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Papillary cystic tumours of the pancreas: an analysis by nuclear morphometry

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Abstract. Papillary cystic tumour (PCT) is a rare, low-grade malignant pancreatic neoplasm, in which the histological criteria for malignancy are still uncertain. We performed a histological examination of 3 metastasizing PCTs, while comparing them with 18 non-metastasizing PCTs, using a computed image analyser. The mean maximum nuclear diameter, the mean standard deviation (SD) of the nuclear diameter, the mean nuclear area and the nuclear-nonnuclear (N/NN) ratio obtained by the image analyser of the metastasizing PCTs (7.23 μm, 2.21 μm, 30.45 μm^2, 36.41%) were all significantly larger than those of the non-metastasizing PCT (6.34 μm, 1.59 μm, 23.66 μm^2, 23.74%; $P<0.005$, $P<0.005$, $P<0.005$, $P<0.001$ respectively). However, there were no statistical differences in either the nuclear ellipsoidity or nuclear regularity. These results suggested that nuclear morphometry might be a useful parameter to define metastatic potential, in addition to histological variables such as venous invasion, nuclear grade and mitotic rate.

Key words: Papillary cystic tumour – Pancreatic neoplasms – Metastatic potential – Nuclear morphometry – Image processing

Introduction

Papillary cystic tumour (PCT) of the pancreas is a morphologically distinct and rare pancreatic neoplasm that occurs mainly in adolescents and young females (Compagno et al. 1979; Klöppel et al. 1981; Cubilla and Fitzgerald 1984; Morohoshi et al. 1987). Patients usually present with large abdominal masses with little evidence of metastatic spread and are associated with a favourable prognosis. There have been 19 cases of such neoplasms with metastases (Compagno et al. 1979; Matsunou and Konishi 1990; Nishihara et al. 1993); however, only a few histological markers for metastatic potential of PCT have been described (Compagno et al. 1979; Cappellari et al. 1990).

Recently, we have described histological characteristics which indicate metastatic potential. These include venous permeation, nuclear grade, necrobiotic nests and mitotic rate (Nishihara et al. 1993); these are still subjective. However, nuclear morphometry in many different organ systems including the pancreas (Klöppel et al. 1985), colorectum (Mitmaker et al. 1991), urinary bladder (Blomjous et al. 1989), prostate (Diamond et al. 1982), ovary (Ludescher et al. 1990), kidney (Tosi et al. 1986) and breast (Baak et al. 1982; Lipponen and Eskelinen 1990) has been reported, to reflect prognosis and metastatic potential.

The purpose of this study was to analyse the nuclear morphometry of 21 PCTs by using an image analyser, as well as to clarify the relationship between the metastatic potential of PCT and nuclear morphometry.

Materials and methods

Twenty-one patients with a PCT of the pancreas were treated at Kyushu University Hospital and at the following 15 hospitals: University of Occupational and Environmental Health, Medical College of Oita, Nagasaki University, National Nagasaki Central Hospital, Nagasaki Atomic Bomb Hospital, National Kyushu Cancer Center, National Fukuoka Central Hospital, National Shimonoseki Hospital, Hofu Gastrointestinal Hospital, Fukuoka Red Cross Hospital, Chihaya Hospital, Kitakyushu City. Kokura Hospital, Higashi Kunisaki Kokuho Sogo Hospital, Fukuoka Children Hospital and Uwajima City Hospital. Some of these cases have been reported by other authors (Yamaguchi et al. 1989, 1990; Nagai et al. 1991). All specimens were fixed in 10% formalin and embedded in paraffin. Sections 5 μm thick were then stained with haematoxylin and eosin (H & E) as a routine procedure.

Clinical data were available for all 21 patients, and complete follow-up data could be obtained. The follow-up period ranged from 3 months to 14 years; the mean follow-up period of all 21 cases was 5 years and 8 months, while that of 18 non-metastasizing cases was 5 years and 1 month.

Morphometric analysis was performed on H & E stained sections in the following manner. The histological images were re-

