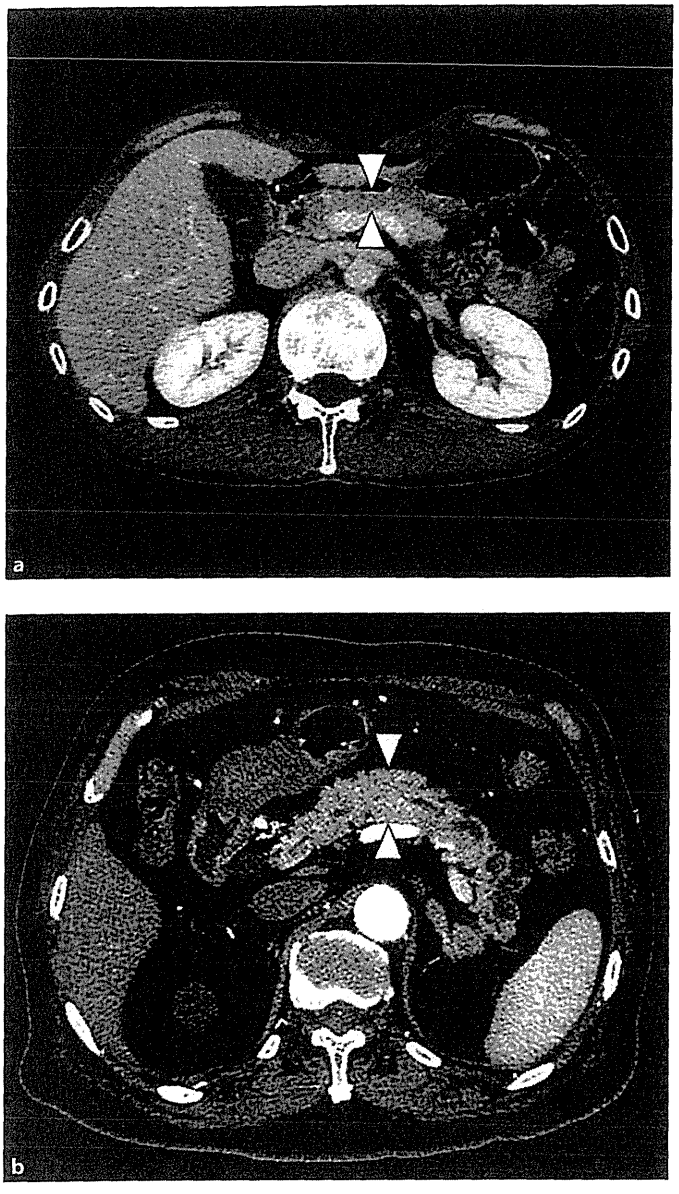

Fig. 1. Measurement of the thickness of the pancreatic remnant by preoperative CT. In pancreatic transaction at the body level (arrowheads), the thickness differs between the patients.

Clinical Characteristics

The cut-line of the pancreas was planned based on preoperative CT; however, the true cut-line was recorded during surgery and the thickness of the true pancreatic cut-line was measured postoperatively by preoperative CT using Centricity Enterprise software (version 3.0; GE Medical Systems, Tokyo, Japan; fig. 1). Regardless of the CT density of pancreatic parenchyma, a thick pancreas was retrospectively defined as more than 13 mm because the median thickness of all enrolled patients was 13 mm. The texture of the pancreatic parenchyma was defined as either soft or hard, according to the surgeon's judgment. The amylase concentrations in the peripheral blood and in the drain fluid were measured on postoperative days 1, 3 and 7.

Statistical Analyses and Ethical Considerations

All data were reported as the mean ± SD and/or median. Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data were used. Multiple logistic regression analysis was used to identify the independent risk factors for pancreatic fistula. Statistically significant factors by univariable analyses were entered into the multivariable model. For each variable, the OR with 95% CI was determined. Data analyses were performed based on an intention-to-treat basis using the SPSS software package (SPSS Inc., Chicago, Ill., USA), and a p value of less than 0.05 was considered to be statistically significant. The study protocol was approved by the Human Ethics Review Committee of Osaka University Graduate School of Medicine and a signed consent form was obtained from each patient.

Results

No statistical differences were observed between the hand-sewn group and the stapler group in the male/female ratio, age, indications for surgery, extent of pancreatic resection, percentage of laparoscopic or laparoscopy-assisted surgery, texture of the pancreas (soft or hard), thickness of the pancreas, amylase level in the drain fluid, or duration of postoperative hospital stay (table 1). All patients in the hand-sewn group successfully underwent a hand-sewn closure, while a stapler closure was impossible in 2 patients in the stapler group because the surgical cut-lines were too close to the gastroduodenal artery. A pancreatic fistula (grade B or C) was observed in 7 patients (27%) in the hand-sewn group, whereas 5 patients (23%) developed a pancreatic fistula in the stapler group (p = n.s.). Two patients in the stapler group in whom a staple closure failed did not develop a pancreatic fistula. The cartridge for stapler in the stapler group was chosen by the surgeon: a white cartridge (1 mm) was used in 2, blue (1.5 mm) in 2, gold (1.8 mm) in 11 and green (2 mm) in 5. The 5 patients that had a pancreatic fistula in the stapler group included patients treated with white (1 patient), gold (2 patients) and green cartridges (2 patients). A subclinical pancreatic fistula was observed in 22 patients (84.6%) in the hand-sewn group and 14 patients (63.6%) in the stapler group (p = n.s.). These subclinical pancreatic fistulas were not added to the following analyses. No patients died perioperatively.

The patients' characteristics were compared between the patients with a pancreatic fistula and those without a fistula in order to identify the risk factors for pancreatic fistula in all patients. Univariate analyses demon-

Table 1. Patient characteristics

	Hand-sewn group	Stapler group	p
Number of cases	26	22	
Gender, male:female	8:18	12:10	0.10
Age, years ± SD	56.8 ± 18.3	64.3 ± 12.2	0.21
Indications, pancreatic cancer:other	11:15	13:9	0.25
Resection, body and tail:tail	19:7	21:1	0.06
Laparotomy:laparoscopy-assisted	22:4	18:4	>0.99
Soft pancreas:hard pancreas	19:7	18:4	0.47
Thickness, mm ± SD	13.7 ± 5.0	12.6 ± 4.3	0.44
Pancreatic fistula, yes:no (%)	7:19 (27:73)	5:17 (23:77)	0.74
Amylase level in drain fluid, U/l ± SD	5,937 ± 15,423	2,062 ± 4,225	0.13
Postoperative hospital stay, days	31.4 ± 24.0	27.2 ± 14.4	0.94

Table 2. Factors associated with postoperative pancreatic fistula in all patients (univariate analysis)

	Pancreatic fistula		p
	yes	no	
Number of cases	12	36	
Gender, male:female	6:6	14:22	0.50
Age, years ± SD	53.0 ± 13.4	62.6 ± 16.4	0.03*
Indications, pancreatic cancer:other	4:8	20:16	0.18
Resection, body and tail:tail	9:3	31:5	0.39
Laparotomy:laparoscopy-assisted	9:3	31:5	0.39
Soft pancreas:hard pancreas	11:1	26:10	0.25
Thickness, mm ± SD	16.7 ± 4.4	12.0 ± 4.2	0.003*
Closure technique, hand-sewn:stapler	7:5	19:17	0.74
Amylase level in drain fluid, U/l ± SD	13,924 ± 21,095	907 ± 1,520	<0.0001*

* $p < 0.05$.

strated that patients' age ($p = 0.03$) and the thickness of the pancreatic remnant ($p = 0.003$) were significant factors (table 2). Neither the male/female ratio, indications for surgery, extent of pancreatic resection nor texture of the pancreas were different between the groups. By logistic regression analysis of risk factors for pancreatic fistula, younger age (OR = 0.949, $p = 0.048$) and the thickness of the pancreatic remnant (OR = 1.342, $p = 0.006$) were identified as independent risk factors (table 3).

Table 3. Logistic regression analysis of risk factors for pancreatic fistula

	OR	95% CI	p
Age, years	0.949	0.901–0.999	0.048*
Thickness, mm	1.342	1.090–1.652	0.006*

* $p < 0.05$.

Statistical analyses in all patients elucidated that a thick pancreas was one of the independent risk factors for pancreatic fistula; however, it is conceivable that a thick pancreas may be a more serious factor when the pancreatic remnant is closed by a stapler instead of a hand-sewn closure because a thick pancreas may be crushed when compressed by a stapler. We therefore separately calculated risk factors for pancreatic fistula in patients who underwent hand-sewn closure (table 4) or stapler closure (table 5). Neither the male/female ratio, age, indications for surgery, extent of pancreatic resection, texture of the

Table 4. Factors associated with postoperative pancreatic fistula in patients who underwent hand-sewn closure

	Pancreatic fistula		p
	yes	no	
Number of cases	7	19	
Gender, male:female	4:3	4:15	0.15
Age, years ± SD	49.9 ± 16.6	59.3 ± 18.7	0.24
Indications, pancreatic cancer:other	2:5	9:10	0.66
Resection, body and tail:tail	5:2	14:5	0.99
Laparotomy:laparoscopy-assisted	4:3	18:1	0.047*
Soft pancreas:hard pancreas	7:0	12:7	0.13
Thickness, mm ± SD	15.9 ± 5.6	12.9 ± 4.7	0.21
Amylase level in drain fluid, U/l ± SD	18,846 ± 26,773	1,182 ± 1,666	0.0002*

* $p < 0.05$.

