



Original article

Risk factors for pancreas-related abscess after total gastrectomy

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Abstract

Background. European clinical trials of gastrectomy have shown that pancreas-related complications are the major cause of mortality. The aim of this study was to determine the risk factors for pancreas-related abscess after gastrectomy and to evaluate the effects of the abscess on postoperative mortality.

Methods. Between 1992 and 1999, 663 consecutive patients with gastric carcinoma underwent total gastrectomy. Data from these patients were analyzed, to identify the predictors of pancreas-related abscess caused by pancreatic juice leakage, by a multiple logistic regression model.

Results. On multivariate analysis, increasing age ($P = 0.018$) and body mass index ($P = 0.006$) were independent preoperative risk factors. Dissection along the distal splenic artery was an intraoperative risk factor. The hazard ratios were increased 9.13-fold ($P = 0.000$) with a pancreas-preserving operation and 16.72-fold ($P = 0.000$) by distal pancreatectomy. Patients with the abscess had a higher postoperative mortality rate ($P = 0.008$), and a higher re-operation rate ($P < 0.001$) than patients without the abscess.

Conclusion. Pancreas-related abscess is more likely to occur in older, obese patients undergoing node dissection along the distal splenic artery. Abscess formation is associated with a higher mortality and re-operation rate. Spleen preservation should be evaluated in Japan.

Key words Gastric cancer · Morbidity

Introduction

The most frequent major complication after gastrectomy with extended dissection is pancreatic juice leakage [1], because recently, the incidence of anastomotic

leakage has decreased remarkably [2]. Pancreatic juice leakage is often followed by contamination, resulting in a peripancreatic abscess. Secondary hemorrhage from major arteries damaged by contamination can be fatal. European clinical trials of gastrectomy have shown that pancreas-related complications are a major cause of mortality [3,4].

The prediction and early detection of pancreas-related complications may be helpful. The aim of this study was to determine risk factors for pancreas-related abscess after gastrectomy, caused by pancreatic juice leakage, and to evaluate the effects of the abscess on postoperative mortality.

Patients and methods

Six hundred and sixty-three consecutive patients with gastric carcinoma underwent total gastrectomy, between 1992 and 1999, at the National Cancer Center Hospital, Tokyo. Data for these patients were analyzed to identify the predictors of pancreas-related abscess caused by pancreatic juice leakage, using a multivariate logistic regression model.

The diagnosis of a pancreas-related abscess was made when purulent fluid containing turbid necrotic debris drained from the peripancreatic area for more than 7 days. The abscess cavity was assessed by computed tomography (CT) scan and contrast study through drains. We recorded an abscess regardless of its cavity size. When we found anastomotic leakage radiologically on initial diagnosis of the abscess, we excluded these patients from the pancreas-related abscess group.

The preoperative and perioperative data were collected from the patients' records and stored on our gastric surgical database.

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Operative techniques

Total gastrectomy with Roux-en-Y esophagojejunostomy was performed in 623 patients (94.0%), as the standard operation. Forty patients (6.0%) underwent jejunal interposition. Pouch formations were added in 7 patients (1.1%). The extent of nodal dissection along the distal splenic artery and splenic hilum varied, including no dissection of these nodes. Distal pancreatectomy or the Maruyama pancreas-preserving method [5] was usually performed for advanced tumor (T2, T3, and T4). The splenic arteries were sacrificed distally to the dorsal pancreatic arteries, in all patients, when we performed pancreas-preserving total gastrectomy. At least one drainage tube was applied in the left subphrenic space in all patients. In most cases, the amylase level of the drainage fluid was determined on the first postoperative day. All patients received antibiotic prophylaxis for the same period.

Statistical methods

Univariate analyses were performed in order to predict those preoperative and perioperative variables that were associated with a pancreas-related abscess. Fischer's exact test and the Mann-Whitney test were used as appropriate.

To develop a model for predicting postoperative pancreas-related abscess in terms of pre- and perioperative variables, three preoperative and six perioperative variables were entered in multiple logistic regression analysis. All the statistical procedures were performed with the SPSS 11.5 statistical package (SPSS Japan, Tokyo, Japan). The limit for statistical significance was $P < 0.05$.

Results

The overall incidence of pancreas-related abscess was 11.5%. The median amylase level of the drainage fluid on the first postoperative day was 1942 I/U (range, 22–387000) U/I overall, and it was 1682 (22–303800) U/I in patients without abscess and 6590 (96–387000) U/I in patients with abscess.

The male-to-female ratio was 2.5:1, and the mean age was 59.9 ± 11.6 years. The proportion of patients with early gastric cancer (T1) was 21.1%. Operation with curative intent was performed in 82.5% of the patients. Nodal dissection along the distal splenic artery was performed in 68.0% of the patients and D2 dissection or more was carried out in 67.6% of the patients. The median operation time was 263 min (90–580 min). Median blood loss was 567 ml (250–4457 ml).

Univariate analysis identified several preoperative patient-related factors as having a high association with pancreas-related abscess. The preoperative demographic data are shown in Table 1, for patients with and without the abscess. Increasing age ($P = 0.004$) and increasing body mass index ($P = 0.008$) had a strong association with postoperative pancreas-related abscess.

Perioperative data are also presented in Table 1. Univariate analysis showed that depth of tumor invasion ($P = 0.007$), operation time ($P = 0.024$), extent of dissection ($P = 0.000$), and dissection along the distal splenic artery ($P = 0.000$) were all associated with a greater incidence of abscess formation. The method of dissection along the distal splenic artery was categorized into one of five variations.

Multivariate analysis identified three independent factors as predictors of postoperative pancreas-related abscess formation (Table 2). Increasing age and increasing body mass index increased the risk of the abscess by 1.4- and 1.1-fold, respectively.

Dissection of nodes along the distal splenic artery and in the splenic hilum was an intraoperative risk factor. If the relative risk for the abscess was set at 1 for patients with neither splenectomy nor pancreatectomy, the hazard ratios were 9.1 for pancreas-preserving operation and 16.7 for distal pancreatectomy.

The postoperative outcomes of the patients with and without pancreas-related abscess were compared (Table 3). The patients with the abscess had a higher postoperative mortality rate. Patients with pancreas-related abscess had 7.6-fold increased mortality compared to patients without the abscess. The re-operation rate for patients with pancreas-related abscess was 32-fold greater than that for patients without the abscess.

Discussion

Increasing body mass index increases the risks of pancreas-related abscess. The literature also reports fat volume as being a risk factor in increasing postoperative complications [6,7]. Nodal dissection along the distal pancreas and in the splenic hilum in obese patients is a difficult task, even in the hands of experienced surgeons specializing in the treatment of gastric carcinoma.

Patients in the West usually have a higher body mass index than those in Japan [8]. The observed high morbidity rates in Western randomized trials for D2 dissection may be related to the greater obesity of these patients.

Increasing age also increases the risk of abscess formation. Patients in the West receiving gastrectomies are usually older than those in Japan, as well as having a

Table 1. Univariate analysis of variables associated with pancreas-related abscess

	No abscess (<i>n</i> = 587)	Abscess (<i>n</i> = 76)	<i>P</i> value; patients with vs without abscess
Preoperative variables			
Sex			
Male	413 (87.1%)	61 (12.9%)	0.080
Female	174 (92.1%)	15 (7.9%)	
Age (years)	59.5 (22–91) ^a	62.8 (44–84) ^a	0.004
Body mass index (kg/m ²)	21.7 (12.2–37.7) ^a	22.6 (15.0–31.5) ^a	0.008
Perioperative variables			
Depth of tumor invasion			
Early (T1)	133 (95.0%)	7 (5.0%)	0.007
Advanced (T2, T3, T4)	454 (86.8%)	69 (13.2%)	
Curability of operation			
Curative (R0)	480 (87.8%)	67 (12.2%)	0.200
Noncurative (R ≥ 1)	107 (92.2%)	9 (7.8%)	
Operation time (min)	260 (90–580) ^a	286 (140–540) ^a	0.024
Blood loss (ml)	565 (25–3776) ^a	587.5 (70–4457) ^a	0.123
Extent of dissection			
D0, D1	207 (96.3%)	8 (3.7%)	0.000
D2, D3	380 (84.8%)	68 (15.2%)	