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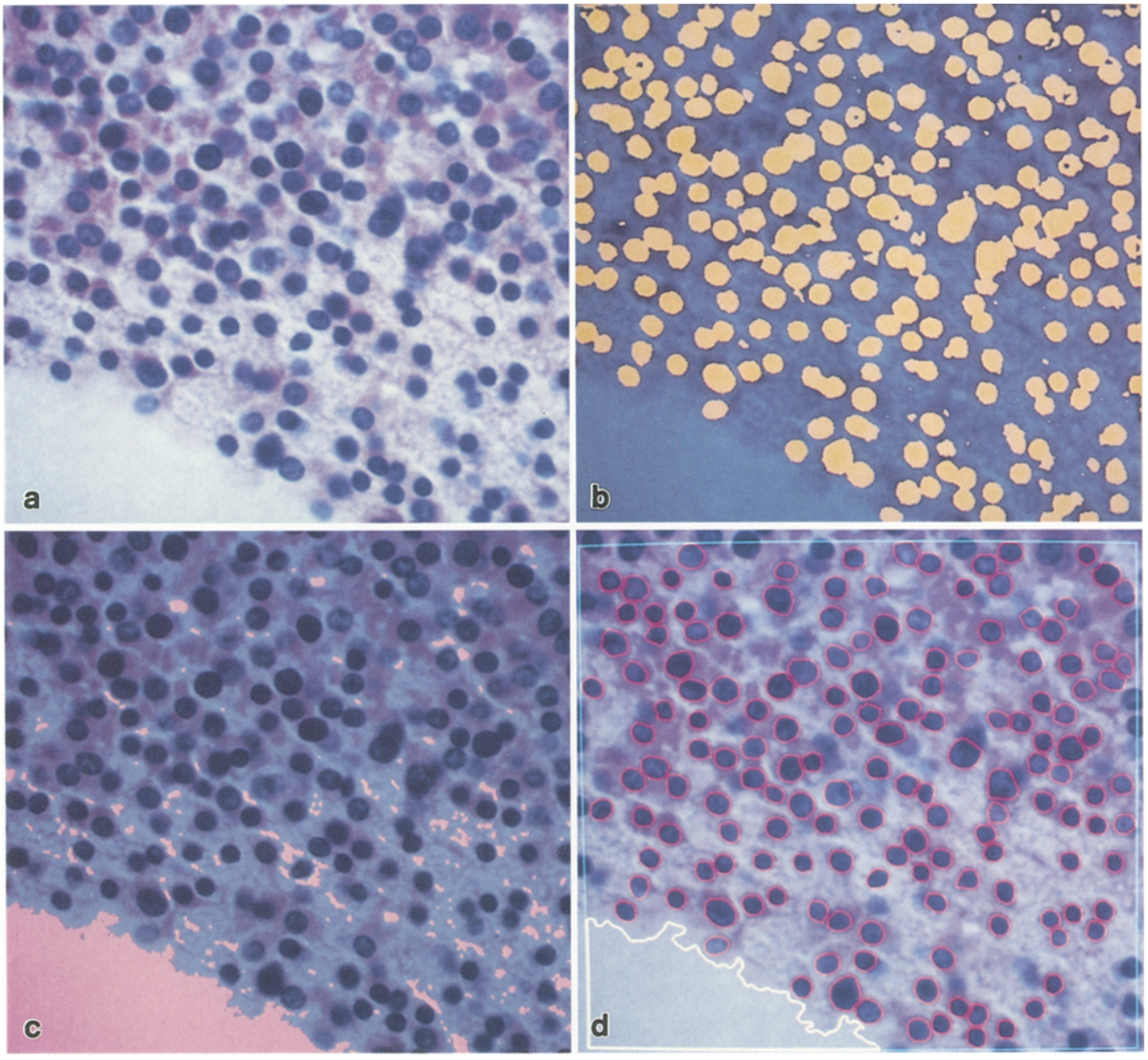

Fig. 1a–d. The procedure of image processing. Each figure part (**a–d**) is taken from the same area. **a** The original histological image is input into the image analyser (case 15). Most of the field shows solid areas of the tumour, while a cystic space is seen at the lower left. **b** The image obrained when the brightness segments of the nucleus is picked up. The orange area reveals the nuclear area. **c** The image obtained when the brightness segment of non-cellular area is picked up. The pink area shows the non-cellular area. **d** The results of computed analysis by image analyser. The nuclear area is surrounded by red lines, and the non-cellular area is bounded by white lines. Nuclear number is 154, the mean nuclear diameter is 5.12 μm, the mean nuclear area is 19.37 μm^2, and the nuclear-nonnuclear (N/NN) ratio is 26.15%

corded on a Nikon Optiphot-2 microscope (Nikon, Tokyo, Japan) with a 40× Plan Nikon objective lens, connected to a Sony DXC-325 TV camera (Sony, Tokyo, Japan) (Fig. 1a). By using an NEC personal computer PC-9801 DX2 (NEC, Tokyo, Japan) with the Nexus Qube image analysis processor (Nexus, Tokyo, Japan), the image processing steps were done semi-automatically consisting of the following steps. The nuclear image was sampled with the threshold technique, where the threshold level is automatically derived from the blue value histogram through the mode method (Fig. 1b). Thereafter, a closing operation was applied to fill in any small holes smaller than 12.6 μm^2. Then, small artefacts, such as dirt, nuclear debris or degenerative nuclei smaller than 1.89 μm^2 were eliminated. The overlapping nuclei were then automatically segmented with the shrinking method by computer; that is, nuclear notches were detected, and the nuclei were diminished in size until they separate out from one another, and then the nuclei expanded to the previous size. Next, the non-cellular part where the red value was extremely low was sampled with the threshold technique (Fig. 1c). Then a closing operation was automatically done, and small artefacts were eliminated by the computer as part of the nuclear procedures. Thereafter, the figures were manually corrected; the detected area consisting of the cellular part were deleted, while the true non-cellular area remained.

Quantitative nuclear features [maximum nuclear diameter, nuclear area, nuclear ellipsoidity (from Ell), nuclear regularity (form Ar)] and nuclear-nonnuclear (N/NN) ratio were all automatically calculated by computer thereafter. The final colour images were observed by a Sony Trinitron® colour video monitor PVM-1442Q, at a final magnification of ×1600 (Fig. 1d).

The areas for measurement were carefully selected on the basis

of the following criteria: the highest cellularity, the most severe atypicality, a lack of inflammation or necrosis, and few interstitial components such as vessels and stroma.

