However, one should consider that PPCs are lethal complications frequently requiring extended intensive care, including reintubation and continuous positive airway pressure.

Smetana et al. interestingly reported that BMI was not associated with increased clinical PPCs after surgery in a systematic review.[14] However, obesity is thought to be a risk factor for PPCs and may lead to restrictive pulmonary physiology and further reduction of lung volume.[15, 16] Thus, obesity interrupts the ability to take a deep breath after surgery, and visceral fat (VF) plays an important factor in obesity. Patients with a high volume of VF have high abdominal pressure, resulting in a risk factor for PPCs. Therefore, a new strategy is required for evaluating obesity for the improvement of surgical outcomes after pancreaticoduodenectomy. We conducted this study to determine whether postoperative complications, including PPCs, are associated with BMI and visceral fat area (VFA) after pancreaticoduodenectomy.

## Material and Methods

### Patients

Between February 2003 and December 2009, 324 consecutive patients underwent pancreaticoduodenectomy in Wakayama Medical University Hospital (WMUH). In the present study, seven patients were excluded because of undergoing hepatopancreaticoduodenectomy ($n$=3), additional pancreatic tail resection ($n$=2), total gastrectomy ($n$=1), or splenectomy ($n$=1). The 317 enrolled patients in the present study have a median age of 70 years (range 35–91); 181 are male and 136 are female. Patients' characteristics and perioperative and postoperative parameters were reviewed for the following clinical variables: age, gender, concomitant disease, including cardiovascular disease, chronic obstructive pulmonary disease (COPD), and diabetes mellitus, recent smoking history (smoking within 4 weeks prior to surgery),[17] pulmonary function on spirograms (percentage predicted vital capacity, %VC, and the ratio of forced expiratory volume in 1 s to forced vital capacity, FEV1/FVC), preoperative biliary drainage, type of resection (pylorus-preserving pancreaticoduodenectomy, PpPD, or conventional pancreaticoduodenectomy, PD), additional portal vein resection, BMI, VFA, operative time, intraoperative bleeding, red blood cell transfusion, pancreatic texture (soft or hard), and histologic diagnosis (malignant or benign). Informed consents were obtained from all the patients in accordance with the guidelines of the Ethical Committee on Human Research of WMUH.

### BMI and Visceral Fat Area

BMI was calculated by patient height and body weight measured preoperatively. The World Health Organization criteria for overweight and obesity were used (overweight, BMI 25.0–29.9; obesity, BMI≥30.0).[18] VFA was measured using a cross-sectional CT scan at the level of the umbilicus by FatScan software version 3.0 (N2 systems Inc., Osaka, Japan),[19] and patients were classified into a high-VFA group (VFA≥130 $cm^2$) and a low-VFA group (VFA<130 $cm^2$). In Fig. 1, we show samples in this study population of the amount of visceral fat by FatScan

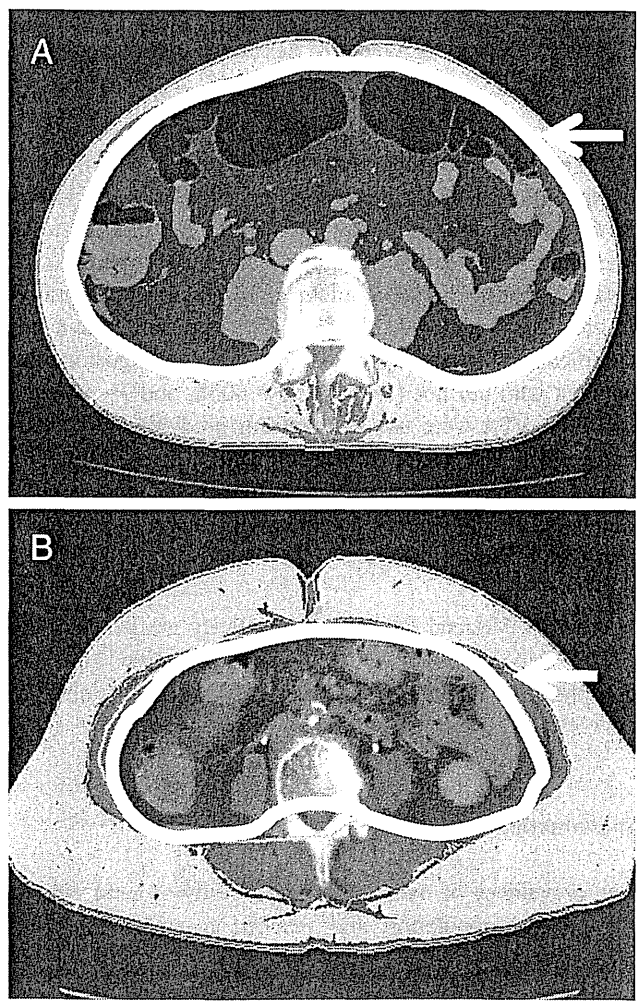


**Fig. 1** Distribution of visceral fat area (VFA) by FatScan software on preoperative CT scan. The white line (*white arrow*) outlines the intraperitoneal area. Visceral fat tissue was calculated in the region outlined by the white line by FatScan software. A, VFA was 194.4 $cm^2$ and body mass index (BMI) was 19.6 $kg/m^2$, representing high VFA but low BMI. B, VFA was 71.1 $cm^2$ and BMI was 25.3 $kg/m^2$, representing low VFA but high BMI (high VFA≥130 $cm^2$ and low VFA<130 $cm^2$ and high BMI≥25 $kg/m^2$ and low BMI<25 $kg/m^2$)

software on preoperative CT scan. We have no financial relationship to disclose with the FatScan software used.

### Surgical Treatment

All patients underwent PpPD with Traverso reconstruction or PD with Child reconstruction, with various extents of lymph node dissection, as described previously.[20, 21] All operations were performed by two experienced pancreatic surgeons (H.Y. and M.T.). Pancreaticojejunostomies were performed with duct-to-mucosa, end-to-side anastomosis in all patients.[22] A 5-French polyethylene pancreatic duct drainage tube (Sumitomo Bakelite, Tokyo, Japan) was used in an external or internal drainage stent for pancreaticojejunostomy. Hepaticojejunal anastomosis was performed end-to-side without stent, followed by pancreaticojejunostomies. Reconstruction of the duodenojejunostomies was performed by the antecolic route.[20] A single prophylactic closed-suction drain was routinely placed in the right upper quadrant around the pancreatic and biliary anastomosis.