Table 5. Factors associated with postoperative pancreatic fistula in patients who underwent stapler closure

	Pancreatic fistula		p
	yes	no	
Number of cases	5	17	
Gender, male:female	2:3	10:7	0.62
Age, years ± SD	57.4 ± 6.3	66.4 ± 12.8	0.05
Indications, pancreatic cancer:other	2:3	11:6	0.61
Resection, body and tail:tail	4:1	17:0	0.23
Laparotomy:laparoscopy-assisted	5:0	13:4	0.54
Soft pancreas:hard pancreas	4:1	14:3	>0.99
Thickness, mm ± SD	17.8 ± 2.3	11.1 ± 3.4	0.002*
Amylase level in drain fluid, U/l ± SD	7,033 ± 6,840	600 ± 1,319	0.002*

* $p < 0.05$.

pancreas nor thickness of the pancreas were different between the groups in the hand-sewn group. In the hand-sewn closure group, 3 of 4 patients who underwent a laparoscopy-assisted pancreatectomy developed a pancreatic fistula, which was statistically higher than those who underwent a conventional pancreatectomy ($p = 0.047$). The amylase level in patients with a pancreatic fistula was 18,846 ± 26,773 U/l, but was 1,182 ± 1,666 U/l in those without a fistula ($p = 0.0002$). In the stapler group, the thickness of the pancreatic remnant was statistically greater in patients with a pancreatic fistula than those without a fistula ($p = 0.002$; table 5). There was no difference associated with the male/female ratio, age, indications for surgery, extent of pancreatic resection, percentage of laparoscopic or laparoscopy-assisted surgery, or texture of the pancreas. The amylase level in patients with a pancreatic fistula was higher than that in those without a fistula ($p = 0.002$). Even when 2 patients in whom a staple closure was unsuccessful were excluded from these analyses, the thickness and the amylase level were still statistically higher in patients with a pancreatic fistula ($p = 0.002$ and 0.003, respectively).

Figure 2 shows the relationship between the thickness of the pancreatic remnant and the presence or absence of a pancreatic fistula. None of the patients in the stapler group with a thin pancreatic remnant (13 mm or less) developed a pancreatic fistula, whereas 50% of patients with a thicker remnant (more than 13 mm) developed a fistula, which was statistically significant by intention-to-treat analysis ($p = 0.01$). This difference was still statisti-

cally significant when 2 patients in whom a staple closure failed were excluded (p = 0.008). The incidence of fistula in patients in the hand-sewn group with a thick remnant was 38%, which was lower than those with thick remnants in the stapler group, although not statistically significant.

Discussion

The present study retrospectively investigated the risk factors for pancreatic fistula and identified that younger age and a thick pancreas were independent risk factors. Patient age has been reported as an independent risk factor, but thickness has not yet been discussed so far. Moreover, previous studies include several kinds of closure techniques, such as hand-sewn and stapling techniques, and therefore the true risk factors of using a stapler remain to be elucidated. Surgeons speculate that a thick and hard pancreas is more likely to be crushed when compressed by a stapler; nevertheless, no investigation to confirm this hypothesis has yet been carried out. The present study revealed that 50% of patients with a thick pancreas developed a pancreatic fistula when the pancreatic remnant is closed by a stapler, while no patients with a thin pancreas developed this. The results indicate that patients with a thin pancreas should be recommended to undergo a stapler closure while a thick pancreas is a risk factor for pancreatic fistula regardless of the closure techniques.

Both previous studies and the current results also indicated that the hand-sewn closure of a hard pancreas was less likely to induce a pancreatic fistula (no cases in 7; table 2) than a soft pancreas (7 cases in 19), although this difference was not statistically significant. Although the initial hypothesis was that a hard pancreas would be more likely to be crushed when compressed by a stapler, the current results indicate the same incidence of pancreatic fistula in patients with a soft pancreas as observed in those with a hard pancreas when the stapler is used (table 5). There is insufficient evidence to propose an underlying mechanism for this observation; however, the equal incidence may result from the fact that the accompanying pancreatitis in a distal pancreatectomy is generally less severe than in a pancreaticoduodenectomy, so that the pancreas can be compressed even when it is diagnosed to be hard.

Okano et al. [15] noted that the most important and technically difficult step of a stapler dissection was to prevent the pancreatic tissue from tearing during compression. Therefore, they clamped the stapler jaw carefully and slowly over more than 5 min at a fixed speed. The procedures in the present study clamped the stapler in the same manner. Even with this careful procedure, the result clearly confirmed that patients with a thick pancreas had a higher risk for pancreatic fistula. It is unclear why a thick pancreas, but not a hard pancreas, is a risk factor for pancreatic fistula. Macroscopically, the serosa of the pancreatic remnant was intact just after stapling in all these cases. Thereafter either microscopic tissue tearing during surgery or delayed tearing after surgery may occur if the remnant is too thick.

It is also unclear if the selection of the cartridge for stapler has any influence on the outcome. In the present study, 1 patient whose pancreas was closed by a stapler with a white cartridge developed a pancreatic fistula. It is not yet clarified whether that the selection of the cartridge can be a very important determinant for inducing a pancreatic fistula; therefore, it should be elucidated by a prospective study. Nevertheless, except for 1 patient, all patients with a thick pancreas in the stapler group were treated using a cartridge of greater staple height (green cartridge or gold cartridge) in order to avoid compression which is too strong. Even with these selections, however, the incidence of pancreatic fistula was high in patients with a thick pancreas, indicating that the thickness itself is the risk factor for pancreatic fistula, at least when employing currently available stapling devices. Moreover,

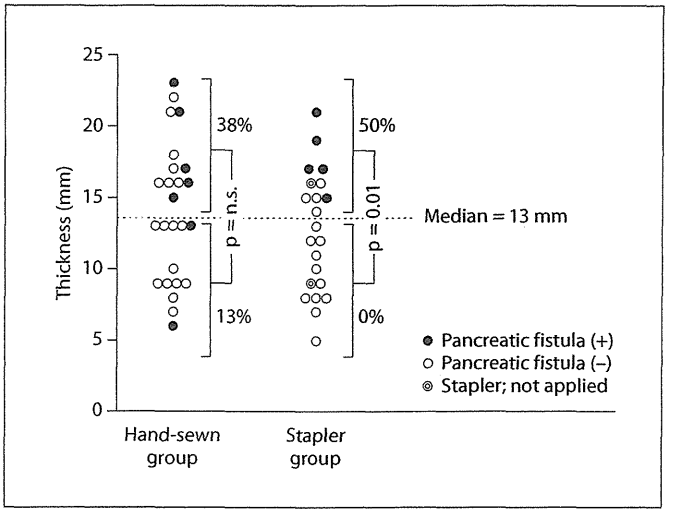

Fig. 2. Distribution of patients according to thickness and closing techniques. Closed circles indicate patients with pancreatic fistula. Two patients in whom a staple closure failed in the stapler group did not develop pancreatic fistula (double circles).

we should note that 2 patients who had been scheduled for stapler closure could not be stapled because their surgical cut-lines were too close to the gastroduodenal artery. Fortunately, these 2 patients underwent a hand-sewn closure and did not develop a pancreatic fistula; however, a hand-sewn closure is also difficult to such patients. Another closure technique should be established for such patients.

In the present study, 8 patients underwent laparoscopic or laparoscopy-assisted distal pancreatectomy. Although these surgical procedures were not identified as risk factors for pancreatic fistula, it should be noted that 3 out of 4 patients who underwent a laparoscopy-assisted hand-sewn closure developed a pancreatic fistula. This higher incidence may have been caused by a surgically inappropriate procedure, as a laparoscopy-assisted hand-sewn closure was performed through the very small upper-abdominal incision.

The present study defined 13 mm as the cutoff value because 13 mm was the median thickness in this series of patients and it was concluded that a thick pancreas of more than 13 mm was a risk factor for pancreatic fistula. However, a true cutoff value still remains to be determined, which requires evaluating a larger number of patients.

In summary, this study clarifies that a thick pancreas, but not a hard pancreas, is one of the risk factors for a postoperative pancreatic fistula regardless of the closure technique and that patients with a thick pancreas have a higher risk of pancreatic fistula than those with a thin pancreas when the pancreatic remnant is closed by a stapler. A randomized clinical trial with a large number of patients to confirm these findings is suggested, as well as the identification of an appropriate cutoff value for the thickness of the pancreas for which a stapler can be safely used.

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BRIEF ARTICLE

Advantage of autologous blood transfusion in surgery for hepatocellular carcinoma

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Abstract

AIM: To evaluate the significance of autologous blood transfusion (AT) in reducing homologous blood transfusion (HT) in surgery for hepatocellular carcinoma (HCC).