Nuclear ellipsoidity (form Ell) and nuclear regularity (form Ar) were calculated by the following formula by using the method of Tosi et al. (1986) method dealing with renal cell carcinoma:

$$\text{Form Ell} = \frac{\text{minor diameter}}{\text{major diameter}} \times 1000$$

Its value = 1000 is for a circle, less than 1000 for elliptical structures.

$$\text{Form Ar} = \frac{\text{area}}{\pi/4 \times \text{major diameter} \times \text{minor diameter}} \times 1000$$

where major and minor diameters are calculated by the moments of inertia of an elliptical-type structure. Its value = 1000 is for a circle and an ellipse, and less than 1000 for an irregular structure.

It was difficult to distinguish the pinkish colour of the cellular matrix from that of the interstitial matrix by the image analyser, so the interstitial areas, such as the vessels and stroma, were not included in the measurement area as far as possible. The N/NN ratio was calculated by the following formula:

$$\text{N/NN ratio} = \frac{\text{area of the nuclei}}{\text{total area} - \text{area of the nuclei} - \text{non-cellular area}} \times 100\ (\%)$$

In order to investigate the presence of field-to-field variations within one section, a representative slide was selected. In the section, all the nuclei in ten random fields were measured, and the morphometrical parameters were calculated for each field. Analyses of variance showed no significant field-to-field differences in each parameter [normal probability plot test coefficient of variation (CV) of the diameter = 0.7011%, CV of the area = 3.191%, CV of Ell = 2.438%, CV of Ar = 0.6878%, CV of N/C ratio = 8.045% ($P < 0.0001$)].

Three non-parametric statistical tests, the Mann-Whitney-Wilcoxon test, Kruskal-Wallis test and Scheffe test were used to evaluate the difference between the mean values of the groups. Values of $P < 0.05$ for every test were regarded as having statistical significance. Multiple regression analyses were also performed using the profound parameters produced.

Results

The sex and age of the patients, the anatomical site, the size of tumours, their biological characteristics and follow-up data have all been described in a previous report (Nishihara et al. 1993). The 21 patients with PCT were aged 12–60 years with a mean age of 27.5 years. There were 19 women and 2 men. All cases fulfilled the established histological criteria (Cubilla and Fitzgerald 1984). The three metastasizing cases were a 21-year-old Japanese woman (case 19) having a 8.5 × 4.5 cm mass located in an area between the body and the tail