Dissection methods for nodes along the distal splenic artery

	Splenectomy	Distal pancreatectomy	Dissection along distal splenic artery			
1.	No	No	No	155 (98.1%)	3 (1.9%)	0.000
2.	Yes	No	No	49 (90.7%)	5 (9.3%)	
3.	No	No	Yes	10 (83.3%)	2 (16.7%)	
4.	Yes	No	Yes	309 (86.3%)	49 (13.7%)	
5.	Yes	Yes	Yes	64 (79.0%)	17 (21.0%)	

Splenectomy (yes), pancreatectomy (no), dissection along distal splenic artery (yes) indicates pancreas-preserving total gastrectomy method

^aMedian values, with ranges in parentheses**Table 2.** Multivariate predictors of pancreas-related abscess

Variables	<i>P</i> value	Odds ratio	95% Confidence interval of odds ratio			
Preoperative variables						
Age (continuous)	0.018	1.414	1.060–1.886			
Body mass index (continuous)	0.006	1.126	1.035–1.225			
Perioperative variables						
Dissection methods for nodes along the distal splenic artery						
	Splenectomy	Distal pancreatectomy	Dissection along distal splenic artery			
1.	No	No	No		1	
2.	Yes	No	No	0.012	6.601	1.505–28.953
3.	No	No	Yes	0.011	11.973	1.760–81.468
4.	Yes	No	Yes	0.000	9.130	2.791–29.864
5.	Yes	Yes	Yes	0.000	16.724	4.675–59.823

Table 3. Relationship of postoperative events to pancreas-related abscess

Variables	No abscess (n = 587)	Abscess (n = 76)	P value
Re-operation	4 (0.7%)	17 (22.4%)	< 0.001
Operation-related death	4 (0.7%)	4 (5.3%)	0.008

higher body mass index [9,10]. The observed high morbidity rates in Western trials were related to the age distribution [11], similar to our findings here.

Our study shows that the dissection of nodes alongside the distal splenic artery and nodes in the splenic hilum is an intraoperative risk factor. Distal pancreatectomy with splenectomy had the highest odds ratio. However, even when we performed pancreas-preserving total gastrectomy to avoid pancreas-related complications, there was still a considerably higher odds ratio of abscess formation. Pancreas-preserving splenectomy is part of the standard operation in specialized centers in Japan. Splenectomy without dissection along the distal splenic artery also had a high risk of abscess formation.

Japanese retrospective studies have shown that 20%–30% of patients with advanced cancer in the proximal stomach have nodal metastasis in the splenic hilum, and that gastrectomy with resection of these nodes can yield a 5-year survival of 20%–25% [12]. Consequently, in Japan, dissection of nodes in these areas is performed routinely.

Although mortality rates from gastrectomy complicated by pancreas-related abscess are lower in Japan than those reported in Western series [3,4], pancreas-related abscess formation remains a strong factor in the mortality and morbidity rates in both Japanese and Western centers.

Evaluation of the role of splenectomy for proximal gastric cancer is important. Spleen preservation, avoiding thorough nodal dissection in the splenic hilum as well as in the distal splenic artery, as described by groups in the United Kingdom [13,14], should be evaluated in Japan. The Japan Clinical Oncology Group have recently started a randomized controlled trial to evaluate the effect of splenectomy on postoperative morbidity and longterm cancer-free survival [15].

Conclusions

Pancreas-related abscess after gastrectomy is more likely to occur in older, obese patients undergoing node dissection along the distal splenic artery. Because the abscesses are associated with high mortality and re-operation rates, the role and oncologic value of splenec-

tomy has to be considered more carefully. This now forms the basis of a nationwide trial.

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Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer

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Background: Extended lymphadenectomy for gastric carcinoma has been associated with high mortality and morbidity rates in several multicentre randomized trials.

Methods: Using data from 523 patients registered for a prospective randomized trial comparing extended (D2) and superextended (D3) lymphadenectomies, risk factors for overall complications and major surgical complications (anastomotic leakage, intra-abdominal abscess and pancreatic fistula) were identified by multivariate logistic regression analysis.

Results: Mortality and morbidity rates were 0.8 per cent (four of 523) and 24.5 per cent (128 of 523) respectively. Pancreatectomy (relative risk 5.62 (95 per cent confidence interval (c.i.) 1.94 to 16.27)) and prolonged operating time (relative risk 2.65 (95 per cent confidence interval 1.34 to 5.23)) were the most important risk factors for overall complications. A body mass index of 25 kg/m² or above, pancreatectomy and age greater than 65 years were significant predictors of major surgical complications.

Conclusion: Pancreatectomy should be reserved for patients with stage T4 disease. Age and obesity should be considered when planning surgery.

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Introduction

Despite a declining incidence in Western Europe¹ and the USA², gastric carcinoma remains the second commonest cause of cancer death worldwide, with over 600 000 deaths per year³. Given the poor outcome of irresectable disease treated by other therapeutic modalities in phase II and III trials^{4,5}, the curative treatment of gastric carcinoma remains primarily surgical. Although the presence of distant metastases usually precludes curative surgery, this does not necessarily apply to disease in the regional lymph nodes, which can be dissected *en bloc* with the primary lesion^{6,7}. This type of resection may allow cure, provided that metastases are within the margins of dissection. Removal of a wider range of lymph nodes by extended lymph node dissection might increase the

chance of cure, but is inappropriate if the cancer has spread systemically.

In Japan, gastrectomy plus extended systematic lymphadenectomy (D2 resection) has long been the standard treatment, even for superficial cancers⁸. Success with D2 resection has led to the evolution of a superextended lymphadenectomy (D3 resection) and several feasibility studies evaluating dissection of para-aortic lymph nodes have been performed⁹⁻¹². A randomized trial (Japan Clinical Oncology Group (JCOG) 9501) was launched in 1995, primarily to explore the potential survival benefit of D3 over D2 dissection¹³. This trial has provided the opportunity to evaluate prospectively collected data on gastric cancer surgery in Japan. The present study represents a detailed analysis of risk factors for overall and surgical complications following D2 and D3 resections.

Patients and methods

Between June 1995 and April 2001, 523 patients registered in the JCOG 9501 study were allocated randomly to either D2 (263 patients) or D3 (D2 plus para-aortic lymph node dissection; 260 patients) resection. Eligibility criteria and the method of randomization have already been reported in detail¹³. In brief, patients aged less than 75 years of age with histologically proven and resectable primary gastric carcinoma with an estimated depth of SS (penetrating the muscle layer), SE (penetrating the serosa) or SI (invasion to an adjacent organ) were recruited after giving informed consent. Patients found positive for free cancer cells by cytological examination of peritoneal washes and those with Borrmann type 4 tumours (linitis plastica type) were excluded. Twelve institutions participated in the trial initially and 12 other institutions were added to increase patient recruitment.

After laparotomy, cytological examination of peritoneal washes was performed, followed by gross examination of the abdominal cavity and the primary lesion. Only patients who were negative for free cancer cells in the abdominal cavity and without evidence of gross para-aortic lymph node spread, peritoneal carcinomatosis or other distant metastasis were eligible to participate. The patients were allocated randomly to either D2 or D3 resection by the minimization method of balancing the groups according to T stage (T2 *versus* T3/T4), gross appearance (Borrmann types 1 and 2 *versus* Borrmann types 3 and 5) and institution. The surgeons were notified immediately of the allocation results and completed the operation accordingly.

Patients underwent appropriate gastrectomy with systematic lymphadenectomy as allocated. Perigastric lymph nodes (nodal stations 1, 3, 4, 5 and 6 according to the Japanese Classification of Gastric Cancer¹⁴) and nodes at the base of the left gastric artery (7), along the common hepatic artery (8) and at the base of the splenic artery (11) were resected routinely. Lymph nodes along the hepatoduodenal ligament and behind the pancreatic head (12 and 13) were resected when the primary lesion was located in the lower third of the stomach. Lymph nodes along the left side of the cardia (2), within the splenogastric ligament (4sa) and at the splenic hilum (10) were resected with the spleen when total or proximal gastrectomy was performed. Concurrent resection of the pancreatic tail was not routine during either D2 or D3 resection and was reserved for patients with direct invasion to the pancreas. In patients randomized to superextended lymphadenectomy, para-aortic lymph nodes from the level of the coeliac trunk down to the root of the inferior mesenteric artery (16a2 and 16b1) were dissected. The mode of reconstruction following resection was not specified.