### Postoperative Complications

POPFs were defined according to the definition of the International Study Group on Pancreatic Fistula.[23] DGE and PPH were also defined according to definitions of the International Study Group of Pancreatic Surgery.[24, 25] In detail, POPF was defined as a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than three times the serum amylase activity.[23] DGE was defined by the need for maintenance of the nasogastric tube (NGT) for 3 days, need for reinsertion of NGT for persistent vomiting after postoperative day 3, or inability to tolerate a solid diet by postoperative day 7.[24] PPH is defined by three parameters: onset, location, and severity. The onset is either early (≤24 h after the end of the index operation) or late (<24 h), the location is either intraluminal or extraluminal, and the severity of bleed may be either mild or severe. Three different grades of PPH (grades A, B, and C) are defined according to these parameters.[25] PPCs were defined as pneumonia with evidence by radiologic pulmonary infiltrates and/or the presence of pathogenic bacteria in the sputum culture, and pulmonary atelectasis required frequent bronchoscopic toilet or prolonged ventilator support.[26] Pulmonary edema, pulmonary embolus, and acute respiratory distress syndrome were excluded, similar to previous reports.[27] Other postoperative complications were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v.3.0). In this study, adverse events of grades 2–5 within 30 days after surgery were expediently judged as postoperative complications. Adverse events of grade 1 were excluded because no medical treatment was required. Mortality was defined as death within 30 days after surgery.

### Statistical Analysis

Any significance in the correlation between all variables and two variables (BMI and VFA) was evaluated by Mann–Whitney $U$ test and linear regression analysis, where applicable. A $P$ value of less than 0.05 was considered statistically significant. Risk factors for complications were analyzed by logistic regression analysis. Multivariate logistic regression analysis was performed incorporating all factors with $P<0.20$ on univariate analysis. All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 13.0 (SPSS, Chicago, Illinois).

## Results

### Clinicopathological Characteristics

Table 1 shows the clinicopathological characteristics of patients. Median BMI and VFA were 21.5 kg/m$^2$ (range 14.8–33.5) and 77.5 cm$^2$ (range 9.2–261.2), respectively. Association between characteristics and BMI/VFA were summarized in Table 2. BMI was significantly lower in patients with %VC<80 on spirogram ($P$=.0429) and was higher in patients of benign disease than malignant disease ($P$=.0334). Otherwise, gender and diabetes mellitus were demonstrated to have significant differences in VFA ($P$ <.0001 and $P$=.0177, respectively). Other variables were statistically identical with both BMI and VFA.

### Surgical Outcome

Median operative time was 358 min (range 185–723) and median estimated blood loss was 735 ml (range 45–9,100; Table 1). Relations between intraoperative outcome and BMI/VFA are shown in Table 3. The linear relationship was demonstrated to have a significant correlation between operative time and both BMI and VFA ($P$=.0088 and $P$<.0001, respectively). Estimated blood loss and required red blood cell transfusion were also demonstrated to have a significant correlation with VFA ($P$=.0008 and $P$=.0276), whereas for BMI the relation of estimated blood loss was only marginally correlated ($P$=.0575), and there was no difference between blood transfusion and BMI ($P$=.3341).

**Table 1** Clinicopathological characteristics and intraoperative outcome of patients after pancreaticoduodenectomy

| Variable | *N*=317 |
|---|---|
| Age (years), median (range) | 70 (35–91) |
| Gender (male/female) | 181/136 |
| Concomitant disease (yes/no) | |
| Cardiovascular disease | 21/296 |
| COPD | 15/302 |
| Diabetes mellitus | 98/219 |
| Recent smoking history[a] (yes/no) | 87/230 |
| Pulmonary function on spirogram | |
| %VC<80 (yes/no) | 31/286 |
| FEV1/FVC ratio<0.70 (yes/no) | 64/253 |
| Preoperative biliary drainage (yes/no) | 127/190 |
| Type of resection (PpPD/PD) | 269/48 |
| Additional portal vein resection (yes/no) | 43/274 |
| Pancreatic texture (soft/hard) | 137/180 |
| Histologic diagnosis (malignant/benign) | 232/85 |
| BMI median (range) | 21.5 (14.8–33.5) |
| BMI (≥25/<25) | 46/271 |
| VFA median (range) | 77.5 (9.2–261.2) |
| VFA (≥130/<130) | 60/257 |
| Operative time (min), median (range) | 358 (185–723) |
| Estimated blood loss (ml), median (range) | 735 (45–9100) |
| Red blood cell transfusion (yes/no) | 114/203 |

*COPD* chronic obstructive pulmonary disease, *%VC* percentage predicted vital capacity, *FEV1/FVC ratio* ratio of forced expiratory volume in 1 s to forced vital capacity, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *BMI* body mass index, *VFA* visceral fat area

[a] Recent smoking history means smoking within 4 weeks prior to surgery[17]

## Postoperative Complications

Of all patients, 130 patients had postoperative complications (41.0%). The complications are listed in Table 4. The most common postoperative complication was POPF in 92 patients (29.0%), consisting of 61 grade A (19.2%), 27 grade B (8.5%), and four grade C (1.3%). The incidence of DGE was 35 patients (11.0%), consisting of six grade A (1.9%), ten grade B (3.2%), and 15 grade C (4.7%), and the incidence of PPH was 11 patients (3.5%), consisting of six grade B (1.9%) and five grade C (1.6%). PPCs occurred in 14 patients (4.4%). In the 14 patients with PPCs, seven were unexpectedly admitted to the intensive care unit, and the other five patients required intensive therapy by continuous positive airway pressure in the surgical ward. Mortality occurred in five patients (1.6%); causes were extraluminal hemorrhage (2), sepsis (1), disseminated intravascular coagulation (1), and nonobstructive mesenteric ischemia (1).