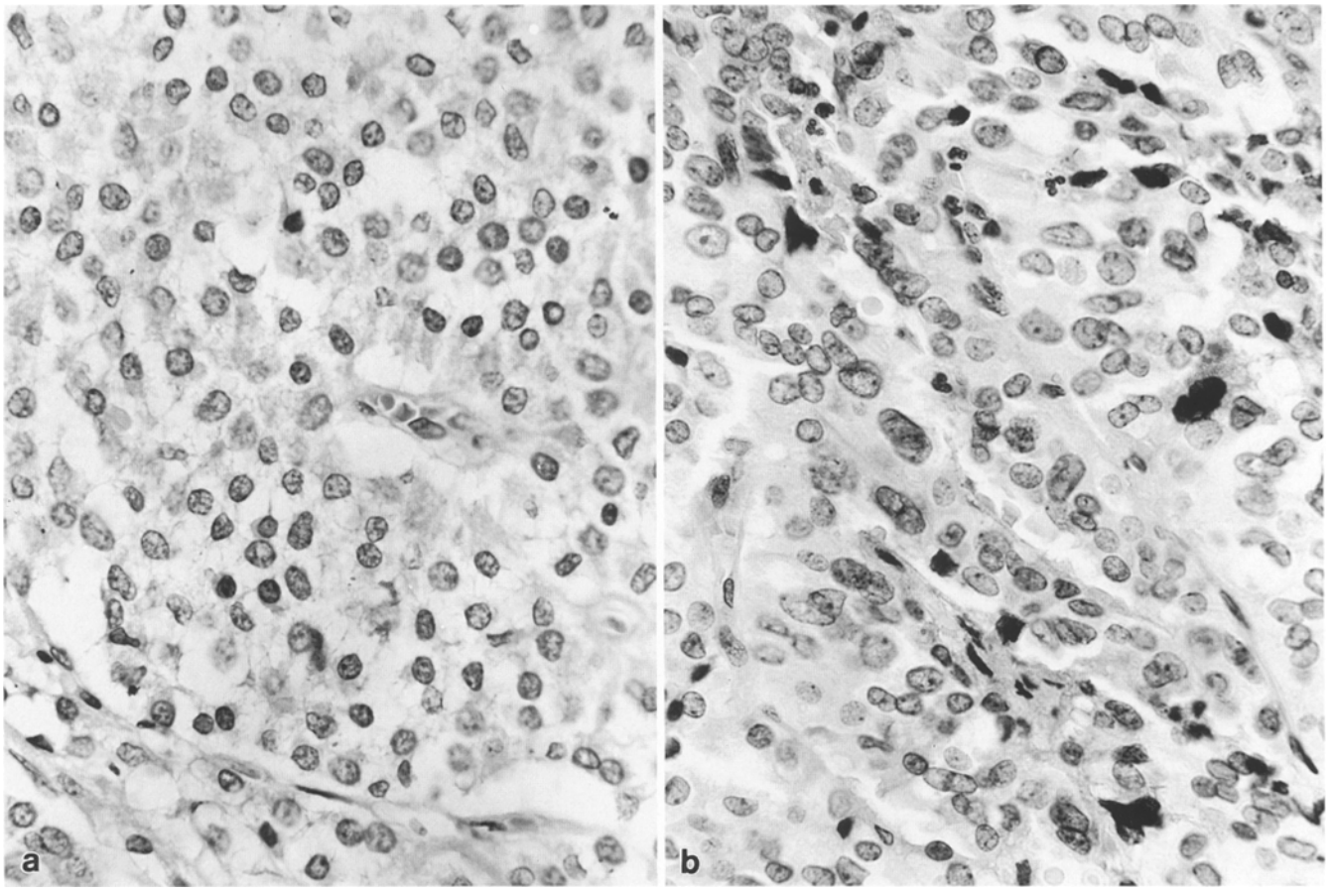

Fig. 2. a Nuclear grade 1. The nuclei of case 1 show a mean diameter of 6.3 μm, fine chromatin, small and inconspicuous nucleoli, minimal nuclear atypia and minimal nuclear pleomorphism by light microscope observation. The features indicate a nuclear grade 1. **b** Nuclear grade 3. The nuclei of case 19 reveal a mean diameter of 7.5 μm, mildly vesicular chromatin, moderate-sized nucleoli, severe nuclear atypia and moderate nuclear pleomorphism by light microscope observation, not using an image analyser. The features indicate a nuclear grade 3. H & E, × 570

Table 1. Morphometric data of the papillary cystic tumour of the pancreas

Case	Mean number of nuclei	Mean nuclear maximum diameter (μm)	Mean nuclear area (μm²)	Mean Ell	Mean Ar	N/NN(%)
Non-metastasizing cases						
1	107.9	6.19±1.26	24.04± 9.08	791	958	28.05
2	114.1	6.11±1.34	21.15± 9.68	788	957	24.33
3	82.1	6.57±1.52	25.34± 9.41	747	947	19.68
4	114.3	5.18±1.13	17.00± 5.69	804	955	19.29
5	91.6	6.48±1.30	25.00±10.71	754	939	21.83
6	117.9	6.51±1.66	25.42±11.95	771	936	27.52
7	76.2	4.93±1.00	14.77± 4.96	754	981	16.29
8	122.8	6.49±1.74	25.14±11.86	746	890	31.43
9	99.0	6.56±2.12	24.53±13.04	707	863	23.43
10	105.0	6.82±1.60	26.31±10.44	739	923	28.55
11	106.1	6.70±1.89	25.85±12.03	708	920	27.16
12	88.5	6.44±1.47	23.98±11.12	754	914	21.30
13	94.0	6.49±1.63	22.50± 9.28	677	956	20.86
14	125.4	6.79±1.70	25.94±12.77	728	934	29.22
15	103.1	5.34±1.06	20.00± 5.75	865	983	19.76
16	99.5	6.33±1.93	22.65±12.44	733	888	19.78
17	83.6	6.52±1.90	23.71±12.49	735	917	23.20
18	80.0	7.66±2.36	32.53±18.47	713	902	25.57
Mean	100.6	6.34*±1.59*	23.66*±10.62	751	931	23.74**
Metastasizing cases						
19	116.8	7.45±2.37	31.05±18.79	711	924	34.12
20	96.7	7.14±2.04	31.19±10.93	819	942	29.27
21	160.4	7.09±2.21	29.11±16.39	734	910	45.85
Mean	124.6	7.23*±2.21*	30.45*±15.37	755	925	36.41**

* $P<0.005$, ** $P<0.001$ (Mann-Whitney-Wilcoxon test)

The image analyses were performed in ten fields for each tumour. The number of nuclei reveals the number of nuclei counted by an image analyser.
Ell, Nuclear ellipsoidity; Ar, nuclear regularity; N/NN: nuclear/nonnuclear ratio

of the pancreas with a metastatic regional lymph node, a 28-year-old Japanese woman (case 20) who was found to have metastatic lymph nodes at the second operation and a 36-year-old Japanese women (case 21) who did of multiple hepatic metastases and peritoneal dissemination. The other 18 cases are now doing well and are clinically free of tumours.

A comparison of the data in the pathological findings between metastasizing and non-metastasizing PCTs was previously reported (Nishihara et al. 1993). Briefly, venous invasion was observed in all 3 metastasizing tumours (MTs), while only 1 of the 18 non-metastasizing tumours (NMTs) had such invasion. The nuclear grade of the PCT was divided into three groups based on the nuclear size, quantity of chromatin, size of nucleoli, and the extent of nuclear atypia and pleomorphism (Nishihara et al. 1993). One MT and 10 NMTs showed nuclear grade 1, 7 NMTs revealed nuclear grade 2, while 2 MTs and 1 NMT showed nuclear grade 3 (Fig. 2). Each MT had 4, 9 and 10 mitotic figures per 20 high power fields (hpf) (×400), whereas 6 NMTs revealed no mitotic figures, 11 NMTs had 1–3 such figures per 20 hpf, and 1 NMT showed 8 mitotic figures per 20 hpf. Therefore, the metastatic potential of the PCT was considered to be related to the venous invasion, nuclear grade and mitotic rate. However, there was no significant difference between the two groups regarding necrosis, capsular invasion, direct extension to the pancreatic parenchyma or perineural growth.

