Selective Use of Staging Laparoscopy Based on Carbohydrate Antigen 19-9 Level and Tumor Size in Patients With Radiographically Defined Potentially or Borderline Resectable Pancreatic Cancer

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Objective: The aims of this study were to verify whether the selective use of staging laparoscopy can prevent unnecessary laparotomy and to find a surrogate marker for surgical unresectability in patients with potentially or borderline resectable pancreatic cancer.

Methods: Group A consisted of consecutive 33 patients evaluated between 2005 and 2006 and who directly underwent open laparotomy for planned surgical resection. Group B consisted of consecutive 61 patients evaluated between 2007 and 2009 and of whom 16 patients (26%) had a staging laparoscopy due to the presence of high-risk markers of unresectability defined as carbohydrate antigen 19-9 level 150 U/mL or greater and tumor size 30 mm or greater.

Results: The frequency of unnecessary laparotomies for occult distant organ metastasis was significantly different between groups A and B (18% and 3%, respectively; $P = 0.021$). Of 16 patients who underwent staging laparoscopy in group B, 5 patients (31%) had occult metastases. The multivariate analysis showed that the presence of high-risk markers and extrapancreatic plexus invasion on multidetector-row computed tomography were significant independent risk factors for unresectability.

Conclusions: The presence of high-risk markers was associated with surgical unresectability in patients with potentially or borderline resectable pancreatic cancer. The selective use of staging laparoscopy decreased the frequency of unnecessary laparotomy by detecting minute metastases.

Key Words: staging laparoscopy, CA-19-9, tumor size, pancreatic cancer, occult distant metastasis

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Pancreatic cancer is a lethal disease with poor prognosis, even in patients who have undergone resection with curative intent. The results of surgical therapy alone for ductal pancreatic adenocarcinoma are disappointing, and the 5-year survival rate is only about 10% even after curative resection.[1–4] Recently, favorable results of preoperative chemoradiation followed by surgical resection have been reported by some authors.[5–7] However, these institutions reported that approximately 20% of patients did not undergo surgery because of the detection of distant metastases or local progression during the perichemoradiation period. At the time of pancreatic cancer diagnosis, only 15% to 20% of patients have a potentially resectable disease without evidence of a major vessel involvement or extrapancreatic spread of the tumor.[8,9] Despite the advances and resolution improvement of imaging technologies,[10] noninvasive staging modalities are still limited in their ability to identify accurately metastatic disease of small volume. Even multidetector-row computed tomography (MDCT) cannot accurately detect liver and peritoneal metastases less than 10 mm in diameter or provide qualitative diagnosis of small amounts of ascites, resulting in unnecessary laparotomy and inappropriate patient selection for therapy.

Staging laparoscopy is a minimally invasive procedure that can identify occult distant metastases, resulting in appropriate patient selection for preoperative chemotherapy or chemoradiation therapy and preventing unnecessary laparotomies. Stefanidis et al[11] stated in their review that staging laparoscopy was clearly beneficial in some patients with pancreatic cancer and that the selective use of staging laparoscopy might be appropriate. It has been reported that tumor size more than 3 cm in diameter on preoperative imaging[12] or level of the tumor marker, carbohydrate antigen 19-9 (CA-19-9) greater than 150 U/mL,[13] was the predictive factor for unresectability in patients with pancreatic cancer.

Consequently, we have defined a high risk of unresectability as a combination of CA-19-9 level of 150 U/mL or greater and tumor size of 30 mm or greater in patients radiographically predicted to have potentially or borderline resectable pancreatic cancer based on MDCT. Using this classification system, we introduced a selective staging laparoscopy starting in 2007. In the current study, we prospectively assessed the role of selective use of staging laparoscopy and retrospectively compared clinical data on unresectability before and after our introduction of staging laparoscopy. The other aim of this study was to evaluate the reliability of a surrogate marker for surgical unresectability in patients with pancreatic cancer radiographically defined as potentially or borderline resectable.

MATERIALS AND METHODS

The study included 94 consecutive patients with pathologically invasive adenocarcinoma of the pancreas who were evaluated between January 2005 and July 2009 at Kansai Medical University Hospital, Osaka, Japan (Table 1). Patients with an endocrine tumor of the pancreas, intraductal papillary mucinous cancer, acinar cell cancer, or anaplastic cancer were excluded. In short, all patients with a clinical diagnosis of pancreatic cancer using ultrasonography, contrast-enhanced computed tomography (CT), magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography, cytological examination

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TABLE 1. Patient Characteristics and Operative Factors in Groups A and B

	Group A (n = 33)	Group B (n = 61)	*P*
Age, y	69 (50–85)	65 (36–82)	0.23
Sex (male-female)	14 (42):19 (58)	23 (38):38 (62)	0.66
CA-19-9 (U/mL)	72 (1–7729)	146 (1–15380)	0.38
CA-19-9 (≥38 vs <38 U/mL)	23 (70):10 (30)	47 (77):14 (23)	0.46
CA-19-9 (≥150 vs <150 U/mL)	12 (36):21 (64)	29 (48):32 (52)	0.38
Diabetes mellitus (+:−)	21 (64):12 (36)	40 (66):21 (34)	1.00
Obstructive jaundice (+:−)	24 (73):9 (27)	38 (62):23 (38)	0.37
Preoperative blood tests			
Total bilirubin, mg/dL	0.8 (0.4–4.7)	0.7 (0.2–5.4)	0.09
Albumin, g/dL	3.7 (2.3–4.3)	3.8 (1.9–4.5)	0.64
Tumor characteristics			
Pancreatic head–body-tail	24 (73):9 (27)	29 (8–70)	0.64
Tumor size (≥30 vs <30 mm)	20 (61):13 (39)	29 (48):32 (52)	0.28
Risk classification (tumor size ≥30 mm and CA-19-9 ≥150 U/mL)			
High risk vs low risk	11 (33):22 (67)	17 (28):44 (72)	0.64
Tumor staging on MDCT			
PV +:−	14 (42):19 (58)	22 (36):39 (64)	0.66
A +:−	5 (15):28 (85)	11 (18):50 (82)	0.78
PL +:−	11 (33):22 (67)	13 (21):48 (79)	0.22
T 1–3 vs 4	16 (48):17 (52)	34 (56):27 (44)	0.52
PR-borderline (defined by NCCN)	16 (48):17 (52)	31 (49):30 (51)	1.00
Operative factors	n = 26	n = 54	
Type of surgery (PD/TP/DP)	19 (73):0 (0):7 (27)	36 (66):2 (4):16 (30)	0.57
PV resection (+:−)	7 (27):19 (73)	19 (35):35 (65)	0.61
CA resection (+:−)	1 (4):25 (96)	1 (2):53 (98)	0.55
Operative duration, min	523 (281–795)	514 (181–711)	0.3619
Extent of blood loss, mL	1045 (200–6420)	983 (258–5238)	0.6703
Transfusion (auto/allo/none)	21 (81):4 (15):1 (4)	32 (59):13 (24):9 (17)	0.17
Residual tumor grading (R0/1:R2)	25 (96):1 (4)	52 (96):2 (4)	1.00

Data are expressed as the median (range) or n (%).

The vascular involvement (A/PV) was defined as greater than 50% contiguity of tumor to the common hepatic, superior mesenteric, and celiac arteries, or portal and superior mesenteric veins. The extrapancreatic plexus invasion (PL) was defined as disappearance of the fat layer between the pancreas and the celiac and superior mesenteric arteries.

PR indicates potentially resectable; borderline, borderline resectable; NCCN, National Comprehensive Cancer Network criteria defining resectability status; PD, pancreaticoduodenectomy; TP, total pancreatectomy; DP, distal pancreatectomy; PV, portal vein; CA, celiac axis; auto, autologous blood transfusion; allo, allogeneic blood transfusion.

of the bile juice, and/or biopsy of the bile duct mucosa were referred to our center for the standard staging imaging according to the same protocol. It was focused on (1) the detection of distant organ metastasis and (2) identifying the tumor's vascular involvement. It consisted of cine MDCT imaging, using the Aquilion CT system (Toshiba Medical Systems, Tochigi, Japan). Arterial- and portal-phase images were collected using a 1.0-mm × 64-detector configuration. After reconstruction of the raw scans, data from serial 1.0-mm-thick slices with a 0.5-mm interval were transferred to a workstation (AquariusNet Viewer; TeraRecon Inc, San Mateo, Calif).[10] After creating 2- and 3-dimensional coronal and sagittal anatomical reconstructions, the cine images were evaluated by an experienced hepatopancreatobiliary surgeon and a consultant radiologist.

In this study, potentially or borderline resectable pancreatic cancer was defined as no distant organ metastasis detected in the abdomen and thorax, no vascular involvement of a major peripancreatic artery (defined as tumor ingrowth with <50% vessel contiguity in the celiac trunk, common or proper hepatic artery, or superior mesenteric artery), and no localized obstruction of the portal vein or the superior mesenteric vein and without cavernous transformation of the porta hepatis. Patients with cancer of the pancreatic body and tail, with celiac trunk invasion, and without superior mesenteric artery invasion were also classified as potential candidates for resection with curative intent. Since 2005, we have followed a policy of not to proceed with surgery that would leave a macroscopic residual tumor (R2 resection). The positron emission tomography scanning was used for patients with suspected metastatic disease at lung, cervical, and para-aortic lymph nodes by MDCT. All patients with a suspected distant organ metastasis diagnosed by positron emission tomography scanning were excluded after confirmation of adenocarcinoma in the biopsy specimens from locations such as the liver, lung, cervical lymph nodes, and bone.

Entire population of 94 patients who were classified as having potentially or borderline resectable pancreatic cancer based on MDCT was divided into 2 groups. Group A consisted of 33 patients treated between 2005 and 2006, and all these patients directly underwent open laparotomy for planned surgical resection (Table 1). Group B consisted of 61 patients treated

between 2007 and 2009, who were selectively considered for a staging laparoscopy if the level of CA-19-9 is 150 U/mL or greater and tumor size is 30 mm or greater. Seventeen patients within group B met these criteria, and the staging laparoscopy was performed in 16 of them (1 patient refused the procedure).

