
Images for this section:

**Fig. 2:** This graph shows Bland Altman test assessing the agreement of measurements between CT late arterial phase and CT venous phase, both in downstaged and upfront tumours

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**Fig. 3:** This graph shows Bland Altman test assessing the agreement of measurements between CT late arterial phase and pathology, both in downstaged and upfront tumours

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**Fig. 4:** This graph shows Bland Altman test assessing the agreement of measurements between CT venous phase and pathology, both in downstaged and upfront tumours.

Table 1: This table shows Fisher test evaluating if the accuracy of CT for measuring the tumour diameter is affected by preoperative downstaging.

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Conclusion

Downstaging chemotherapy does not appear to affect the accuracy of CT (both in arterial and venous phase) in measuring the largest tumour diameter in pancreatic adenocarcinoma and thus assessing the T-stage to the tumour. There was not a significant difference in the percentage of T-category change in downstaged patients when compared with upfront patients.

These results have to be confirmed analysing a larger group of downstaged resected patients.
Personal information

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References