All information on complications was extracted from the case-report forms for the trial. Anastomotic leakage, intra-abdominal abscess and pancreatic fistula were considered to be major surgical complications. Anastomotic leakage was defined as dehiscence confirmed by radiographic examination using contrast medium. Pancreatic fistula was diagnosed if there was prolonged purulent discharge containing pancreatic juice from the drainage tube.

Factors that might affect the risk of overall and major surgical complications were evaluated by univariate analysis using cross-tabulations. Variables analysed included extent of lymphadenectomy, splenectomy, pancreatectomy, type of gastrectomy, pathological (p) T category (pT2 and pT3 *versus* pT4), sex, age, body mass index (BMI), operating time, amount of blood loss and need for autologous blood transfusion. Operating time and blood loss were divided into tertiles for analysis. Two factors associated with surgical experience were also evaluated: institutions that enrolled over 20 patients *versus* those with fewer patients and first and second halves of the trial (1995–1998 *versus* 1999–2001). The χ^2 test was used to assess differences in proportions. The independent contribution of various factors was assessed by multivariate logistic regression analysis, with mutual adjustment of potential risk factors for complications. All factors analysed in the univariate analysis were included as variables in the multivariate analysis. Two-sided *P* values are presented. Statistical analysis was performed using SAS[®] version 8.12 (SAS Institute, Tokyo, Japan).

Results

Total gastrectomy was performed in 199 (38.0 per cent) of 523 patients and proximal gastrectomy in four;

Table 1 Complications

Severe abdominal complications	
Pancreatic fistula	30
Abdominal abscess	29
Anastomotic leakage	11
Other complications	
Pneumonia	16
Anastomotic stenosis	14
Bowel obstruction/ileus	16
Lymphorrhoea	10
Thoracic effusion requiring thoracic drainage	7
Severe feeding problem requiring prolonged hyperalimentation	6
Wound abscess	5
Postoperative bleeding	3
Severe diarrhoea	3
Urinary tract infection	3
Catheter-induced sepsis	3
Pulmonary embolism	2
Cardiac failure	1
Cholecystitis requiring percutaneous drainage	1

the remaining patients underwent distal gastrectomy. Splenectomy was performed in 191 patients (36.5 per cent) and distal pancreatectomy in 22 (4.2 per cent). There was no significant difference in the type of gastrectomy and incidence of combined resection between the two groups. Details of patient demographics and tumour stages have been reported previously¹³.

There were four hospital deaths (0.8 per cent), two in each group. Two patients suffered from rapid disease progression and died 3 and 5 months after

surgery without being discharged from hospital. One patient died from pneumonia at 46 days and another died from massive bleeding from the gastroduodenal artery 24 days after operation. Complications were identified in 128 patients (24.5 per cent) and major surgical complications in 49 patients (9.4 per cent) (Table 1).

The results of univariate analyses of risk factors for overall postoperative complications are summarized in Table 2. Only pancreatic resection ($P = 0.001$) and

Table 2 Univariate and multivariate analysis of risk factors for overall complications

	n	No. with complications	Univariate analysis		Multivariate analysis	
			Relative risk	P	Relative risk	P
Extent of lymphadenectomy						
D2	263	55	1		1	
D3	260	73	1.48 (0.99, 2.21)	0.057	0.93 (0.58, 1.51)	0.776
Splenectomy						
No	332	64	1		1	
Yes	191	64	2.11 (1.41, 3.17)	<0.001	2.05 (0.52, 8.01)	0.304
Pancreatectomy						
No	501	115	1		1	
Yes	22	13	4.85 (2.02, 11.63)	<0.001	5.62 (1.94, 16.27)	0.001
Extent of gastrectomy						
Distal	320	62	1		1	
Total or proximal	203	66	2.01 (1.34, 3.00)	<0.001	0.84 (0.22, 3.27)	0.804
Invasion to adjacent organs						
T2, T3	501	123	1		1	
T4	22	5	0.90 (0.33, 2.50)	0.846	0.37 (0.11, 1.24)	0.107
Sex						
M	358	94	1		1	
F	165	34	0.73 (0.47, 1.14)	0.163	0.73 (0.45, 1.19)	0.207
Age (years)						
<56	160	33	1		1	
56-65	207	48	1.16 (0.70, 1.92)	0.557	1.26 (0.73, 2.17)	0.403
>65	156	47	1.66 (0.99, 2.77)	0.053	1.63 (0.92, 2.89)	0.092
Body mass index						
<25	446	101	1		1	
≥25	77	27	1.85 (1.10, 3.10)	0.019	1.75 (0.99, 3.08)	0.054
Operating time (min)						
<240	167	23	1		1	
240-297	179	43	1.98 (1.13, 3.46)	0.016	1.77 (0.96, 3.25)	0.068
>297	177	62	3.38 (1.97, 5.78)	<0.001	2.65 (1.34, 5.23)	0.005
Blood loss (ml)						
<395	174	27	1		1	
395-710	174	42	1.73 (1.01, 2.97)	0.045	1.05 (0.58, 1.90)	0.886
>710	175	59	2.77 (1.65, 4.64)	<0.001	1.11 (0.58, 2.12)	0.754
Blood transfusion						
Yes	408	87	1		1	
No	115	41	2.04 (1.31, 3.20)	0.002	1.53 (0.92, 2.56)	0.102
Case volume*						
<20	147	41	1		1	
≥20	376	87	0.78 (0.51, 1.20)	0.256	0.83 (0.51, 1.34)	0.437
Period						
1995-1998	295	75	1		1	
1999-2001	228	53	0.9 (0.59, 1.33)	0.566	0.87 (0.56, 1.35)	0.539

Values in parentheses are 95 per cent confidence intervals. *No. of patients registered.

Table 3 Univariate and multivariate analysis of risk factors for major surgical complications

	n	No. with major complications	Univariate analysis		Multivariate analysis	
			Relative risk	P	Relative risk	P
Extent of lymphadenectomy						
D2	263	23	1		1	
D3	260	26	1.16 (0.64, 2.09)	0.623	0.67 (0.32, 1.39)	0.279
Splenectomy						
No	332	20	1		1	
Yes	191	29	2.79 (1.53, 5.09)	<0.001	1.08 (0.15, 7.56)	0.941
Pancreatectomy						
No	501	43	1		1	
Yes	22	6	3.99 (1.49, 10.74)	0.003	6.90 (1.86, 25.58)	0.004
Extent of gastrectomy						
Distal	320	19	1		1	
Total or proximal	203	30	2.74 (1.50, 5.03)	<0.001	2.15 (0.31, 15.20)	0.442
Invasion to adjacent organs						
T2, T3	501	47	1		1	
T4	22	2	0.97 (0.22, 4.26)	0.964	0.37 (0.067, 2.01)	0.246
Sex						
M	358	38	1		1	
F	165	11	0.60 (0.30, 1.21)	0.150	0.57 (0.25, 1.27)	0.169
Age (years)						
<56	160	7	1		1	
56–65	207	20	2.34 (0.96, 5.67)	0.061	3.06 (1.15, 8.20)	0.026
>65	156	22	3.59 (1.49, 8.66)	0.005	4.04 (1.48, 11.02)	0.006
Body mass index						
<25	446	34	1		1	
≥25	77	15	2.93 (1.51, 5.69)	0.001	3.32 (1.54, 7.12)	0.002
Operating time (min)						
<240	167	8	1		1	
240–297	179	14	1.69 (0.69, 4.13)	0.252	1.60 (0.60, 4.27)	0.350
>297	177	27	3.58 (1.58, 8.12)	0.002	2.96 (1.03, 8.55)	0.045
Blood loss (ml)						
<395	174	10	1		1	
395–710	174	11	1.11 (0.46, 2.68)	0.822	0.47 (0.17, 1.30)	0.145
>710	175	28	3.12 (1.47, 6.65)	0.003	0.86 (0.32, 2.31)	0.767
Blood transfusion						
Yes	408	29	1		1	
No	115	20	2.75 (1.49, 5.08)	<0.001	1.99 (0.97, 4.08)	0.061
Case volume*						
<20	147	16	1		1	
≥20	376	33	0.79 (0.42, 1.48)	0.457	0.76 (0.36, 1.57)	0.454
Period						
1995–1998	295	30	1		1	
1999–2001	228	19	0.80 (0.44, 1.47)	0.475	0.83 (0.43, 1.61)	0.575

Values in parentheses are 95 per cent confidence intervals. *No. of patients registered.

prolonged operating time (patients in the upper tertile for whom the operating time was more than 297 min; $P = 0.005$) were identified as significant independent risk factors for overall complications (Table 2). A BMI of 25 or more was close to significance ($P = 0.054$).