The level of CA-19-9 could be influenced by the total bilirubin level.[14] In principle, a preoperative blood sample for measuring the CA-19-9 level was to be taken at several times in patients with obstructive jaundice who underwent biliary drainage. Especially in patients with CA-19-9 level of 150 U/mL or greater upon hospital admission, the CA-19-9 level was repeatedly measured until the total bilirubin level was less than 3.0 mg/dL. In 4 of the 94 patients in this study, total bilirubin levels were greater than 3 mg/dL during the preoperative period. Three of these 4 patients had CA-19-9 levels pf less than 150 U/mL, and the remaining patient had a CA-19-9 level of 7729 U/mL at a total bilirubin level of 4.1 mg/dL. Because the tumor diameter in this patient was less than 30 mm, he was not classified as being at high risk for unresectability. Therefore, the CA-19-9 level in all patients with the high-risk marker for unresectability was evaluated at a total bilirubin level of less than 3.0 mg/dL.

Informed consent was obtained from each patient included in the study, in accordance with the provisions of the Declaration of Helsinki. Patient data were obtained from the prospective database of pancreatic disease at Kansai Medical University Hospital.

Staging Laparoscopy

After establishing the capnoperitoneum through a 12-mm trocar inserted at the umbilical area, a flexible laparoscope was inserted, and 2 additional 5-mm ports were placed. First, inspection focused on the presence or absence of nodules on the parietal peritoneum, and the liver surface was carefully performed. Second, a cytological examination was performed if any ascites was present. When there was no ascitic fluid, the peritoneal cavity was washed with 100 mL of physiological saline solution. After placing the patient in Trendelenburg position, the presence or absence of nodules in the Douglas cavity was checked by inserting the laparoscope through filled water into the Douglas cavity. Subsequently, cytological washings from the Douglas cavity were obtained for pathological examination. Third, the entire mesentery was examined by grasping the small intestine from the first jejunal loop to the ileocecal junction to locate the minute peritoneal nodules. Finally, laparoscopic ultrasonography was performed searching for deep hepatic nodules that could be missed by visual inspection and to diagnose the presence or absence of tumor vascular invasion in patients at high risk of surgical unresectability. Biopsies were taken from any regions suspected of containing metastatic nodules. Neither the lesser nor greater sac was opened in this study.

Statistical Analysis

Data are expressed as median values and ranges. Categorical variables were compared by Mann-Whitney U test, χ^2 test, or Fisher exact test, as appropriate. The significant factors identified by univariate analysis were further examined by multivariate analysis using logistic regression analysis to determine independent significant risk factors for surgical unresectability. $P < 0.05$ was considered to be statistically significant. Data analysis was performed using StatView software, version 5.0 for Windows (SAS Inc, Cary, NC).

RESULTS

Establishment of High-Risk Classification of Unresectability in Patients With Potentially or Borderline Resectable Pancreatic Cancer

To predict the likelihood of surgical unresectability, we retrospectively examined the statistical association of the categories of CA-19-9 level, tumor size, and risk classification (high risk: CA-19-9 level ≥150 U/mL and tumor size ≥30 mm) with actual surgical unresectability in group A (Table 2). The high-risk classification was found to have a significant association with surgical unresectability and the highest rate of predictive accuracy. Therefore, the high-risk classification was established using the parameters of CA-19-9 level of 150 U/mL or greater and tumor size of 30 mm or greater, and 17 patients in group B met these criteria. The association between preoperative parameters and surgical unresectability in group B was examined in Table 2. The univariate analysis showed that large tumor size and the high-risk classification were each independent risk factors for surgical unresectability. The category of risk classification showed the highest rate of predictive accuracy. More patients with potentially or borderline resectable disease were subjected to an unnecessary intervention when using a category of CA-19-9 or tumor size.

TABLE 2. Association of CA-19-9 Level and/or Tumor Size With Surgical Unresectability in Groups A and B

	Sensitivity	Specificity	Accuracy	PPV	NPV
Group A					
CA-19-9 ≥150 U/L (n = 12)	71	73	73	42	90
Tumor size ≥30 mm (n = 20)	86	46	55	30	92
Risk classification* (n = 11)	71	77	76	45	91
Group B					
CA-19-9 ≥150 U/L (n = 29)	71	56	57	17	94
Tumor size ≥30 mm† (n = 29)	100	59	52	24	100
Risk classification‡ (n = 17)	71	78	77	29	95

Risk classification indicates high risk of unresectability based on CA-19-9 level of 150 U/L or greater and tumor size of 30 mm or greater. Values are percentages.

*$P = 0.0274$.

†$P = 0.0036$.

‡$P = 0.0147$.

PPV indicates positive predictive value; NPV, negative predictive value.

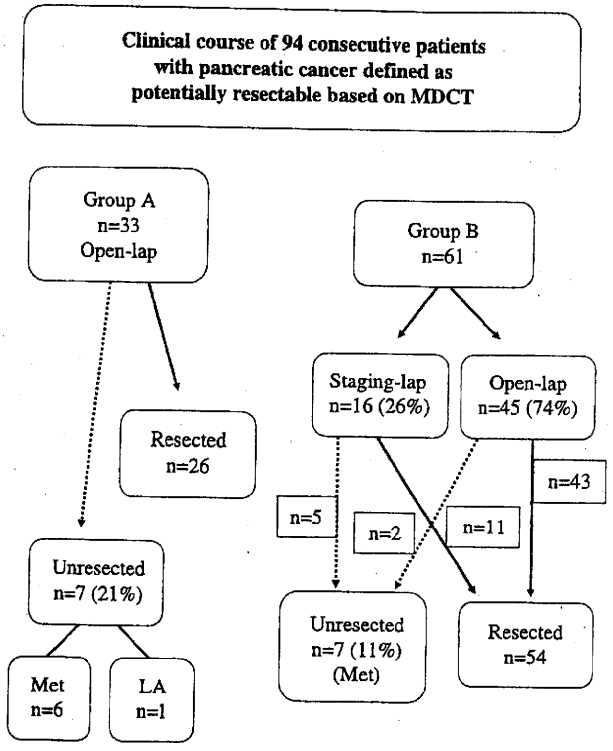

FIGURE 1. Clinical course of 94 consecutive patients with pancreatic cancer defined as potentially or borderline resectable based on MDCT. LA, locally advanced disease; Met, distant metastasis; Open-lap, open laparotomy; Staging-lap, staging laparoscopy.

Comparison of Surgical Unresectability Upon Laparotomy in Groups A and B

Figure 1 illustrates the clinical course of the 94 consecutive patients with potentially or borderline resectable pancreatic cancer. In group A, the 26 patients of the 33 underwent surgical resection, and 7 patients were found during laparotomy as having an unresectable disease (6 with distant metastasis and 1 with locally advanced disease). In group B, the 16 of the 61 patients (26%) fulfilled the criteria (CA-19-9 level ≥150 U/mL and tumor size ≥30 mm) to perform the staging laparoscopy prior to open surgery. Of these 16 patients, 5 patients were found to have a distant metastasis, and 11 patients underwent surgical resection. On the other hand, only 2 patients from the 45 patients in group B who directly underwent open laparotomy had distant metastasis that precluded surgical resection. The surgical unresectability was found in 7 of 33 patients in group A and 7 of 61 patients in group B, with no significant difference found. The unnecessary laparotomy versus B was performed in 7 of 33 patients in group A and 2 of 61 patients in group B, which represented a statistically significant difference ($P < 0.05$). Moreover, when the reason for unresectability was limited to patients with distant organ metastasis, unnecessary laparotomy was performed in 6 of 33 patients in group A and 2 of 61 patients in group B, which also represented a statistically significant difference ($P < 0.05$). Of the 16 patients in group B who underwent staging laparoscopy, 11 patients required resection, so this could be viewed as having undergone unnecessary staging laparoscopy.

Among 14 patients with unresectable tumors in this study (Table 3), 9 patients had liver or peritoneal metastasis less than 5 mm in diameter, and 10 patients had multiple metastasis. None of the patients in this study had a lesion in the small pelvis, single peritoneal metastasis, or nodules located deep in the liver parenchyma. During the follow-up period, potential recurrence in distant organs in resected patients (n = 80) was monitored postoperatively for 3 months, with liver metastases detected in 4 patients in group A and 3 patients in group B.

There was no significant difference in clinical background between groups A and B, as shown in Table 1. The proportion of patients with CA-19-9 level greater than the reference value (38 U/mL) was 23 of 33 patients in group A and 47 of 61 patients in group B. The proportion of patients with CA-19-9 level of 150 U/mL or greater, which was one of the risk factors for

TABLE 3. Clinical Background and Course of Patients Who Had Unresectable Pancreatic Cancer Detected Upon Open Laparotomy or Staging Laparoscopy

Group	Patient No.	Tumor Location	Tumor Size, mm	CA-19-9, U/mL	Procedure	Location of Distant Metastasis	No./Size of Distant Metastasis	Hospital Stay, d	Days Until Chemotherapy
A	1	Ph	40	1768	Open	Liver	Sol/15 mm	5	13
A	2	Ph	35	3355	Open	Peritoneum	Multi/3 mm	5	22
A	3	Ph	15	102	Open	Peritoneum	Multi/3 mm	8	27
A	4	Pbt	30	216	Open	Liver	Multi/3 mm	19	Not done
A	5	Ph	48	676	Open	Peritoneum	Multi/3 mm	16	Not done
A	6	Ph	35	33	Open	Liver	Multi/8 mm	11	22
A	7	Pbt	41	861	Open	Local	—	19	Not done
B	1	Ph	32	81	Open	Liver	Multi/3 mm	9	15
B	2	Pbt	36	83	Open	Peritoneum	Multi/3 mm	6	8
B	3	Pbt	42	525	Stag-lap	Ascites	—	4	8
B	4	Ph	35	15380	Stag-lap	Liver	Sol/8 mm	6	27
B	5	Ph	40	275	Stag-lap	Peritoneum	Multi/3 mm	4	9
B	6	Ph	31	347	Stag-lap	Liver	Multi/5 mm	4	12
B	7	Ph	70	5768	Stag-lap	Peritoneum	Multi/2 mm	2	6

Pt indicates patient; Ph, pancreatic head; Pbt, pancreatic body and/or tail; Open, open laparotomy; Stag-lap, staging laparoscopy; Multi, multiple metastases (>2 lesions); Sol, solitary metastasis.

surgical unresectability, was 12 of 33 patients in group A and 29 of 61 patients in group B. Moreover, the frequency of tumor size of 30 mm or greater in diameter, another risk factor for surgical unresectability, was 20 of 33 patients in group A and 29 of 61 patients in group B. Together, 11 of 33 patients in group A and 17 of 61 patients in group B fulfilled the high-risk classification. There were no significant differences in the above parameters between groups A and B.

