

# Primary Tumor of Pancreatic Cancer as a Measurable Target Lesion in Chemotherapy Trials

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Received June 16, 2005; accepted August 10, 2005; published online September 19, 2005

**Background:** It is unclear whether primary pancreatic cancer (PC) tumors can be accepted as measurable target lesions in chemotherapy trials. We reviewed recent PC patients to clarify the significance of their computed tomography (CT) responses of the primary tumor after chemotherapy.

**Methods:** The patient selection criteria were (i) having been admitted between January 2002 and December 2004, (ii) diagnosed as having histologically or cytologically proven adenocarcinoma of the pancreas, (iii) treated with chemotherapy with no previous anticancer treatment and (iv) having been evaluated by follow-up CT to assess the response according to the Response Evaluation Criteria in Solid Tumors criteria.

**Results:** A total of 143 patients met the selection criteria. It was possible to measure the largest diameter of the primary tumor in 119 (83%) of the 143, and primary tumor shrinkage was observed in 10 (8%) of the 119. When regarding the primary as measurable as opposed to non-measurable, the number of patients with measurable disease became 127 from 67, and the frequencies of partial response (PR), stable disease (SD) and progressive disease (PD) became 11, 74 and 15% of the 127 from 18, 52 and 30% of the 67, respectively. In the former situation, large primary tumor sometimes canceled the shrinkage or progression of small metastasis. In each setting, PR or SD represented a favorable prognosis compared with PD, however, there were no statistical differences between the PR and the SD.

**Conclusion:** Measuring the primary tumor is acceptable in ~80% of PC patients. However, we must be aware that the frequency of SD may increase compared with the PR or PD.

*Key words: pancreatic neoplasm – RECIST – computed tomography – measurement – response*

## INTRODUCTION

The computed tomography (CT) response to treatment is an important indicator of the therapeutic effect of anticancer agents. In daily practice, response assessment is combined with other indicators of the patient's condition to contribute to the decision-making process. In clinical trials, it is widely used to identify and quantify the antitumor activity of investigational chemotherapy. A valid assessment of the response is based on an accurate measurement of the tumor on CT.

In pancreatic cancer (PC), however, it is difficult to accurately measure the size of the primary tumor mainly due to its invasive growth (1,2). In addition, the appearance of the tumor on a CT scan may not reflect the true proportion of the tumor response due to a vigorous desmoplastic reaction, including inflammation and fibrosis, within and around the tumor (3). Therefore, a primary PC tumor has been regarded

as a non-measurable lesion in chemotherapy, and the antitumor effect of CT has been assessed mainly by measurable distant metastasis (4).

Recently, the consensus about the measurability of the primary PC tumor has become unclear. Shrinkage of the primary PC tumor has been more frequently observed since the introduction of gemcitabine (GEM)-based chemotherapy. There have been a number of trials that included not only patients with metastatic disease but also those with locally advanced disease, even though their end point is an objective CT response (5-7). In these reports, the primary PC tumor might be regarded as a measurable lesion, at least in locally advanced PC patients.

The current retrospective study was conducted to clarify whether the primary PC tumor could be accepted as a measurable target lesion in chemotherapy trials.

## PATIENTS AND METHODS

The patient selection criteria were (i) having been admitted between January 2002 and December 2004, (ii) diagnosed as

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having histologically or cytologically proven adenocarcinoma of the pancreas, (iii) treated with chemotherapy with no previous anticancer treatment and (iv) having been evaluated by follow-up CT to assess the response. We listed all patients who met the above criteria and surveyed their records to clarify the significance of the primary tumor measurement in PC chemotherapy.