METHODS: The proportion of patients who received HT was compared between two groups determined by the time of AT introduction; period A (1991-1994, n = 93) and period B (1995-2000, n = 201). Multivariate logistic regression analysis was performed in order to identify independent significant predictors of the need for HT. We also investigated the impact of AT and HT on long-term postoperative outcome after curative surgery for HCC.

RESULTS: The proportion of patients with HT was significantly lower in period B than period A (18.9% *vs* 60.2%, $P < 0.0001$). Multivariate logistic regression analysis identified AT administration as a significant independent predictor of the need for HT ($P < 0.0001$). Disease-free survival in patients with AT was comparable to that without any transfusion. Multivariate analysis identified HT administration as an independent significant factor for poorer disease-free survival (P = 0.0380).

CONCLUSION: AT administration significantly decreased the need for HT. Considering the postoperative survival disadvantage of HT, AT administration could improve the long-term outcome of HCC patients.

Key words: Hepatocellular carcinoma; Surgery; Autologous blood transfusion; Homologous blood transfusion

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INTRODUCTION

Surgical resection is a safe and effective treatment for hepatocellular carcinoma (HCC). Because HCC usually develops in patients with liver cirrhosis, most of such patients present with bleeding tendencies related to

chronic liver dysfunction[1-3]. Therefore, surgery for HCC frequently requires intraoperative transfusion. Homologous blood transfusion (HT) is necessary for patients with excessive intraoperative bleeding, though this is still associated with risks of infections and/or immunological complications[4,5]. Moreover, evidence suggests that HT may be adversely associated with tumor recurrence and poor postoperative survival in various kinds of cancers[6-13]. Autologous transfusion (AT), which represents collection and reinfusion of the patient's own blood or blood components before surgery, and has been developed as a strategy to reduce the need for HT, is currently used for patients scheduled for surgery for various diseases including HCC[11,14-17]. It has been the policy in our hospital since 1995 to prepare for AT for patients scheduled for HCC surgery. To date, several investigators have examined the significance of AT in terms of reducing the need for HT and of postoperative outcome, but only a few were conducted with proper statistical analyses to identify the significance of AT[16,17].

In the present study, we reviewed the frequency of HT and AT administration in patients undergoing surgery for HCC, and statistically analyzed the significant factors that could predict the need for HT. We also compared the difference between the effects of AT and HT on long-term postoperative outcome after curative surgery for HCC.

MATERIALS AND METHODS

The present study included 294 patients with HCC who underwent hepatic resection at the Department of Surgery, Osaka University Hospital between January 1991 and December 2000. In 93 patients between 1991 and 1994 (period A), AT was not administered, and, when blood was needed, HT was administered. Between 1995 and 2000 (period B), AT was carried out preoperatively in the remaining 201 patients provided: (1) they agreed to the storage; (2) their hemoglobin (Hb) level was $\geq$ 11.0 g/dL before storage; and (3) they were free of severe cardiopulmonary and/or cerebrovascular diseases, or infection. Autologous blood was collected 1 to 3 times, with 200-400 mL of blood at a time. The blood was stored in a liquid state without freezing. Iron supplements were given daily to the patients who deposited the autologous blood in the post-storage period. In addition, if the total volume of the collected blood was $\geq$ 800 mL, recombinant human erythropoietin was administered. All through the study period, during hepatic resection, blood transfusion was carried out when the Hb level fell to < 8.0 g/dL in patients with normal cardiopulmonary function or < 9.0 g/dL in patients with severe cardiopulmonary or cerebrovascular diseases. In patients who had previously deposited autologous blood, autologous blood was first used prior to homologous blood. In this study, patients who required HT were defined as the HT group, irrespective of prior AT, and the remaining patients without HT were defined as the non-HT group. Furthermore, patients in whom only AT was performed were defined as the AT group, and patients without AT or HT were as defined as the non-transfusion group.

Hospital records were collected retrospectively to gather clinical information including clinical factors, tumor-related factors and surgery-related factors. In patients with autologous blood storage, preoperative Hb was indicated as Hb before the storage. The surgical procedure was selected based on the extent of the tumor and residual liver function. The indication for surgery and selection of surgical procedure were not different between period A and period B. The histological grade of differentiation of HCC was determined according to the Edmondson-Steiner classification, and was based on the areas of the tumor with the highest grade[18]. Data were expressed as mean ± standard deviation. Differences between groups were assessed by the chi-square test, Fisher's exact test or the Mann-Whitney *U* test. Survival rates were calculated according to the Kaplan-Meier method, and compared using the log-rank test. Multivariate logistic regression analysis was performed for the selection of significant variables. Statistical analysis was performed using StatView (version 5.0; SAS Institute Inc., Cary, NC). A P value < 0.05 was considered significant. The study protocol was approved by the Human Ethics Review Committee of Osaka University Hospital and a signed consent form was obtained from each patient.

RESULTS

Table 1 shows the clinicopathological characteristics of patients in period A (n = 93) and in period B (n = 201). The clinical features, tumor-related features, and surgery-related factors were not significantly different between patients of the 2 groups. HT was administered in 56 of the 93 patients (60.2%) in period A. In period B, HT was administered in 38 patients (18.9%) (HT group), AT in 134 patients (66.7%), and neither AT nor HT in 45 patients (22.4%) (non-transfusion group). In 134 AT patients, the amount of transfused autologous blood was 200 mL in 3 patients, 400 mL in 63 patients, 600 mL in 2 patients, 800 mL in 62 patients, 1000 mL in 1 patient, and 1200 mL in 3 patients. Among the 134 patients with AT, only AT was administered in 118 patients (58.7%) (AT group), and both AT and HT in the remaining 16 patients (8.0%). Figure 1 shows the distribution of patients according to blood transfusion. Thus, the proportion of patients who received HT was significantly lower in period B than in period A (P < 0.0001). With regard to disease-free survival examined only in patients with curative surgery for HCC, there were no significant differences between period A and period B; the 1-, 3-, 5-, and 10-year disease-free survival rates were 73.9%, 39.5%, 24.7%, and 7.2% for patients in period A, and 65.9%, 34.8%, 21.9%, and 7.2% for patients in period B (P = 0.5688), respectively. The 1-, 3-, 5- and 10-year overall survival rates were 85.7%, 75.6%, 63.1%, and 28.5% for patients in period A, and 92.9%, 70.6%,

Table 1 Clinicopathological characteristics of patients of periods A and B with hepatocellular carcinoma

	Period A (1991-1994) (n = 93)	Period B (1995-2000) (n = 201)	P-value
Clinical factors			
Gender (male/female)	81/12	161/40	0.144
Age (yr)[1]	61 ± 9	62 ± 9	0.102
HBs-Ag (±)	73/20	169/32	0.243
Anti-HCV Ab (±/unknown)	29/62/2	71/125/5	0.471
Child-Pugh classification (A/B)	79/14	160/41	0.275
Preoperative Hb (g/dL)[1]	13.6 ± 1.5	13.3 ± 1.6	0.213
Tumor-related factors			
Number of tumors (single/multiple)	70/23	146/55	0.635
Maximum tumor size (cm)[1]	3.8 ± 2.7	4.1 ± 3.1	0.450
Vascular invasion (±)	83/10	172/29	0.388
Histological grade (Ⅰ, Ⅱ/Ⅲ, Ⅳ/unknown)	40/41/12	89/92/20	0.975
Surgery-related factors			
Procedure (nonanatomical/anatomical)	45/48	101/100	0.767
Operation time (min)[1]	291 ± 144	295 ± 151	0.853
Resected liver volume (g)[1]	218 ± 406	214 ± 289	0.925
Intraoperative blood loss (mL)[1]	2190 ± 5689	1621 ± 2209	0.219

[1]Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin.

Table 2 Clinicopathological characteristics of patients with hepatocellular carcinoma according to homologous blood transfusion

	Non-HT group (n = 200)	HT group (n = 94)	P-value
Clinical factors			
Gender (male/female)	162/38	80/14	0.390
Age (yr)[1]	62 ± 9	60 ± 9	0.084
HBs-Ag (±)	168/32	74/20	0.269
Anti-HCV Ab (±/unknown)	65/130/5	35/57/2	0.437
Child-Pugh classification (A/B)	167/33	72/22	0.157
Preoperative Hb (g/dL)[1]	13.5 ± 1.6	13.2 ± 1.7	0.171
AT administration (±)	82/118	78/16	< 0.0001
Tumor-related factors			
Number of tumors (single/multiple)	149/51	67/27	0.559
Maximum tumor size (cm)[1]	3.6 ± 2.4	4.9 ± 3.7	0.000
Vascular invasion (±)	177/23	78/16	0.193
Histological grade (Ⅰ, Ⅱ/Ⅲ, Ⅳ/unknown)	91/88/21	38/45/11	0.446
Surgery-related factors			
Procedure (nonanatomical/anatomical)	111/89	35/59	0.004
Operation time (min)[1]	264 ± 130	356 ± 166	< 0.0001
Resected liver volume (g)[1]	159 ± 196	336 ± 490	< 0.0001
Intraoperative blood loss (mL)[1]	993 ± 707	3522 ± 6104	< 0.0001

[1]Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin; AT: Autologous transfusion; HT: Homologous transfusion.