## Differences Between Postoperative Complications and BMI/VFA

Table 5 shows the statistical differences between the occurrence of postoperative complications and variables of BMI/VFA. Both BMI and VFA in patients with complications were significantly higher than in those without complications ($P$=.0434 and $P$=.0189, respectively). Regarding POPF, BMI and VFA demonstrated no significant differences; however, the patients who developed grade B/C POPF had higher VFA than the patients who did not develop POPF ($P$=.0282). BMI and VFA were demonstrated

**Table 2** Association between clinicopathological characteristics and BMI/VFA

| Variable | BMI (median, range) | *P* value | VFA (median, range) | *P* value |
|---|---|---|---|---|
| Age, years (≥70/<70) | 21.5 (15.4–33.5)/21.6 (14.8–30.5) | .8392 | 81.5 (9.2–261.2)/75.7 (10.4–241.1) | .2856 |
| Gender (male/female) | 21.5 (15.4–31.2)/21.5 (14.8–33.5) | .6235 | 93.5 (10.9–261.2)/68.8 (9.2–201.0) | <.0001 |
| Concomitant disease (yes/no) | | | | |
| Cardiovascular disease | 21.1 (15.4–31.2)/21.5 (14.8–33.5) | .7506 | 81.3 (16.5–183.3)/76.2 (9.2–261.2) | .2040 |
| COPD | 21.2 (15.4–26.1)/21.5 (14.8–33.5) | .1443 | 88.1 (16.5–144.2)/77.1 (9.2–261.2) | .9290 |
| Diabetes mellitus | 21.5 (15.8–33.5)/21.5 (14.8–30.0) | .3623 | 90.6 (10.4–261.2)/75.8 (9.2–230.9) | .0177 |
| Recent smoking history (yes/no) | 21.3 (15.8–31.2)/21.6 (14.8–33.5) | .9967 | 86.1 (18.5–241.1)/75.2 (9.2–261.2) | .1201 |
| Pulmonary function on spirogram | | | | |
| %VC<80 (yes/no) | 21.0 (15.4–26.7)/21.6 (14.8–33.5) | .0429 | 89.4 (16.5–241.1)/77.0 (9.2–261.2) | .5670 |
| FEV1/FVC ratio<0.70 (yes/no) | 21.6 (14.8–30.5)/21.5 (15.4–33.5) | .2694 | 75.9 (16.0–252.0)/78.8 (9.2–261.2) | .8427 |
| Preoperative biliary drainage (yes/no) | 21.4 (15.8–30.5)/21.6 (14.8–33.5) | .7919 | 74.5 (10.4–241.1)/81.7 (9.2–261.2) | .5363 |
| Type of resection (PpPD/PD) | 21.6 (14.8–33.5)/20.6 (15.4–31.2) | .0731 | 77.5 (10.0–261.2)/78.2 (9.2–209.3) | .3410 |
| Additional portal vein resection (yes/no) | 21.4 (16.2–28.3)/21.5 (14.8–33.5) | .8756 | 84.7 (10.4–208.5)/76.2 (9.2–261.2) | .7399 |
| Pancreatic texture (soft/hard) | 21.6 (14.8–31.2)/21.4 (15.4–33.5) | .4697 | 76.5 (10.0–241.1)/78.9 (9.2–261.2) | .6291 |
| Histologic diagnosis (malignant/benign) | 21.2 (15.4–33.5)/22.4 (14.8–30.0) | .0334 | 75.5 (10.4–252.0)/87.4 (9.2–261.2) | .1853 |

**Table 3** Relation with intraoperative outcome

| Variable | BMI | | | VFA | | |
|---|---|---|---|---|---|---|
| | Regression coefficient | $R^2$ | *P* value | Regression coefficient | $R^2$ | *P* value |
| Operative time (min) | 3.878 | .022 | .0088 | 0.377 | .054 | <.0001 |
| Estimated blood loss (ml) | 65.417 | .011 | .0575 | 7.023 | .035 | .0008 |
| Red blood cell transfusion (units) | .088 | .003 | .3341 | .012 | .015 | .0276 |

*BMI* body mass index, *VFA* visceral fat area

to have no statistical differences regardless of the occurrences of DGE and PPH. Median VFA of patients with PPCs was 135.7 (range 49.2–174.3), significantly higher than patients without PPCs (75.9; range 9.2–261.2) ($P$=.0058), whereas there was no difference in BMI. Both BMI and VFA showed no significant differences regardless of the occurrence of the other complications including intra-abdominal abscess, cardiovascular complication, bile leakage, sepsis, bowel obstruction, and wound infection. The mortality group had significantly higher BMI and VFA compared with the nonmortality group ($P$=.0143 and $P$=.0173, respectively).

## Risk Factors Influencing the Incidence of POPF Grade B/C

BMI and VFA were categorized into two groups and assessed; 46 patients (14.5%) were categorized to high BMI (≥25.0 kg/m$^2$) and the other 271 patients (85.5%) were categorized to low BMI (<25.0 kg/m$^2$); similarly, 60 (18.9%) patients were categorized into high VFA (≥130 cm$^2$) and the other 257 (81.1%) into low VFA (<130 cm$^2$). Of all 31 patients with POPF grade B/C, five patients were in the high-BMI and high-VFA groups; however, two patients were in only the high-BMI group and two patients were in only the high-VFA group. Multivariate analysis demonstrated that preoperative biliary drainage and soft pancreas predicted the independent risk factor for POPF grade B/C ($P$=.0407 and $P$=.0004, respectively; Table 6).