The results of univariate analyses of risk factors for major surgical complications are summarized in Table 3. Multivariate analysis identified BMI ($P = 0.002$), pancreatic resection ($P = 0.004$), age (56–65 years, $P = 0.026$; over 65 years, $P = 0.006$) and operating time

over 297 min ($P = 0.045$) as significant independent risk factors for major surgical complications (Table 3).

Discussion

Gastrectomy plus extended systemic lymphadenectomy (D2 resection) is the standard procedure for gastric carcinoma in Japan. This approach has resulted in superior stage-by-stage survival than that observed in most Western countries and has led to cure for a

proportion of patients with nodal disease beyond the perigastric region, although this has not been confirmed in Western randomized trials^{15,16}. Although long-term follow-up revealed significantly better disease-free survival for the D2 group in the subset with node-positive cancer¹⁷, this difference did not extend to all patients in the trial, in part owing to the unacceptably high mortality rate associated with D2 resection⁸. JCOG 9501, a Japanese multi-institutional prospective randomized trial comparing D2 with more extended resection, has superior quality control of surgical procedures and reliability of data¹³ than retrospective Japanese studies and Western prospective trials.

The most significant risk factor for both surgical and overall complications in the present study was pancreatic resection, although it should be noted that this was performed in only 4.2 per cent of patients, compared with 30.3 and 15.2 per cent in the UK Medical Research Council (MRC) and Dutch trials respectively^{15,16}. The rate of pancreatectomy was lower in the present series because a pancreas-preserving technique^{18,19} was generally used, whereas distal pancreatectomy and splenectomy were integral parts of D2 dissection in the Dutch trial unless cancer was located in the distal stomach. The low morbidity rate in the present study may well be related to pancreas preservation^{18,19}. The success of this approach has also been reported in a multicentre phase II trial of D2 dissection in Northern Italy²⁰.

Splenectomy, on the other hand, was not an independent determinant of risk, possibly because it was never performed with distal gastrectomy in the present series. In the Dutch randomized trial a high mortality rate after distal gastrectomy was attributed in part to necrosis of the remnant stomach as a result of splenectomy and division of the short gastric arteries²¹. The survival benefit of splenectomy performed solely to facilitate dissection of lymph nodes close to the splenic hilum has been questioned, however, and a randomized trial to explore this issue is ongoing²².

Age was not an independent risk factor for overall complications in this study, in contrast to the Dutch trial in which age over 65 years was a significant risk factor for hospital death and overall complications²¹. This discrepancy may be attributed to the fact that only patients aged 75 years or less were eligible for inclusion in the JCOG 9501¹³, whereas other trials have included older patients^{15,16}. Japanese patients were, on average, 8 years younger than Dutch patients²³; consequently the proportion of patients over 65 years of age was 29.8 per cent in the present series as opposed to 51.3 per cent in the Dutch trial¹⁶. This age distribution

may account for the very low incidence of perioperative cardiovascular events in the present series, another factor that may have influenced the low morbidity and mortality rates.

Extended lymph node dissection may be hampered by excess bodyweight^{24–26} and in the present study BMI was a significant risk factor for major surgical complications. Caucasians in general have a higher BMI than Japanese and the incidence of morbid obesity is significant among patients in the USA and Europe. Only 14.7 per cent of the present patients had a BMI of 25 kg/m² or greater, whereas one-third of the US population is obese (BMI over 27 kg/m²)²⁷. These data suggest that the patients' physique favours Japanese patients when major gastric cancer surgery is performed.

The extent of lymph node dissection (D2 *versus* D3), surgical volume and the period in which the operation was performed had no impact, suggesting that there were no learning curve issues. Although D2 resection has long been a standard procedure in Japan, all surgeons in the trial were experts from specialized centres who had sufficient experience with D3 resection through numerous other studies. Of the variables reflecting difficulties encountered during surgery, prolonged operating time was identified as a significant independent risk factor for both overall and major surgical complications. However, amount of blood loss and blood transfusion were significant only in univariate analysis; this may be attributable to multicollinearity, as these two factors are closely related.

Gastrectomy with extended lymphadenectomy is feasible and safe in Japan, provided that older patients with comorbidity are excluded and pancreatectomy is reserved for lesions with direct invasion to the pancreas. Obese patients should be treated with caution, however, as they have a significant risk of developing major surgical complications. Hopefully, with careful patient selection, appropriate surgical expertise and pancreas and spleen preservation⁸ where possible, equally good results, rarely achieved previously^{20,28}, will be realized in the West.

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Grade of Stromal Invasion in Small Adenocarcinoma of the Lung

Histopathological Minimal Invasion and Prognosis

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Abstract: The pathologic features of invasion such as stromal disruption and pleural/vascular involvement have been shown to be of prognostic value in adenocarcinoma. However, the relationship between the degree of invasion, histologic subtype of adenocarcinoma, and prognosis remains unclear. We retrospectively studied 380 peripheral adenocarcinomas of ≤ 2.0 cm in diameter with regard to histology and clinical profiles. Their degree of invasive growth was classified into four grades as follows according to the structural deformity and its location in the adenocarcinoma lesion: Grade 0 had a pure bronchioloalveolar growth pattern and no evidence of stromal invasion. Grade 1 had stromal invasion in the area of bronchioloalveolar growth. Grade 2 had stromal invasion localized on the periphery of a fibrotic focus. Grade 3 had stromal invasion into the center of a fibrotic focus. The clinicopathological data were obtained from medical records. The distribution of the histologic grade of invasion was as follows: grade 0 in 85 tumors (22%), grade 1 in 37 (10%), grade 2 in 46 (12%), and grade 3 in 212 (56%). This histologic grade of invasion was closely related to other indicators of tumor spread. Vascular/lymphatic permeation was seen in none of grade 0, in 1 lesion each of grade 1 and grade 2, and 144 (68%) of grade 3. Lymph node metastasis was seen in 57 (27%) lesions of grade 3 but not in grades 0, 1, or 2. The 5-year disease-free survival rates were 100%, 100%, 100%, and 59.6% for tumors with grade 0, grade 1, grade 2, and grade 3 invasion, respectively. Tumors with grade 1 and grade 2 invasion, like tumors with grade 0 invasion (bronchioloalveolar carcinoma), showed an excellent prognosis. Therefore, tumors with grade 1 and grade 2 invasion could be considered "minimally invasive" or "early" adenocarcinomas.

Key Words: adenocarcinoma, pathology, prognosis, early cancer, lung

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Because of the advent of high-resolution computed tomography (CT) and the consequent availability of more detailed images and screening programs, small lung cancers are being found more often.¹² Most of these have an adenocarcinoma histology and arise in the periphery of the lung parenchyma.¹ It has also been repeatedly reported that lymph node metastasis is found in approximately 20% of peripheral adenocarcinomas, even if the tumor diameter is small, such as <2.0 cm.^{2,11,13,15,17,22}

On the other hand, another histologic category of adenocarcinoma, bronchioloalveolar carcinoma (BAC), has also been discussed with regard to its histologic features and prognosis.^{5,6,8,14,23} This subcategory is classified as a subtype of adenocarcinoma, which histologically shows a unique replacing growth pattern of tumor cells along the alveolar wall. According to radiologic studies by high-resolution CT, the replacing growth pattern of adenocarcinoma cells seen in BAC presents as a focal, hazy increase in attenuation called "ground-glass opacity."³ Radiologic-pathologic studies have demonstrated that the ground-glass opacity appearance represents patent alveolar spaces and the preservation of bronchial and vascular margins.^{16,18}

In the recently revised histologic classification of lung and pleural tumors by the World Health Organization (WHO),²⁹ adenocarcinomas have been classified into five histologic subtypes: BAC, acinar, papillary, solid with mucin, and adenocarcinoma with mixed subtypes. The WHO classification describes BAC as a form of adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular, or pleural invasion. Accordingly, BAC is the only subtype without any invasive features. Obviously, an excellent prognosis can reasonably be expected for noninvasive BACs, and invasive features seen in adenocarcinoma are thought to be

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prognostic. However, the relationship between the degree of pathologic invasion and prognosis has not yet been clarified.