58.2%, and 40.3% for patients in period B (P = 0.3202).

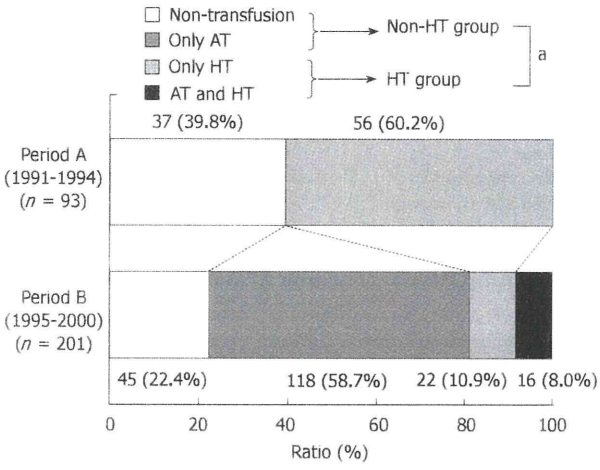

Figure 1 Distribution of patients according to transfusion status during periods A and B. The proportion of patients who received HT was significantly lower in period B than period A (^aP < 0.0001). AT: Autologous transfusion; HT: Homologous transfusion.

In order to identify the factors that can predict the need for HT, various clinical parameters, tumor-related factors, and surgery-related factors were compared between the non-HT group and the HT group (Table 2). The preoperative Hb level was not significantly different between the 2 groups (13.5 ± 1.6 g/dL *vs* 13.2 ± 1.7 g/dL, P = 0.1708). The proportion of patients who received AT was significantly lower in the HT group than the non-HT group [59.0% (118/200) *vs* 17.0% (16/94), P < 0.0001]. The maximum tumor size was significantly larger in the HT group than in the non-HT group (4.9 ± 3.7 cm *vs* 3.6 ± 2.4 cm, P = 0.0003). As for surgery-related factors, there were significant differences in surgical procedure (P = 0.0035), operation time (P < 0.0001), resected liver volume (P < 0.0001), and intraoperative blood loss (P < 0.0001), suggesting that surgery in the HT group was major compared to that in the non-HT group.

To identify significant factors that could predict the need for HT, multivariate logistic regression analysis was performed (Table 3). The analysis was carried out using the 6 significant factors identified in the comparison of the non-HT group and the HT group. The analysis identified AT administration, intraoperative blood loss, and resected liver volume as significant independent predictors for the need of HT (P < 0.0001, P < 0.0001, P = 0.0362, respectively). Long-term postoperative outcome after surgery for HCC was examined. In this analysis, patients were limited to those with curative resection, which was defined as complete removal of all macroscopically evident tumors [non-HT group: 193 patients (non-transfusion group: 78 patients; AT group: 115 patients), HT group: 83 patients]. Among the 276 patients, 37 patients (13.4%) were followed-up for more than 10 years. The clinicopathological features of the groups are shown in Table 4. First, we compared the long-term postoperative outcome between the non-transfusion group and the AT group. The preoperative Hb level was significantly higher in the AT group than in the non-

Table 3 Results of multivariate logistic regression analysis for the need for homologous blood transfusion

		OR	95% CI	*P*-value
AT administration	±	28.571	9.615-83.333	< 0.0001
Maximum tumor size (cm)	< 5/≥ 5	1.126	0.500-2.538	0.774
Procedure	Nonanatomical/anatomical	1.016	0.449-2.202	0.967
Operation time (min)	< 300/≥ 300	0.986	0.435-2.242	0.974
Resected liver volume (g)	< 200/≥ 200	2.532	1.062-6.061	0.036
Intraoperative blood loss (mL)	< 2000/≥ 2000	30.303	9.346-100.000	< 0.0001

OR: Odds ratio; CI: Confidence interval; AT: Autologous transfusion.

Table 4 Clinicopathological characteristics of patients who underwent curative surgery for hepatocellular carcinoma

	Non-HT group (n = 193)	HT group (n = 83)	*P*-value (Non-HT *vs* HT)	Non-HT group		
				Non-transfusion group (n = 78)	AT group (n = 115)	*P*-value (Non-transfusion *vs* AT)
Clinical factors						
Gender (male/female)	156/37	70/13	0.488	63/15	93/22	0.986
Age (yr)[1]	62 ± 8	61 ± 9	0.115	62 ± 8	61 ± 9	0.878
HBs-Ag (±)	163/30	67/16	0.445	Nov-67	96/19	0.649
Anti-HCV Ab (±/unknown)	62/127/4	31/51/1	0.426	21/54/3	41/73/1	0.254
Child-Pugh classification (A/B)	161/32	65/18	0.262	66/12	95/20	0.833
Preoperative Hb (g/dL)[1]	13.5 ± 1.5	13.4 ± 1.6	0.425	12.8 ± 1.8	14.1 ± 1.1	< 0.0001
Tumor-related factors						
Number of tumors (single/multiple)	147/46	64/19	0.866	62/16	85/30	0.372
Maximum tumor size (cm)[1]	3.5 ± 2.4	4.8 ± 3.7	0.000	3.3 ± 2.2	3.6 ± 2.4	0.287
Vascular invasion (±)	172/21	70/13	0.268	73/5	99/16	0.101
Histological grade (Ⅰ, Ⅱ/Ⅲ, Ⅳ/unknown)	89/83/21	33/41/9	0.304	36/34/8	53/49/13	0.412

[1]Data are expressed as number of patients and mean ± standard deviation. HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin; AT: Autologous transfusion; HT: Homologous transfusion.

transfusion group (14.1 ± 1.1 g/dL *vs* 12.8 ± 1.8 g/dL, $P < 0.0001$). Tumor-related factors were similar in the 2 groups. There were no significant differences in the disease-free survival rates between the AT group (1-, 3-, 5-, and 10-year: 70.6%, 37.1%, 22.3%, and 11.2%, respectively) and the non-transfusion group (73.1%, 41.3%, 30.7%, and 9.6%, respectively) ($P = 0.3874$) (Figure 2A). Next, we compared the long-term survival rates of the non-HT group and the HT group. Although the cumulative disease-free survival rate of the non-HT group was significantly better than that of the HT group ($P = 0.0305$) (Figure 2B), since the maximum tumor size was significantly different in the comparison (3.5 ± 2.4 cm *vs* 4.8 ± 3.7 cm, $P = 0.0004$), additional comparison was also performed based on the tumor size. The disease-free survival rates for the non-HT group (1-, 3-, 5-, and 10-year: 75.6%, 42.6%, 29.4%, and 10.8%, respectively) was significantly better than those of the HT group (69.0%, 31.6%, 16.7%, and 4.5%, respectively) of the subgroup with tumor size 5.0 cm or smaller than 5.0 cm ($P = 0.0452$) (Figure 2C), but not in patients with tumor size larger than 5.0 cm (1-, 3-, 5-, and 10-year: 56.4%, 24.1%, 10.8%, and 5.4% in the non-HT group, and 39.4%, 26.3%, 13.1%, and 0.0% in the HT group, respectively, $P = 0.7391$) (Figure 2D). Furthermore, multivariate analyses using significant factors identified in the univariate analyses demonstrated that transfusion status (non-HT/HT) was one of the independent significant factors for disease-free survival ($P = 0.0380$) (Table 5), suggesting disadvantages of HT on postoperative prognosis.

DISCUSSION

The results of the present study demonstrated a reduction in HT administration in surgery for HCC after the introduction of AT. Our results are in agreement with those of previous reports which emphasized the significance of AT in reducing the need for HT in surgery for HCC[16,17]. However, in these previous reports, only 20-30 patients were included in the AT group. Furthermore, although the Hb level immediately before surgery was reported in the AT group, the Hb level before storage was not indicated, suggesting a different clinical background of patients who received HT and those of other groups. On the other hand, in the present study, despite its retrospective design, the clinicopathological background, including the Hb level, was similar in the 2 groups as shown in Table 1. In this regard, the present study is significant as it identified the benefits of AT in the reduction of HT administration.