**Table 4** Incidence of postoperative complications after pancreaticoduodenectomy

| Complication | Number of patients | % |
|---|---|---|
| Overall complications | 130 | 41.0 |
| POPF | | |
| All grades | 92 | 29.0 |
| Grade A/B/C | 61/27/4 | 19.2/8.5/1.3 |
| DGE | 32 | 10.1 |
| PPH | 11 | 3.5 |
| Extraluminal hemorrhage | 5 | 1.6 |
| Intraluminal hemorrhage | 6 | 1.9 |
| Intra-abdominal abscess | 38 | 12.0 |
| PPCs | 14 | 4.4 |
| Cardiovascular complication | 10 | 3.2 |
| Bile leakage | 9 | 2.8 |
| Sepsis | 11 | 3.5 |
| Bowel obstruction | 10 | 3.2 |
| Wound infection | 19 | 6.0 |
| Mortality | 5 | 1.6 |

*POPF* postoperative pancreatic fistula, *DGE* delayed gastric empting, *PPH* postpancreatectomy hemorrhage, *PPCs* postoperative pulmonary complications

## Risk Factors Influencing the Incidence of PPCs

In the 14 patients who developed PPCs, four patients were in the high-BMI group (8.7%). On the other hand, eight patients were in the high-VFA group (13.3%). Six parameters that had a $P$ value ≤ 0.20 by univariate analysis were selected for multivariate analysis, gender, additional portal vein resection, high BMI, high VFA, operative time, and estimated blood loss, and only high VFA was predicted as an independent risk factor influencing the incidence of PPCs ($P$=.0390, odds ratio 4.246, 95% confidence interval 1.076–16.759; Table 7).

## Risk Factors Influencing Mortality

There were five postoperative mortalities (1.6%). Three patients were in the high-BMI group and two were in the low-BMI group, whereas four patients were in the high-VFA group and one was in the low-VFA group. Multivariate analysis demonstrated that recent smoking history (smoking within 4 weeks prior to surgery) was the only independent predictive factor ($P$=.0321, odds ratio 28.954, 95% confidence interval 1.332–629.405), although high BMI and high VFA were not consequently risk factors for postoperative mortality ($P$=.1145 and $P$=.7514, respectively; Table 8).

## Discussion

In this study, VFA was demonstrated to be the independent risk factor for the incidence of PPCs after pancreaticoduo-

**Table 5** Difference of BMI and VFA in postoperative complications

| Complication | BMI (median, range) | | | VFA (median, range) | | |
|---|---|---|---|---|---|---|
| | (+) | (−) | *P* value | (+) | (−) | *P* value |
| Overall complications | 21.9 (15.6–33.5) | 21.3 (14.8–31.2) | .0434 | 86.8 (15.0–261.2) | 73.0 (9.2–252.0) | .0178 |
| POPF | | | | | | |
| All grades | 21.7 (15.8–29.8) | 21.4 (14.8–33.5) | .1364 | 87.7 (9.2–261.2) | 74.0 (10.0–252.0) | .1420 |
| Grade B/C | 22.2 (16.2–29.8) | 21.5 (14.8–33.5) | .0814 | 93.5 (20.1–261.2) | 75.2 (9.2–252.0) | .0282 |
| DGE | 21.5 (15.6–28.4) | 21.5 (14.8–33.5) | .7626 | 93.1 (22.3–201.0) | 75.9 (9.2–261.2) | .1895 |
| PPH | | | | | | |
| Extraluminal hemorrhage | 23.0 (19.4–26.6) | 21.5 (14.8–33.5) | .3934 | 93.5 (73.5–160.9) | 76.6 (9.2–261.2) | .2498 |
| Intraluminal hemorrhage | 24.9 (15.8–28.4) | 21.5 (14.8–33.5) | .0507 | 144.6 (19.9–208.5) | 76.6 (9.2–261.2) | .1219 |
| Intra-abdominal abscess | 22.2 (15.8–29.8) | 21.5 (14.8–33.5) | .3191 | 89.6 (19.4–261.2) | 75.8 (9.2–252.0) | .1088 |
| PPCs | 21.6 (19.6–28.3) | 21.5 (14.8–33.5) | .1668 | 135.7 (49.2–174.3) | 75.9 (9.2–261.2) | .0058 |
| Cardiovascular complication | 20.8 (18.7–28.6) | 21.5 (14.8–33.5) | .9972 | 61.1 (28.7–261.2) | 78.3 (9.2–252.0) | .9650 |
| Bile leakage | 19.3 (16.8–29.8) | 21.5 (14.8–33.5) | .2588 | 79.3 (19.4–209.3) | 77.1 (9.2–261.2) | .5888 |
| Sepsis | 20.6 (19.3–30.5) | 21.5 (14.8–33.5) | .9306 | 114.2 (49.6–162.8) | 76.2 (9.2–261.2) | .0680 |
| Bowel obstruction | 21.4 (19.6–28.6) | 21.5 (14.8–33.5) | .6650 | 78.7 (18.8–261.2) | 77.5 (9.2–252.0) | .6727 |
| Wound infection | 21.9 (16.8–33.5) | 21.5 (14.8–31.2) | .4235 | 81.2 (15.0–194.8) | 76.6 (9.2–261.2) | .8323 |
| Mortality | 25.3 (22.6–30.5) | 21.5 (14.8–33.5) | .0143 | 142.7 (73.5–208.5) | 76.6 (9.2–261.2) | .0173 |