In the preoperative staging of tumor extension based on MDCT, there were no significant differences in the grading of adjacent organ invasion between groups A and B, as shown in Table 1. When patients were classified into potentially or borderline resectable status, as defined by the National Comprehensive Cancer Network,[15] there was no significant between-group difference. Moreover, no significant differences in operative parameters and residual tumor grading were found between the groups. Significant difference was not found in the frequency of R2 resection between them.

Multivariate Analysis of Preoperative Parameters for Surgical Unresectability

The preoperative parameters (ie, patient characteristics, tumor features, and radiological findings, as shown in Table 1) were analyzed by logistic regression to determine the risk factors for surgical unresectability. Univariate analysis showed that the high-risk classification based on CA-19-9 and tumor size, vascular involvement of the portal vein, and extrapancreatic plexus invasion shown on MDCT were covariates that were significantly associated with surgical unresectability. The risk factors used for multivariate analysis were selected based on the results of univariate analyses (Table 4). The high-risk classification and extrapancreatic plexus invasion on MDCT were found to be statistically significant independent risk factors for surgical unresectability.

Morbidity and Mortality After Staging Laparoscopy

Of the 16 patients who underwent staging laparoscopy, 6 patients had a history of previous surgeries, which consisted of 4 pelvic surgeries and 3 upper gastrointestinal surgeries. Two patients underwent conversion to open surgery because of the previous upper gastrointestinal surgery and need for further pathological exploration of the pancreatic cancer. The median duration of staging laparoscopy was 67 minutes (range, 20–159 minutes). There was no postoperative morbidity, mortality, or port-site tumor recurrence in this study.

Between-Group Comparisons of Duration of Hospital Stay and Time Until Initiating Chemotherapy After Surgical or Laparoscopic Staging in Unresected Patients

As shown in Table 3, 7 of 16 patients in group A were found to have unresectable disease upon open laparotomy (6 patients with metastatic disease and 1 with locally advanced disease). In group B, of the 7 patients with metastatic disease, 5 patients were diagnosed with unresectable disease during the staging laparoscopy, and 2 patients had incidental distant organ metastasis detected upon open laparotomy. The duration of postoperative hospital stay in unresected patients in group B (median, 4 days; range, 2–9 days) was significantly shorter than that in group A (11 days, 5–19 days; $P < 0.05$). Across both groups, the duration of hospital stay in the 5 unresected patients who underwent staging laparoscopy (4 days, 2–6 days) was significantly shorter than that in the 9 unresected patients who underwent open laparotomy (9 days, 5–19 days; $P < 0.05$). The length of time until initiating chemotherapy after surgical or laparoscopic staging was also compared in both groups. Three unresected patients in group A did not undergo chemotherapy because of poor performance status or patient expectations. Compared with the time until initiating chemotherapy in the 4 remaining patients in group A (median, 22 days; range, 13–27 days), the length of time in the 7 unresected patients in group B (9 days, 6–27 days) tended to be shorter, but the difference was not statistically significant. Across both groups, the time until initiating chemotherapy in the 5 patients who underwent staging laparoscopy (9 days, 6–27 days) was also nonsignificantly shorter relative to that in the 6 patients who underwent open laparotomy (19 days, 8–27 days).

TABLE 4. Logistic Regression Analysis of Preoperative Risk Factors for Unresectability

Category	Risk Factors	*P*	Relative Risk	95% CI
Risk classification	Low		1	
	High	0.0115	6.736	1.535–29.569
PL on MDCT	Negative		1	
	Positive	0.0343	4.332	1.114–16.839
PV on MDCT	Negative		1	
	Positive	0.6315	1.456	0.313–6.766

This table summarizes the most significant risk factors in each category identified by multivariate analysis. The risk factors used for multivariate analysis were selected based on the results of univariate analyses. Risk classification indicates high risk of unresectability (tumor size ≥30 mm and CA-19-9 level ≥150 U/L) or low risk of unresectability. The vascular involvement of the PV was defined as greater than 50% contiguity of tumor to vessel. The extrapancreatic PL was defined as disappearance of the fat layer between the pancreas and the celiac and superior mesenteric arteries.

CI indicates confidence interval; PV, portal vein; PL, plexus invasion.

DISCUSSION

It is widely accepted that surgical resection, that is, the only potentially curative treatment of pancreatic cancer, should be offered only to patients with prospect for curative radical resection.[16,17] Recent reports indicate that approximately one third of patients diagnosed with resectable pancreatic tumors upon CT were subsequently found to have unresectable tumors upon surgery.[18–20] Accurate staging to select patients who may benefit from resection is of paramount importance.

Preoperative radiographic modalities have advanced in recent years. Since 2002, we have introduced the routine use of cine-imaging MDCT for staging of tumor extension in patients with pancreatic cancer. It provides increased imaging speed, allowing greater contrast bolus injection and correspondingly minimal volume resolution. Multidetector-row computed tomography cine images with thin collimation in the axial, coronal, and sagittal phases can provide detailed information in regions around major peripancreatic vessels.[10] Other investigators have reported that the sensitivity and specificity of diagnosing vascular involvement are 80% to 100% with MDCT.[21,22] Starting in 2005, we no longer allowed noncurative surgical resection in patients with pancreatic cancer, because cine-imaging MDCT enabled the accurate diagnosis of vascular invasion of pancreatic cancer.[10] In this study, the frequency of R2 resection was 3%, and pancreatectomy with portal vein

or celiac trunk resection was performed in 29% of patients in whom resection had been predicted to generate surgical- or pathological-free margins. During the duration of this study, the surgical indication was fixed, and 2 experienced surgeons supervised all resections.

Still, it is difficult to reliably detect small liver and peritoneal metastases up to 10 mm in diameter. For this reason, many surgeons advocate to perform routinely preoperative staging laparoscopy to avoid unnecessary laparotomy that could be present in 15% to 51% of patients according to Stefanidis et al.[9,11,18–20] The main controversy today, however, is whether laparoscopic staging should be used routinely or selectively in patients with pancreatic cancer defined as resectable based on preoperative imaging. Several authors proposed a selective use of staging laparoscopy due to the declining yield of staging laparoscopy associated with quality of preoperative imaging.[9,23–25] Finally, performing staging laparoscopy for all patients is difficult because of limits in available operating room access, logistics, and high costs. Morganti et al[12] found that patients with tumor size greater than 3 cm measured on preoperative imaging had significantly more unsuspected metastases upon surgical exploration compared with those with tumors less than 3 cm. Schlieman et al[13] calculated that a CA-19-9 level of greater than 150 U/mL had a positive predictive value of 88% in identifying unresectability in patients believed to be resectable according to preoperative imaging and concluded that this subgroup might benefit the most from staging laparoscopy. These data were supported by Connor et al,[26] who studied 159 patients with resectable pancreatic cancer defined by CT who had undergone staging laparoscopy. They found that a preoperative CA-19-9 level 150 U/L or less had a positive predictive value of 95% in predicting resectability at laparoscopic assessment.

Based on the available evidence, what is the most reliable surrogate marker to use for selecting patients for staging laparoscopy to predict surgical unresectability in patients with radiographically defined potentially or borderline resectable pancreatic cancer.? The primary purpose of our study was to verify the value of selective use of staging laparoscopy to prevent unnecessary laparotomy. We compared the frequency of unnecessary laparotomy in patients who underwent MDCT alone versus MDCT in combination with preoperative laparoscopy in patients suspected to have unresectable disease based on tumor size and CA-19-9 levels.

In this study, there was no significant difference in the surgical unresectability rate between group A (used as a historical control; 21%) and group B (11%). However, the 3% rate of unnecessary laparotomy for occult distant organ metastasis in group B patients, who underwent staging laparoscopy because of their high-risk classification, was significantly lower than that in group A (18%; $P = 0.0207$). Thus, the introduction of staging laparoscopy in the patients classified as high risk was useful for appropriate patient selection and minimizing unnecessary laparotomy.

Although we carefully examined the surface of the mesentery of the small and large intestines during staging laparoscopy, there was no evidence of solitary peritoneal metastasis or of peritoneal metastasis localized in the Douglas cavity. Therefore, examination of the mesentery may not be necessary in patients with potentially or borderline resectable pancreatic cancer. However, it seems that staging laparoscopy might not detect deep liver metastasis of minute size in the liver parenchyma. Although we have introduced intraoperative ultrasonography for staging laparoscopy, it is still difficult to diagnose minute hypoechoic nodules in the liver parenchyma and to provide pathological diagnosis of these lesions. We carefully followed up the study patients postoperatively to detect any new occurrence of liver metastasis. Within 3 months postoperatively, liver metastases were found in 4 of the resected patients (15%) in group A and in 3 resected patients (6%) in group B. Unfortunately, these patients might have had occult and minute liver metastasis in the liver parenchyma at the time of open laparotomy, or their pancreatic cancer could have exhibited highly metastatic potential.

The high-risk classification of CA-19-9 level of 150 U/L or greater and tumor size of 30 mm or greater proved to be one of the significant independent risk factors for surgical unresectability in the study population. Some authors have stressed the need to carefully interpret CA-19-9 levels in patients with obstructive jaundice.[14,27] To prevent an artificial increase of CA-19-9 influenced by high levels of total bilirubin, we measured CA-19-9 when total bilirubin was less than 3 mg/dL, after biliary drainage, in 96% of all patients. Although there is no clear evidence for setting this threshold of 3.0 mg/dL, this level of bilirubin did not affect the patient classification of high risk in this study.

The beneficial aspects of staging laparoscopy have been reported to include faster recovery and earlier administration of chemotherapy agents.[11] In this study, the postoperative hospital stay in patients with distant organ metastasis diagnosed by staging laparoscopy was significantly shorter than in those diagnosed by open laparotomy ($P < 0.05$). Two patients underwent conversion to open laparotomy with small incisions due to previous surgery and need for further pathological exploration.

In conclusion, in patients with pancreatic cancer radiographically defined as potentially or borderline resectable, the selective use of staging laparoscopy detected minute metastasis and thereby decreased by 15% the frequency of unnecessary laparotomy. The significant risk factors for surgical unresectability included the presence of extrapancreatic plexus invasion upon MDCT and the high-risk classification consisting of tumor size of 30 mm or greater and CA-19-9 level of 150 U/L or greater (measured at a level of total bilirubin <3 mg/dL). The use of this risk classification to select patients for staging laparoscopy can be useful to avoid unnecessary laparotomy.