In the present study, we analyzed the data for significant predictors of HT use. The results showed that AT administration was an independent significant predictor of the need for HT, and support the significance of AT in reducing the need for HT. In the analysis, preoperative Hb, which is reported to be significantly associated with the need for HT[19,20], was not an independent significant factor. While the reason for this difference in the results

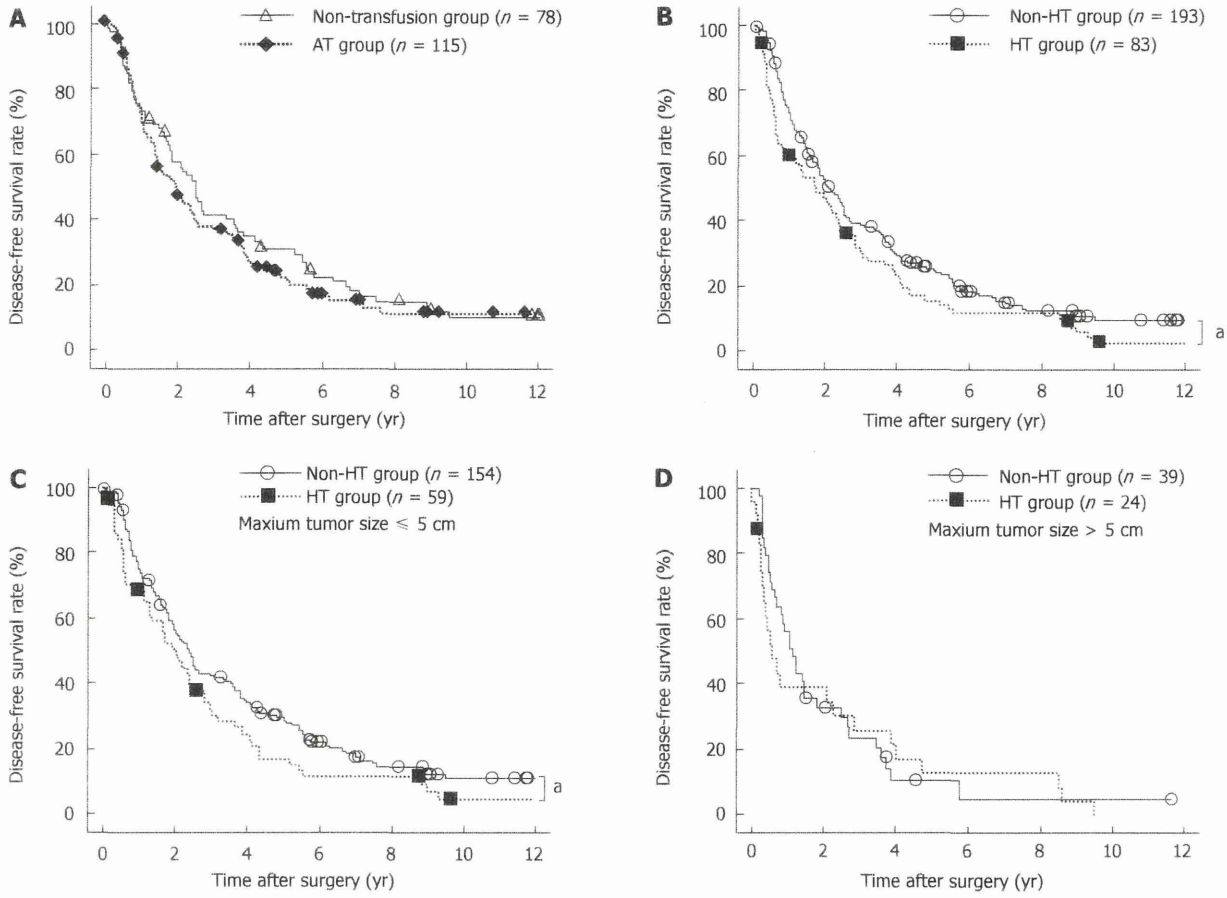

Figure 2 Disease-free survival after curative surgery for hepatocellular carcinoma. A: There were no significant differences between the non-transfusion group (solid line) and the Autologous transfusion (AT) group (dotted line) (P = 0.3874); B: The cumulative disease-free survival in the non-Homologous transfusion (HT) group (solid line) was significantly better than in the HT group (dotted line) (^aP = 0.0305); C: The disease-free survival in the non-HT group (solid line) was significantly better in than the HT group (dotted line) in patients with maximum tumor size of ≤ 5.0 cm (^aP = 0.0452); D: No significant differences were noted between the non-HT group (solid line) and the HT group (dotted line) in patients with the maximum tumor size > 5.0 cm (P = 0.7391).

Table 5 Statistical analysis of disease-free survival of patients with curative resection for hepatocellular carcinoma

	Univariate		Multivariate	
	P-value	OR	95% CI	*P*-value
Clinical factors				
Gender (male/female)	0.840			
Age (yr) (≤ 63/> 63)	0.402			
HBs-Ag (±)	0.279			
Anti-HCV Ab (±)	0.045	1.401	1.032-1.901	0.031
Child-Pugh classification (A/B)	0.079			
Preoperative Hb (g/dL) (≤ 12/> 12)	0.824			
Transfusion (non-HT group/HT group)	0.031	1.372	1.018-1.849	0.038
Tumor-related factors				
Number of tumors (single/multiple)	0.000	1.819	1.290-2.564	0.001
Maximum tumor size (cm) (≤ 5/> 5)	0.001	1.07	0.750-1.525	0.709
Vascular invasion (±)	< 0.0001	2.473	1.606-3.806	< 0.0001
Histological grade (Ⅰ, Ⅱ/Ⅲ, Ⅳ)	0.017	1.188	0.898-1.570	0.227

OR: Odds ratio; CI: Confidence interval; HBs-Ag: Hepatitis B surface antigen; Anti-HCV Ab: Anti-hepatic C virus antibody; Hb: Hemoglobin; HT: Homologous transfusion.

remains unclear, it could be due to the effect of recombinant human erythropoietin administered after the storage of autologous blood. Alternatively, it is possible that, since the subjects of the above previous studies did not receive AT, the significance of preoperative Hb is overestimated. Thus, the present study is significant in terms of identifying the effect of AT in reducing HT using appropriate statistical analysis.

We also investigated the effects of AT and HT on postoperative outcome after curative surgery for HCC. The study revealed that the disease-free survival rates were comparable between the non-transfusion group and the AT group when the clinical background was similar. Furthermore, the disease-free survival rates of the HT group were significantly worse than those of the non-HT group, based on the results of univariate analysis. Since there was a significant difference in the maximum tumor size between the 2 groups, which suggests the possibility of different tumor biology and recurrences between the HT group and the non-HT group, the survival rate was compared in subgroups based on tumor size, and showed significant differences in the pa-

tients with tumor size ≤ 5.0 cm. In addition, the difference was confirmed to be independently significant by multivariate analyses.

Since the report of a survival advantage of HT in patients undergoing colectomy for colon cancer[21], some investigators have indicated that HT triggers recurrence in various kinds of cancers[6-8]. This HT-induced disadvantage is speculated to be derived from transfusion-associated immunomodulation. Actually, several investigators suggested that HT induces downregulation of natural killer cell activity and cytotoxic T-cell function, resulting in a subclinical state of anergy or tolerance[22-24].

The correlation has been reported also in patients with HCC[9-14,25]. Although the results of the present study were comparable to these previous reports, we think that the present study reports a new finding based on the inclusion of patients who were followed-up for more than 10 years. With regard to the long-term survival advantages, to our knowledge, there are only a few reports describing the survival advantage of HT on long-term prognosis (> 10 years). Hirano *et al*[14] investigated the long-term (> 10 years) survival disadvantage of HT over AT, but their reports did not include the clinical background of patients and described the results of only univariate analysis, suggesting inadequate analysis. Also in this regard, the present study provides significant data.

Thus, the present study revealed that AT is significant in reducing the need for HT, which is associated with a long-term postoperative survival disadvantage after HCC surgery. In this study, however, in order to investigate the long-term postoperative outcome for more than 10 years, we limited inclusion in the study to patients who underwent surgery between 1991 and 2000. Based on this limitation, it is possible that the selected time period does not reflect recent advances in both surgical and anesthetic techniques, which could explain the recent decrease in intraoperative blood loss. Considering such recent advances affecting intraoperative blood loss, one can speculate that there are increasingly more patients with HCC who do not need AT. It was also reported recently that the practice of using autologous blood requires more administrative work and laborious collection procedures, and is not without disadvantages[26-29]. Taken together, AT actually has advantage an over HT, but currently, it may be necessary to deliberate on the need for AT itself during surgery for HCC.

In summary, the present study showed that AT administration significantly decreased the need for HT in surgery for HCC, and that AT was one of the significant independent predictor of the need for HT. Considering that HT was disadvantageous with regard to long-term postoperative survival, one can assume that AT administration can lead to improvement in the long-term postoperative outcome of patients with HCC.

COMMENTS

Background

Some evidences suggest that homologous blood transfusion (HT) may be adversely associated with tumor recurrence and poor survival in various kinds of cancers, and autologous blood transfusion (AT) is currently used for patients scheduled for surgery. To date, several investigators have examined the significance of AT in terms of reducing the need for HT and postoperative outcome, but few were conducted with proper statistical analyses to identify the significance of AT in surgery for hepatocellular carcinoma (HCC).

Research frontiers

The authors compared the proportion of patients who received HT between 2 groups determined by the time of AT introduction; period A (1991-1994, n = 93) and period B (1995-2000, n = 201), and performed multivariate logistic regression analysis for identification of independent significant predictors of the need for HT. Furthermore, they investigated the impact of AT and HT on long-term postoperative outcome after curative surgery for HCC.

Innovations and breakthroughs

The present study showed that the proportion of patients having HT was decreased after AT introduction, that AT administration was a significant independent predictor of the need for HT, and identified HT administration as an independent significant factor for poorer disease-free survival.

Applications

Considering the results of the present study, it could be suggested that AT administration could improve the long-term outcome of patients with HCC.

Peer review

This is a large series of patients treated in several ways with respect to the need for blood transfusion during their surgery for HCC. Unfortunately the authors have a mix of numbers that they have used in different ways to make the conclusion they wanted to make.