The tumor response was assessed by CT according to the Response Evaluation Criteria in Solid Tumors (RECIST) response criteria (8). In brief, a complete response was defined as the disappearance of all lesions. A partial response (PR) was defined as at least a 30% reduction in the tumor load, estimated as the sum of the longest diameters of all measurable lesions, taking as a reference the baseline sum of the longest diameters. Progressive disease (PD) was defined as at least a 20% increase in the tumor load, taking as a reference the smallest sum of the longest diameters recorded since the treatment started or development new lesions in a previously uninvolved site. Stable disease (SD) was defined as disease that showed neither sufficient shrinkage nor increase to qualify as either PR or PD.

CT scanning was performed with a four-section multi-detector row CT scanner (Aquilion; Toshiba Medical System, Tokyo, Japan). Dynamic contrast-enhanced CT was performed in all patients with the mechanical injection of 100 ml of iopamidol (370 mg/ml of iodine) into the antecubital vein at a rate of 3 ml/s. CT scanning commenced 40–70 s after the start of injection of the contrast medium. Scanning parameters were as follows: 0.5 s gantry rotation time, a beam collimation of  $4 \times 2$  mm, helical pitch of 5 and a reconstruction thickness of 5–7.5 mm.

The CT stage of each patient before chemotherapy was determined prospectively at our film conference held every Tuesday with the attendance of 2–4 staff from each section, i.e. diagnostic radiology, upper abdominal surgery and medical oncology. The measurability of the primary PC tumor on pretreatment CT was judged retrospectively (measurable or non-measurable) by three oncologists (H.I., J.F. and K.N) independently, with no clinical information of the patients. In this retrospective part, the radiologists did not participate in the judgment of measurability for primary lesions. The results were classified into three categories, i.e. ‘measurable’, ‘marginal’ or ‘non-measurable’, the definition of which was as follows: ‘measurable’ when three of the three judged the primary tumor as measurable, ‘marginal’ when two of the three judged the primary tumor as measurable and ‘non-measurable’ when one or none of the three judged the primary as measurable. Finally, the ‘marginal’ cases were determined to be measurable or non-measurable based on the consensus of the three (Fig. 1).

In the current study, responses were assessed by two methods, i.e. regarding the primary PC tumor as a non-measurable lesion (referential method) or as a measurable target lesion in cases with ‘measurable’ primary tumors (alternative method). In the latter, the maximum size of the pancreatic mass on CT was measured on the serial axial slices containing the largest portion of the mass. According to the RECIST criteria, shrinkage of the primary PC tumor was defined as 30% or greater

reduction of the largest size, and PR was confirmed when the shrinkage continued for more than 4 weeks.

Survival curves were calculated using the Kaplan–Meier method (9). Overall survival was measured from the beginning of chemotherapy to the time of the final follow-up or death. Differences in survival were evaluated with log-rank tests. All analyses were performed using the statistical software SPSS 11.0J for Windows. Statistical significance was defined as a two-sided *P*-value of  $\leq 0.05$ .

## RESULTS

Between January 2002 and December 2004, a total of 327 histologically confirmed PC patients were admitted to our hospital. Of them, 63 underwent surgical resection, 20 were treated with chemoradiotherapy, 26 received best supportive care and 218 were treated with chemotherapy. Of the 218, 47 had anticancer treatment earlier, i.e. surgical resection of primary PC in 24 and chemotherapy in 23. Of the remaining 171, 28 were not evaluated by CT after chemotherapy because of their early deteriorations. Accordingly, the remaining 143 met the selection criteria in the current study.