**Table 6** Univariate and multivariate analyses of risk factors for POPF grade B/C

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | *P* value | Odds ratio (95% CI) | *P* value | Odds ratio (95% CI) |
| Age, years (≥70 or <70) | .4370 | 1.346 (0.636–2.851) | – | – |
| Gender (male/female) | .6199 | 1.212 (0.567–2.591) | – | – |
| Concomitant disease (yes/no) | | | | |
| Cardiovascular disease | .4353 | 0.443 (0.057–3.422) | – | – |
| COPD | .7067 | 1.236 (0.410–3.720) | – | – |
| Diabetes mellitus | .1490 | 0.506 (0.201–1.276) | .4037 | 0.661 (0.251–1.746) |
| Recent smoking history[a] (yes/no) | .1447 | 0.478 (0.178–1.289) | .1291 | 0.451 (0.161–1.261) |
| Pulmonary function on spirogram | | | | |
| %VC<80% (yes/no) | .5154 | 0.611 (0.139–2.695) | – | – |
| FEV1/FVC ratio<0.70 (yes/no) | .7272 | 1.172 (0.481–2.855) | – | – |
| Preoperative biliary drainage (yes/no) | .0348 | 2.248 (1.060–4.771) | .0407 | 2.292 (1.036–5.071) |
| Type of resection (PpPD/PD) | .3771 | 1.743 (0.508–5.978) | – | – |
| Additional portal vein resection (yes/no) | .9099 | 0.938 (0.311–2.828) | – | – |
| Pancreatic texture (soft/hard) | .0002 | 5.296 (2.208–12.703) | .0004 | 5.100 (2.084–12.481) |
| Histologic diagnosis (malignant/benign) | .9263 | 0.975 (0.564–1.683) | – | – |
| BMI (≥25 or <25) | .1849 | 1.847 (0.746–4.576) | .0685 | 2.508 (0.932–6.743) |
| VFA (≥130 or <130) | .5854 | 1.282 (0.525–3.133) | – | – |
| Operative time (min; ≥350 or <350) | .5205 | 1.283 (0.600–2.741) | – | – |
| Intraoperative bleeding (ml; ≥1,000 or <1,000) | .7384 | 1.141 (0.525–2.481) | – | – |
| Red blood cell transfusion (yes/no) | .9534 | 0.977 (0.450–2.120) | – | – |

*COPD* chronic obstructive pulmonary disease, *%VC* percentage predicted vital capacity, *FEV1/FVC ratio* ratio of forced expiratory volume in 1 s to forced vital capacity, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *BMI* body mass index, *VFA* visceral fat area, *CI* confidence interval

[a] Recent smoking history = smoking within 4 weeks prior to surgery[17]

**Table 7** Univariate and multivariate analyses of risk factors for PPCs

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | *P* value | Odds ratio (95% CI) | *P* value | Odds ratio (95% CI) |
| Age, years (≥70 or <70) | .3300 | 1.742 (0.570–5.318) | – | – |
| Gender (male/female) | .0435 | 4.757 (1.047–21.625) | .1863 | 2.956 (0.592–14.750) |
| Concomitant disease (yes/no) | | | | |
| Cardiovascular disease | .9365 | 1.088 (0.135–8.748) | – | |
| COPD | .6666 | 1.588 (0.194–13.015) | – | – |
| Diabetes mellitus | .4367 | 0.597 (0.163–2.190) | – | – |
| Recent smoking history[a] (yes/no) | .4808 | 1.497 (0.487–4.600) | – | – |
| Pulmonary function on spirogram | | | | |
| %VC<80% (yes/no) | .7354 | 0.700 (0.088–5.541) | – | – |
| FEV1/FVC ratio<0.70 (yes/no) | .5763 | 0.648 (0.141–2.971) | – | – |
| Preoperative biliary drainage (yes/no) | .7345 | 0.824 (0.270–2.519) | – | – |
| Type of resection (PpPD/PD) | .5053 | 0.640 (0.172–2.383) | – | – |
| Additional portal vein resection (yes/no) | .1059 | 2.708 (0.810–9.057) | .2929 | 2.034 (0.542–7.635) |
| Pancreatic texture (soft/hard) | .2712 | 0.515 (0.158–1.679) | – | – |
| Histologic diagnosis (malignant/benign) | .4451 | 0.646 (0.210–1.985) | – | – |
| BMI (≥25 or <25) | .1384 | 2.486 (0.745–8.291) | .8179 | 0.841 (0.193–3.673) |
| VFA (≥130 or <130) | .0009 | 6.436 (2.142–19.333) | .0390 | 4.246 (1.076–16.759) |
| Operative time (min; ≥350 or <350) | .0216 | 11.018 (1.423–85.304) | .0678 | 7.258 (0.865–60.932) |
| Intraoperative bleeding (ml; ≥1,000 or <1,000) | .1697 | 2.124 (0.725–6.224) | .6801 | 0.778 (0.236–2.566) |
| Red blood cell transfusion (yes/no) | .2692 | 1.832 (0.626–5.361) | – | – |

*CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *%VC* percentage predicted vital capacity, *FEV1/FVC ratio* ratio of forced expiratory volume in 1 s to forced vital capacity, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *BMI* body mass index, *VFA* visceral fat area

[a] Recent smoking history = smoking within 4 weeks prior to surgery[17]

denectomy. Additionally, BMI did not statistically correlate with the incidence of PPCs. Smetana et al. concluded that obesity was not a risk factor for PPCs[14] because many studies reported that obesity had not increased the risk for PPCs after noncardiothoracic surgery.[28, 29] However, obesity was defined by BMI. As shown in Fig. 1, visceral fat has an individual distribution. In the high-VFA group, 29 patients (48.3%) were interestingly of normal BMI, and 15 patients of high BMI (32.6%) had VFA less than 130 $cm^2$; these results indicate that BMI and VFA are independent factors from each other for evaluation of the obesity status, and BMI could not always reflect the amount of visceral fat for surgeons.

After abdominal surgery, various factors have been considered to modify postoperative pulmonary dysfunction, that is, rapid shallow breathing, prolonged supine position,[30] pain and anesthesia-induced diaphragmatic dysfunction,[31] and impaired mucociliary clearance.[32] Visceral fat accumulation increases intra-abdominal pressure[33] to pump the diaphragmatic muscle upward, compressing the parenchyma of the lung. Consequently, patients with visceral obesity are affected by a restrictive respiratory impairment with decreased expiratory reserve volume and functional residual capacity.[15, 16] It was considered that the restrictive respiratory impairment caused by visceral fat accumulation may further impair pulmonary function in the perioperative period and lead to PPCs.

In the present study, overall POPF were not associated with BMI and VFA; however, the patients who developed POPF grade B/C showed significantly higher VFA than patients without grade B/C POPF, regardless of risk factors for POPF grade B/C. House et al. showed that the patients with retrorenal visceral fat thickness were associated with the incidence of pancreatic fistula after pancreaticoduodenectomy.[34] Moreover, fatty infiltration into the pancreatic parenchyma was demonstrated as a risk factor for POPF after pancreaticoduodenectomy;[35, 36] therefore, further studies are expected to associate VFA, fatty infiltration, and POPF.

Patients with postoperative mortality had significantly higher BMI and higher VFA than other patients, whereas neither BMI nor VFA was a risk factor for mortality.