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Clinical Science

Mural nodule in branch duct–type intraductal papillary mucinous neoplasms of the pancreas is a marker of malignant transformation and indication for surgery

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KEYWORDS:
IPMN;
Branch duct type;
Mural nodule;
Malignancy;
Predictive factor

Abstract

BACKGROUND: The management of branch duct–type intraductal papillary mucinous neoplasms (IPMNs) remains controversial. This study aimed to elucidate the preoperative clinical factors that identify high-risk malignant transformation in branch duct–type IPMN.

METHODS: We retrospectively evaluated 38 patients diagnosed with branch duct–type IPMN who underwent pancreatectomy, identifying different preoperative factors between adenoma (intraductal papillary mucinous adenoma [IPMA]) and carcinoma (intraductal papillary mucinous carcinoma [IPMC]).

RESULTS: Twelve patients were diagnosed with IPMC. The mean tumor size was 31.9 ± 11.8 mm for IPMA and 35.7 ± 17.1 mm for IPMC ($P = .467$). No significant differences were found between IPMA and IPMC patients with regard to age, sex, symptoms, and tumor number. The mean diameter of the main pancreatic duct was significantly larger in IPMCs (8.3 ± 5.9 mm) compared with IPMAs (4.7 ± 2.3 mm; $P = .011$). The mural nodule was a good predictor of malignancy ($P = .0002$) and was identified as the only independent and significant marker of IPMC in multivariate analysis.

CONCLUSIONS: The presence of mural nodules is a potentially suitable marker for differentiating IPMC from IPMA, and is important for making decisions about surgical interventions.

Recent advances in diagnostic imaging have resulted in an increased frequency of diagnosis for cystic mucin-producing pancreatic neoplasms.[1–4] In 2000, the World Health Organization and the Armed Forces Institute of Pathology classified these tumors into 2 distinct entities: intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms.[5,6] IPMNs are premalignant lesions originating from a large pancreatic duct that progresses from adenoma (intraductal papillary mucinous adenoma [IPMA]) to carcinoma (intraductal papillary mucinous carcinoma [IPMC]).[7,8] Many recent clinicopathologic studies have reported that the rate of malig-

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nancy for IPMN varies according to the region of the pancreatic duct where the tumor originates. An IPMN arising from the main pancreatic duct (MPD) is more aggressive than those arising from the branch duct. In fact, the reported rate of malignancy for the MPD type ranges from 57% to 92%,[4,9–12] and surgical resection is recommended for all MPD types. By contrast, the rate of malignancy for the branch duct type is relatively low, reportedly 6% to 46%.[2,13–15] Thus, differentiating between IPMC and IPMA is clinically relevant and important. In this regard, several tumor features are reported to allow discrimination of IPMC from IPMA, including tumor size, MPD diameter, and the presence of a mural nodule in the cystic lesion.[8,10,15] However, the significance of these parameters is currently debated and further investigation is necessary.

The purpose of the present study was to elucidate the preoperative clinical features of IPMA and IPMC and use multivariate regression analysis for the differentiation of the 2 lesion types, and consequently the choice of surgery or other alternative therapies.

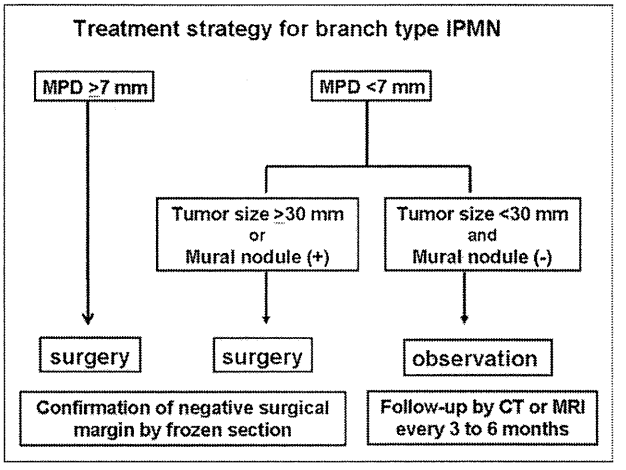

Figure 1 Therapeutic strategy for branch duct–type IPMN. Surgical resection was performed for all patients with an MPD diameter greater than 7 mm and patients with an MPD diameter that was not more than 7 mm but who had a tumor size greater than 30 mm or an apparent mural nodule in the tumor. Patients with an MPD smaller than 7 mm, tumor size less than 30 mm, and no apparent mural nodule in the tumor were not indicated for surgery but were followed up by CT or MRI every 3 to 6 months.

Patients and Methods

Patients

This study was performed retrospectively. From March 1992 to November 2007, 46 patients who were diagnosed preoperatively with IPMN underwent surgical treatment at Osaka University Hospital. Before surgery, all patients received clinical evaluation and routine laboratory tests including tumor markers and imaging studies (abdominal ultrasonography, computed tomography [CT], and endoscopic retrograde cholangiopancreatography). Magnetic resonance imaging (MRI) and magnetic resonance imaging cholangiopancreatography (MRCP) also were performed in most patients. Pancreatic juice cytology and intraductal ultrasonography were performed when possible.

Definition of IPMN type and surgical indication

The type of IPMN was established by imaging studies and consultation with radiologists, internists, and surgeons. The following definitions were used. The MPD type was diagnosed in the presence of a mural nodule in the main duct only together with pancreatic duct dilatation. The complex type represented a mural nodule in the main duct with dilatation of a branch of the pancreatic duct. The branch pancreatic duct type was diagnosed in the presence of a dilated branch of the pancreatic duct and a lack of a mural nodule in the tumor in the main duct, with or without dilatation of the main duct. A pancreatic duct measuring more than 4 mm was regarded as dilated.

Based on the international consensus guidelines established in 2006,[8] the treatment strategy for IPMN in our institute was as follows. The main pancreatic duct type and complex type were indication for surgery at diagnosis. For the branch type, all patients with an MPD diameter of 7 mm or greater were indicated for resection. An MPD diameter of less than 7 mm, tumor size of 30 mm or greater, or the presence of a mural nodule also was an indication for surgery. Patients with an MPD diameter of less than 7 mm, tumor size of less than 30 mm, and no apparent mural nodule in the tumor were followed up by CT or MRI every 3 to 6 months (Fig. 1). Most patients enrolled in this study underwent surgery in accordance with this algorithm, and 8 patients underwent resection after more than 1 year of follow-up evaluation because the tumors in these patients were not resected at the first diagnosis, so they were followed up. More than 1 year after the first diagnosis, the patients had surgery because of tumor growth of more than 30 mm in 5 patients, the dilatation of MPD of more than 7 mm in 5 patients, and the appearance of a mural nodule in 4 patients. More than 2 factors appeared in the same patient, so the total number is more than 8. Inevitably, the earlier-described criteria varied slightly in some of the patients included in this study because resection was performed before the guidelines became available. All surgeries included confirmation of a negative surgical margin using frozen sections during surgery.

Patient enrollment

Among the 46 patients diagnosed with IPMN, 38 were classified as branch pancreatic duct type and all were enrolled in this study. Table 1 presents the patient characteristics. The sample included 20 men and 18 women with a

Table 1 Characteristics of patients with branch pancreatic duct-type IPMN

Age, y	62.6 ± 8.9
Sex, male/female	20/18
Symptoms, yes/no	18/19
Tumor size, mm	36.0 ± 15
Mural nodule, yes/no	15/23
Dilatation of MPD, yes/no	24/14
Postoperative diagnosis	
IPMA/IPMC (invasive IPMC)/others	20/12 (9)/6
Pathologic MPD invasion, yes/no	7/25
Number of tumors, single/multiple	32/6
Surgery, PD/DP/others	22/9/4
Recurrence, yes/no	5/33

Data are the mean ± SD or the number of patients.
DP = distal pancreatectomy; PD = pancreatoduodenectomy.

mean age ± standard deviation of 62.6 ± 8.9 years. Approximately half of the patients were asymptomatic at the first visit. The mean tumor size was 36.0 ± 15.0 mm, and a mural nodule was observed in 15 patients. Dilatation of the MPD was observed in 24 patients, and the mean diameter was 6.1 ± 4.4 mm. Pancreatoduodenectomy, including subtotal stomach-preserved pancreatoduodenectomy and pylorus-preserved pancreatoduodenectomy, was performed in 22 patients, distal pancreatectomy was performed in 9 patients, and other surgical techniques, including middle pancreatectomy, was performed in 4 patients. The postoperative pathologic findings confirmed the diagnosis of IPMN in 32 patients, including invasive ductal carcinoma derived from IPMN, but 6 patients were diagnosed with other diseases: serous cyst adenoma in 3 patients, mucinous cystic neoplasms in 2 patients, and chronic pancreatitis in 1 patient. Thus, we excluded these 6 patients from further analysis.

Statistical analysis and ethical issues

Data are expressed as mean ± standard deviation. Differences in continuous preoperative factors between IPMA and IPMC patients were analyzed using the Student *t* test.