An image analysis was performed in the field of 109 μm × 118 μm (1.29×10^4 μm²), and 10 fields were examined for each tumour (Table 1). The mean number of the nuclei counted ranged from 76.2 to 160.4 (mean 104.1). The mean maximum diameter showed values of between 4.93 μm and 7.66 μm with the mean ± SD being 6.47 ± 0.67 μm. The mean maximum nuclear diameter (7.23 μm) and the standard deviation of the mean nuclear diameter (2.21 μm) of the MTs were larger than those of the NMTs (6.34 μm, 1.59 μm), respectively ($P<0.005$, $P<0.005$) (Fig. 3a, b).

The mean nuclear areas had values of between 14.77 μm² and 32.53 μm² with the mean ± SD being 24.63 ± 4.32 μm². The mean nuclear area (30.45 μm²) and N/NN ratio (36.41%) of the MTs were all statistically larger than those of the NMTs (23.66 μm², 23.74%) ($P<0.005$, $P<0.001$) (Fig. 3c, d).

The number of nuclei counted in the MTs (124.6) was slightly larger than that in the NMTs (100.6). The

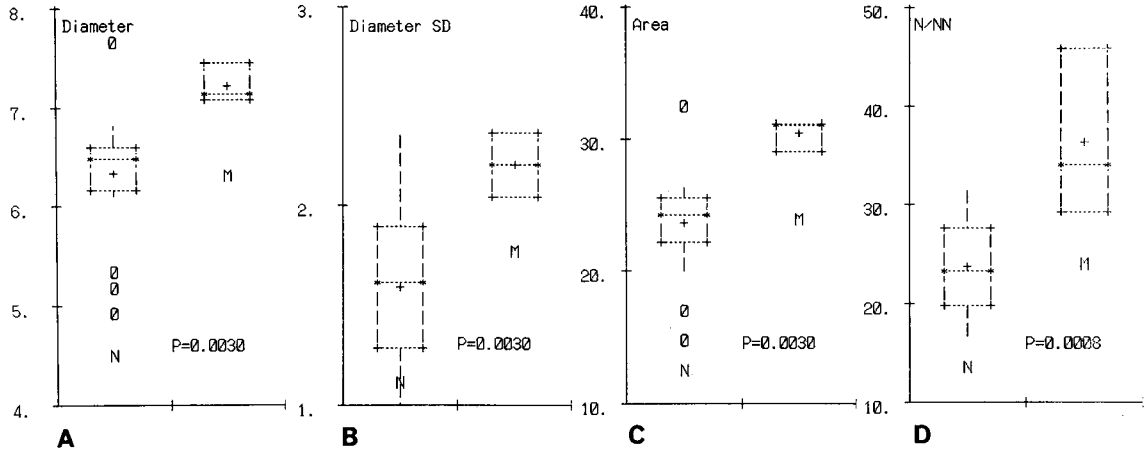

Fig. 3a–d. Box plots of nuclear parameters of metastasizing (*M*) and non-metastasizing (*N*) papillary cystic tumours of the pancreas. **a** The mean nuclear diameter. **b** The mean standard deviation (SD) of the nuclear diameter. **c** The mean nuclear area. **d** The nuclear-nonnuclear (N/NN) ratio. The median of the batchs of data is marked with a "+", and the upper and lower highest edges of the box represent the two middle quartiles. The ends of the whiskers denote the outermost range of values with outside values marked with an "∅". *P* values were calculated by the Mann-Whitney-Wilcoxon test

mean form Ell (nuclear ellipsoidity score) or the MTs (755) was slightly larger than that of the NMTs (751); however there was no statistical difference between the two groups regarding these two factors. The mean form Ar (nuclear regularity score) of the MTs (925) was shown to have almost the same value as that of the NMTs (931).

As mentioned above, the nuclear diameter, SD of the nuclear diameter, nuclear area and N/NN ratio proved to be reproducible parameters, and these were also significantly different; the four parameters were then used for further multiple regression analyses (Fig. 4). As shown by Fig. 4, each parameter could separate the MTs from the NMTs (1–4 in Fig. 4); however, the combination of nuclear area (NA) and N/NN ratio $((-0.2265 \times \mathrm{NA}) + (-0.4597 \times \mathrm{N/NN\ ratio}) + 19.9536)$ was the best multiple regression formula to distinguish between the two groups ($P < 0.005$) (6 in Fig. 4).

Comparing the nuclear grade with the morphometric parameters (Table 2), the mean nuclear maximum diameter of nuclear grade 1, 2 and 3 PCTs was 6.29, 6.50 and 7.02 μm, respectively. Furthermore, the mean nuclear area of nuclear grade 1, 2 and 3 PCTs was 23.38, 24.68 and 29.08 μm^2, respectively. Therefore, the mean nuclear maximum diameter and the mean nuclear area were observed to be gradually enlarging according to the grade. Statistically, the mean nuclear area of grade 3 cases (29.08 μm^2) was significantly larger than that of grade 1 cases (23.38 μm^2) ($P < 0.05$).

