## Original Article
# Study on clinical target volume (CTV) of pancreatic cancer: under the scope of CT scanning and pathology

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Abstract: Objective: The current study aimed to investigate differences between computed tomography (CT) scanning pictures of pancreatic cancer primary tumors and the actual sizes of tumors measured by pathologists after surgical resections, probing the micronidus-invaded area within normal pancreatic tissues out of primary tumors. Methods and materials: This study evaluated 19 patients with resected pancreatic cancer at two different hospitals. MDR-CT scans and maximum cross-sectional diameters of primary tumors of whole specimens were checked. The actual tumor-invaded area was microscopically detected through pathological examinations. Results: Of included patients, fifteen possessed preoperative MDR-CT scans that were available. There were significant differences between the pathology and maximum diameters of CT scan-measured primary tumors (33.6 vs. 30.1 mm, $P < 0.001$). Discrepancies between the actual maximum tumor-invaded distance of the nineteen specimens and the maximum measuring distance were statistically significant (3.50 vs. 3.19 mm, $P < 0.001$). The actual maximum tumor-invaded distance was 5.21 mm, while the median value was 3.34 mm (range, 2.19 to 5.21 mm). The mean value reached $3.50 \pm 0.88$ mm. Conclusion: Since CT scanning has significantly underestimated pancreatic cancer primary tumor sizes, in the process of radiation therapy, a 5 mm marginal expansion of the clinical target volume (CTV) from the gross target volume (GTV) is probably insufficient in CT simulation. Based on results of the micronidus-invaded area from this study, an additional CTV expansion of 1~3 mm is necessary.

Keywords: Pancreatic cancer, radiation therapy, clinical target volume, tomography, X-ray computed, pathology

## Introduction

Pancreatic cancer is a fatal disease with an overall 5-year survival rate of less than 5% [1]. Surgical resection is one of the main treatment methods. Five-year survival rates after receiving the radical operation are approximately 5%-20% [2]. Locoregional recurrence remains common after resections [3-5]. Up to 40% of pancreatic cancer patients have localized but inoperable tumors. These are commonly treated with upfront radiotherapy [6-9].

An accurate determination of the target volume area (including visible nidus, micronidus, and necessary marginal expansion) is one of the most crucial steps during precise radiation therapy. According to the International Commission on Radiation Units and Measurements (ICRU, Item 62), gross tumor volume (GTV) provides the tumor-invaded area for clinical exami-

nation and image analysis. In clinical practice, radiotherapy planning, formulated based on multidetector row computed tomography (MDR-CT) scanning pictures, has already been widely used. Therefore, pancreatic cancer primary tumor GTVs indicate the tumor area shown on CT scanning pictures. Although some studies have discussed the function of MDR-CT scanning before pancreatic cancer surgical resections, an accurate estimation of tumor size has not been previously reported.

According to ICRU, clinical target volume (CTV), which is an expansion of GTV, has established itself as an anatomicopathological concept with the coverage of suspicious but un-vouched structures involved (micronidus) in clinical practice. Very few studies have discussed the actual involved area of the micronidus of pancreatic cancer. Therefore, the current study aimed to reveal whether there exists significant differ-

ences between CT scanning pictures of pancreatic cancer primary tumors and actual sizes of tumors measured by pathologists after surgical resections, probing the micronidus-invaded area within normal pancreatic tissues out of primary tumors. These provide necessary experimental data for deciding the margin of CTV expansion in target volume delineation of pancreatic cancer radiation therapy.

**Materials and methods**

*Patients*

From December 2013 to October 2014, 19 consecutive patients with resected pancreatic cancer were selected from the Department of Hepatobiliary Surgery, both in PLA General Hospital and PLA Air Force General Hospital. **Table 1** shows all patient information in detail. Patients were selected based on the following criteria: 1) Patients had not received any radiation therapy, chemotherapy, or surgical operations before the resection; 2) Pre-resection image analysis indicated single protuberance without any metastasis beyond the pancreas; 3) Patients underwent radical pancreatic cancer resections; 4) Post-pathological diagnosis resulted in pancreatic cancer. Of these, four patients only held PET-CT scanning pictures, which occupied 21% of the whole sample. The reason was that they had already undertaken MDR-CT scanning in other hospitals and refused repetitive examinations. The rest of the patients had pre-contrast MDR-CT and contrast scanning pictures. The time span between CT scanning and the median of surgical resection reached 5 days, with an average time ranging from 1 day to 26 days.