Table 2 Clinicopathologic characteristics of patients according to the type of pancreatic tumor

	IPMA	IPMC	*P* value
Total patients	20	12	
Age, y	65.3 ± 8.5	62.6 ± 7.5	.376
Sex, male/female	13/7	6/6	.474
Symptoms, yes/no	7/12	8/4	.149
Tumor size, mm	31.9 ± 11.8	35.7 ± 17.1	.467
Diameter of MPD, mm	4.7 ± 2.3	8.7 ± 5.9	.011
Number of tumors, single/multiple	16/4	10/2	.99
Mural nodule, no/yes	17/3	2/10	.0002

Data are the mean ± SD or the number of patients.

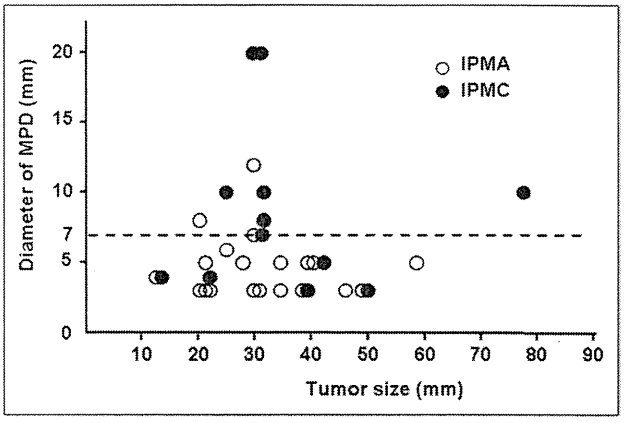

Figure 2 The distribution of IPMN patients by tumor size and MPD diameter. The relationship between the diameter of the MPD and tumor size was not significant. IPMA is indicated by a white circle (○) and IPMC is indicated by a black circle (●). In 22 patients with an MPD diameter less than 7 mm, 5 (22.7%) had IPMC, whereas 7 patients (70.0%) among 10 with an MPD diameter greater than 7 mm had IPMC (P = .018).

The Fisher exact test was used to compare discrete variables. A P value of less than .05 indicated significance.

The study protocol was approved by the Human Ethics Review Committee of Osaka University Hospital, and a signed consent form was obtained from each subject.

Results

In 32 patients with branch-type IPMN, 12 patients were diagnosed with IPMC; 3 patients had noninvasive or microinvasive IPMC and 9 had invasive IPMC, including invasive ductal adenocarcinoma derived from IPMC (Table 1). The mean age of the 20 patients with IPMA was 65.3 ± 8.6 years, whereas the mean age of patients with IPMC was 62.6 ± 7.5 years. There were no significant differences between the 2 groups with regard to age, sex, symptoms, and the number of tumors (Table 2). Although the difference between the mean tumor size in IPMA and IPMC patients was not significant (31.9 ± 11.8 mm vs 35.7 ± 17.1 mm, respectively; P = .467), the mean diameter of the MPD in IPMA patients was significantly smaller than that of IPMC patients (4.7 ± 2.3 mm vs 8.3 ± 5.9 mm, respec-

Table 3 Differences between benign and malignant pancreatic tumors according to the diameter of the MPD

	MPD, mm	
	<7	≥7
IPMA	17	3
IPMC	5	7

P = .018

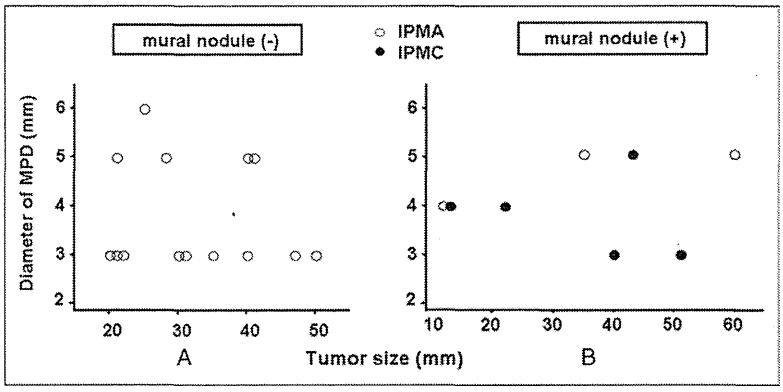

Figure 3 The distribution of IPMN patients with an MPD diameter less than 7 mm. (A) patients lacking a mural nodule; (B) patients with a mural nodule. All 14 patients lacking a mural nodule had IPMA, regardless of tumor size, whereas among the 8 patients with mural nodules, 5 (63%) had IPMC (P = .0021).

tively; P = .011). A mural nodule was observed in preoperative imaging in 13 patients, 10 of whom (76.9%) had IPMC, whereas only 2 patients (10.5%) among 19 patients without mural nodules had IPMC, and the relationship between the presence of a mural nodule and IPMC was significant (P = .0002; Table 2). The relationship between the MPD diameter and tumor size was not significant (Fig. 2).

When the patients were divided into 2 groups based on the diameter of the MPD, 22 patients had a diameter less than 7 mm. Among these patients, 5 patients (22.7%) had IPMC. Ten patients had an MPD diameter of 7 mm or greater, 7 of whom (70.0%) had IPMC. The difference in IPMC occurrence between the 2 groups was significant (P = .018; Table 3).

The tumor size did not allow us to distinguish between IPMA and IPMC (data not shown). Among the 22 patients with an MPD diameter less than 7 mm, mural nodules were not observed in 14 patients and all had IPMA. By contrast, 5 patients (63%) among the remaining 8 patients with apparent mural nodules had IPMC (P = .0021; Fig. 3). Multivariate analysis identified the presence of a mural nodule as the only independent and significant factor that allows differentiation between IPMC and IPMA, whereas the MPD diameter was a marginal predictive factor (P = .063; Table 4).

In 8 patients who underwent surgery after more than 1 year of follow-up evaluation, 6 (75%) patients had IPMC. Five (83%) of these cases were noninvasive or showed microinvasion. In the remaining 24 patients who underwent surgery without a follow-up period, 6 (25%) patients had IPMC, only 2 (33%) of which were noninvasive or showed microinvasion (P = .014).

Comments

IPMNs are a well-recognized type of pancreatic tumor and represent roughly 1% of pancreatic exocrine tumors and 12% of cystic pancreatic tumors.[16] Despite being larger than ductal adenocarcinomas, IPMNs appear to be biologically less aggressive than ductal adenocarcinomas, with a lower incidence of nodal positivity, perineural invasion, and vascular invasion, and a significantly better 5-year survival rate (62% vs 19%). Levy et al[17] reported that the actual risk of developing high-grade dysplasia or invasive carcinoma from IPMA at 2 years and 5 years for the branch duct type was 9% and 15%, respectively, whereas the risks for the main duct type, including combined type, were 58% and 63%, respectively. These data suggest that one can take a wait-and-see approach in most patients with branch duct–type IPMN.[18] By contrast, IPMC has been reported to acquire aggressive behavior similar to that of general invasive ductal adenocarcinoma of the pancreas once it invades the pancreatic parenchyma.[19] Therefore, discriminating between IPMC and IPMA is important, especially in the case of the branch duct type with low incidence of malignancy.

Table 4 Results of univariate and multivariate analyses

	IPMA	IPMC	Univariate analysis, P value	Multivariate analysis expected P value (odds ratio, range)
Tumor size, <30/≥30 mm	8/12	3/9	.4647	.813 (1.24, .21–7.32)
MPD diameter, <7/≥7 mm	17/3	5/7	.0184	.063 (5.67, .91–35.2)
Symptoms, yes/no	12/7	4/8	.1489	.512 (1.79, .10–3.19)
Mural nodule, no/yes	17/3	2/10	.0002	.019 (25.0, 3.29–200)

The management of branch pancreatic duct–type IPMN continues to be a topic of considerable controversy, although an increasing number of reports have provided information about its clinicopathologic characteristics. Tumor size, MPD diameter, and the presence of a mural nodule in the tumor are reported to be important in predicting malignancy.[8,15,20] Some studies have reported that a tumor size of more than 30 mm is associated with an increased risk of malignant change,[10,15,20] and recently Jang et al[21] reported that 20 mm is a useful cut-off value for tumor size when evaluating malignancy. Although an increase in tumor size undoubtedly is associated with increased malignant risk, we sometimes experience cases with no signs of malignancy despite a gradual increase in the size of the cystic lesions.

The frequencies of mural nodules and MPD dilatation are likely to increase with increased tumor size; thus, we need to examine the true importance of these factors in regards to the risk of malignancy in IPMNs. In addition, with recent advances in imaging modalities, small nodules can be detected, and the identification of mural nodules may allow for the discrimination of IPMC from IPMA.[22,23] In the present retrospective study, the selection of various cut-off values for tumor size did not allow for the diagnosis of IPMC. This result may have occurred in part because, in our hospital, the criteria for resection was applicable to almost all enrolled patients. Therefore, our study included many cases with tumors measuring more than 30 mm in diameter. In other words, the present study showed that tumors without dilatation of the MPD or the presence of mural nodules are associated with a low risk of malignancy, even when the tumor size is more than 30 mm. Multivariate analysis identified the presence of a mural nodule as the only significant factor related to the risk of malignancy and the most useful in predicting malignant changes. Among 8 patients with more than 1 year of follow-up evaluation, 6 (75%) patients had IPMC, 5 of whom (83%) had noninvasive tumors or tumors that showed microinvasion, whereas 6 (25%) of the remaining 24 patients without any follow-up evaluation had IPMC, only 2 of which (33%) were noninvasive or showed microinvasion. These findings indicate that, in patients followed up before surgery, IPMC was diagnosed selectively and at early stages, so the algorithm for IPMN treatment in this study is adequate. Furthermore, among these 8 patients, the 4 patients with a mural nodule had IPMC, whereas 4 of the 5 patients with MPD dilatation and 3 of the 5 patients with tumor growth had IPMC. This result also indicated that the presence of a mural nodule is useful for follow-up evaluation.