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Effect of Aging on Risk for Hepatocellular Carcinoma in Chronic Hepatitis C Virus Infection

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An increase in the aging population is an impending problem. A large cohort study was carried out to determine the influence of aging and other factors on hepatocarcinogenesis in patients treated with interferon. Biopsy-proven 2547 chronic hepatitis C patients registered at our referral center since 1992 were included. Of these, 2166 were treated with interferon-based therapy. Incidences of hepatocellular carcinoma (HCC) associated with interferon were analyzed by Kaplan-Meier and person-years methods for an average follow-up of 7.5 years. Factors associated with HCC risk were determined by Cox proportional hazard analysis. HCC developed in 177 interferon-treated patients. The risk for HCC depended on age at primary biopsy and increased more than 15-fold after 65 years of age. Even when stratified by stage of fibrosis, the cumulative and annual incidences of HCC were significantly higher in older patients than in younger patients ($P < 0.001$) at the same stage of fibrosis, except for cirrhosis. Progression of fibrosis over time was significantly accelerated in older patients. The impact of viral eradication on HCC prevention was less significant in older patients than in younger patients. Multivariate analysis confirmed that age, gender, liver fibrosis, liver steatosis, total cholesterol level, fasting blood sugar level, baseline and postinterferon alpha-fetoprotein level, and virological response to interferon were independent risk factors associated with HCC. Aging was the strongest risk factor for a nonvirological response to interferon-based antiviral therapy. *Conclusion:* Elderly patients are at a higher risk for HCC. Hepatitis C viral eradication had a smaller effect on hepatocarcinogenesis in older patients. Patients should therefore be identified at an earlier age and treatment should be initiated. (HEPATOLOGY 2010;52:518-527)

Primary liver cancer is the third most common cause of cancer mortality worldwide,[1] and hepatocellular carcinoma (HCC) is one of the most frequent primary liver cancers.[2,3] Infection with hepatitis C virus (HCV) is a common cause of chronic hepatitis, which progresses to HCC in many patients.[4] The prevalence of older patients has been increasing in Japan, and this is an impending problem in other countries where viral spread has occurred more recently.[5] The number of Americans older than 65 years is expected to double by the year 2030.[6] In Western Europe, people older than 65 years already constitute 15%-18% of the population[7]; thus, aging patient who is chronically infected with HCV is

Abbreviations: AFP, alpha-fetoprotein; HBc, hepatitis B core; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; SVR, sustained virological response.

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one of the most important issues confronted by physicians.

Viral eradication with interferon-based therapy for chronic hepatitis C has been shown to prevent HCC by studies conducted in Japan and Italy.[8-11] However, this finding is controversial according to another study conducted in Europe and Canada,[12] in which viral eradication did not significantly reduce the risk for HCC in 479 consecutively treated patients. The likelihood of development of HCC among interferon-treated patients is difficult to determine because of the paucity of adequate long-term cohort studies. Moreover, in patients who are treated with interferon the effect of certain factors, including aging, on the risk for HCC remains unclear. Furthermore, the benefit of viral eradication with interferon-based therapy, including pegylated interferon and ribavirin combination therapy, in older patients remains unknown. To further clarify this, we conducted a large-scale, long-term cohort study and analyzed the influence of aging and other host and virological factors in patients treated with interferon.

Patients and Methods

Patients. Consecutive patients (n = 2547) chronically infected with HCV who underwent liver biopsy between 1992 and January 2008 at our referral center were enrolled. Of these, 2166 patients were treated with interferon-based antiviral therapy, whereas 381 patients did not receive interferon treatment (Fig. 1). All patients had histologically proven chronic hepatitis or cirrhosis. HCV infection was proven in all patients by identification of HCV RNA. Patients with a history of HCC, autoimmune hepatitis, or primary biliary cirrhosis were excluded. We also excluded patients who had a history of excessive alcohol consumption (50 g/day) and confirmed alcohol abstinence during follow-up. No patient was positive for hepatitis B surface antigen or antihuman immunodeficiency virus antibody. Written informed consent was obtained from all patients. The study was approved by the Ethical Committee of Musashino Red Cross Hospital in accordance with the Declaration of Helsinki.

Histological Evaluation. A liver biopsy specimen was obtained laparoscopically using 13G needles. When laparoscopy was impossible, ultrasound-guided liver biopsy was performed with 15G needles (n = 254). The mean length of the specimen was 18 mm (range 12-40 mm), and the mean number of portal tracts was 17 (range 8-34). Liver biopsy specimens

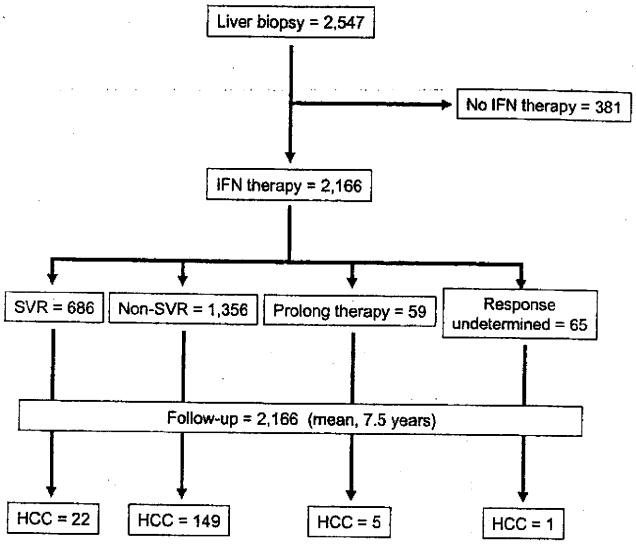

Fig. 1. Clinical outcomes of the patients enrolled in the present study. HCC, hepatocellular carcinoma; SVR, sustained virological response.

were scored by board-certified pathologists for stage of fibrosis and grade of inflammatory activity according to the classification of Desmet et al.[13] Additional macroscopic pathological information was obtained from laparoscopic findings. The percentage of steatosis was quantified by determining the average proportion of hepatocytes affected by steatosis. In this study, superimposed nonalcoholic steatohepatitis (NASH) was defined as a central pattern of colocalization of hepatic steatosis and hepatocyte ballooning with pericellular/perisinusoidal fibrosis or Mallory hyaline.

Interferon Treatment. Among the 2166 patients treated with interferon-based antiviral therapy, 1062 patients received interferon-alpha or beta monotherapy either for 24 weeks (n = 1003) or for 2 to 5 years (n = 59); 386 patients received interferon-alpha and ribavirin combination therapy for 24 weeks; 306 received pegylated interferon-alpha monotherapy for 48 weeks; and 412 received pegylated interferon-alpha and ribavirin combination therapy for 48 weeks. All interferon treatment was initiated within 48 weeks after liver biopsy.

Definitions of Response to Interferon Therapy. A patient negative for serum HCV RNA after the first 6 months of completion of interferon-based therapy was defined as a sustained viral responder. HCV RNA was determined by the qualitative Amplicor or TaqMan HCV assay (Roche Molecular Diagnostics, Tokyo, Japan).

Data Collection and Patient Follow-up. Data on patient characteristics, biochemical data, hematological

data, virological data, histological data, and treatment details were collected at enrollment. Age was determined at primary liver biopsy. Patients were examined for HCC with abdominal ultrasonography, dynamic computed tomography, and/or magnetic resonance imaging every 3-6 months. Serum alpha-fetoprotein (AFP) levels were measured every 1-2 months. This screening program constitutes the standard of care in Japan. To evaluate the effect of interferon-induced AFP reduction on hepatocarcinogenesis, the average AFP level after interferon treatment was calculated in each patient. HCC diagnosis was confirmed with needle biopsy, surgically resected specimens, or typical radiological findings diagnosed by board-certified radiologists. Figure 1 shows the schema for patient follow-up and clinical outcomes.

The start date of follow-up was the date of primary liver biopsy and the endpoint of follow-up was the development of HCC or the latest medical attendance until January 2009. The mean follow-up period was 7.5 years (range 0.5-17 years). The factors associated with development of HCC were retrospectively analyzed.

Change in Fibrosis Staging Over Time. To evaluate change in fibrosis staging over time, 271 patients who had not achieved a sustained virological response (SVR) with interferon therapy underwent a sequential biopsy after the initial biopsy. The interval between the paired biopsies was on average 4.8 years (range 0.7-14 years). The yearly rate of progression of fibrosis was calculated as the change in fibrosis staging divided by the time between paired biopsies.

Statistical Analysis. Categorical data were compared by the chi-square test and Fisher's exact test. Distributions of continuous variables were analyzed with Student's t test or the Mann-Whitney U test for two groups. All tests of significance were two-tailed and a P value of <0.05 was considered statistically significant. The cumulative incidence curve was determined with the Kaplan-Meier method and differences among groups were assessed using the log-rank test. Factors associated with HCC risk and virological response to interferon therapy were determined by the Cox proportional hazard model and logistic regression analysis, respectively. To depict the role of aging in developing risk for HCC, the multivariate Cox proportional hazard model was used after adjusting for stage of liver fibrosis, steatosis, and virological response to interferon. A polynomial regression was used to fit risk ratios for segments of the age distribution. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 11.0 (SPSS, Chicago, IL).

Results

Patient Characteristics. Patient characteristics at the time of enrollment are shown in Table 1. The distribution of stages of liver fibrosis differed between younger and older patients, indicating the need to adjust for stage of liver fibrosis when comparing the two subgroups.

Response to Interferon Therapy. The response to interferon therapy was determined in 2042 (97.2%) of the interferon-treated patients, excluding those who received prolonged interferon treatment at the endpoint. SVR rates are shown in Table 1. The percentage of patients showing SVR was significantly lower in older patients (≥65 years) than in younger patients (<65 years) ($P < 0.001$). Overall response rates to the different types of interferon therapy were as follows: interferon monotherapy, 31.5% (312/992); interferon-alpha and ribavirin combination therapy, 28.6% (108/378); pegylated interferon-alpha monotherapy, 37.9% (108/285); and pegylated interferon-alpha and ribavirin combination therapy, 41.1% (159/387). Response rates in genotype-1 patients (n = 1347) were 20.6% (114/554), 17.9% (29/162), 18.9% (56/297), and 36.8% (123/334), and those in nongenotype-1 patients (n = 565) were 52.2% (163/312), 63.1% (77/122), 65.0% (52/80), and 70.6% (36/51). Overall response rates of interferon and pegylated interferon monotherapy seem to be high because of the high response rates in the nongenotype-1 patients treated with these regimens.