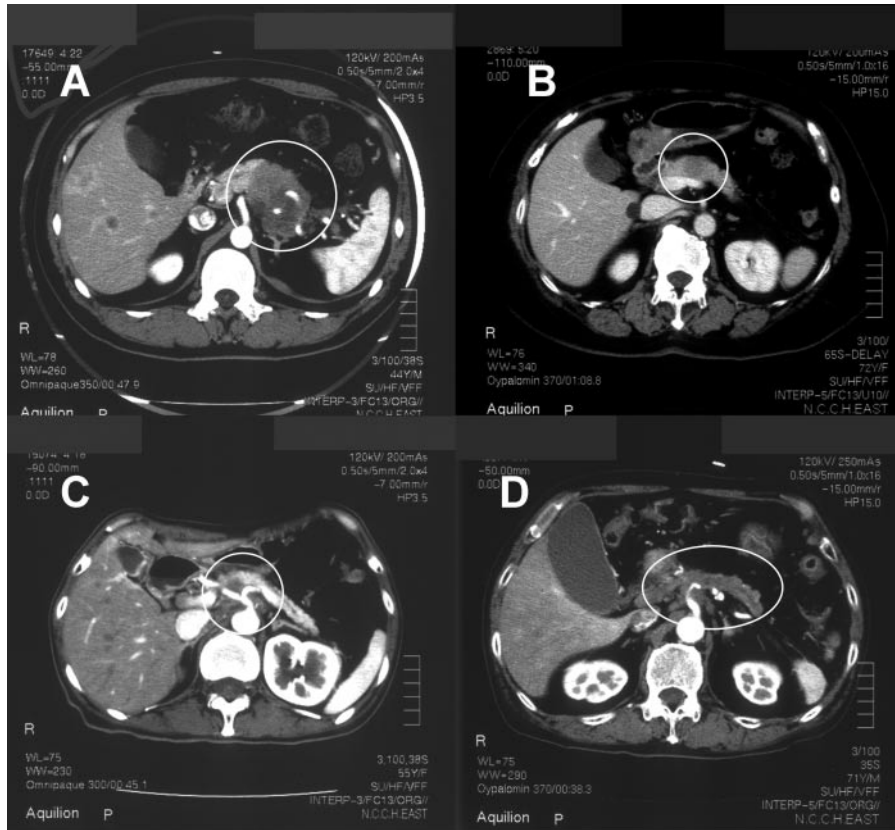
The patient backgrounds are shown in Table 1. Of the 143, 67 had measurable metastasis and the remaining 76 had no measurable metastasis. Among them, 101 received GEM monotherapy as a clinical practice (1000 mg/m<sup>2</sup>/30 min, Day 1, 8 and 15, every 4 week). The remaining 42 received chemotherapy as part of multicenter clinical trials: Phase 1/2 study of the fixed dose rate infusion of GEM ( $n = 11$ ), and combination of GEM and S-1 ( $n = 11$ ), Phase 2 study of combination of GEM and infusional fluorouracil ( $n = 5$ ), S-1 ( $n = 6$ ), NK911 (micelle forming polymeric doxorubicin,  $n = 6$ ) and CPT-11 ( $n = 3$ ).

### RESPONSE BY THE REFERENTIAL METHOD

Of 67 patients with measurable metastasis, 12 (18%) showed a PR, 35 (52%) remained SD, and 20 (30%) showed PD. All 12 PR cases showed liver metastasis shrinkage. Of 76 with no measurable metastasis, 68 remained SD and 8 showed PD. Therefore, the overall responses in the 143 were 12 PRs, 103 SD and 28 PD, according to a referential method, i.e. regarding the primary PC tumor as a non-target lesion.

### RESPONSE BY THE ALTERNATIVE METHOD

The frequencies of patients with a ‘measurable’ primary tumor in the 143 were 76, 85 and 87% according to each of the three blinded reviewers. As a result, the frequencies of ‘measurable’, ‘marginal’ and ‘non-measurable’ primary tumors were 74, 13 and 13%, respectively. Of the 19 ‘marginal’ cases, 13 were reconsidered to be ‘measurable’ cases by discussion. Finally, 119 (83%) were diagnosed as having a measurable primary PC tumor. In the 119, the maximum size of the primary tumor ranged from 21 to 121 mm and the quartiles at 25, 50 and 75% were 37, 47 and 65 mm, respectively. Shrinkage of the primary tumor was observed in 10 of the 119. The relationship between the primary tumor measurability and presence



**Figure 1.** CT images of the ‘measurable’, ‘marginal’ or ‘non-measurable’ primary tumor (indicated in the center of an each white circle). (A) A case with the ‘measurable’ pancreatic body-tail tumor. (B) A case with the ‘marginal’ pancreatic body tumor, which was finally determined to be ‘measurable’. (C) A case with the ‘marginal’ pancreatic body tumor, which was finally determined to be ‘non-measurable’ because of its irregular shape. (D) A case with the ‘non-measurable’ pancreatic tumor because of its indistinct margin.