*Primary tumor size on CT scanning and measuring methods*

A Germany-imported dual electrical source SIEMENS CT machine, with 64 rows of spirals, was used. It used 120 kV of tube voltage and 220 mAs of tube current. The sphere of CT contrast enhancement scanning was the upper abdomen. Ultravist was chosen as the iodine contrast-medium, with specifications of 300 mgI/mL. A high-pressure injector was utilized, injecting contrast-medium speedily with a large dose through forearm veins within one injection. The speed was 2.5~3.0 mL/s. Therapy dosage was 1~3 mL/kg and the total amount added up to 60~80 mL. Scanning began 25 seconds after the high-speed injection of con-trast-medium in the arterial phase, 65~75 seconds in the portal vein phase, and 3 minutes after injection in the period of delayed scanning. In terms of the dealing with pictures, the recombination was obtained with 4-mm slice thickness and 4-mm layer spacing, respectively. Reconstructed slice thickness in the pancreatic area reached 2~4 mm. In cases of special requirements, slice thickness can be only 1 mm. Imaging experts then compared cross sectional CT scanning pictures of pancreatic cancer primary tumors, slice by slice, examining the maximum diameters of cross-sectional pancreatic cancer primary tumors. The width measured 150 Hu and the level reached 40~60 Hu (**Figure 1**).

*Measurement and source of pathological specimens*

Specimens of the resected pancreatic cancer primary tumors were placed into the tissue fixative liquid (formalin 10%) for 24 hours. Given the position of primary tumors and the anatomical relationship with the resected normal tissues at the periphery, the spatial position of the pancreas was imitated *in vitro* in the abdominal cavity (**Figure 2A**). Aiming at CT scanning levels, researchers cut along the transaction of pancreas *in vitro* at a fixed slice thickness of 2~4 mm into histological sections. They continually observed them until the occurrence of the maximum cross-sectional slice with radial lines of pancreatic tumors appeared. Hereafter, this is called the interesting slice in this study. They measured the maximum diameter in cross-sectional slices of primary tumors (**Figure 2B**).

The volume of the pathological materials measured roughly 2 cm × 2 cm × 0.2 cm with a comparatively clear dividing line, including that of tumor tissues, as well as enough normal pancreatic tissues. Serial numbers were recorded (**Figure 2C**). Since the contents of pancreatic tissue fat and protein vary in different specimens and tissues are likely to retract in various degrees after dehydration and wax-dipping, every patient was offered a designed tissue to examine retraction rates (**Figure 2D**).

*Production of pathological tissue and immunohistochemistry*

Wax stones were constructed out of the pathological tissues through a process of dehydration, transparentizing, waxing, and embedding. They were placed in the section cutter (German

**Table 1.** Patient characteristics (n = 19)

| Patient characteristics | Data |
|---|---|
| Treating institution (no. of patients) | |
| PLA. General Hospita | 15 |
| PLA. Air Force General Hospital | 4 |
| Gender | |
| Male | 10 |
| Female | 9 |
| Median age at surgery (y) | 61 (range, 48 to 77) |
| Neoadjuvant radiotherapy | 0 |
| Neoadjuvant chemotherapy | 0 |
| Year of surgery | Dec.2013 to Oct.2014 |
| Method of surgery | |
| Pancreaticoduodenectomy | 10 |
| Resection of pancreatic body/tail and spleen | 8 |
| Resection of pancreatic body/tail | 1 |
| Preoperative MDR-CT scan availa ble | 15 (79%) |
| Median days between MDR-CT and surgery | 5 (range, 1 to 26) |

Abbreviation: MDR-CT = multidetector row computed tomography.
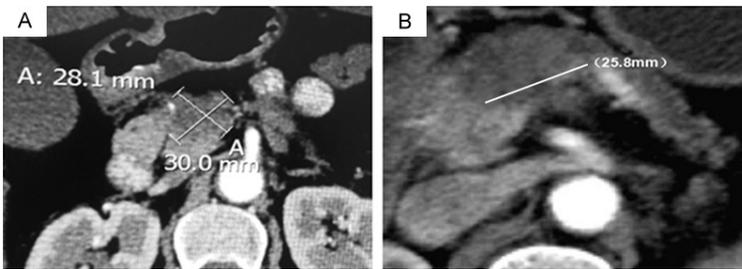


**Figure 1.** Cross-sectional CT scanning images of the pancreatic cancer primary tumor from a patient in (A) Air Force General Hospital, Beijing, China; and (B) General Hospital, Beijing, China.