The procedure used to detect the mural nodule also may be important. In our institute, the presence of a mural nodule is diagnosed mainly by CT (high-resolution CT) or MRI (MRCP) because CT and MRI (MRCP) can provide clearer images than US or endoscopic retrograde cholangiopancreatography. Liu et al[23] also reported that CT is recommended to evaluate IPMN. Jang et al[21] reported the presence of mural nodules in many patients with benign IPMN, and the malignant ratio for patients with mural nodules in our study was much different from the ratio in the study by Jang et al[21] (76.9% vs 33.3%, respectively). However, the rate of malignancy in the report by Jang et al[21] seemed low. For example, Rodriguez et al[20] had 19 patients (82.6%) who were diagnosed with malignancy among 23 patients with mural nodules, and Sugiyama et al[10] had 8 patients (80.0%) who were diagnosed with malignancy among 10 patients with mural nodules. We do not know why this discrepancy occurred. The presence of a mural nodule was diagnosed by CT or MRI in our institute, but the method of mural nodule detection by Jang et al[21] was not stated clearly, so the diagnostic criteria may have been different from ours.

IPMN will be of increasing significance as a premalignant lesion originating from a large pancreatic duct. Additional studies are needed to elucidate the risk of malignancy in IPMN, especially in the branch type regarded as a relatively low-risk group, and we believe that a mural nodule could play an important role in predicting cancerous changes and deciding treatment strategy.

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CURRENT TOPICS REVIEW ARTICLE

Multimodal treatment for resectable esophageal cancer

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Abstract Surgical resection has been traditionally the mainstay of treatment for localized esophageal cancers. However, survival after surgery alone for advanced esophageal cancer is not satisfactory. In Japan, the development of multimodal therapy for esophageal cancers has centered mainly on systemic chemotherapy plus surgery to control distant metastasis. Based on the results of the recent Japan Clinical Oncology Group (JCOG) 9907 study, preoperative chemotherapy (consisting of 5-FU and cisplatin) followed by surgery has emerged as the standard treatment. In Western countries, where chemoradiotherapy followed by surgery has been mainly explored for patients with resectable esophageal cancers, two large controlled trials that evaluated the effectiveness of preoperative chemotherapy reported conflicting results. However, a recent meta-analysis reported significant survival benefits for preoperative chemotherapy in patients with adenocarcinoma of the esophagus. We need to find new effective preoperative chemotherapeutic regimens, including molecular target agents, with response rates higher than that of the conventional chemotherapy of 5-FU and cisplatin. However, we also must compare the survival benefits of preoperative chemotherapy with preoperative chemoradiotherapy.

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Introduction

Esophageal cancer remains an extremely difficult tumor to cure. Esophagectomy has been recognized as the standard treatment for resectable esophageal cancers. However, survival after surgery alone is still not satisfactory although new surgical techniques and perioperative care have been developed.[1–3] Approximately half the patients who undergo curative resection for esophageal cancers develop local or distant recurrence postoperatively.[4–8] To improve prognosis, multimodal therapy, including chemotherapy and radiotherapy, in addition to surgery has been developed. In Japan, three-field lymphadenectomy, which comprises cervical, mediastinal, and upper abdominal lymph node dissection, was introduced in the early 1980s, and there is a general agreement that this form of extended lymphadenectomy can achieve local tumor control.[2,9–12] Therefore, in Japan, surgery combined with chemotherapy is mainly applied for the control of distant metastasis. On the other hand, in Western countries, efforts have been directed since the late 1980s toward analysis of the benefits of neoadjuvant chemoradiotherapy followed by surgery in improving local tumor control and eradicating distant micrometastases.[13–20] In general, preoperative chemoradiation therapy, in particular, high-dose radiation therapy, is associated with increased perioperative morbidity although preoperative chemotherapy does not increase postoperative complications. By histopathological type, squamous cell carcinoma still accounts for the majority of esophageal cancers in Japan, the incidence of adenocarcinoma of the

Table 1 Randomized trials of preoperative or postoperative chemotherapy for squamous cell carcinoma of the esophagus in Japan

Study	Arm	*n*	DFS	*P* value	5-year OS	*P* value
JCOG8806	Surgery alone	100	NA		45.1%	
	Surgery + CDDP/VDS	105	NA		48.3%	0.60
JCOG9204	Surgery alone	122	45%*		52%	
	Surgery + 5-FU/CDDP	120	55%*	0.037	61%	0.13
JCOG9907	Surgery + 5-FU/CDDP	166	2.0 years**		38.4%	
	5-FU/CDDP + surgery	164	3.0 years**	0.044	60.1%	0.013

CDDP, cisplatin; 5-FU, fluorouracil; VDS, vindesine; DFS, disease-free survival rate; OS, overall survival rate; NA, not available
*Five-year disease-free survival; **median progression-free survival.

esophagus has increased dramatically during the past three decades in Western countries, and adenocarcinoma has become the dominant histopathological type of esophageal cancer rather than squamous cell carcinoma.[21,22] In operative procedures, the transhiatal approach has been widely performed in Western countries whereas it is rarely performed in Japan. Thus, this article reviews the accumulated evidence of systemic chemotherapy plus surgery in consideration of the differences in background between Japan and Western countries.

Systemic chemotherapy and surgery in Japan

In Japan, surgical resection has been the mainstay of treatment for clinical stage II and III esophageal cancers. The introduction of three-field lymphadenectomy improved the prognosis of patients with resectable esophageal cancers, but the 5-year survival rate remains relatively modest at less than 40%.[23] To compensate for this limitation of surgery, the role of adjuvant systemic chemotherapy was first explored in the late 1980s. The Japan Clinical Oncology Group (JCOG) conducted a randomized controlled trial (JCOG 8806) to compare the outcome of surgery alone and surgery followed by chemotherapy, consisting of fluorouracil (5-FU) and vindesin. The trial results indicated no significant benefits for postoperative chemotherapy[24] (Table 1).

Subsequently, the JCOG 9204 study compared postoperative adjuvant chemotherapy with surgery alone in patients who underwent curative resection (R0) for pathological stage II–IV esophageal cancers.[25] Patients in the postoperative chemotherapy group received two courses of chemotherapy comprising cisplatin at 80 mg/m^2 and 5-FU at 800 mg/m^2 for 5 days, separated by a 3-week interval. In that study, the overall survival was not significantly different between the two groups. However, the disease-free survival was significantly better in the postoperative chemotherapy group compared with surgery alone (5 year disease-free survival, 55% vs. 45%, $P=0.037$). These results suggest that postoperative chemotherapy seems to reduce recurrence after curative resection. In subgroup analysis, postoperative chemotherapy showed survival benefit in patients with lymph node metastasis (pN1), but not those without lymph node metastasis (pN0). Based on these results, two cycles of postoperative chemotherapy consisting of 5-FU and cisplatin were recommended for patients with pathologically confirmed lymph node metastasis who underwent surgery for esophageal cancers.

Following the results of JCOG 9204, another study, the JCOG 9907 study, compared preoperative chemotherapy, consisting of 5-FU and cisplatin, with postoperative chemotherapy, applying a regimen similar to that used in patients with clinical stage II–III esophageal cancers.[26] In the study, all patients of the preoperative chemotherapy group received 5-FU and cisplatin regardless of the clinical diagnosis of lymph node metastasis; in the postoperative chemotherapy group, only patients who were confirmed pathologically to have lymph node metastasis received the treatment. The results showed that survival was significantly better for the preoperative chemotherapy group than the postoperative chemotherapy group (5-year overall survival, 60.1% vs. 38.4%). Furthermore, the preoperative group of the JCOG9907 study was superior with regard to the overall survival compared with the definitive chemoradiotherapy group of the JCOG 9906 study,[27] which was conducted to assess the effectiveness of definitive chemoradiotherapy in the same population of the JCOG 9907 (resectable clinical stage II/III) (5-year survival rate, 60.1% vs. 37%).[26,27] Based on these results, preoperative chemotherapy consisting of 5-FU and cisplatin became the standard treatment for clinical stage II/III esophageal cancers in Japan. However, the JCOG 9907 study had several weak points that may be subject to criticism. Only 57% of patients received postoperative chemotherapy in the postoperative group because node-negative patients (pN0) were excluded from postoperative chemotherapy although most of the preoperative group received preoperative chemotherapy. The superiority of preoperative to postoperative chemotherapy was also evident in stage II patients, including node-negative patients, compared to those in stage III.