**Table 1.** Patient characteristics in the 143 pancreatic cancer patients treated with chemotherapy

Gender (Man/woman)	76/67
Age [Median (range)]	63 (37–90)
Performance status (0/1/2/3)	101/37/4/1
Tumor location (Head/body-tail)	64/79
Stage	
Locally advanced disease	44
with measurable regional lymph node	2
without measurable regional lymph node	42
Metastatic disease	99
with measurable lesion	65
without measurable lesion	34
CA19-9 <sup>†</sup> (U/ml)[Median, (25–75 percentile)]	713 (79-2,788)

<sup>†</sup>Carbohydrate antigen 19-9, cut-off index is less than 37 U/ml in our hospital.

or absence of measurable metastasis is shown in Table 2. Of the 127 with measurable primary or metastatic tumors, 14 (11%) showed a PR, 94 (74%) remained SD and 19 (15%) showed PD. Of the remaining 16 with no measurable lesions, 13 remained

**Table 2.** Relationship between the primary tumor measurability and the presence or absence of measurable metastasis

	Measurable metastasis		Total
	Absent	Present	
Primary tumor			
Non-measurable	16 (11%)	8 (6%)	24 (17%)
Measurable	60 (42%)	59 (41%)	119 (83%)
Total	76 (53%)	67 (47%)	143 (100%)

SD and 3 showed PD. As a result, the overall responses in the 143 were 14 PRs, 107 SD and 22 PD, according to the alternative method.

COMPARISON OF THE TWO METHODS

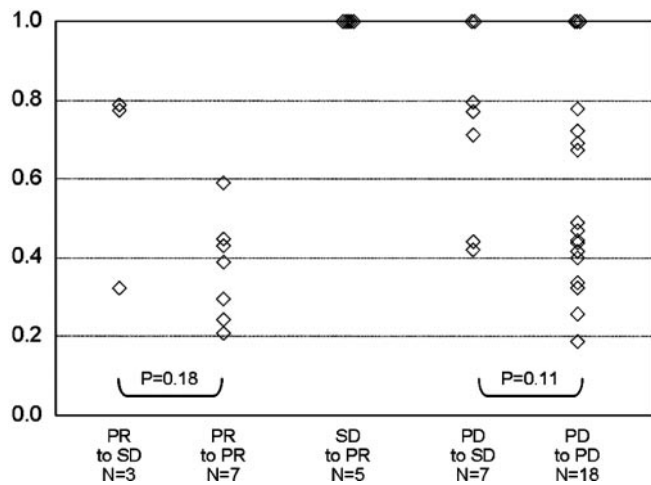
The relationship between the referential and the alternative responses is shown in Table 3. A discrepancy between the responses was observed in 14 (10%) cases.

All five cases from SD (referential) to PR (alternative) had no target metastatic metastasis (locally advanced, 2; minute liver metastasis, 2; peritoneal dissemination, 1),

**Table 3.** CT response with or without measuring the primary tumor as a measurable target lesion

Response	Primary tumor as a measurable target lesion			Total
	PR <sup>†</sup>	SD <sup>‡</sup>	PD <sup>§</sup>	
Primary tumor as a non-measurable lesion				
PR	9	3		12
SD	5	98		103
PD		6	22	28
Total	14	107	22	143

<sup>†</sup>Partial response.  
<sup>‡</sup>Stable disease.  
<sup>§</sup>Progressive disease.