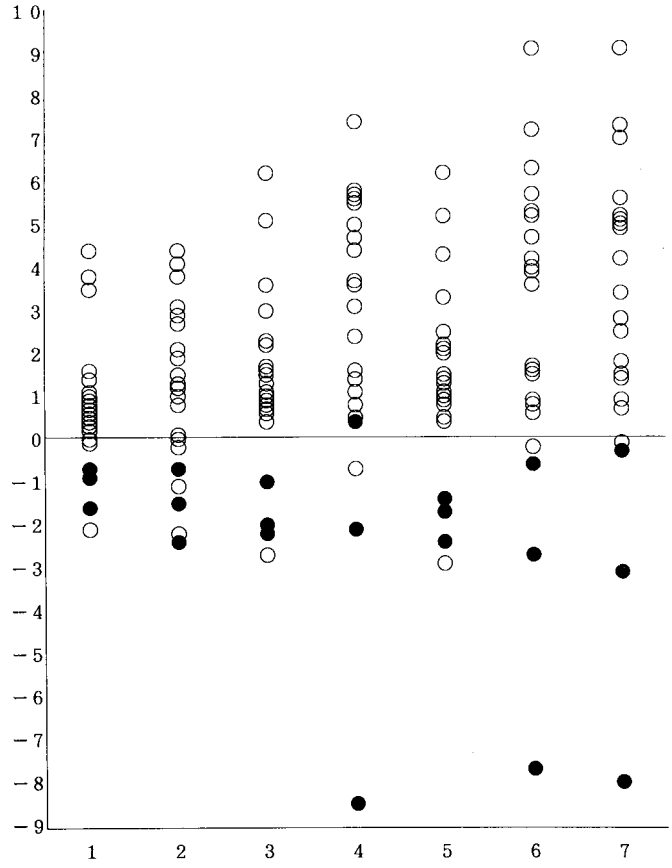

Fig. 4. The separation between 21 patients with papillary cystic tumours, 19 of which (*open circles*) are non-metastasizing tumours and 3 of which (*closed circles*) are metastasizing tumours. The *Y-axis* represents the value provided by the multiple regression equations: *1* $(-2.3988 \times \mathrm{MD}) + 16.2712$; *2* $(-4.9139 \times \mathrm{SDMD}) + 9.3268$; *3* $(-0.5065 \times \mathrm{MA}) + 13.7027$; *4* $(-0.5383 \times \mathrm{N/NN}) + 16.1880$; *5* $(-2.2814 \times \mathrm{SDMD}) + (-0.3420 \times \mathrm{MA}) + 13.5817$; *6* $(-0.2265 \times \mathrm{MA}) + (-0.4597 \times \mathrm{N/NN}) + 19.9536$; *7* $(-2.0742 \times \mathrm{SDMD}) + (-0.0786 \times \mathrm{MA}) + (-0.4569 \times \mathrm{N/NN}) + 19.8051$. MD, The mean maximum diameter (μm); SDMD, the mean standard deviation of the nuclear diameter (μm); MA, the mean nuclear area (μm^2); N/NN, the nuclear-nonnuclear ratio (%)

Discussion

PCT of the pancreas is a rare pancreatic neoplasm, and is known to have a generally favourable prognosis. There have been 17 reports, including 19 cases of metastasizing PCTs (Compagno et al. 1979; Benjamin and Wright 1980; Warren 1985; Kaufman et al. 1986; Rustin et al. 1986; Matsuda et al. 1987; Choi et al. 1988; Todani et al. 1988; Hernandez-Maldonado et al. 1989; Ya-

Table 2. The relationship between nuclear grade and morphometrical parameters in papillary cystic tumours of the pancreas

Nuclear grade	Mean number of nuclei	Mean nuclear maximum diameter (μm)	Mean nuclear area (μm²)	Mean Ell	Mean Ar	N/NN(%)
Grade 1	106.1	6.29±1.60	23.38*±10.47	753	933	25.76
Grade 2	101.9	6.50±1.70	24.68 ±11.67	745	924	23.99
Grade 3	101.7	7.02±1.90	29.08*±13.48	761	935	28.41

* $P<0.05$ (Mann-Whitney-Wilcoxon test)

Ell, Nuclear ellipsoidity; Ar, nuclear regularity; N/NN, nuclear/nonnuclear ratio

maguchi et al. 1989; Cappellari et al. 1990; Matsunou and Konishi 1990; Zinner et al. 1990; Chu et al. 1991; Sclafani et al. 1991; Stömmer et al. 1991; Nishihara et al. 1993). Clinicopathological descriptions of malignant PCT are few. Compagno et al. (1979) reported histological evidence of aggressive behaviour with capsular invasion and extension of tumour cells to the adjacent parenchyma in a short conference abstract. Matsunou et al. (1990) described that the malignant biological behaviour of PCT was associated with the age of the patient. Cappellari et al. (1990) reported a metastasizing PCT with an increase in pleomorphism, hyperchromasia, and in the number of mitoses and bizarre tumour giant cells. In our previous report, the nuclear grade, mitotic rate and venous invasion correlated with the metastatic potential of PCT (Nishihara et al. 1993); however, no one variable alone was able to separate the MTs from the NMTs, and they were still subjective.