In this retrospective study, we histopathologically graded the degree of invasion and explored the relationship between invasion and the prognosis of patients with adenocarcinoma, which might contribute to establishing the concept of "curable" lung cancer.

MATERIALS AND METHODS

Patients

For the 8-year period from January 1993 to December 2000, a total of 1045 pulmonary resections were performed for adenocarcinoma of the lung at the National Cancer Center Hospital, Tokyo. These comprised 60% of all resections for primary lung carcinomas performed during the same period (1738 resections). Among these 1045 adenocarcinomas, 384 tumors were ≤ 2.0 cm in diameter and located in the periphery of the lung parenchyma. Three cases with a past history of resection for other lesions and one case with preoperative treatment were excluded from this study. A total of 380 peripheral adenocarcinomas of ≤ 2.0 cm in diameter (36%) were studied to explore the relationship between the degree of invasive growth and prognosis. Clinicopathologic information was obtained by reviewing the medical chart in detail with regard to age, sex, mode of resection, recurrence, and survival. The surgical and postsurgical stages were determined according to the TNM system of the UICC.²⁶ The backgrounds of these 380 patients are summarized in Table 1. The patients ranged in age from 23 to 89 years with an average of 61.3 years. A total of 182 patients (48%) were male and 198 patients (52%) were female. Most of the patients (98%) underwent complete resection. As the mode of surgical resection, at least lobectomy was performed in 83%.

Pathologic Evaluations

The resected specimens were routinely fixed with 10% formalin after lung inflation by intubation from the bronchus and embedded in paraffin. The entire nodules were blocked for histologic examination. Each of the specimens, including the largest cut surface of the tumor, was cut into 3- μ m-thick sections. Sections of the tumor were stained by hematoxylin and eosin, periodic acid-Schiff, and elastica, and then examined by light microscopy. The histologic subtype was determined according to the WHO classification as BAC, acinar, papillary, solid with mucin, or adenocarcinoma with mixed subtypes. We strictly assigned a diagnosis of BAC for noninvasive tumors as defined by the WHO classification, where it is defined as "an adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion." In this study, histopathological "invasion" was defined when the tumor cells were arranged in acinic/papillotubular struc-

TABLE 1. Characteristics of Patients With Small Adenocarcinoma

Characteristic	Data
No. of patients	380
Age (years)	
Mean	61.3
Range	23-89
Gender	
Male	182 (48%)
Female	198 (52%)
Operative mode	
Pneumonectomy/lobectomy	314 (83%)
Segmentectomy/partial	66 (17%)
Lymph node dissection	
Mediastinohilar	227 (60%)
Hilar only/none	153 (40%)
Curability of surgery	
Complete	373 (98%)
Incomplete	7 (2%)
Histologic subtype by the WHO classification	
BAC	85 (22%)
Acinar	4 (1%)
Papillary	7 (2%)
Solid with mucin	27 (7%)
Mixed subtypes	257 (68%)
Pathologic stage	
IA	312 (82%)
IB	6 (1%)
IIA	21 (6%)
IIB	5 (1%)
IIIA	22 (6%)
IIIB/IV	14 (4%)

WHO, World Health Organization; BAC, bronchioloalveolar carcinoma.

tures or solid nests in a fibroblastic stroma, often accompanied by collagenization, and when the alveolar structures were no longer discernible (Fig. 1).^{7,29} To categorize the degree of invasive growth in adenocarcinoma, four grades (0-3) were defined according to the location of the above-mentioned invasive features in adenocarcinoma lesions (Table 2). Lesions that were defined as having grade 0 invasion were consistent with BAC by the WHO classification. Typical histologic findings in each grade of invasion are shown in Figures 2 to 5. The following histopathologic findings were also evaluated in the same slides; tumor size (maximum tumor dimension), the size of the fibrotic focus within the tumor, degree of pleural involvement, vascular/lymphatic permeation, lymph node involvement, and pathologic stage. The size of the fibrotic focus was measured at the maximum dimension of the tumor after the fibrotic focus was diagnosed histologically in a low-power

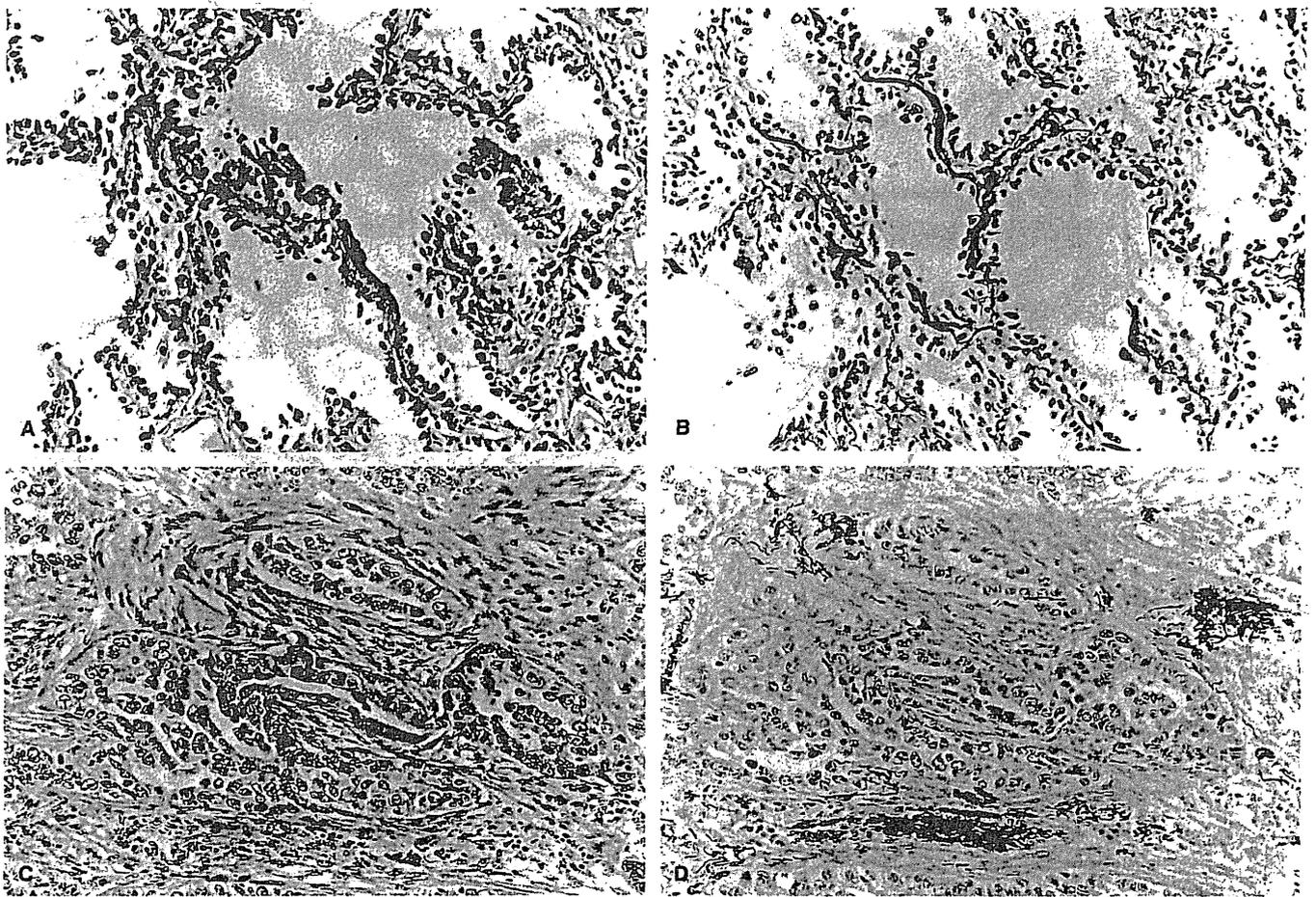


FIGURE 1. Features of histologic noninvasion (A, B) and invasion (C, D) in adenocarcinoma lesions. A and B, The tumor shows a pure bronchioloalveolar growth pattern and no evidence of stromal invasion. The elastic fiber framework is preserved. C and D: The tumor cells are arranged in acinic/papillotubular structures in a fibroblastic stroma, and the elastic framework is disrupted. The elastic stain highlights the elastic framework. Hematoxylin and eosin staining (A, C) and Elastica staining (B, D): original magnification $\times 200$.

view as previously reported.²⁷ Pleural involvement was classified as positive when the tumor was exposed on the pleural surface or when the tumor invaded the parietal pleura or chest wall. Vascular and lymphatic permeation was evaluated based on the presence of identifiable tumor cells in the blood vessel lumen or lymphatic lumen, respectively.