Overall Cumulative Incidence of HCC. During follow-up, HCC developed in 177 interferon-treated patients (Fig. 1). The cumulative incidence of HCC 5, 10, and 15 years after interferon therapy was 4.7%, 11.6%, and 15.5%, respectively. The cumulative incidence in SVR patients was 2.1%, 4.3%, and 4.3%, respectively, which was significantly lower than that in non-SVR patients (5.8%, 14.9%, and 20.2%, respectively; log-rank test, $P < 0.001$).

Effect of Aging on Risk for HCC. The risk ratio determined by multivariate Cox proportional hazards analysis after adjustment for stage of liver fibrosis, degree of liver steatosis, and virological response to interferon demonstrated that the risk for HCC after interferon treatment was age-dependent and increased predominantly when the age at primary liver biopsy was >65 years (Fig. 2A). Hence, we defined older patients as those ≥65 years of age at primary liver biopsy and younger patients as those aged <65 years. As shown in Fig. 2B, the cumulative incidence of HCC was significantly higher in older patients than in younger patients (log-rank test, $P < 0.001$).

Table 1. Characteristics of Patients Enrolled in the Present Study

Characteristics	Total	<65 year	≥65 year	P Value*
Patients, n	2166	1614	552	
Sex, n (%)				<0.001†
Male	1080 (49.9)	840 (52.0)	240 (43.6)	
Female	1086 (50.1)	774 (48.0)	312 (56.4)	
Age (SD), year	55.4 (12.1)	51.1 (10.8)	68.4 (2.9)	<0.001‡
BMI (SD), kg/m^2	23.3 (3.1)	23.4 (3.0)	23.3 (3.1)	0.9‡
Fibrosis stage, n (%)				<0.001†
F0	27 (1.3)	24 (1.5)	3 (0.5)	
F1	860 (39.7)	704 (43.6)	156 (28.2)	
F2	733 (33.8)	515 (31.9)	218 (39.5)	
F3	444 (20.5)	301 (18.6)	143 (25.9)	
F4	102 (4.7)	70 (4.3)	32 (5.8)	
%Severe steatosis (≥10%)	27.6	27.1	29.3	0.4†
ALT level (SD), IU/L	95 (18)	101 (119)	76 (58)	<0.001‡
HCV load (SD), KIU/mL	880 (1046)	861 (1016)	924 (1116)	0.2‡
HCV genotype, n (%)				<0.001†
1a	7 (0.3)	5 (0.3)	2 (0.4)	
1b	1414 (69.6)	1036 (68.9)	378 (71.3)	
2a	373 (18.3)	273 (18.2)	100 (18.9)	
2b	211 (10.4)	164 (10.9)	47 (8.9)	
Others	28 (1.4)	25 (1.7)	3 (0.6)	
Duration (SD), year	7.5 (4.4)	8.1 (4.4)	5.8 (3.7)	<0.001‡
IFN regimen, n (%)				<0.001†
IFN mono	1062 (49.0)	833 (51.6)	229 (41.5)	
PEG-IFN mono	306 (14.1)	200 (12.4)	106 (19.2)	
IFN + RBV	386 (17.8)	291 (18.0)	95 (17.2)	
PEG-IFN + RBV	412 (19.0)	290 (18.0)	122 (22.1)	
SVR, n (%)	686 (33.6)§	565 (36.6)‖	121 (24.3)¶	<0.001‡

Unless otherwise indicated, data are given as the mean (SD).

ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; N/A, not applicable; PEG, pegylated; RBV, ribavirin; SVR, sustained virological response.

*Comparison between <65 years and ≥65 years.

†Chi-squared test.

‡Student t test.

§Virological responses were determined in 2042 patients.

‖Virological responses were determined in 1545 patients.

¶Virological responses were determined in 497 patients.

As shown in Fig. 2C-E, even when stratified by stage of fibrosis the cumulative incidences among patients at stages F0/F1, F2, and F3 were significantly greater in older patients than in younger patients (log-rank test, $P < 0.001$). These differences were not significant among patients with cirrhosis (Fig. 2F, log-rank test, $P = 0.7$).

The annual incidence of HCC after interferon treatment was calculated by the person-years method (Table 2); it increased with the degree of liver fibrosis from 0.2% (F0 or F1) to 4.6% (F4) and was higher among older patients at the same stage of liver fibrosis.

Among the 177 patients with HCC, 92 showed evidence of a single blood transfusion. We analyzed the relationship between duration of infection and age in these 92 patients. A significant and strong negative correlation was found between the interval from blood transfusion to development of HCC and the age of the patients at the time of blood transfusion ($r = -0.74$, $P < 0.001$) (Fig. 3A). The mean duration of chronic infection was 22.0 years in patients who had received blood transfusion at >40 years of age, which was significantly shorter than that in patients who received it at ≤40 years of age (40.6 years, $P < 0.001$).

The presence of cirrhosis at the time of development of HCC, which was defined as having any of the following criteria, was evaluated: (1) histological evidence for cirrhosis, (2) findings of cirrhosis in any radiological study, or (3) presence of marked portal hypertension (i.e., presence of esophagogastric varices). Following this, 142 of the 177 with HCC (80.2%) were diagnosed as having cirrhosis, of which 42 were diagnosed histologically, 69 radiologically, and 31 based on the presence of marked portal hypertension. No significant difference was found in the proportion of patients with cirrhosis between older and younger patients, at the rate of 78.3% (94/120) in older

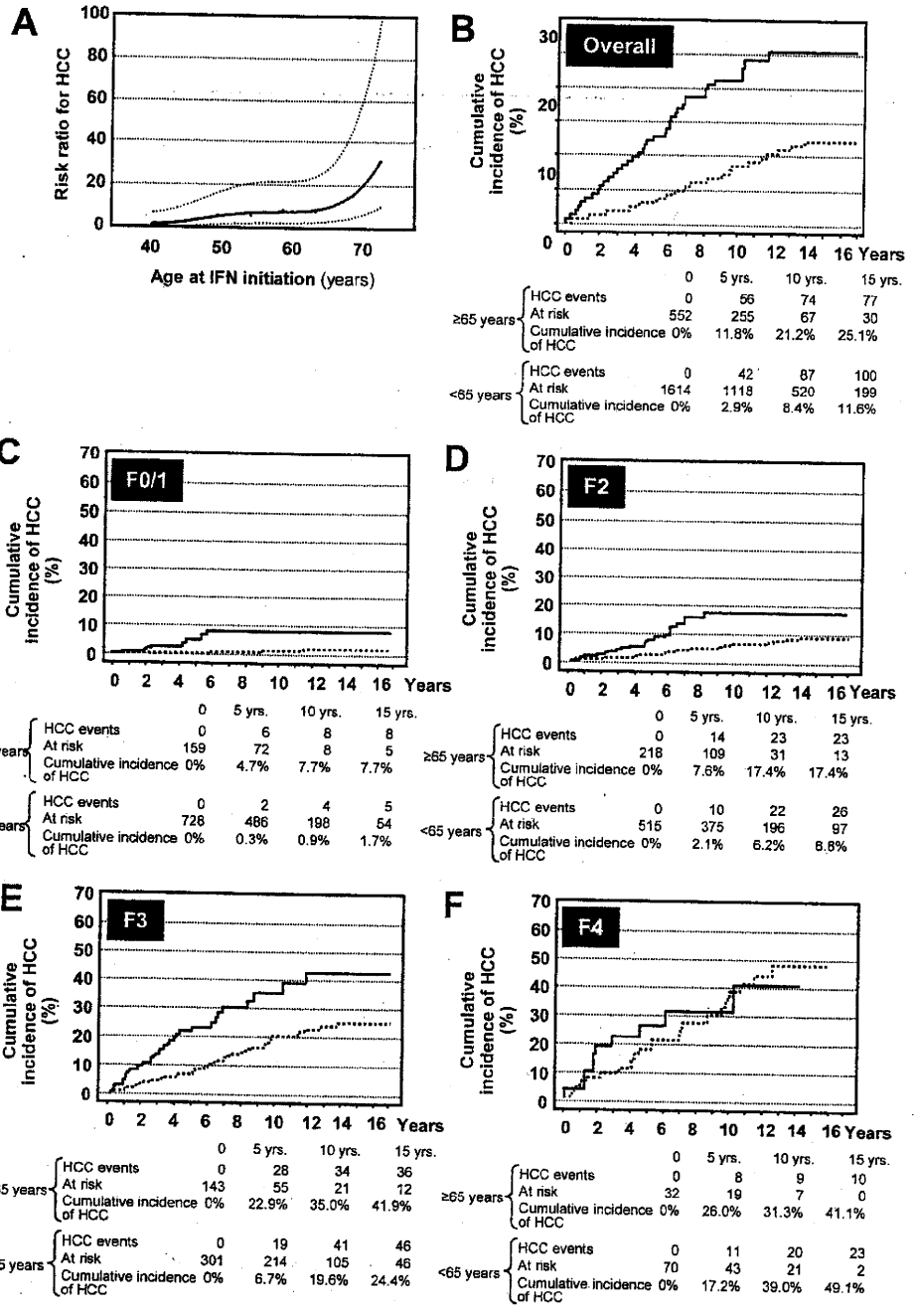

Fig. 2. Effect of aging on the risk for HCC. (A) Risk ratio (solid line) and 95% CI (dotted lines) for the risk of HCC according to age. To show the age-dependent relationship, a multivariate Cox proportional hazard model was used after adjustment for gender, stage of liver fibrosis, body mass index, and virological response to interferon therapy. Curves were fitted using polynomial regression. (B-F) Cumulative incidence of HCC after interferon therapy among younger (<65 years, n = 552, dotted line) and older patients (≥65 years, n = 1614, solid line). (B) Overall data, $P < 0.001$. (C) Patients with stage F0 or F1 liver fibrosis (no or mild fibrosis with portal expansion), $P < 0.001$. (D) Patients with stage F2 liver fibrosis (bridging fibrosis without architectural distortion), $P < 0.001$. (E) Patients with stage F3 liver fibrosis (bridging fibrosis with architectural distortion), $P < 0.001$. (F) Patients with stage F4 liver fibrosis (cirrhosis), $P = 0.7$. All P values were obtained by the log-rank test. The numbers of HCC events and patients at risk at each timepoint are shown below the graphs.

patients and 84.2% (48/57) in younger patients ($P = 0.36$, comparison at the age of HCC development).