**Table 8** Univariate and multivariate analyses of risk factors for mortality

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | *P* value | Odds ratio (95% CI) | *P* value | Odds ratio (95% CI) |
| Age, years (≥70 or <70) | .6097 | 0.625 (0.103–3.794) | – | – |
| Gender (male/female) | .3201 | 3.051 (0.337–27.615) | – | – |
| Concomitant disease (yes/no) | | | | |
| Cardiovascular disease | .9796 | NE | – | – |
| COPD | .9828 | NE | – | – |
| Diabetes mellitus | .9690 | NE | – | – |
| Recent smoking history[a] (yes/no) | .0329 | 11.036 (1.216–100.187) | .0321 | 28.954 (1.332–629.405) |
| Pulmonary function on spirogram | | | | |
| %VC<80% (yes/no) | .4513 | 2.350 (0.254–21.716) | – | – |
| FEV1/FVC ratio<0.70 (yes/no) | .2844 | 2.688 (0.440–16.440) | – | – |
| Preoperative biliary drainage (yes/no) | .3719 | 2.274 (0.375–13.809) | – | – |
| Type of resection (PpPD/PD) | .9795 | NE | – | – |
| Additional portal vein resection (yes/no) | .1101 | 4.407 (0.714–27.176) | .0695 | 14.656 (0.807–266.262) |
| Pancreatic texture (soft/hard) | .3185 | 0.326 (0.036–2.950) | – | – |
| Histologic diagnosis (malignant/benign) | .1191 | 0.238 (0.039–1.448) | .0684 | 0.048 (0.002–1.258) |
| BMI (≥25 or <25) | .0158 | 9.384 (1.523–57.805) | .1145 | 26.257 (0.453–1520.454) |
| VFA (≥130 or <130) | .0100 | 18.286 (2.005–166.773) | .7514 | 1.695 (0.065–44.353) |
| Operative time (min; ≥350 or <350) | .9763 | NE | – | – |
| Intraoperative bleeding (ml; ≥1,000 or <1,000) | .2148 | 3.134 (0.515–19.053) | – | – |
| Red blood cell transfusion (yes/no) | .0761 | 7.345 (0.811–66.545) | .1175 | 15.023 (0.505–447.051) |

*CI* confidence interval, *NE* not able to estimate, *COPD* chronic obstructive pulmonary disease, *%VC* percentage predicted vital capacity, *FEV1/FVC ratio* ratio of forced expiratory volume in 1 s to forced vital capacity, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *BMI* body mass index, *VFA* visceral fat area

[a] Recent smoking history = smoking within 4 weeks prior to surgery[17]

Fortunately, our study had a low incidence of mortality ($n$= 5, 1.6%); therefore, the influence of VFA on mortality cannot be evaluated.

The limitations of our study include the facts that the racial responses to relative levels of obesity with the population in Japan differ across much of the Western countries. WHO defines obesity as BMI≥30.0, but the prevalence of the population with such a BMI is less than 3% of the general population in Japan.[37] The Western Pacific Region of the WHO has recommended lowering the BMI cutoff levels for Asian people to 25.0 for obesity[37] because of occurring of obesity-related disorders at a much lower BMI than in Caucasian populations. For this point, we defined high BMI as BMI≥25.0 kg/m$^2$ in this study.

In the present study, we categorized the patients into high- and low-VFA groups using the cutoff value of VFA determined to be 130 cm$^2$ for logistic regression analysis because VFA≥130 cm$^2$ has been reported to be a risk factor for cardiovascular disease,[38] metabolic syndrome,[39] and the complication of laparoscopic sigmoidectomy.[40] However, the optimal cutoff value for VFA still remains unclear, and it is essential to determine the optimal cutoff value of VFA for pancreatic surgery.

It has been demonstrated that adipose tissue is not only for fat storage but is also a metabolically active organ secreting several hormones, adipocytokines, including adiponectin, leptin, tumor necrosis factor-α, interleukin-6, angiotensinogen, and plasminogen activator inhibitor 1. Circulating adiponectin levels correlate inversely with VFA, and hypoadiponectinemia with visceral adiposity is associated with a low-grade systemic inflammatory environment.[41] Indeed, a low preoperative adiponectin level was an independent risk factor for the development of postoperative infections after colorectal cancer surgery.[42] These results suggest that adipocytokines with visceral obesity may influence postoperative complications, including PPCs.

To prevent PPCs, prophylactic respiratory physiotherapy, management of immune status, and fast-track recovery pathways including early mobilization are thought to be effective; therefore, careful perioperative management may be more essential for patients with visceral obesity.

In conclusion, visceral obesity was the independent risk factor for the incidence of PPCs after pancreaticoduodenectomy. Preoperative VFA measurements using CT scan may be a useful tool for the prediction of the development of PPCs compared to BMI calculation and may reduce the incidence of PPCs through careful management of patients with high VFA.

**Acknowledgments** This work was supported in part by grants from the Japanese Society for Advancement of Surgical Techniques.