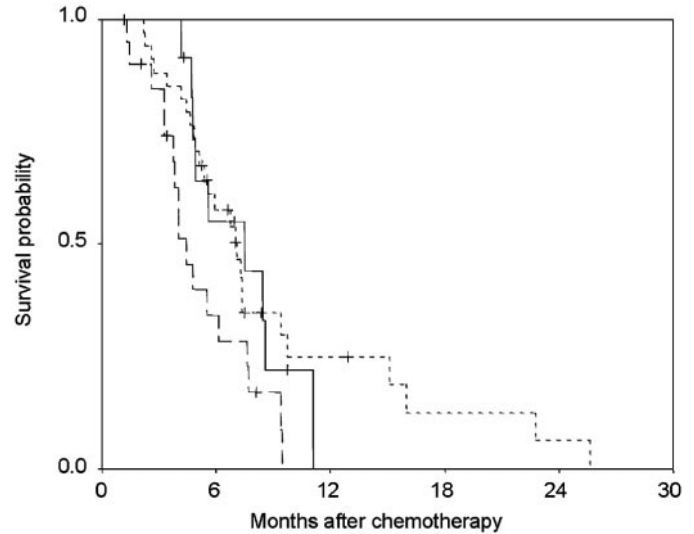


**Figure 2.** The proportion of the primary tumor size to all sum of the longest measurable lesion including the primary tumor. In cases from PR to SD, or from PD to SD, there was a trend to have a relatively large primary tumor compared with those from PR to PR, or from PD to PD, respectively. The *P*-values were calculated by Mann–Whitney *U*-tests.

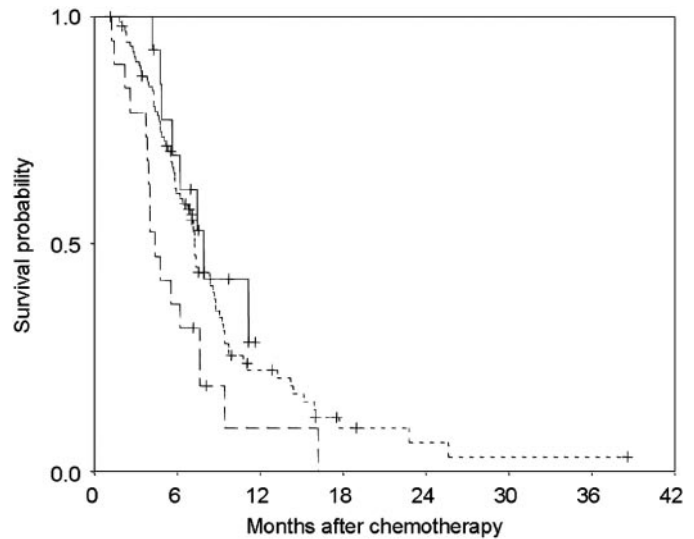
i.e. shrinkage was observed in the primary tumor as the sole target lesion.

Cases from PR to SD, or from PD to SD, had relatively large primary tumors compared with metastasis (Fig. 2). In these cases, the primary tumor was so large to be set off against shrinkage or progression of small metastasis. Therefore, reduction of the total sum of the largest diameter of the targets did not reach over 30% in cases from PR to SD, or the enlargement of the total sum remained within 20% in cases from PD to SD, using the alternative method.

Survival curves of measurable cases according to each response are shown in Figs 3 and 4. They showed a situation that was commonly seen in a Phase 2 chemotherapy trial for advanced PC, i.e. a trial for metastatic PC using the referential method and for locally advanced or metastatic PC by the alternative method. PR and SD were superior to PD; however, there were no significant differences between PR and SD in both situations.



**Figure 3.** The overall survival curve of 67 patients with measurable metastasis according to the CT response when assessing the primary tumor as a non-target lesion (referential method). The plain line indicates cases with a PR, the fine dotted line indicates cases with SD and the dotted line indicates cases with PD. The *P*-values of the log-rank test for cases with PR versus SD, PR versus PD and SD versus PD were 0.80, 0.05 and 0.02, respectively.