Using a histoquantitative technique in PCT, Cappellari et al. (1990) described malignant PCT as being aneuploid by flow cytometry; however, there have been no previous reports dealing with nuclear morphometry in PCT. Morphometric study of several carcinomas including pancreas (Klöppel et al. 1985), breast (Baak et al. 1982; Lipponen and Eskelinen 1990), urinary bladder (Blomjous et al. 1989), prostate (Diamond et al. 1982), colorectal (Mitmaker et al. 1991), ovarian (Ludescher et al. 1990) and renal cell (Tosi et al. 1986) have also been reported, and the results indicated that certain findings were important in prognosis and metastatic potential. We also attempted a morphometrical study of the PCT nuclei in order to make an objective description of our subjective impressions obtained by light microscopy.

Nuclear size and area have been described as correlating with prognosis in some malignant neoplasms (Baak et al. 1982; Diamond et al. 1982; Klöppel et al. 1985; Tosi et al. 1986; Lipponen and Eskelinen 1990; Ludescher et al. 1990). For instance, Tosi et al. (1986) mentioned that patients with a nuclear area larger than 32 μm² had a worse prognois than those with a smaller nuclear area in stage I renal cell carcinoma. In the present study, the mean maximum diameter and the mean nuclear area of metastasizing PCTs were significantly larger than those of non-metastasizing PCTs ($P<0.005$, $P<0.005$); therefore these parameters were considered to be metastatic predictors of PCT.

Cellularity is also known to be one of the important prognostic factors in malignant tumours (Baak et al. 1982; Ludescher et al. 1990). Ludescher et al. (1990) showed nuclear density to be prognostically significant in advanced ovarian cancer. Three metastasizing PCTs also had more cellurality (mean number of nuclei, 124.6) than 18 non-metastasizing PCTs (100.6). In the present series, however, no significant difference could be seen.

Nuclear shape in morphometry has been reported to reflect metastatic potential (Baak et al. 1982; Diamond et al. 1982) and prognosis (Baak et al. 1982; Tosi et al. 1986; Mitmaker et al. 1991). Baak et al. (1982) described the relationship between axillary lymph node metastases and mean nuclear shape factor in breast cancer, and Mitmaker et al. (1991) reported the nuclear shape factor to be associated with prognosis in large bowel carcinoma. We tried to determine whether nuclear shape was useful in distinguishing metastasizing PCT from non-metastasizing PCT by the Tosi et al. method (1986), however, there was no significant difference in the nuclear regularity or ellipsoidity between the two groups. Neither nuclear ellipsoidity, nor regularity were considered useful in distinguishing MTs from NMTs in the current study.

It is suggested that the standard deviation (SD) of nuclear diameter and/or that of nuclear area represents nuclear pleomorphism. A few papers have shown a relationship between the SD of the nuclear area and prognosis in breast cancer (Baak et al. 1982) and urinary bladder carcinoma (Lipponen and Eskelinen 1990). In the present series, the SD of the nuclear diameter of PCT in MTs (2.21 μm) was significantly greater than that in NMTs (1.59 μm) ($P<0.005$), thus MTs were considered to show more prominent nuclear pleomorphism than NMTs. However, we could not reveal any significant difference between the SD in the nuclear area of MTs and that of NMTs.

As shown in Table 2, the nuclear grade of PCT obtained by light microscope observation was related to the mean maximum diameter and the mean nuclear area calculated by the image analyser. Thus, one advantage of the application of morphometry is that it provides an objective description of subjective impressions.

In conclusion, the histological variables indicative metastatic potential in PCT were venous invasion, nuclear grade and mitotic rate. In addition, of the several nuclear morphometric parameters, the mean nuclear diameter, standard deviation of nuclear diameter, mean

nuclear area and N/NN ratio revealed significant differences between the metastasizing and non-metastasizing PCTs. However, larger number of cases will be needed if the nuclear morphometry is to be used as an additional factor in determining metastatic potential.

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References

Baak JPA, Kurver PHJ, Snoo-Niewlaat AJE de, Graef S de, Makkink B, Boon ME (1982) Prognostic indicators in breast cancer-morphometric methods. Histopathology 6:327–339

Benjamin E, Wright DH (1980) Adenocarcinoma of the pancreas of childhood: a report of two cases. Histopatholoy 4:87–104

Blomjous CEM, Schipper NW, Vos W, Baak JPA, Voogt HJ de, Meijer CJLM (1989) Comparison of quantitative and classic prognosticators in urinary bladder carcinoma. A multivariate analysis of DNA flow cytometric, nuclear morphometric and clinicopathological features. Virchows Arch [A] 415:421–428

Cappellari JO, Geisinger KR, Albertson DA, Wolfman NT, Kute TE (1990) Malignant papillary cystic tumor of the pancreas. Cancer 66:193–198

Choi BI, Kim KW, Han MC, Kim YI, Kim C-W (1988) Solid and papillary epithelial neoplasms of the pancreas: CT findings. Radiology 166:413–416

Chu H-W, Ho WL, Chang S-M (1991) Malignant papillary cystic tumor of the pancreas: report of a case and review of the literature. Chin Med J 47:139–144

Compagno J, Oertel JE, Kremzar M (1979) Solid and papillary epithelial neoplasm of the pancreas, probably of small duct origin: a clinicopathologic study of 52 cases. Lab Invest 40:248–249

