The Intraductal Carcinoma Component Is a Significant Prognostic Parameter in Patients with Invasive Ductal Carcinoma of the Pancreas

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We have sometimes encountered invasive ductal carcinomas (IDCs) of the pancreas containing intraductal carcinoma components in the intra- and/or extra-tumor area. The purpose of this study was to investigate whether intraductal carcinoma components would be useful for predicting the outcome of IDC patients. Forty-seven surgically treated IDCs were examined, and all histological tumor sections were stained with Elastica to accurately confirm intraductal carcinoma components. Well-known clinicopathological parameters that exhibited a significant correlation in the univariate analyses for predicting disease-free survival (DFS) and overall survival (OS) were entered into the Cox proportional hazard multivariate analysis. Since the lowest P-value predicting DFS or OS periods was observed in IDCs with more than 10% intraductal carcinoma components and those with 10% or less intraductal carcinoma components (P=0.028 and P=0.019), we established the cutoff value of intraductal carcinoma components at 10%. In the multivariate analyses for DFS and OS, the presence of more than 10% intraductal carcinoma components showed a marginally significant increase in the hazard rate (HR) of tumor recurrence (P=0.067) and significantly increased the HR of mortality (P=0.040). The present study demonstrated that IDCs with more than 10% intraductal carcinoma components were associated with a significantly better patient outcome than those with 10% or less intraductal carcinoma components.

Key words: Ductal carcinoma — Pancreas — Intraductal component — Prognosis — Histology

The major histological type of pancreatic tumors is invasive ductal carcinoma (IDC), and the outcome of patients with IDCs is very poor.1 However, we have sometimes encountered IDCs containing intraductal carcinoma components and exhibiting papillary or low-papillary features resembling the noninvasive components of invasive papillary-mucinous carcinoma of the pancreas.2, 3) Invasive papillary-mucinous carcinomas have ample intraductal carcinoma components, and the clinical course of patients with invasive papillary-mucinous carcinoma is better than that of patients with IDC. In breast cancer, a tendency was observed for decreased nodal metastases and a more favorable prognosis when the intraductal component in the tumor was relatively more abundant.4) This suggested to us that the rate of intraductal carcinoma components in IDCs plays an important role in the outcome for patients with IDC of the pancreas.

The purpose of this study was to investigate whether there is a cutoff value for the area of intraductal carcinoma components that would be useful for predicting the outcome in IDC patients. In addition, a comparative study was performed between patients with IDCs with intraductal carcinoma components at or above the cutoff value and patients with invasive papillary-mucinous carcinoma, which is associated with a better clinical course than IDC,5, 6) to clarify whether the clinical course of the former is similar to that of the latter. The results demonstrated that the IDCs with more than 10% intraductal carcinoma components were associated with a significantly better patient outcome than the IDCs with 10% or less intraductal carcinoma components. In addition, the former clearly demonstrated a clinical course similar to that of invasive papillary-mucinous carcinoma of the pancreas.

MATERIALS AND METHODS

Cases of IDCs Forty-seven consecutive cases that had been surgically treated at the National Cancer Center Hospital East between July 1992 and May 2000 were examined. All tumors were classified according to the guidelines of the World Health Organization7) and the pathological TNM (pTNM) classification.8) The patient characteristics are listed in Table I. All of the patients were Japanese. Tumor size ranged from 15 to 110 mm (35.3±16.0 mm), and many of the tumors were located in the pancreatic head. The majority of the cases were classified as stage 3 or
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4A. None of the patients had received preoperative radiotherapy or chemotherapy. Pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy was performed in 38 cases, and distal pancreatectomy was performed in the other nine cases. Intraoperative radiotherapy was performed in all IDC cases, and nine IDCs were incompletely resected.

Cases of invasive papillary-mucinous carcinoma Nine cases treated in our hospital between July 1992 and May 2000 were investigated to compare their survival times with those of the IDC patients according to whether the noninvasive components were above or below the cutoff value. There were six males and three females. Their mean age and tumor size were 71.3±5.6 years and 69.0±30.0 mm, respectively. Six tumors were located in the pancreatic head and three in the pancreatic body to tail. The histological type of the invasive components was well-differentiated adenocarcinoma in four cases, mucinous adenocarcinoma in three cases, papillary adenocarcinoma in one case, and poorly differentiated adenocarcinoma in one case. Lymph node metastases were observed in eight cases. According to the pTNM stage distribution, one case was in stage 1, six cases were in stage 3, and two cases were in stage 4B. All cases were treated by the same methods used to treat the IDC cases, and four of them were incompletely resected.