LEICA RM2235) and cut continuously every 0.1~0.2 mm. They were sliced until the whole pancreatic tissue wax stones were used up. Pathological tissues for diagnosis were analyzed by immunohistochemical staining, in which process Dako k5007 was used as the reagent. However, tissues for identifying the micronidus were only analyzed with normal H&E staining.

*Reading of pathological sections and marking of the micronidus*

Reading of pathological sections included identifying the pathological types of tumors, degrees of tissue grading, vascular tumor thrombus, and neural invasion. While pathologists read every pathological section, they first gla-

nced over the whole section through a low power view and drew the edging line of the primary tumor. If primary tumor edges were invaded with burrs, then the researchers drew the line closely along the root of the burrs (**Figure 3A**). Second, the observing focus transferred to the micronidus, which exists within the pancreatic tissue outside the primary tumor, by means of a high-power view. The farthest invaded micronidus was marked and located under the view of a microscope (**Figure 3B**, **3C**). Next, the shortest straight line was connected between the marked furthest micronidus. The edging line of the primary tumor distance was measured, called the measuring distance. A Vernier caliper was used (**Figure 3D**). Third, considering pre- and post-fixation tissue retraction rates, the practical distance between this micronidus and the edge of primary tumor was identified. This means the practical distance equals the measuring distance divided by retraction rate.

*Statistical analysis*

SPSS 17.0 statistical software was used for analysis. The maximum diameter of pancreatic cancer was t-tested. Results showed that 95% of the microscopic cancer-invaded area was confidence interval, out of the edging line of the pancreatic cancer primary tumor.

**Results**

*Pathological features of patients*

Pathological results of the 19 patients are shown in **Table 2**. Twelve of the pancreatic cancer primary tumors (63.2%) were located in the head of the pancreas. Eighteen patients (94.8%) had pathological T-stages between T1 and T3. In terms of grade of tumor differentiation, the number of middle and middle-lower
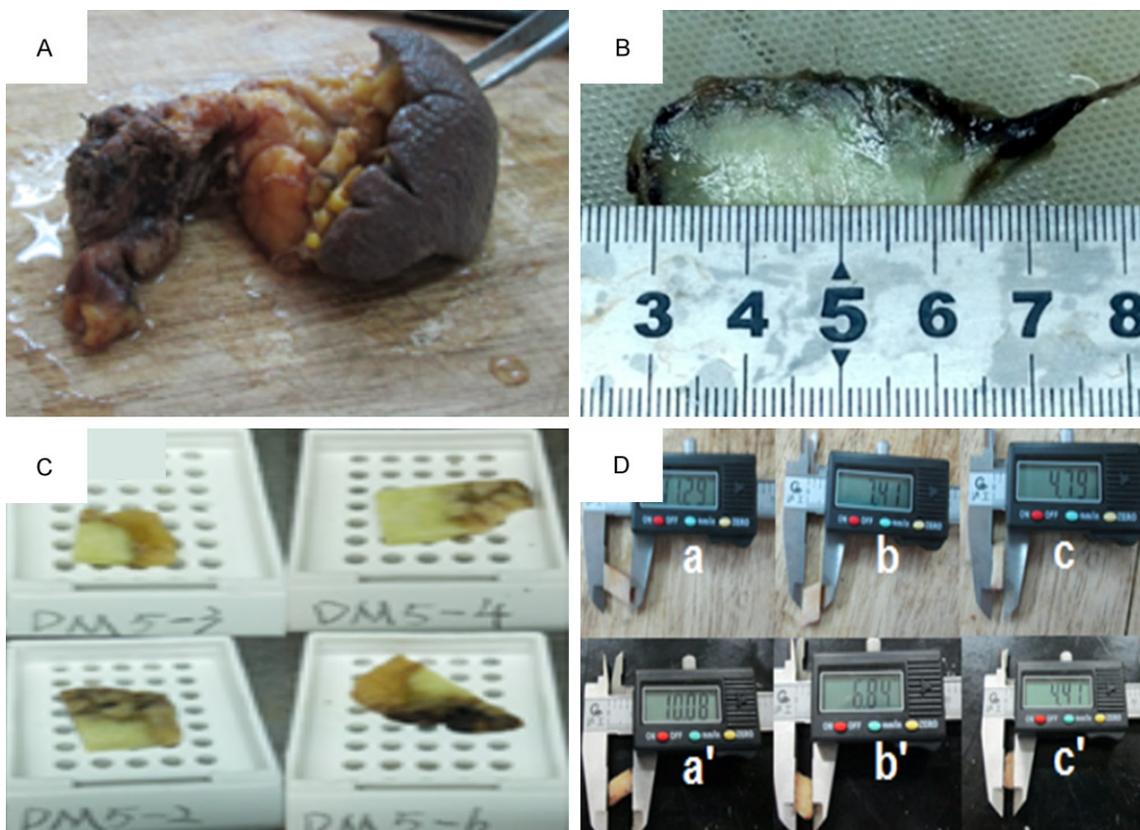
**Figure 2.** A. Spatial position of pancreatic specimens in vitro; B. The maximum cross-sectional slice with radial lines of pancreatic tumor; C. Images of pathological tissues; D. The length, width, and height before (a, b and c) and after (a', b' and c') dehydration/wax-dipping. Vernier calipers have a precision of 0.01 mm.