TABLE 2. Histologic Grade of Invasion in Adenocarcinoma

Grade	Description
0	Pure bronchioloalveolar growth pattern and no evidence of stromal invasion
1	Stromal invasion in the area of bronchioloalveolar growth
2	Stromal invasion localized on the periphery of a fibrotic focus
3	Stromal invasion into the center of a fibrotic focus

Statistics

To compare the frequencies among different groups, a χ^2 test or Tukey's significant difference test was used. Survival curves were estimated by the Kaplan-Meier method using the date of resection as the starting point and the date of recurrence or last follow-up as the end point. Deaths by causes other than lung cancer were considered censored. Survival curves were compared by the log-rank test. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Pathologic Findings

The distribution of histologic grade of invasion (grade 0-3) was as follows: 85 (22%) in grade 0, 37 (10%) in grade 1, 46 (12%) in grade 2, and 212 (56%) in grade 3. The pathologic characteristics of each grade are summarized in Table 3. The histologic grade of invasion defined in this study was closely

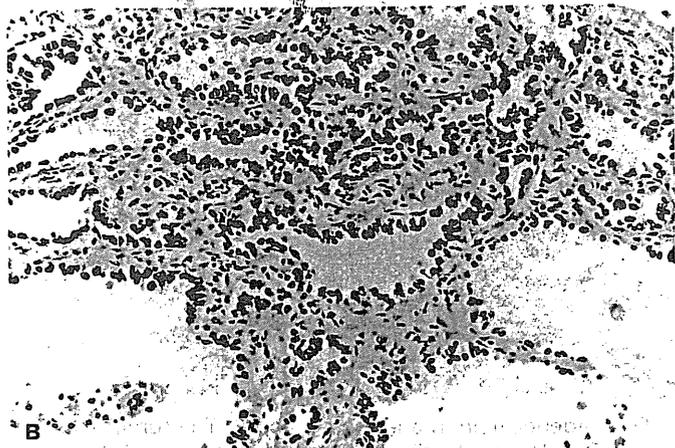
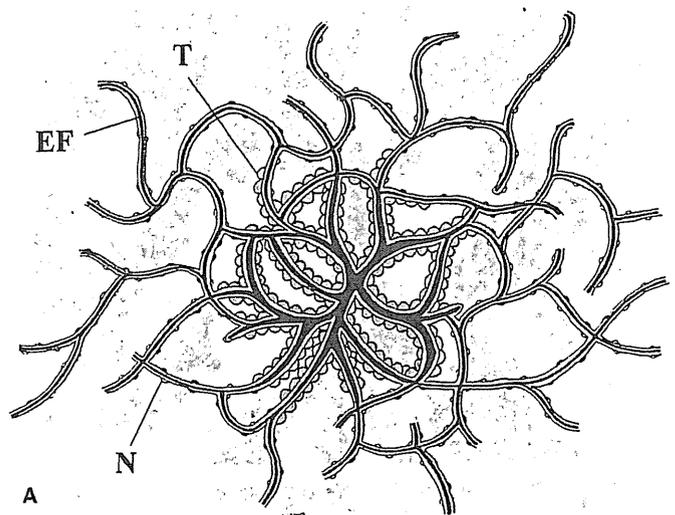


FIGURE 2. Schematic drawing (A) and microphotograph of grade 0 invasion (B, C). The tumor shows a bronchioloalveolar growth pattern with no stromal invasion. Hematoxylin and eosin staining (B) and Elastica staining (C): original magnification $\times 200$. N, normal alveolar cells; T, tumor cells; EF, elastic fiber framework.

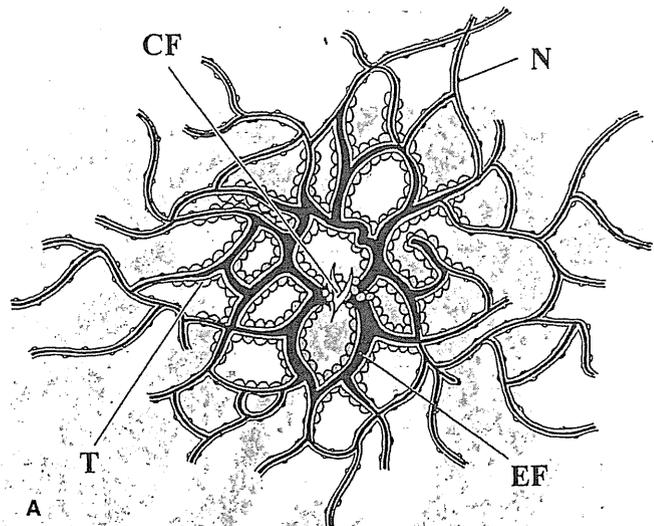


FIGURE 3. Schematic drawing (A) and microphotograph (B, C) of grade 1 invasion. The tumor shows features of histologic invasion in the area of bronchioloalveolar growth (arrows). Hematoxylin and eosin staining (B): original magnification $\times 40$. Elastica staining (C): original magnification $\times 200$. CF, collagen fiber (collagenization).