## References


1. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006; 355:763–778.
2. Ojima T, Iwahashi M, Nakamori M, Nakamura M, Naka T, Ishida K, Ueda K, Katsuda M, Iida T, Tsuji T, Yamaue H. Influence of overweight on patients with gastric cancer after undergoing curative gastrectomy: an analysis of 689 consecutive cases managed by a single center. Arch Surg 2009; 144:351–358.
3. Leroy J, Ananian P, Rubino F, Claudon B, Mutter D, Marescaux J. The impact of obesity on technical feasibility and postoperative outcomes of laparoscopic left colectomy. Ann Surg 2005; 241:69–76.
4. Doyle SL, Lysaght J, Reynolds JV. Obesity and post-operative complications in patients undergoing non-bariatric surgery. Obes Rev 2010; 11:875–886.
5. Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. Lancet 2003; 361:2032–2035.
6. Tokunaga M, Hiki N, Fukunaga T, Ogura T, Miyata S, Yamaguchi T. Effect of individual fat areas on early surgical outcomes after open gastrectomy for gastric cancer. Br J Surg 2009; 96:496–500.
7. Lee JH, Paik YH, Lee JS, Ryu KW, Kim CG, Park SR, Kim YW, Kook MC, Nam BH, Bae JM. Abdominal shape of gastric cancer patients influences short-term surgical outcomes. Ann Surg Oncol 2007; 14:1288–1294.
8. Hiki N, Fukunaga T, Yamaguchi T, Ogura T, Miyata S, Tokunaga M, Ohyama S, Sano T. Increased fat content and body shape have little effect on the accuracy of lymph node retrieval and blood loss in laparoscopic distal gastrectomy for gastric cancer. J Gastrointest Surg 2009; 13:626–633.
9. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997; 226:248–257.
10. Turaga K, Kaushik M, Forse RA,Sasson AR. In hospital outcomes after pancreatectomies: an analysis of a national database from 1996 to 2004. J Surg Oncol 2008; 98:156–160.
11. Simons JP, Shah SA, Ng SC, Whalen GF, Tseng JF. National complication rates after pancreatectomy: beyond mere mortality. J Gastrointest Surg 2009; 13:1798–1805.
12. Grobmyer SR, Pieracci FM, Allen PJ, Brennan MF, Jaques DP. Defining morbidity after pancreaticoduodenectomy: use of a prospective complication grading system. J Am Coll Surg 2007; 204:356–364.
13. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006; 244:10–15.
14. Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med 2006; 144:581–595.
15. Canoy D, Luben R, Welch A, Bingham S, Wareham N, Day N, Khaw KT. Abdominal obesity and respiratory function in men and women in the EPIC-Norfolk Study, United Kingdom. Am J Epidemiol 2004; 159:1140–1149.
16. Busetto L, Sergi G. Visceral fat and respiratory complications. Diab Obes Metab 2005; 7:301–306.
17. Lindstrom D, Sadr Azodi O, Wladis A, Tonnesen H, Linder S, Nasell H, Ponzer S, Adami J. Effects of a perioperative smoking cessation intervention on postoperative complications: a randomized trial. Ann Surg 2008; 248:739–745.
18. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000; 894:i–xii, 1–253.
19. Tanaka K, Miyashiro I, Yano M, Kishi K, Motoori M, Seki Y, Noura S, Ohue M, Yamada T, Ohigashi H, Ishikawa O. Accumulation of excess visceral fat is a risk factor for pancreatic fistula formation after total gastrectomy. Ann Surg Oncol 2009; 16:1520–1525.
20. Tani M, Terasawa H, Kawai M, et al. Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. Ann Surg 2006; 243:316–320.
21. Kawai M, Tani M, Terasawa H, Ina S, Hirono S, Nishioka R, Miyazawa M, Uchiyama K, Yamaue H . Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients. Ann Surg 2006; 244:1–7.
22. Tani M, Onishi H, Kinoshita H, Kawai M, Ueno M, Hama T, Uchiyama K, Yamaue H. The evaluation of duct-to-mucosal pancreaticojejunostomy in pancreaticoduodenectomy. World J Surg 2005; 29:76–79.
23. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138:8–13.
24. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo C, Buchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007; 142:761–768.
25. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Buchler MW. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007; 142:20–25.
26. Lee JM, Lo AC, Yang SY, Tsau HS, Chen RJ, Lee YC. Association of angiotensin-converting enzyme insertion/deletion polymorphism with serum level and development of pulmonary complications following esophagectomy. Ann Surg 2005; 241:659–665.
27. Hall JC, Tarala RA, Hall JL, Mander J. A multivariate analysis of the risk of pulmonary complications after laparotomy. Chest 1991; 99:923–927.
28. Mullen JT, Davenport DL, Hutter MM, Hosokawa PW, Henderson WG, Khuri SF, Moorman DW. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. Ann Surg Oncol 2008; 15:2164–2172.
29. Kuwano H, Sumiyoshi K, Sonoda K, Kitamura K, Tsutsui S, Toh Y, Kitamura M, Sugimachi K. Relationship between preoperative assessment of organ function and postoperative morbidity in patients with oesophageal cancer. Eur J Surg 1998; 164:581–586.

30. Lumb AB, Nunn JF. Respiratory function and ribcage contribution to ventilation in body positions commonly used during anesthesia. Anesth Analg 1991; 73:422–426.
31. Vassilakopoulos T, Mastora Z, Katsaounou P, Doukas G, Klimopoulos S, Roussos C, Zakynthinos S. Contribution of pain to inspiratory muscle dysfunction after upper abdominal surgery: a randomized controlled trial. Am J Respir Crit Care Med 2000; 161:1372–1375.
32. Konrad F, Schreiber T, Grunert A, Clausen M, Ahnefeld FW. Measurement of mucociliary transport velocity in ventilated patients: short-term effect of general anesthesia on mucociliary transport. Chest 1992; 102:1377–1383.
33. Sugerman H, Windsor A, Bessos M, Wolfe L. Intra-abdominal pressure, sagittal abdominal diameter and obesity comorbidity. J Intern Med 1997; 241:71–79.
34. House MG, Fong Y, Arnaoutakis DJ, Sharma R, Winston CB, Protic M, Gonen M, Olson SH, Kurtz RC, Brennan MF, Allen PJ. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. J Gastrointest Surg 2008; 12:270–278.
35. Rosso E, Casnedi S, Pessaux P, Oussoultzoglou E, Panaro F, Mahfud M, Jaeck D, Bachellier P. The role of "fatty pancreas" and of BMI in the occurrence of pancreatic fistula after pancreaticoduodenectomy. J Gastrointest Surg 2009; 13:1845–1851.
36. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ, Nakeeb A, Zyromski NJ, Lillemoe KD. Fatty pancreas: a factor in postoperative pancreatic fistula. Ann Surg 2007; 246:1058–1064.
37. World Health Organization. Western Pacific Region, International Association for the Study of Obesity. The Asia-Pacific Perspective. Redefining Obesity and its Treatment. Sydney: Health Communications Australia, 2000.
38. Hunter GR, Snyder SW, Kekes-Szabo T, Nicholson C, Berland L. Intra-abdominal adipose tissue values associated with risk of possessing elevated blood lipids and blood pressure. Obes Res 1994; 2:563–568.
39. Despres JP, Lamarche B. Effects of diet and physical activity on adiposity and body fat distribution: implications for the prevention of cardiovascular disease. Nutr Res Rev 1993; 6:137–159.
40. Tsujinaka S, Konishi F, Kawamura YJ, Saito M, Tajima N, Tanaka O, Lefor AT. Visceral obesity predicts surgical outcomes after laparoscopic colectomy for sigmoid colon cancer. Dis Colon Rectum 2008; 51:1757–1765.
41. Yatagai T, Nagasaka S, Taniguchi A, Fukushima M, Nakamura T, Kuroe A, Nakai Y, Ishibashi S. Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in Japanese men with type 2 diabetes mellitus. Metabolism 2003; 52:1274–1278.
42. Matsuda A, Matsutani T, Sasajima K, Furukawa K, Tajiri T, Tamura K, Kogo H. Preoperative plasma adiponectin level is a risk factor for postoperative infection following colorectal cancer surgery. J Surg Res 2009; 157:227–234.