grade specimens was 8 and 9, respectively, accounting for 42.1% and 47.4% of all patients. Neural invasion was detected in 2/3 of the patients (63.2%). Only 3 specimens (15.8%) were confirmed as node-positive pancreas cancer via clearing the surrounding lymph nodes.

*The maximum diameter of pathological specimens was significantly longer, compared with CT scanning*

Fifteen patients with pancreatic cancer underwent pre-resection MDR-CT enhancement scanning in the hospital. The other four patients had examinations in other hospitals and refused repetitive testing. Results of the maximum diameter of the primary tumor between CT measurement and pathological specimens are shown in **Table 3**. Based on the fifteen patients, it was found that the measured diameter of the latter was longer than that of the former. The pathological measured diameter median (30.0 mm, range: 20 to 90 mm) was

longer than the CT scanning median (25.8 mm, range: 17 to 85 mm). The maximum tumor diameter measured by pathological examinations (33.6 mm) was significantly larger, compared with CT scanning (30.1 mm, $t = 6.969$, $P < 0.001$). The median and mean value of differences between pathological and CT scanning value was 3.1 mm (range: 1.2-8 mm) and 3.6 ± 2.0 mm (95% confidence interval: 1.2-6.0 mm).

*Maximum actual distance of micronidus invasion was significantly longer than the maximum measurement distance via CT scanning*