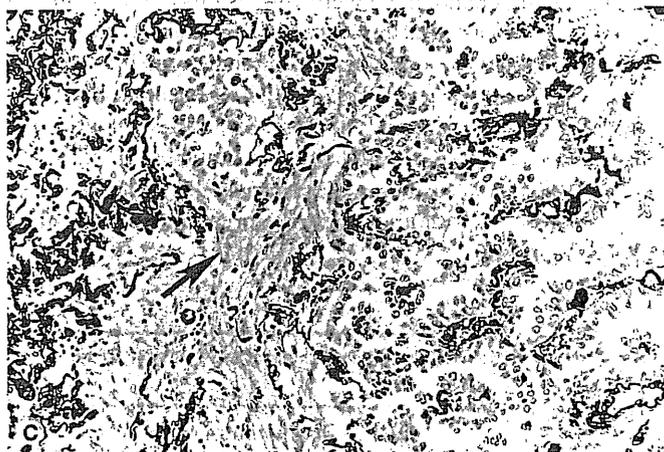
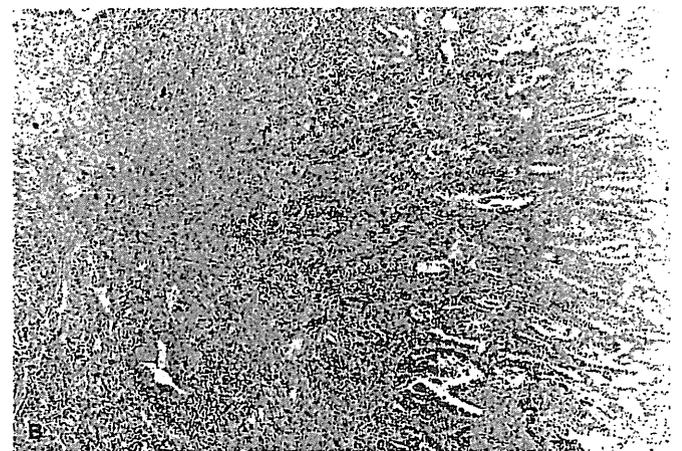
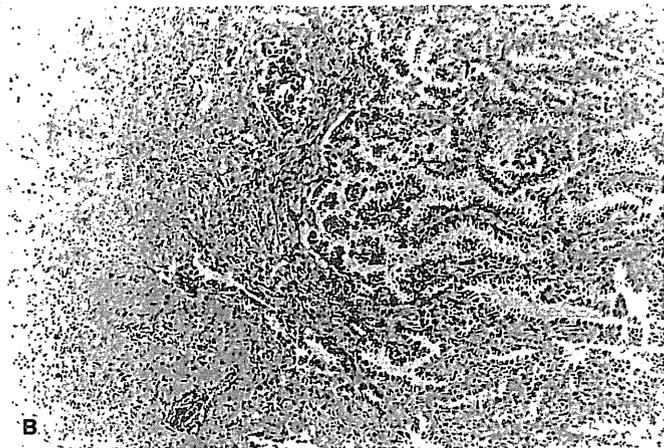
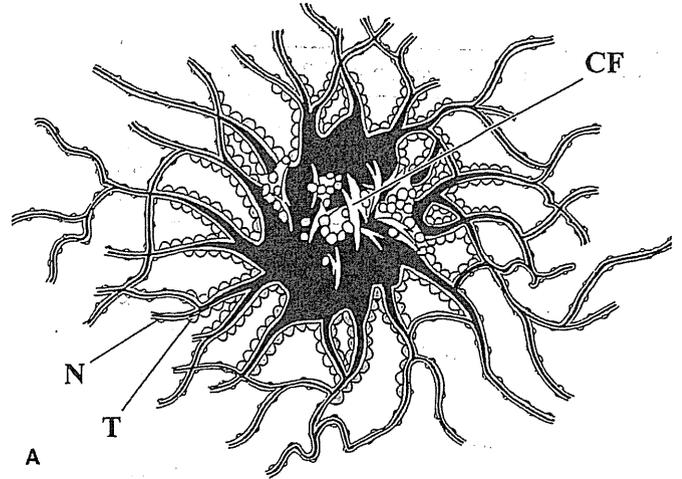
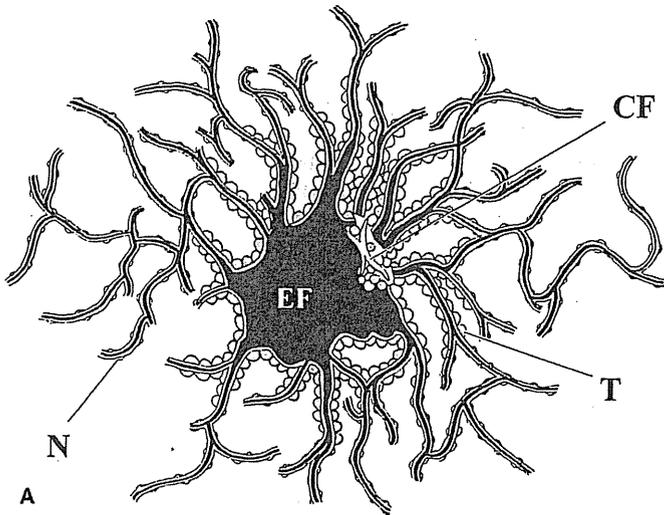


FIGURE 4. Schematic drawing (A) and microphotograph (B, C) of grade 2 invasion. The tumor shows features of histologic invasion localized on the periphery of a central fibrosis (arrow). The invasive foci are seen at the boundary between the central collapsed fibrosis and the surrounding tumor cells showing bronchioloalveolar growth. Hematoxylin and eosin staining (B): original magnification $\times 40$. Elastica staining (C): original magnification $\times 200$. EF is the black area.

FIGURE 5. Schematic drawing (A) and microphotograph (B, C) of grade 3 invasion. The tumor shows features of histologic invasion into the center of a fibrotic focus (arrows). Hematoxylin and eosin staining (B): original magnification $\times 40$. Elastica staining (C): original magnification $\times 200$.

TABLE 3. Grade of Invasion and Pathologic Characteristics

	Grade of Invasion			
	Grade 0 (n = 85)	Grade 1 (n = 37)	Grade 2 (n = 46)	Grade 3 (n = 212)
Tumor size (cm)				
Mean	1.2	1.6	1.5	1.6
Range	0.4–2.0	0.7–2.0	0.7–2.0	0.8–2.0
Size of fibrotic focus (mm)				
Mean	2.0	3.8	6.7	7.9
Range	0–11	0–17	2–16	1–19
Pleural involvement				
Negative	85 (100%)	32 (100%)	46 (100%)	194 (92%)
Positive	0 (0%)	0 (0%)	0 (0%)	18 (8%)
Vascular/lymphatic permeation				
Negative	85 (100%)	36 (97%)	45 (98%)	68 (32%)
Positive	0 (0%)	1 (3%)	1 (2%)	144 (68%)
Nodal involvement				
N0	85 (100%)	37 (100%)	46 (100%)	155 (73%)
N1–N3	0 (0%)	0 (0%)	0 (0%)	57 (27%)
Pathologic stage				
I	85 (100%)	37 (100%)	46 (100%)	150 (71%)
II	0 (0%)	0 (0%)	0 (0%)	26 (12%)
III–IV	0 (0%)	0 (0%)	0 (0%)	36 (17%)

related to the progression of adenocarcinoma, as represented by tumor size, size of the fibrotic focus, pleural involvement, vascular/lymphatic permeation, nodal involvement, and pathologic stage. The tumor size was smaller in grade 0 than in other grades of invasion. This difference was statistically significant between grade 0 and grade 1 (Tukey's significant difference test, $P < 0.0001$), between grade 0 and grade 2 (Tukey's significant difference test, $P = 0.0005$), and between grade 0 and grade 3 (Tukey's significant difference test, $P < 0.0001$), but there were no significant differences among grades of invasion other than grade 0. The size of the fibrotic focus within the lesion tended to increase in tumors with a more advanced grade of invasion. Although this difference was only marginally significant between grade 2 and grade 3 (Tukey's significant difference test, $P = 0.056$), it was significant between grade 0 and grade 1 (Tukey's significant difference test, $P = 0.0009$) and between grade 1 and grade 2 (Tukey's significant difference test, $P = 0.0009$). Pleural involvement was only seen in tumors with grade 3 invasion, whereas no pleural involvement was seen in tumors with grade 0, grade 1, or grade 2 invasion. Vascular/lymphatic permeation was seen for one lesion (3%) of grade 1, one (2%) of grade 2, and 144 (68%) of grade 3, but not for grade 0. Lymph node involvement was seen for 57 tumors (27%) with grade 3 invasion: 24 in N1 stations, 32 in N2 stations, and one in N3 stations. However, there was no lymph node involvement for tu-

mors with grade 0, grade 1, or grade 2 invasion. The pathologic stage was IA in all of the lesions in grade 0, grade 1, and grade 2. On the other hand, there were 144 lesions (68%) of stage IA in grade 3. The relationship between the grade of invasion and the histologic subtype as adenocarcinoma defined by the WHO classification is shown in Table 4. All of the acinar, papillary, and solid adenocarcinomas had grade 3 invasion. On the other hand, adenocarcinomas with mixed subtypes ($n = 257$) had various grades of invasion: 37 lesions (14%) with grade 1 invasion, 46 (18%) with grade 2 invasion, and 174 (68%) with grade 3 invasion.

TABLE 4. Relationship Between Grade of Invasion and WHO Classification

Grade	WHO Classification (n = 380)				
	BAC	Acinar	Papillary	Solid	Mixed Subtypes
0	85	0	0	0	0
1	0	0	0	0	37
2	0	0	0	0	46
3	0	4	7	27	174
Total	85	4	7	27	257

WHO, World Health Organization; BAC, bronchioloalveolar carcinoma.

Prognosis

The postoperative median follow-up period was 4.5 years. There were no operative deaths. The 3- and 5-year disease-free survival rates of all 380 patients with adenocarcinoma ≤ 2.0 cm in diameter were 82.3% and 76.4%, respectively (Fig. 6). The disease-free survival curves, according to the histologic subtype by the WHO classification, are shown in Figure 7. The 5-year disease-free survival rates were 100% (BAC), 72.4% (mixed subtypes), 55.6% (solid), and 42.9% (papillary), respectively. No significant difference in disease-free survival was found among these histologic subtypes. The disease-free survival curves according to the histologic grade of invasion (grade 0-3) are shown in Figure 8. The 5-year disease-free survival rates were 100%, 100%, 100%, and 59.6% for grade 0, grade 1, grade 2, and grade 3, respectively. Tumors with grade 0, grade 1, or grade 2 invasion all had a very excellent prognosis, which indicated that tumors with grade 1 and grade 2 invasion could be considered minimally invasive lesions.