Influence of Aging on Progression in Fibrosis Staging Over Time. In 271 patients who underwent paired biopsies, fibrosis staging progressed in 69 patients (25.5%), remained unchanged in 154 (56.8%), and regressed in 48 patients (17.7%). The overall rate of progression of fibrosis in these patients was 0.06 ± 0.02 fibrosis stages per year. Progression of fibrosis over time was significantly accelerated in older patients than in younger patients (0.21 ± 0.10 versus 0.03 ± 0.21 fibrosis stages per year, $P = 0.03$, Mann-Whitney U test) (Fig. 3B).

Effect of Viral Eradication on Risk for HCC in Older Patients. As shown in Fig. 4, the effect of viral eradication on the prevention of HCC was less significant in older patients than in younger patients. The annual incidence was higher among older patients than among younger patients with the same virological response (Table 2).

Influence of Liver Steatosis on Risk for HCC. The cumulative incidence of HCC after interferon therapy was significantly higher in patients with severe steatosis (≥10%) than in those with milder steatosis (at 5, 10, and 15 years: 8.6%, 19.1%, 32.0% versus 1.8%, 4.8%, 7.0%, respectively, log-rank test, $P < 0.001$).

Table 2. Annual Incidence of HCC After IFN Treatment

Factors	Total	<65 Years	≥65 Years
Fibrosis stage			
F0/F1	0.2%	0.1%	0.9%
F2	0.8%	0.6%	1.7%
F3	2.5%	1.8%	4.6%
F4	4.6%	4.4%	5.1%
Total	1.1%	0.8%	2.4%
Degree of liver steatosis			
<10%	0.5%	0.2%	1.4%
≥10%	2.0%	1.8%	3.0%
Virological response			
SVR	0.4%	0.2%	1.3%
Non-SVR	1.4%	1.0%	2.9%

Data were calculated by the person-years method. IFN, interferon; SVR, sustained virological response.

The annual incidence was higher in older patients than in younger patients with the same degree of liver steatosis (Table 2). In patients with severe steatosis (≥10%), superimposed NASH was diagnosed in 6.0% (26/435). Overall, superimposed NASH was significantly associated with hepatocarcinogenesis on univariate analysis (risk ratio, 4.1; 95% confidence interval [CI], 1.8-9.4; $P < 0.001$), but not on multivariate analysis. Superimposed NASH was significantly associated with high body mass index (27.2 ± 4.6 kg/m^2 versus 23.0 ± 3.1 kg/m^2, $P < 0.001$), hyperglycemia (186 ± 67 mg/dL versus 115 ± 39 mg/dL, $P < 0.001$), and advanced fibrosis (F3) (risk ratio, 2.9; 95% CI, 1.4-6.0; $P = 0.005$).

Factors Associated with Hepatocarcinogenesis After Interferon Therapy. Univariate analysis demonstrated factors that increase the risk ratio for the development of HCC (Table 3). Multivariate analysis using Cox proportional hazards regression confirmed that aging was one of the most significant independent factors associated with the development of HCC after interferon therapy. In this analysis, advanced fibrosis, presence of steatosis, male gender, lower total cholesterol level, higher fasting blood sugar level, higher baseline AFP level, insignificant improvement of mean AFP level after interferon therapy, and nonresponse to interferon therapy were also significantly associated with risk for HCC (Table 3).

We identified 22 patients in whom HCC developed even after achieving SVR. Univariate and multivariate logistic regression analyses indicated that both liver steatosis and aging were independently associated with the development of HCC among patients who achieved SVR (n = 686) (Table 4). Anti-HBc was detected in only 4 out of 22 patients and the age distribution was similar among anti-HBc-positive and anti-HBc-negative patients.

Response to Interferon Therapy in Older Patients. Multivariate logistic regression analysis confirmed that aging, female gender, severe liver fibrosis, extremely severe liver steatosis, genotype-1, high HCV load, and nonuse of pegylated interferon and ribavirin were independent risk factors for non-SVR (Supporting Table 1). The odds ratio, determined by multivariate logistic regression analysis after adjustment for these factors, demonstrated that the risk for non-SVR was age-dependent (Supporting Fig. 1). It was also ≈2.5 times higher in patients aged ≥65 years than in those aged <35 years.

In patients with genotype-1b and a high viral load who were treated with pegylated interferon and ribavirin combination therapy, the SVR rate was significantly lower in older patients than in younger patients (<49 years, 59.3%; 50-59 years, 50.5%; 60-65 years, 27.3%; ≥65 years, 25.2%; intention-to-treat analysis). Multivariate logistic regression analysis showed that

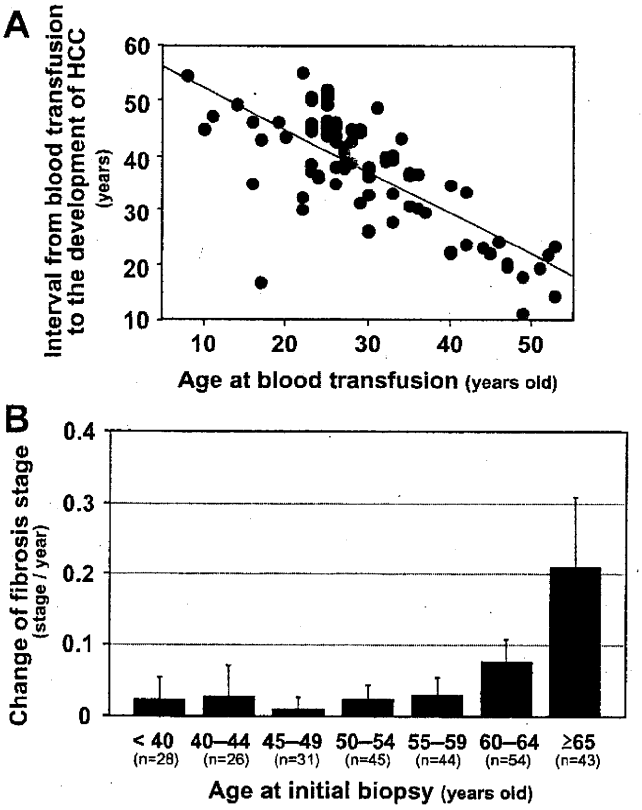

Fig. 3. (A) Relationship between the interval from blood transfusion to development of HCC and the age at blood transfusion (n = 92). A significant and strong negative correlation was observed ($r = -0.74$, $P < 0.001$). (B) Change in fibrosis staging over time. A total of 271 patients who had not achieved SVR by interferon therapy underwent a sequential biopsy after the initial biopsy. The yearly rate of progression of fibrosis was calculated as the change in fibrosis stage divided by the time between the paired biopsies. The yearly rate of progression of fibrosis was significantly higher in older patients (≥65 years) than in younger patients (<65 years) ($P = 0.03$, Mann-Whitney U test).

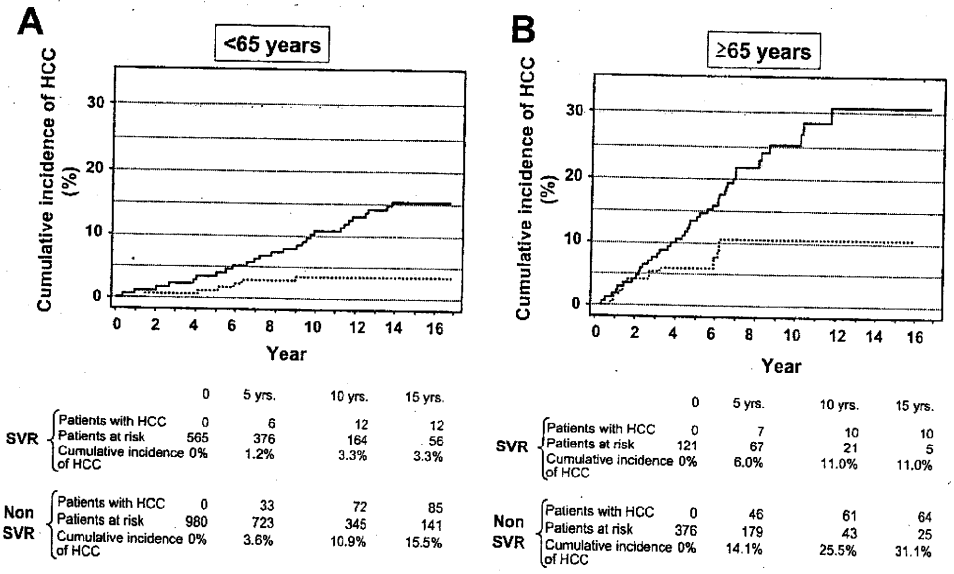

Fig. 4. Cumulative incidence of HCC after interferon therapy among SVRs (dotted lines) and non-SVRs (solid lines) according to age. (A) Younger patients (<65 years). The cumulative incidence of HCC was significantly higher in SVR than in non-SVR (log-rank test, $P < 0.001$). (B) Older patients (≥65 years). The cumulative incidence of HCC was significantly higher in SVR than in non-SVR (log-rank test, $P = 0.02$). However, the difference between SVR and non-SVR was less in older patients than in younger patients. The number of HCC events and patients at risk at each timepoint are shown below the graphs.

aging was the strongest independent factor contributing to SVR in these patients (data not shown). The odds ratio for the risk of non-SVR was 1.8 for each additional 10 years of age (95% CI, 1.5-2.3, $P < 0.001$).

Discussion

In this large cohort study we demonstrated that aging is significantly associated with the development of HCC in patients treated with interferon. The risk ratio increased predominantly in patients older than 65 years, which was more than 15 times that in patients in their 20s. Aging is becoming the most critical risk factor for the development of HCC. Although liver fibrosis was also an important risk factor, we clearly demonstrated that the risk for hepatocarcinogenesis after interferon treatment was significantly higher in older patients at each stage of liver fibrosis except for cirrhosis. Hence, physicians should be aware that older patients can develop HCC regardless of the stage of fibrosis.

Because the present study included a large cohort, it was difficult to determine the duration of infection in all patients, and this might have affected the risk determination for HCC development. Therefore, we analyzed the relationship between duration of chronic infection and HCC development in patients who underwent a single blood transfusion. We found a significant and strong negative correlation between the interval from blood transfusion to development of HCC and the age of the patients at the time of blood transfusion. Consistent with our results, a previous report with posttransfusion HCV demonstrated that the age of patients, rather than the duration of HCV infection, was more significant for HCC development.[14-16] Therefore, older age and not duration of infection is more likely to influence hepatocarcinogenesis. Moreover, our analysis of sequential biopsy specimens demonstrated that the progression rate of liver fibrosis significantly accelerated in patients aged >65 years. Hence, the progression of fibrosis along with aging may also contribute to the increased risk for hepatocarcinogenesis in older patients.