Histological examination of tumors Surgically resected tissue specimens of the IDCs and invasive papillary-mucinous carcinomas were fixed in 20% formalin overnight at room temperature, and the entire tumors were cut into slices at intervals of about 0.5–0.7 cm. The size and gross appearance of the cancer were recorded, and the former was validated by comparison with tumor size on the histological slides. Histological sections were taken from the whole tumor areas in order to measure maximum tumor diameter and area. They were processed routinely and embedded in paraffin, and serial sections of each tumor were cut from paraffin blocks.

One section was stained with hematoxylin and eosin (H-E) and examined pathologically to confirm the diagnosis and to evaluate the tumor histologically. We examined the entire tumor areas of IDCs and determined the approximate areas of intraductal carcinoma components (Fig. 1). The numbers of IDC cases with intraductal components of 0%, 1–10%, 11–20%, 21–30%, 31–40% and 40–50% were 17, 8, 14, 5, 1, and 2, respectively. All histological sections of the tumor were stained with Elastica to confirm noninvasive intra- and extra-tumor components accurately, and only tumor components showing papillary, low-papillary, or cribriform features surrounded by elastic fibers were considered to be true noninvasive intra- and extratumor components (Figs. 2 and 3). Two of the authors (HK and TH) assessed the histological findings and whenever there was a discrepancy between their conclusions, the slides were jointly re-examined to reach a consensus.

Prognosis The survival of the operated IDC and invasive papillary-mucinous carcinoma patients was determined by follow-up until September 2000. Among IDC patients, 31

Table I. Clinicopathological Characteristics of IDCs (n=47)

| Characteristics | Value |
|-----------------|-------|
| Gender          | -     |
| Age (mean±SD)   | 61.0±12.4 years |
| Differentiated type | -     |
| pTNM stage classification | -     |
| Tumor size (mean±SD) | 35.3±16.0 mm |
| Tumor location  | -     |
| Surgical margin | -     |

\[ \text{Histological examination of tumors} \]

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Fig. 2. Histological features of the intraductal carcinoma components of IDC. A, invasive tumor components are observed growing in small solid nests or strands, and there are large tumor nests among them showing low papillary growth and surrounded by dense connective tissue (×20, H-E staining, arrows). B, the dense connective tissue surrounding low papillary tumor components are stained in black and were confirmed to consist of elastic fibers by Elastica staining. This indicates that the components surrounded by elastic fibers are intraductal carcinoma components (×20, Elastica staining). C, intraductal carcinoma components exhibiting low papillary growth (×100, H-E staining).

Fig. 3. Histological features of the intraductal carcinoma components of IDC. A and B, tumor cells extending in low papillary patterns are observed in peripheral pancreatic parenchyma of tumor in some areas (×20 and ×100, H-E staining). C, although all of the tumor components that grow in a low papillary pattern appear to be an intraductal carcinoma component by H-E staining, several of them are not surrounded by elastic fibers (×20, H-E staining, arrows). IDC components not surrounded by elastic fibers can be diagnosed as invasive carcinoma components.
died of their disease, and four died of postoperative complications. Twenty-seven developed local recurrences, 24 developed distant organ metastases, and 20 developed peritoneal dissemination. Six patients were alive and well without tumor recurrence.

Among patients with invasive papillary-mucinous carcinoma, five died of their disease, and one committed suicide on postoperative day 40. Five patients developed local recurrences, three developed distant metastases, and three developed peritoneal dissemination. Two patients were alive and well without tumor recurrence.

**Statistical analyses** Significant correlations between survival curves drawn by the Kaplan-Meier method and noninvasive component cutoff values of 10%, 20%, 30%, 40%, and 50% were examined by means of the log-rank test.

The following clinicopathological parameters were examined as potential predictive parameters for disease-free survival (DFS) or overall survival (OS): 1) gender, 2) age, 3) tumor size, 4) tumor location, 5) tumor histology (well-differentiated vs. moderately/poorly differentiated), 6) pT classification (pT2/3 vs. pT4), 7) pN classification (pN0 vs. pN1a/1b), 8) pM classification (pM0 vs. pM1), 9) pTNM stage classification (stage 2/3 vs. 4A/4B), and 10) surgical margin status (positive vs. negative). The parameters that showed a significant correlation with DFS or OS in the univariate analyses were then entered into the Cox proportional hazards regression model. We also examined the differences in frequency of the above clinicopathological parameters between IDCs with intraductal carcinoma components above the cutoff value and those with intraductal carcinoma components at or below the cutoff value by Fisher’s exact probability test.