DISCUSSION

In 1999, the WHO histologic classification of lung and pleural tumors was revised. With regard to adenocarcinoma, BAC is described as a form of adenocarcinoma with a pure bronchioalveolar growth pattern and no evidence of stromal, vascular, or pleural invasion. If there is histologic evidence of invasive growth, it was considered "adenocarcinoma with mixed subtypes." In recent reports, the pattern of recurrence and survival in patients with resected stage I BAC were investigated.^{4,9,24,30} The 5-year disease-free survival rate was reported to be 73% by Volpino et al,³⁰ 74% by Breathnach et al,⁴ and 81% by Rena et al.²⁴ Despite the clear definition of a "non-invasive" morphology for BACs, these reports included BACs

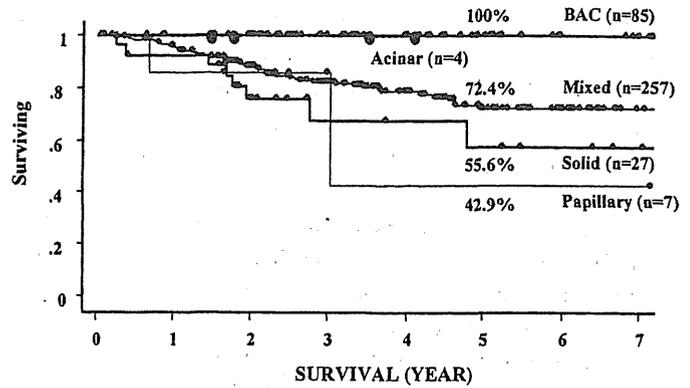


FIGURE 7. Survival curves according to the WHO classification. The 5-year disease-free survival rates are 100% (BAC), 72.4% (mixed subtypes), 55.6% (solid), and 42.9% (papillary), respectively.

with both local and distant recurrence. These results suggested that tumors with postoperative recurrence must have had invasive features and therefore should not be diagnosed as BAC without invasive growth. The difficulties of unequivocally recognizing invasive features by morphology must be addressed.

Several studies have examined the morphologic features related to "tumor development or invasion" in adenocarcinoma.^{10,19-21,25,27,28,31,32} Shimosato et al focused on "scar" formation, which is a characteristic histologic feature in adenocarcinoma of peripheral lung, and demonstrated that the degree of collagenization in the fibrotic focus was closely correlated with tumor growth and prognosis.²⁵ They proposed that tumors with little or no collagenization could be considered to be in an "early stage" of development. Yamashiro et al reported that histologic invasion could be suggested by tumor cells accompanied by a stromal desmoplastic reaction in ad-

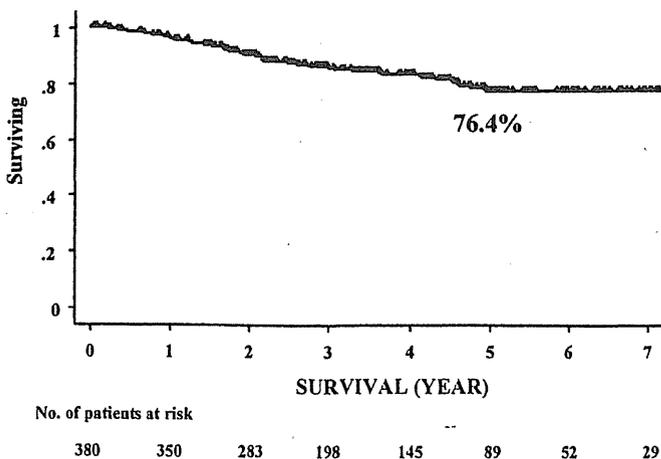


FIGURE 6. Survival curve for all 380 patients with pulmonary adenocarcinoma ≤ 2.0 cm in diameter. The 3- and 5-year disease-free survival rates are 82.3% and 76.4%, respectively.

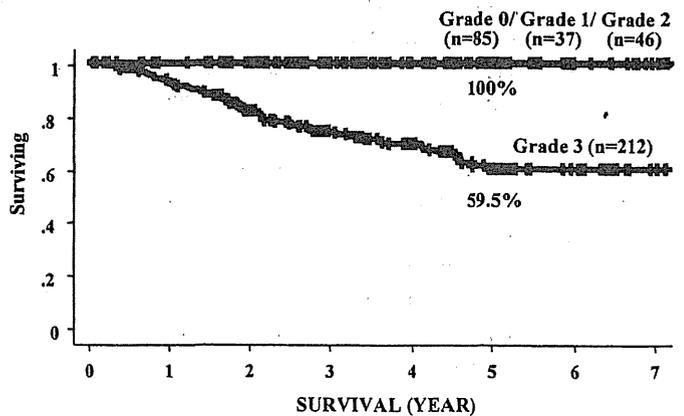


FIGURE 8. Survival curves according to histologic grade of invasion (grade 0-3). The 5-year disease-free survival rates are 100% (grade 0), 100% (grade 1), 100% (grade 2), and 59.6% (grade 3), respectively.

enocarcinoma, and a greater proportion of invasion to the fibrotic focus was correlated with a worse prognosis.³¹ Noguchi et al suggested that active fibroblast proliferation in adenocarcinoma was related to the invasive growth of tumors.²¹ They thought that localized bronchioloalveolar carcinomas without active fibroblastic proliferation could be considered in situ adenocarcinomas with an excellent prognosis (5-year survival rate, 100%). Eto et al analyzed the change in the stromal elastic framework in adenocarcinoma and concluded that the elastic framework was preserved in the early development of the tumor but was disrupted as the tumor grew, indicating stromal invasion.¹⁰ Suzuki et al reported that adenocarcinomas with a fibrotic focus of ≤ 5 mm in size had an excellent prognosis (5-year survival rate, 100%), and the size of the fibrotic focus within the tumor was shown to be a significant prognostic factor.²⁷ In the present study, among 91 patients of adenocarcinoma with fibrotic focus ≤ 5 mm in size, there were 3 (3.3%) patients with recurrence. Terasaki et al measured the size of invasive foci, which were considered by fibroblastic proliferation and architectural distortion of tumor cells, and adenocarcinoma with invasive foci of ≤ 5 mm in size showed low prevalence of vascular, lymphatic, and pleural involvement.²⁸ Indeed, these histologic features were likely to be closely related to the tumor invasion and development. However, practically, a diagnosis of “invasion” often relies on the discretion of the pathologist because the definition of morphologic “invasion” is equivocal.

In the present study, histologic “invasion” was considered cellular arrangement in acinic/papillotubular structures or solid nests in a fibroblastic stroma accompanied by collagenization, as in the 1999 WHO classification. In addition, the structural deformity of the stromal elastic fiber framework was also evaluated. By highlighting the elastic fiber framework using elastic stain, we were able to more precisely analyze the morphologic details. Indeed, vascular/pleural involvement could not be demonstrated in any of the 85 patients without disruption of the stromal framework. As a result, a histologic diagnosis of BAC could be established precisely, and no postoperative recurrence was observed in these patients.

According to our definitions for the grade of invasion in adenocarcinoma, tumors with grade 1 or grade 2 invasion had neither lymph node metastasis nor postoperative recurrence, even though lymphatic permeation was seen in one case each in grades 1 and 2. The prognosis of tumors with grade 1 or grade 2 invasion, like that of BAC, was excellent. Therefore, despite stromal invasion, adenocarcinomas with grade 1 or grade 2 invasion should be considered “minimally invasive lesion” with the same prognosis as BAC.

In summary, the prognosis of BACs was excellent and the 5-year disease-free survival rate was 100%. In addition, adenocarcinomas with grade 1 or grade 2 invasion, ie, “stromal

invasion in the area of bronchioloalveolar growth” and “stromal invasion localized on the periphery of a fibrotic focus,” also had an excellent prognosis. Adenocarcinomas with grade 1 or grade 2 invasion can be considered “minimally invasive adenocarcinomas” or “early adenocarcinomas.”

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