Cubilla AL, Fitzgerald PJ (1984) Tumors of the exocrine pancreas. In: Hartmann WH, Sobin LH (eds) Atlas of tumor pathology, 2nd series, fascicle 19. Armed Forces Institute of Pathology, Washington D.C., pp 201–207

Diamond DA, Berry SJ, Jewett HJ, Eggleston JC, Coffey DS (1982) A new method to assess metastatic potential of human prostate cancer: relative nuclear roundness. J Urol 128:729–734

Hernandez-Maldonado JJ, Rodriguez-Bigas MA, Pesante AG de, Vazquez-Quintana E (1989) Papillary cystic neoplasm of the pancreas. A report of a case presenting with carcinomatosis. Am Surg 55:552–559

Kaufman SL, Reddick RL, Stiegel M, Wild RE, Thomas CG Jr (1986) Papillary cystic neoplasm of the pancreas: a curable pancreatic tumor. World J Surg 10:851–859

Klöppel G, Morohoshi T, John HD, Oehmichen W, Opitz K, Angelkort A, Lietz H, Rückert K (1981) Solid and cystic acinar cell tumor of the pancreas. Virchows Arch [A] 392:171–183

Klöppel G, Lingenthal G, Bülow M von, Kern HF (1985) Histological and fine structural features of pancreatic ductal adenocarcinomas in relation to growth and prognosis: studies in xenografted tumours and clinico-histopathological correlation in a series of 75 cases. Histopathology 9:841–856

Lipponen P, Eskelinen M (1990) Nuclear morphometry in grading transitional cell bladder cancer compared with subjective histological grading. Anticancer Res 10:1725–1730

Ludescher C, Weger A-R, Lindholm J, Oefner D, Hausmaninger H, Reitsamer R, Mikuz G (1990) Prognostic significance of tumor cell morphometry, histopathology, and clinical parameters in advanced ovarian carcinoma. Int J Gynecol Pathol 9:343–351

Matsuda Y, Imai Y, Kawata S, Nishikawa M, Miyoshi S, Saito R, Minami Y, Tarui S (1987) Papillary-cystic neoplasm of the pancreas with multiple hepatic metastases: a case report. Gastroenterol Jpn 22:379–384

Matsunou H, Konishi F (1990) Papillary-cystic neoplasm of the pancreas. A clinicopathologic study concerning the tumor aging and malignancy of nine cases. Cancer 65:283–291

Mitmaker B, Begin LR, Gordon PH (1991) Nuclear shape as a prognostic discriminant in colorectal carcinoma. Dis Colon Rectum 34:249–259

Morohoshi T, Kanda M, Horie A, Chott A, Dreyer T, Klöppel G, Heitz PU (1987) Immunocytochemical markers of uncommon pancreatic tumors. Acinar cell carcinoma, pancreatoblastoma, and solid cystic (papillary-cystic) tumor. Cancer 59:739–747

Nagai E, Tobimatsu M, Hirano T, Nakafusa Y, Andoh H, Saito S, Koga K, Okazawa Y, Wada Y, Kuwazuka T, Ohshima A, Yamaguchi K (1991) A male case of small solid and cystic tumor of the pancreas (in Japanese). J Biliary Tract Pancreas 12:567–571

Nishihara K, Nagoshi M, Tsuneyoshi M, Yamaguchi K, Hayashi I (1993) Papillary cystic tumor of the pancreas: assessment of their malignant potential. Cancer 71:82–92

Rustin RB, Broughan TA, Hermann RE, Grundfest-Broniatowski SF, Petras RE, Hart WR (1986) Papillary cystic epithelial neoplasms of the pancreas. Arch Surg 121:1073–1076

Sclafani LM, Reuter VE, Coit DG, Brennan MF (1991) The malignant nature of papillary and cystic neoplasm of the pancreas. Cancer 68:153–158

Stömmer P, Kraus J, Stolte M, Giedl J (1991) Solid and cystic pancreatic tumors. Clinical, histochemical, and electron microscopic features in ten cases. Cancer 67:1635–1641

Todani T, Shimada K, Watanabe Y, Toki A, Fujii T, Urushihara N (1988) Frantz's tumor: a papillary and cystic tumor of the pancreas in girls. J Pediatr Surg 23:116–121

Tosi P, Luzi P, Baak JPA, Miracco C, Santopietro R, Vindigni C, Mattei FM, Acconcia A, Massai MR (1986) Nuclear morphometry as an important prognostic factor in stage I renal cell carcinoma. Cancer 58:2512–2518

Warren RB (1985) Papillary cystic tumor of the pancreas. Arch Pathol Lab Med 109:706–707

Yamaguchi K, Miyagahara T, Tsuneyoshi M, Enjoji M, Horie A, Nakayama I, Tsuda N, Fujii H, Takahara O (1989) Papillary cystic tumor of the pancreas: an immunohistochemical and ultrastructural study of 14 patients. Jpn J Clin Oncol 19:102–111

Yamaguchi K, Hirakata R, Kitamura K (1990) Papillary cystic tumor of the pancreas: radiological and pathological characteristics in 11 cases. Br J Surg 77:1000–1003

Zinner MJ, Shurbaji MS, Cameron JL (1990) Solid and papillary epithelial neoplasms of the pancreas. Surgery 108:475–480