Median, mean value, maximum measurement distance, retraction rates, and maximum actual invasion distances between the farthest micronidus in the pancreas and the edging line of primary tumors on all consecutive pathological sections are shown in **Table 4**. The maximum actual distance was significantly longer than the maximum measurement distance (3.50 mm vs. 3.19 mm, $t = 14.835$, $P < 0.001$).
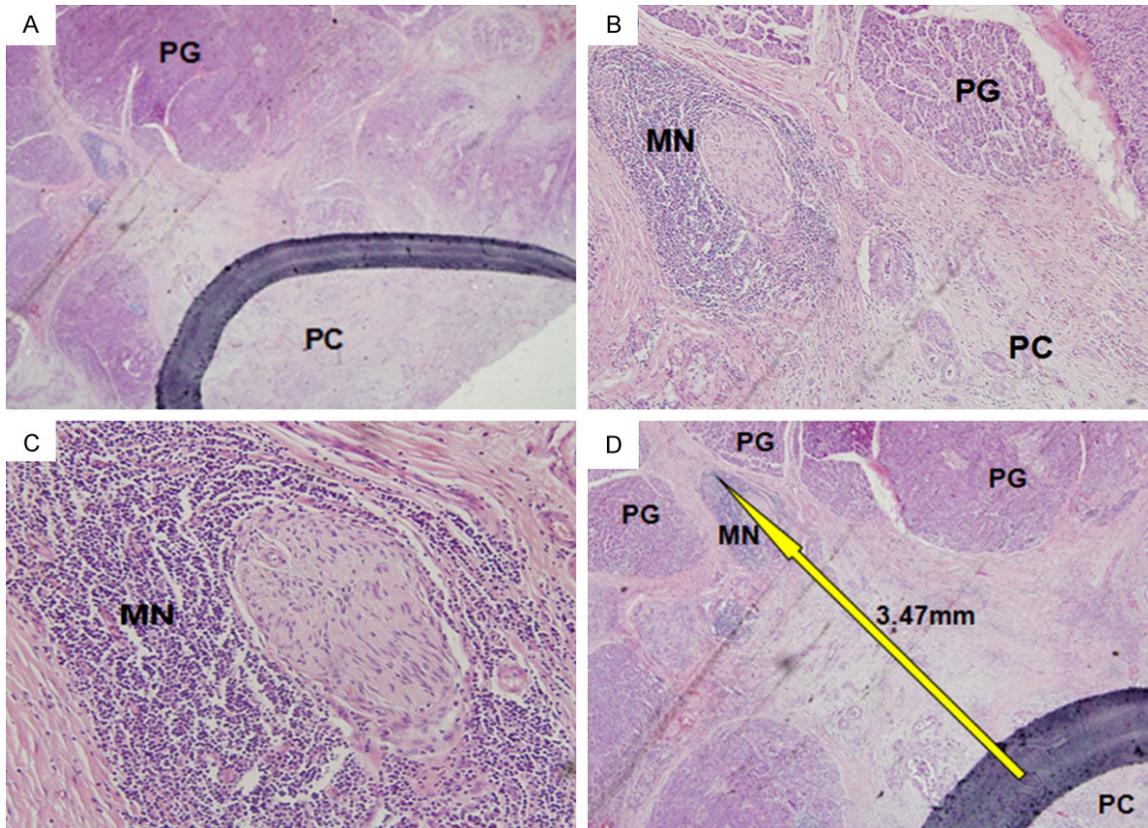
**Figure 3.** Measurement of micronidus infiltration distance. A. The edge of primary pancreatic tumor was outlined under low power field view (2 × 10); B. Micronidus in the pancreas was located under high-power field view (10 × 10); C and D. The farthest micronidus was located and its distance from the edge of primary pancreatic tumor was measured (20 × 10). PC, pancreatic cancer, PG, pancreatic gland, MN, micronidus.

Median and mean values of the differences between actual and measurement distances were 0.31 mm (range: 0.15-0.50 mm) and 0.30 ± 0.09 mm, respectively. The maximum actual invasion distance was 5.21 mm. Median and mean actual invasion distances were 3.34 mm (range: 2.19-5.21 mm, 95% CI: 2.19-5.06 mm) and 3.50 ± 0.88 mm, respectively.

## Discussion

Results of the current study suggest that the tumor size measured by pre-resection enhancement CT scanning pictures is significantly smaller than post-resection pathological measurements. This might be due to several reasons. First, although multi-row spiral-enhanced CT images display the main body of the tumor, it is difficult to distinguish the interface between the tumor and adjacent tissues. Second, the time elapsed between CT examinations and surgery might also contribute to CT scanning measurements and actual tumor size (e.g.

tumor volume doubling time and potential doubling time). Moreover, the fixation process of the pancreatic specimen by formalin might deform the tumor mass.

Since tumor size resulting from pathology has been regarded as the golden standard, the capability of CT scanning in deciding the actual size of pancreatic cancer primary tumors is limited. This finding brings an indication that the GTV location obtained through CT scanning pictures is probably different from that based on pathology in radiotherapy. This is valuable information for the design of radiation treatment planning of unresectable pancreas cancer in limited stages. Previous studies by Arvold [10] retrospectively evaluated 97 patients with resected pancreatic cancer primary tumors. Moreover, 87 patients were used to contrast the pre-resection CT scanning-obtained tumor sizes and that collected from fresh pathological specimens. Consequently, the pathological tumor diameter was longer than that of CT