**Figure 4.** The overall survival curve of 127 patients with any measurable lesion according to the CT response when assessing the primary tumor as a target lesion (alternative method). The plain line indicates cases with a PR, the fine dotted line indicates cases with SD and the dotted line indicates cases with PD. The *P*-values of the log-rank test for cases with PR versus SD, PR versus PD and SD versus PD were 0.44, 0.03 and 0.02, respectively.

**DISCUSSION**

The newly introduced RECIST, which relies on the single largest dimension of the tumor, is intended to simplify the assessment of the tumor response and has become standard in the world. At the end of the preamble in the RECIST article, there is a statement that specific tumors or anatomic sites

presenting unique complexities will be considered in the future. In fact, clinical problems have already been reported in chemotherapy for malignant pleural mesothelioma (10,11) and gastric cancer (12,13) in adopting the unidimensional RECIST criteria. The main cause of the problems arises from the fact that those tumors represent a non-spherical, tridimensional shape at the primary site. PC also demonstrates a non-expanding, invasive growth pattern, and its accurate measuring on CT has been already reported to be difficult (1,2). Therefore, the antitumor effect in Phase 2 chemotherapy trials for PC has been mainly evaluated by the CT assessment of measurable distant metastasis, and primary tumors have generally been regarded as a non-measurable lesion (3).

However, recent reports of Phase 2 trials (5–7) sometimes include not only patients with metastatic disease but also those with locally advanced disease. In patients with locally advanced disease, the primary PC tumor must be measured and assessed using CT. Therefore, the current study focused on the validity of the primary PC tumor measurement and its assessment, because little attention has been given to this issue.

There must be some factors that influence the measurability of the primary PC tumor, such as the quality of CT images, the opinion of each physician and so on. The size of the primary PC tumor may change variously according to the contrast enhanced phase of dynamic CT (1). In the current study, however, an almost uniform method was used to obtain the CT images, thanks to an effort in our diagnostic radiology division. As for the disagreement of each physician's opinion, the current blind test showed a high frequency of agreement about the measurability of the primary tumor. Accordingly, we supposed the primary tumor to be measurable in ~80% of advanced PC patients, also in the other center hospitals.

The assessment of primary tumor shrinkage may be used for measuring the anticancer activity in Phase 2 trials for locally advanced PC. In the current study, however, we could not mention this issue because only two patients with locally advanced disease achieved a PR. Overall survival has been usually employed as the primary end point in Phase 2 trials for locally advanced PC (14,15), because standard chemoradiotherapy reproduced almost constant results, i.e. the median survival time of 10 months or 1 year survival rate of 40% (16–18). Accordingly, it may be unnecessary to measure the primary in trials for locally advanced disease.

Measuring the primary PC tumor may be an advantage for recruiting many patients into clinical trials. In fact, patients with measurable lesions increased from 67 to 127 patients. The result indicated candidates for Phase 2 trials may be doubled by measuring the primary tumor. In this manner, however, we should notice that the frequency of SD might increase compared with the PR or PD. As shown in the results, this phenomenon occurred because the large primary tumor sometimes canceled the shrinkage or progression of small metastasis. Accordingly, whether primary tumor can be accepted as a

measurable target lesion or not should be determined strictly in each protocol to make an easy interpretation of anticancer activity. To date, the non-PD rate may be the best response indicator, because it is unnecessary to differentiate PR from SD until the development of a new effective chemotherapy superior to standard GEM in the treatment of PC. In this respect, we should be aware of regarding a non-PD rate as an end point, because it may tend to be high using the alternative method in the current study.

In conclusion, the measurement and assessment of the primary PC tumor may be accepted in Phase 2 trials, whereas a careful interpretation of the responses is needed for each protocol.

### Acknowledgment

The authors thank our secretary, Ms Yuki Fujishiro, for her devoted preparation and arrangement of CT imaging.

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