We further demonstrated that liver steatosis was an independent risk factor for the development of HCC, which was not mentioned in previous reports.[8-11] The presence of steatosis is related to both viral (genotype-3 or HCV core protein) and host metabolic factors.[17,18] In our cohort, most superimposed NASH was associated with host metabolic factors such as high body mass index and hyperglycemia, whereas infection of genotype-3 was only noted in two patients. In vitro experiments have suggested an association between liver steatosis induced by HCV core protein and hepatocarcinogenesis,[19] and have proposed virus-associated steatohepatitis as a new aspect of chronic hepatitis C.[20,21] Because steatosis was likely to be related to hepatocarcinogenesis, patients with chronic hepatitis C, whose liver histology shows superimposed NASH,

Table 3. Factors Associated with HCC After IFN Therapy

Risk Factor Value	Univariate Analysis		Multivariate Analysis	
	Risk Ratio (95% CI)	*P* Value	Risk Ratio (95% CI)	*P* Value
Age (by every 10 year)	2.2 (1.8-2.7)	<0.001	3.0 (1.9-4.8)	<0.001
Sex				
Female	1		1	
Male	1.2 (0.9-1.6)	0.2	2.0 (1.0-3.8)	0.04
BMI (by every 10 kg/m^2)	2.0 (1.2-1.3)	0.005	1.1 (0.4-3.5)	0.8
Fibrosis stage				
F0/F1/F2	1		1	
F3/F4	5.4 (3.9-7.5)	<0.001	2.5 (1.2-4.9)	0.01
Degree of steatosis				
<10%	1		1	
≥10%	4.5 (3.0-6.9)	<0.001	3.5 (1.9-6.4)	<0.001
Esophagogastric varices				
No	1		1	
Yes	3.3 (2.0-5.3)	<0.001	1.6 (0.6-4.4)	0.3
Virological response				
SVR	1		1	
Non-SVR	3.3 (2.1-5.2)	<0.001	2.6 (1.2-5.5)	0.001
Genotype				
Non-1	1		1	
1	1.7 (1.2-2.5)	0.006	1.0 (0.5-2.3)	0.9
Albumin (by every 1 g/dL)	0.2 (0.1-0.3)	<0.001	0.6 (0.2-2.2)	0.3
ALT (by every 100 IU/L)	1.0 (0.9-1.0)	0.8	0.4 (0.1-1.8)	0.6
AST (by every 100 IU/L)	1.2 (1.1-1.3)	0.001	1.1 (0.6-1.8)	0.8
γ-GTP (by every 100 IU/L)	1.3 (1.1-1.6)	0.009	0.6 (0.3-1.6)	0.3
ALP (by every 100 IU/L)	1.3 (1.2-1.5)	<0.001	0.6 (0.3-1.2)	0.2
Total bilirubin (by every 1 mg/dL)	1.6 (1.3-2.1)	<0.001	1.2 (0.6-2.7)	0.6
Total cholesterol (by every 100 mg/dL)	0.3 (0.2-0.6)	<0.001	0.2 (0.1-0.6)	0.006
Triglyceride (by every 100 mg/dL)	0.8 (0.5-1.1)	0.2	0.1 (0.02-1.1)	0.08
Fasting blood sugar (by every 100 mg/dL)	1.8 (1.5-2.2)	<0.001	1.1 (1.0-1.1)	0.04
WBC (by every 100/μL)	0.1 (0.03-0.3)	<0.001	0.1 (0.01-2.2)	0.2
RBC (by every 10^6/μL)	0.5 (0.4-0.7)	<0.001	1.8 (0.7-4.4)	0.2
Platelet counts (by every 10^6/μL)	0.3 (0.2-0.4)	<0.001	0.6 (0.3-1.5)	0.3
Baseline AFP (by every 10 ng/mL)	1.0 (0.9-1.1)	0.2	1.3 (1.0-1.7)	0.04
Post IFN AFP (by every 10 ng/mL)	1.2 (1.1-1.3)	<0.001	1.9 (1.5-2.4)	<0.001
HCV load (by every 100 KIU/mL)	1.0 (0.9-1.0)	0.4	1.0 (1.0-1.1)	0.06
IFN regimen				
IFN monotherapy	1		1	
IFN + RBV (24 W)	1.2 (0.8-1.8)	0.4	1.5 (0.7-3.2)	0.3
PEG-IFN monotherapy (48 W)	1.1 (0.6-1.9)	0.8	1.5 (0.4-5.5)	0.6
PEG-IFN + RBV	0.4 (0.2-0.9)	0.03	1.0 (0.3-3.1)	0.9

Risk ratios for development of HCC were calculated by Cox proportional hazards regression analysis. AFP, alpha fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspirate aminotransferase; BMI, body mass index; γ-GTP, gamma-glutamyltranspeptidase; HCC, hepatocellular carcinoma; IFN, interferon; PEG, pegylated; RBC, red blood cell counts; RBV, ribavirin; SVR, sustained virological response; WBC, white blood cell count.

may be at a higher risk of developing HCC. Further study is necessary to confirm this association in a clinical situation. Because several developed countries are in the midst of a growing obesity epidemic, the risk related to obesity cannot be ignored in patients with chronic hepatitis C who are treated with interferon.

Several retrospective cohort studies have been conducted to evaluate the effect of interferon on the incidence of HCC among patients with chronic hepatitis C.[8-11] Our results, obtained from one of the largest cohort studies, confirm the efficacy of viral eradication in preventing HCC. In one study conducted in a Western population, no statistically significant reduction was found in the development of HCC among patients with SVR compared with those without SVR (adjusted hazard ratio, 0.46; 95% CI, 0.12-1.70; $P = 0.25$).[12] Because relatively few occurrences of HCC were observed in this cohort, and the duration of follow-up was shorter, the differences in HCC development between patients with and without SVR might be less pronounced.

Interestingly, our results demonstrated that the risk for HCC remains even after achieving SVR in older patients, confirming the findings of previous studies conducted with a smaller number of patients.[22,23] The cumulative incidence of HCC during the first 5 years

Table 4. Factors Associated with Development of HCC After Achieving SVR

Risk Factor	Odds Ratio (95% CI)	*P*-value
Univariate analysis		
Age (by every 10 year)	3.2 (1.8-5.5)	<0.001
Sex		
Female	1	
Male	3.0 (1.0-8.8)	0.04
Fibrosis stage		
F0/F1/F2	1	
F3/F4	5.9 (2.5-14.0)	<0.001
Degree of steatosis		
<10%	1	
≥10%	5.5 (2.0-15.2)	0.001
BMI (by every 10 kg/m^2)	3.2 (0.8-12.6)	0.09
ALT (by every 10 IU/L)	0.9 (0.7-1.3)	0.7
AST (by every 10 IU/L)	1.1 (0.9-1.4)	0.3
Genotype		
Non-1	1	
1	1.2 (0.6-3.0)	0.5
HCV load (by every 100 KIU/mL)	0.9 (0.8-1.0)	0.2
IFN regimen		
IFN monotherapy	1	
IFN + RBV (24 W)	0.7 (0.2-2.3)	0.5
PEG-IFN monotherapy (48 W)	0.8 (0.2-3.6)	0.8
PEG-IFN + RBV	0.3 (0.03-2.0)	0.2
Multivariate analysis		
Age (by every 10 year)	2.7 (1.5-5.1)	0.002
Sex		
Female	1	
Male	4.1 (0.9-18.9)	0.06
Fibrosis stage		
F0/F1/F2	1	
F3/F4	2.6 (0.9-7.5)	0.08
Degree of steatosis		
<10%	1	
≥10%	5.6 (1.9-16.5)	0.002

Odds ratios for SVR were calculated by logistic regression analysis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; HCC, hepatocellular carcinoma; PEG, pegylated; RBV, ribavirin; SVR, sustained virological response.

after completion of interferon therapy was similar between SVR and non-SVR patients in the older age group, and the risk for HCC remained for 9 years after eradication of HCV in our patients. Therefore, HCC patients with SVR who have a risk factor should be screened for at least 5-10 years after the completion of interferon therapy.

It has been reported that coffee consumption has a protective effect against hepatocarcinogenesis[24,25] and liver disease progression in patients with chronic HCV infection.[26] Because we could not review coffee consumption in all the patients and fewer data were available in the previous literature as to whether a habitual change of reducing coffee consumption occurs in older patients, it is unclear whether increased risk for HCC in older patients is an effect of this habitual change in older patients. However, the majority (68%) of Japanese patients who have HCV (n = 1058) drink less than 1 cup of coffee per day, and only 7.6% consume more than 3 cups of coffee per day.[27] Therefore, it is unlikely that a habitual change in older patients affects the increased risk for hepatocarcinogenesis in older patients.

Recently, it was reported that interferon therapy might be less effective in preventing HCC among patients with chronic hepatitis C who are positive for anti-HBc antibody,[28] but this finding is still controversial.[29,30] In the present study, anti-HBc was only detected in 4 of 22 patients in whom HCC developed after viral eradication, and age distribution was similar among anti-HBc-positive and anti-HBc-negative patients. Because no significant difference in mean age was found between anti-HBc-positive and anti-HBc-negative patients in the recent study conducted in Japan,[28] it is unlikely that previous exposure to hepatitis B virus or occult hepatitis B virus infection is responsible for the difference in risk for HCC between younger and elderly patients found in the present study.

In conclusion, aging has become one of the most important risk factors for HCC. Even after stratification by stage of fibrosis, the risk for HCC after antiviral treatment was significantly higher in older patients, and HCV eradication had a smaller effect on HCC-free survival in older patients. Patients with HCV should therefore be identified at an earlier age and antiviral treatment should be initiated. The present results have potentially important clinical implications for physicians that may influence their decisions about the treatment strategy in individual patients.