**Table 2.** Pathologic characteristics (n = 19)

| Pathologic characteristics | Data |
|---|---|
| Tumor location | |
| Head/neck/uncinate | 12 (63.2%) |
| Body/tail | 7 (36.8%) |
| Pathologic T stage | |
| T1 | 1 (5.2%) |
| T2 | 9 (47.4%) |
| T3 | 8 (42.1%) |
| T4 | 1 (5.2%) |
| Histology | |
| Adenocarcinoma | 19 (100%) |
| Adenocarcinoma grade | |
| 1 | 1 (5.2%) |
| 1~2 | 1 (5.2%) |
| 2 | 8 (42.1%) |
| 2~3 | 9 (47.4%) |
| 3 | 0 |
| Vascular invasion | 2 (10.5%) |
| Major vessel invasion | 1 (5.2%) |
| Perineural invasion | 12 (63.2%) |
| Margin invasion | 4 (21.1%) |
| Location of closest or involved margin | |
| Transection margin | 1 (5.2%) |
| Duodenum margin | 4 (21.1%) |
| Common bile duct margin | 2 (10.5%) |
| Lymph node positive | 3 (15.8% |

Abbreviation: Data are presented as no. of patients (%).

scanning in 73 patients (84%). Although the above stated research was retrospective, its results roughly coincide with the present study. Clinicopathological differences obtained from this study are of great significance for the practice of highly conformal radiotherapy of pancreatic cancer. First, in clinical practice, GTV location of pancreatic cancer obtained through CT scanning pictures as the pGTV (pathological gross target volume, pGTV) is probably a question worth discussing. Second, this difference serves as an indication that the simulated locating technique of MRIs (Magnetic Resonance Imaging), which is in the research phase at present, is very valuable in clinical practice. The simulated locating information of MRIs can distinguish between tumors and the surrounding soft tissues and blood vessels, as well as differentiate tumors from the interface of invaded tissues. This makes GTV location obtained from imaging more closely matching that from pathology. Third, implementation of

the simulated locating technique of PET-CT is also very important. It is a combination of imaging anatomy and biological functional imaging. It performs a role which is becoming more and more important in the diagnosis and precise radiotherapy of pancreatic cancer. Since the current analysis is only a comparative study of data obtained from CT scanning and pathological specimens, further studies discussing the typicality of the whole tumor are needed. Moreover, there may have been influencing factors resulting in differences between CT scanning and pathology. These include whether two sets match each other well, the choice of width and location of the observing window, and time differences between CT scanning and the resection (tumor volume doubling time and the potential doubling time). Furthermore, because 10% to 30% of tumors appearing resectable on CTs are found to be unresectable at the time of surgery [11-13], the findings of this study may not represent actual CT-pathology discrepancies very accurately. This study only evaluated resectable cases.

In an attempt to increase the control rate of pancreatic cancer in the limited stage, some experts in stereotactic radiosurgery have tried to shrink the treatment volume to enhance the target dose based on that GTV only plus 2- to 3-mm margin to all directions for PTV [14-17]. However, results of most randomized control tests for pancreatic cancer in the limited stage suggest a local failure as a component of disease progression in 30% to 60% of patients, despite local treatment [6, 7, 9, 18]. Although high doses of stereotactic high-fractionated radiotherapy contribute to an increase of control rates for pancreatic cancer in the limited stage and a time delay of its local progression, local recurrence occurs in 20% of patients with six months of median survival time [16, 17]. Furthermore, based on the micronidus invaded area of the present study, 95% of the micronidus of tumors exists within an area of 5.06 mm outside the edging of primary tumor. Therefore, occurrence of the missing CTV imaging possibly resulted from a shortage of the target extension area in some cases. The extent of microscopic extension in pancreatic cancer does not show in CT scanning pictures. Out of the visible pancreatic cancer primary tumor, large amounts of burr-shaped micronidus are found invading towards the normal pancreatic tissues under microscopy. Of these, part of the microni-

**Table 3.** Primary tumor size on CT vs. pathology (n = 15)

| | Data |
|---|---|
| Primary tumor size (median) | |
|     CT (Preoperative MDR-CT scan available) | 25.8 mm (range, 17 to 85 mm) |
|     Pathologic specimen | 30.0 mm (range, 20 to 90 mm) |
|     Median difference, CT vs. pathology | 3.1 mm larger on pathology (range, 1.2 to 8 mm); P < 0.001 |
|     Primary tumor larger on pathology (no. of patients) | 15 (100%) |

Abbreviation: MDR-CT = multidetector row computed tomography.