**RESULTS**

**Establishment of the cutoff value for intraductal carcinoma components in IDCs** IDCs with intraductal carcinoma components accounting for more than 10%, more than 20%, more than 30%, and more than 40% were associated with a better patient outcome than those with intraductal carcinoma components accounting for less than 10% ($P=0.018$), less than 20% ($P=0.036$), less than 30% ($P=0.037$), and less than 40% ($P=0.046$), respectively. However, there was no significant difference in survival time between IDCs with intraductal carcinoma components greater than 50% and 50% or less ($P=0.439$). Since the lowest $P$-value predicting DFS or OS periods among these cutoff values for areas of intraductal carcinoma components in IDCs was observed in IDCs with intraductal carcinoma components greater than 10% and those with 10% or less intraductal carcinoma components, we established the cutoff value for intraductal carcinoma components at 10% (Fig. 4).

**Clinicopathological characteristics of the IDC patients with more than 10% intraductal carcinoma components** IDC patients with more than 10% intraductal carcinoma components had a significantly higher frequency of well-differentiated tumor histology than those with 10% or less intraductal carcinoma components ($P=0.014$) (Table II). There was no significant difference between them in gender, age, tumor size, tumor location, pTNM stage classification or surgical margin status.

**Comparison of patient outcome between IDCs and invasive papillary-mucinous carcinoma** IDCs with more than 10% intraductal carcinoma components had a clinical course that was almost the same as that of patients with invasive papillary-mucinous carcinoma (Fig. 5).

**Multivariate analyses for DFS and OS** Among the clinicopathological parameters, IDCs with a positive surgi-
cal margin were associated with a significantly shorter DFS and OS in the univariate analyses than those with a negative surgical margin \((P=0.028 \text{ and } 0.047)\). Other clinicopathological parameters, e.g. pTNM stage classification, failed to show a significant association with short DFS or OS in the univariate analyses (data not shown).

In the multivariate analysis for DFS, a positive surgical margin status still significantly increased the hazard rate (HR) of tumor recurrence, and the presence of more than 10% intraductal carcinoma components showed a marginally significant increase of the HR of tumor recurrence (Table III). In regard to OS, although the presence of more than 10% intraductal carcinoma components significantly increased the HR of mortality, the positive surgical margin status failed to significantly increase the HR of mortality in the multivariate analysis.

**DISCUSSION**

Fukushima et al.\(^{12}\) demonstrated that patients with IDCs with intraductal carcinoma components show a significantly longer survival period than those without intraductal carcinoma components. The results of this study confirmed the prognostic significance of the presence of intraductal carcinoma components of IDCs. Fukushima et al.,\(^{12}\) however, evaluated the presence or absence of intraductal carcinoma components only by H-E staining. Intraductal carcinoma components of IDCs that exhibit low-papillary features or cribriform features are mixed with invasive components, and it is very difficult to differentiate the former from the latter by H-E staining alone. It is necessary to perform Elastica staining to accurately evaluate IDCs for the presence of intraductal carcinoma components. Thus, the assessment of intraductal carcinoma components in our study is more accurate than that in Fukushima’s study. Since our study clearly demonstrated that the IDCs with more than 10% intraductal carcinoma components show a better clinical course than those with 10% or less intraductal carcinoma components, the cutoff value of intraductal carcinoma components in this study

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**Table II. Clinicopathological Characteristics of IDCs with More than 10% Intraductal Carcinoma Components and with 10% or Less Intraductal Carcinoma Components**

| Parameters                        | Intraductal carcinoma (>10%) | ≤10% | \(P\)-value |
|-----------------------------------|-----------------------------|-----|-------------|
| Age (years, mean±SD)              | 60.1±11.9                   | 61.9±13.0 | NS          |
| Tumor size (mm, mean±SD)          | 31.6±11.5                   | 38.5±18.6 | NS          |
| Gender (%)                        |                             |     |             |
| Male                              | 13 (27.7)                   | 11 (23.4) | NS          |
| Female                            | 9 (19.1)                    | 14 (29.8) | NS          |
| Tumor location                    |                             |     |             |
| Head                              | 19                          | 19   |             |
| Body/Tail                         | 3                           | 6    | NS          |
| Differentiated type\(^a\)         |                             |     |             |
| Well                              | 11                          | 4    |             |
| Mod/Por                           | 11                          | 21   | 0.014       |
| pTNM stage classification         |                             |     |             |
| Stage 2/3                         | 16                          | 12   |             |
| Stage 4A/4B                       | 6                           | 13   | NS          |
| Surgical margins                  |                             |     |             |
| Positive                          | 3                           | 6    | NS          |
| Negative                          | 19                          | 19   | NS          |

\(^a\) Well, well differentiated; Mod, moderately differentiated, Por, poorly differentiated.