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総　説

C型肝炎の最新治療と医療連携

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はじめに

C型肝炎はわが国における肝がんおよび肝硬変の原因として重要な位置を占めている．わが国では年間約3万4000人が肝がんで死亡しており，これは他の先進国ではみられないわが国における特有の問題である．原発性肝がんの99%は肝細胞がんであり，肝細胞がんの75%はC型肝炎が原因である．したがって，わが国における肝がんの撲滅にはC型肝炎ウイルス（HCV）対策がきわめて重要であり，2010年1月1日からは肝炎対策基本法が施行され，肝炎検診の受診促進，肝炎医療の受療促進等々の理念のもと対策が推し進められている．また2010年4月からは，すでに始まっていたインターフェロン医療費助成制度が拡充され，今回の診療報酬改訂では肝炎医療の均てん化や受療促進を目的とした医療連携にかかわる算定項目も新設された．したがって，われわれ臨床内科医はこれらを十分に活用し実効性のある肝炎診療を実地に行っていく必要がある．

C型肝炎からの肝発がん抑止には，HCVの駆除が最も効果的であるが，これにはインターフェロン治療が基本となる．しかし，わが国のC型慢性肝炎の約70%を占めるHCV genotype 1bはインターフェロンに抵抗性を示すことが知られ，特に高ウイルス量症例やインターフェロン感受性決定領域（Interferon sensitivity determining region；ISDR）にアミノ酸変異がない症例では，インターフェロン単独24週の治療でウイルス学的著効（sustained viral response；SVR）が得られる率はこれまで10%以下であった[1,2]．近年，genotype 1b型かつ高ウイルス症例のいわゆる難治性C型慢性肝炎に対して，ペグインターフェロン・リバビリン併用療法が導入され，約50%の症例でウイルス学的著効が得られるようになった．しかし，わが国におけるC型肝炎は，高齢者が多い，線維化進行例が多い，発がん率が高いなど欧米と異なる特徴を有し，また難治例における治療成績は必ずしも満足できるものではない．

これに対して，最近ではC型慢性肝炎治療のさらなる治療効果向上をめざして，治療開始後の抗ウイルス効果により治療期間を適正に設定する試みが行われ，また新薬の開発もめざましい．さらに，難治要因の解明も進んでいる．本稿では，最新治療の治療成績の実態と，効果に寄与する因子，治療成績向上のための治療法の工夫，最近の新薬の開発状況などについて概説するとともに，C型肝炎診療における医療連携について解説する．

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ペグインターフェロン・リバビリン併用療法の治療成績と治療効果に影響を与える治療前因子

ペグインターフェロン・リバビリン併用療法は，わが国においては2004年12月より保険適応となり，実地診療における治療成績が明らかとなって

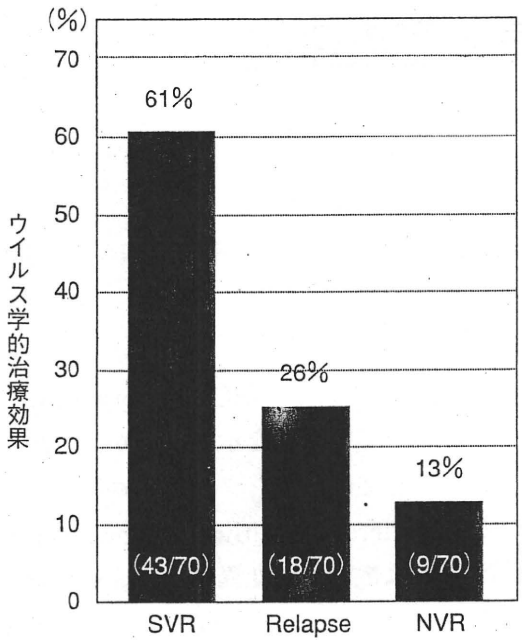

図 1　ペグインターフェロン α2b・リバビリン 48 週併用療法におけるウイルス学的治療効果
予定投与量の 80%以上が投与された症例での検討 (n=292)

きた．そこで，当院においてペグインターフェロン α2b・リバビリン併用療法を施行した 614 例のうち，genotype 1b 型かつ高ウイルス量の 488 例を対象とし，難治要因にかかわる因子を検討した．まず，臨床背景について検討すると，当院におけるペグインターフェロン治療導入時の年齢の中央値は 60 歳で，臨床試験での平均年齢に比し約 10 歳高齢であった．また，F3 の高度線維化例が 23%を占め，前回治療無効例も 14%認め，実地臨床の現場では難治例が多く含まれることがわかる．

すでに最終治療効果を判定しえた症例について検討すると，当院におけるペグインターフェロン α2b・リバビリン併用 48 週投与例の SVR 率は，薬剤減量・中止例も含めた ITT 解析では 37%であったが，予定投与量の 80%以上を投与しえた症例（PP 解析）では 61%と高率であった（図 1）．しかし，予定投与量の 80%以上を投与しえた症例においても，治療終了後の HCV-RNA の再燃を 26%に認め，さらに治療中に HCV-RNA が陰性化しない non-virological responder（NVR）例を 13%に認めた．したがって，さらなる治療成績の向上には，これら再燃・無効要因を明らかとし，それらに対する対策を講じることが重要である．

当院のペグインターフェロン α2b・リバビリン併用 48 週治療における，SVR に関与する治療前因子を単変量解析を用いて解析すると，年齢，性別，過去のインターフェロン治療効果のほか，ヘモグロビン濃度，血小板数，血清クレアチニン濃度，AST 値，γ-GTP 値，LDL コレステロール値，血糖値，さらに肝組織における脂肪化および線維化の程度などが有意な因子としてあげられた．また，HCV NS5A 領域の ISDR 変異数や HCV コア 70 番・91 番変異といったウイルス学的因子も有意であった．これらの因子を基にさらに多変量解析を用いて検討すると，年齢，性別，線維化の程度，ISDR 変異，HCV コア変異が有意な独立因子であった．すなわち，60 歳以上の高齢者，特に高齢女性，F3 以上の線維化進行例，ISDR 変異数 0 または 1 の症例，HCV コア 70 番・91 番のダブル変異例は，それぞれ SVR になりにくい症例と考えられた．

治療中の抗ウイルス効果と治療成績

一方治療中においては，そのウイルス学的反応をモニターすることが最終治療効果を予測するうえできわめて有用である．すなわち，実地臨床ではインターフェロン療法中における HCV-RNA の消失時期が重要であり，HCV-RNA 陰性化時期と SVR 率の間には密接な関連がある．したがって，種々の治療ガイドラインでは HCV-RNA 陰性化時期により治療期間などの治療スケジュールを修正することが推奨されている．

最近では治療中の HCV-RNA のモニターに，より高感度でダイナミックレンジの広いリアルタイム PCR 法を用いるようになったため，より正確に治療効果予測が可能となった．そこで当院の症例において，リアルタイム PCR 法でみた HCV-RNA の陰性化時期と治療完遂例における SVR の関係を検討すると，治療開始 8 週以内に HCV-RNA が陰性化していれば，全例 SVR となり

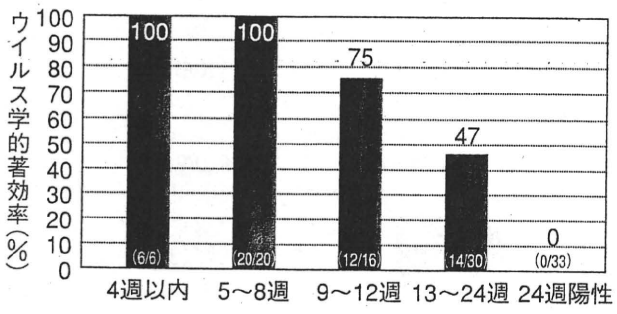

図 2　リアルタイム PCR 法で判定した HCV 消失時期とウイルス学的治療効果
ペグインターフェロン α2b・リバビリン併用 48 週療法での検討．中止例を除く

SVR 率は 100%であった（図 2）．また，9〜12 週の陰性化例でも 75%の症例で SVR 率が得られた．それに対して，13〜24 週に陰性化した症例では再燃率が高く，48 週投与での SVR 率は 47%で，さらに 24 週以降に陰性化した症例からは 1 例も SVR が得られなかった．したがって，HCV-RNA 陰性化時期の遅れた症例における治療後の再燃をいかに減らすかが，治療成績を向上させるためには大変重要な課題となる．

治療中のウイルス学的反応による最適投与期間の設定

そこで最近では，治療前の genotype とウイルス量による画一的な治療法から，個々の症例における治療中のウイルス学的反応性により，最適な治療期間を設定する治療法が行われている．すなわち，HCV-RNA の陰性化が遅れ 13 週以降 36 週以内に消失するいわゆる late virological responder（LVR）に対して 72 週への延長投与が行われており，現在厚生労働省 B 型・C 型肝炎治療標準化研究班（熊田博光班長）のガイドラインでは，治療開始 12 週時点で HCV-RNA の 2 log 低下を認め，リアルタイム PCR 法で 13〜36 週に陰性化した症例に対しては 72 週投与が推奨されている．実際に当院でのインターフェロン α2a・リバビリン併用 72 週療法を検討してみると，投与例の年齢の中央値は 64 歳で女性が 86%を占めており，いわゆる難治例の集団と考えられるにもかかわらず，SVR 率は 60%で 60 歳以上の症例や女性でもそれぞれ 60%，62%と良好な成績が得られている．

再燃に関与する因子の検討と 72 週延長投与の推奨の拡大

HCV-RNA の陰性化時期のほかに，治療後の再燃に関与する治療前因子がないかを検討するために，当院においてペグインターフェロン α2b・リバビリン併用 48 週療法を行った症例について再燃因子を解析した．その結果，単変量解析では，年齢，過去のインターフェロン治療効果，ヘモグロビン値，血小板数，肝組織の脂肪化，ISDR 変異が有意であった．さらに，多変量解析では年齢と ISDR 変異が独立因子として抽出され，すなわち高齢者や ISDR が野生型の症例は 48 週治療後の再燃が多いことがわかった．

先に述べたように，治療後の再燃には治療中の HCV-RNA 消失時期が強く関連するため，HCV-RNA 消失時期別に年齢と ISDR で層別化してその再燃率を検討した（図 3）．それによると，リアルタイム PCR 法で 9〜12 週に HCV-RNA が陰性化した症例において，60 歳未満の症例や ISDR 非野生型の症例では治療後再燃を認めなかったのに対し，60 歳以上かつ ISDR 野生型の症例では 48 週治療では再燃が認められた．一方，リアルタイム PCR 法で 13〜24 週に HCV-RNA が陰性化した LVR 例での再燃率は総じて高率だが，60 歳未満かつ ISDR 非野生型症例の再燃率は低率であった．

したがって，現在の標準治療であるペグインターフェロン α・リバビリン併用療法におけるさらなる治療効果の向上のためには，HCV-RNA の陰性化時期に加えて年齢やウイルス変異といった再燃要因を考慮して，治療期間を決定するなど治療の個別化が必要と考えられた．

ちなみに，本年度の厚生労働省治療ガイドラインでは，50 歳以上の女性や血小板 13 万/μl 未満の線維化進展例では，9〜12 週に HCV-RNA 陰性化が達成された症例においても，72 週への延長投与が推奨されている．