**Table 4.** Distance between primary tumor and the micronidus

| Patient | Median (mm) | Mean (mm) | Maximum measured distance (mm) | Retraction rate | Maximum actual distance (mm) |
|---|---|---|---|---|---|
| 1 | 2.34 | 1.99 | 2.62 | 0.8838 | 2.96 |
| 2 | 2.52 | 2.42 | 2.66 | 0.8895 | 2.99 |
| 3 | 2.75 | 2.77 | 3.47 | 0.9366 | 3.70 |
| 4 | 3.08 | 2.80 | 3.44 | 0.8975 | 3.83 |
| 5 | 1.75 | 1.81 | 3.03 | 0.9084 | 3.34 |
| 6 | 1.30 | 1.51 | 3.11 | 0.9319 | 3.34 |
| 7 | 2.11 | 2.02 | 3.00 | 0.9129 | 3.29 |
| 8 | 2.21 | 2.18 | 2.32 | 0.9293 | 2.50 |
| 9 | 3.82 | 3.75 | 4.68 | 0.9244 | 5.06 |
| 10 | 3.17 | 3.23 | 4.71 | 0.9039 | 5.21 |
| 11 | 1.70 | 1.78 | 2.50 | 0.9238 | 2.71 |
| 12 | 1.90 | 1.90 | 2.36 | 0.9389 | 2.51 |
| 13 | 2.58 | 2.38 | 2.80 | 0.9250 | 3.03 |
| 14 | 1.69 | 1.53 | 1.97 | 0.8980 | 2.19 |
| 15 | 1.92 | 1.88 | 2.81 | 0.9027 | 3.11 |
| 16 | 2.88 | 2.56 | 3.12 | 0.8978 | 3.48 |
| 17 | 2.87 | 2.69 | 3.36 | 0.8976 | 3.74 |
| 18 | 2.47 | 2.75 | 4.07 | 0.9122 | 4.46 |
| 19 | 4.14 | 3.86 | 4.63 | 0.9314 | 4.97 |

by slice, to get the maximum cross-sectional slice with radial lines of pancreatic tumor (the interesting slice). Moreover, since part of the primary tumor bordered the capsule of pancreatic tissues, it was difficult to obtain accurate tissues around the tumor in the following directions: 1) Forward and backward; 2) Left and right; and 3) Up and down. Therefore, further studies are welcomed to investigate whether differences exist in the micronidus-invaded area (the CTV area) of different directions of pancreatic cancer primary tumors. The current study showed that 2/3 (63.2%) of the patients with primary tumors were found to have neural invasion. In Arvold's [10] studies, this data came out to be 77%. Hence, it is necessary to put forward an issue of the existence of the neurotropism of pancreatic cancer. If this hypothesis stands, the subclinical area of pancreas cancer may possibly be larger than that obtained through the present study. At present, it is unclear if it helps to gap pathological differences by enlarging the target volume. Considering that an enlargement of the target volume may increase toxicity after radiotherapy, it is disputable whether the method contributes to a higher control rate of the cancer situation.

dus even detached from the primary tumor and appeared in a far location. However, there is evidence that some patients with primary tumors have shown advanced growth towards the surrounding normal pancreas, without typical burr-shaped invasion. Statistical results of pathology indicate that, in terms of grading of tumor differentiation, the number of middle and middle-lower grade specimens, respectively, reaches 8 (42.1%) and 9 (47.4%). Because of the limitation of sample size, the current study did not analyze pancreatic cancer of different gradings, level by level. Randomized controlled trials with large sample sizes are still needed to investigate whether there are any differences in microscopic invasion areas, in terms of different grading of pancreatic cancer differentiation. Besides, to satisfy the needs of the design of the present study, the sample was cut, slice

### Conclusion

Since computed tomography (CT) scanning has significantly underestimated pancreatic cancer primary tumor sizes, it was assumed that in the process of radiation therapy, a 5 mm marginal

expansion of the clinical target volume (CTV) from the gross target volume (GTV) is probably insufficient in pancreatic cancer CT simulation. Based on results of the micronidus-invaded area from this study, it is suggested that another 1~3 mm of CTV expansion is necessary.

## Disclosure of conflict of interest

None.

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