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**Fig. 5. DFS and OS curves for the IDC patients with 10% or less noninvasive components, those with more than 10% noninvasive component, and patients with invasive papillary-mucinous carcinoma. A and B, the IDC patients with more than 10% noninvasive components had almost the same survival curves as those with invasive papillary-mucinous carcinoma. \(\bullet\), invasive papillary-mucinous carcinoma \((n=9)\); \(\circ\), >10% \((n=22)\); +, \(\leq 10\% \((n=25)\).**
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Table III. Multivariate Analyses for DFS and OS in IDC Patients

| Parameters                      | Total (47 cases) | TR cases (%) | HR       | 95%CI   | P-value |
|--------------------------------|------------------|--------------|----------|---------|---------|
| DFS                            |                  |              |          |         |         |
| Intraductal carcinoma components |                  |              |          |         |         |
| >10%                           | 22               | 14 (63.6)    | Referent |         |         |
| ≤10%                           | 25               | 21 (84.0)    | 1.783    | 0.952–4.428 | 0.067 |
| Surgical resection margins     |                  |              |          |         |         |
| Negative                       | 38               | 26 (68.4)    | Referent |         |         |
| Positive                       | 9                | 9 (100)      | 2.388    | 1.071–5.326 | 0.033 |
| Parameters                      | Total (47 cases) | MR cases (%) | HR       | 95%CI   | P-value |
| OS                             |                  |              |          |         |         |
| Intraductal carcinoma components |                  |              |          |         |         |
| >10%                           | 22               | 13 (59.1)    | Referent |         |         |
| ≤10%                           | 25               | 18 (72.0)    | 2.298    | 1.040–5.075 | 0.040 |
| Surgical resection margins     |                  |              |          |         |         |
| Negative                       | 38               | 27 (71.1)    | Referent |         |         |
| Positive                       | 9                | 8 (88.9)     | 2.139    | 0.907–5.047 | 0.083 |

DFS, disease-free survival; OS, overall survival; IDC, invasive ductal carcinoma; HR, hazard rate; CI, confidence interval; TR, tumor recurrence; MR, mortality rate.

should be useful to objectively evaluate outcomes of patients with IDCs. Therefore, IDC patients should be classified into low- and high-risk groups according to the presence of intraductal carcinoma components, and a cutoff value of 10% for the intraductal carcinoma components in IDCs is suitable for predicting the outcome.

In this study, IDCs with more than 10% intraductal carcinoma components were associated with survival times similar to those of invasive papillary-mucinous carcinoma. The representative type of pancreatic tumors having ample noninvasive components is intraductal papillary-mucinous carcinoma.13–16) Although the intraductal carcinoma components of papillary-mucinous carcinoma of the typical type exhibit mucin hypersecretion and typical papillary features with fibrovascular cores, some of them have small irregular papillae that are not supported by fibrovascular tissue stalks and may display low-papillary feature or cribriform features.7, 16) The histological features of intraductal carcinoma components of IDCs with more than 10% intraductal carcinoma components are very similar to those of the noninvasive components exhibiting low-papillary or cribriform features in invasive papillary-mucinous carcinoma. Thus, IDCs with more than 10% intraductal carcinoma components probably have biological characteristics similar to those of invasive papillary-mucinous carcinoma. Recently, Heinmoller et al.17) and Iacobuzio-Donahue et al.18) noted a significantly higher frequency of Dpc4 protein expression in tumor cells of invasive papillary-mucinous carcinoma than in tumor cells of IDCs. If the intraductal carcinoma components of IDCs with more than 10% intraductal carcinoma components show a significantly higher positive frequency of Dpc4 protein expression than those with 10% or less intraductal carcinoma components, it would strongly support the idea that IDCs with more than 10% intraductal carcinoma components and invasive papillary-mucinous carcinoma share similar biological characteristics.

In conclusion, this is the first study to define a cutoff value of intraductal carcinoma components that is useful to classify patients with IDCs of the pancreas into low- and high-risk groups. All of the IDC patients in this study had been treated by extended pancreatectomy with wide lymphatic and connective tissue dissection and intraoperative radiation therapy. Thus, this combined therapy is probably useful in improving the survival of IDC patients in the low-risk group.

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