Langenbecks Arch Surg (2011) 396:1101–1107
DOI 10.1007/s00423-011-0778-7

ORIGINAL ARTICLE

# Combined intraoperative use of contrast-enhanced ultrasonography imaging using a sonazoid and fluorescence navigation system with indocyanine green during anatomical hepatectomy

**Kazuhisa Uchiyama · Masaki Ueno · Satoru Ozawa · Shigehisa Kiriyama · Yoshinobu Shigekawa · Seiko Hirono · Manabu Kawai · Masaji Tani · Hiroki Yamaue**

Received: 15 August 2010 / Accepted: 8 March 2011 / Published online: 29 March 2011


**Abstract**
*Purpose* The clear demarcation line is ideal for real-time surgical navigation imaging during hepatectomy.
*Methods* The study population was comprised of 22 patients with moderate liver cirrhosis scheduled to undergo an anatomical liver resection for the treatment of hepatocellular carcinoma. This study set out to assess the clinical value of the concomitant intra-operative use of contrast-enhanced intra-operative ultrasound using Sonazoid™, and a fluorescence navigation system (PDE) with ICG, as a novel tool for patients undergoing an anatomical liver resection.
*Results* Following portal pedicle ligation for anatomical resection, 2 min after injection of ICG, the segments to be resected were detected as a negative-brightness area using PDE fluorescence. Sonazoid™ administration provides a parenchymal transectional line, as the margin of a loss of blood flow shows a hypo-enhanced image, and the resectional line of the parenchyma can be confirmed by CE-IOUS. Although the demarcation line of the liver surface after the portal pedicle ligation was apparent in 17 patients, the resection line using PDE was clearly detected in all 22 patients ($p<0.018$).
*Conclusions* The combined use of these methods is therefore considered to be useful and safe for surgeons, as an additional tool for performing a liver resection.

K. Uchiyama · M. Ueno · S. Ozawa · S. Kiriyama · Y. Shigekawa · S. Hirono · M. Kawai · M. Tani · H. Yamaue (✉)
Second Department of Surgery, School of Medicine,
Wakayama Medical University,
811-1 Kimiidera,
Wakayama 641-8510, Japan
e-mail: yamaue-h@wakayama-med.ac.jp

**Keywords** Fluorescence navigation system (Photo Dynamic Eye: PDE) · Contrast-enhanced intra-operative ultrasound (CE-IOUS) · Sonazoid™ · Anatomical hepatic resection · Kupffer-phase image

## Introduction

Intra-operative fluorescent imaging techniques using indocyanine green (ICG) (Diagnogreen Inj., Daiichi Sankyo, Tokyo, Japan) have been used to assess the detection of sentinel lymph nodes metastasis in gastric and breast cancer [1, 2]. Recently, some studies reported that liver tumors such as hepatocellular carcinoma (HCC) and metastatic carcinoma exhibited strong fluorescence in patients who had been administered ICG several days prior to surgery during a routine preoperative liver function test [3]. Previous studies of hepatobiliary surgeries using ICG-fluorescent imaging to identify liver cancers, biliary congested areas, and the biliary tracts during cholecystectomy have been reported [4, 5]. These techniques are based on the finding that ICG binds to plasma proteins, and protein-bound ICG emits light with a peak wavelength of around 830 nm when excited with near-infrared light [4]. In our department, anatomic hepatic resection, defined as the complete removal of at least one Couinaud segment containing the tumor, is the standard treatment for patients with HCC [6]. Two minutes after intravenous ICG injection following portal pedicle ligation via a posterior intrahepatic approach, we found that the demarcation line on the liver surface was clearly detectable using Photo Dynamic Eye (PDE).

Intra-operative ultrasonography (IOUS) has been shown to yield significant new information not identified on preopera-

tive imaging, which either determines the resectability or changes the operative plan; it is considered to be the gold standard, thereby achieving universal usage. Recently, to find occult metastases during a hepatectomy in patients with HCC and liver metastases, contrast-enhanced IOUS (CE-IOUS) was performed using Sonazoid™ (GE Healthcare, Oslo, Norway), a new second-generation ultrasound perflubutane microbubbles agent with a median diameter of 2 to 3 nm that provides a parenchyma-specific contrast image based on its accumulation in the Kupffer cells in the liver [7]. Sonazoid is present on the late Kupffer-phase image with a long duration (approximately 2 h after injection) following vascular- and sinusoidal-phase images. SonoVue (Bracco Spa, Milan, Italy) has already been used as a microbubble agent in CE-IOUS, but the duration of the contrast enhancement was shorter, with a mean duration of 4 to 5 min [8]. After portal pedicle ligation for anatomical resection, intravascularly administered Sonazoid™ provides a parenchyma-specific contrast image based on its accumulation in the Kupffer cells, and we were able to identify the parenchymal transactional line as the margin with loss of blood flow shown as a hypo-enhanced image for over 1 h. Therefore, we were able to confirm the resectional line of the parenchyma with IOUS at any time. The aim of the present study was to assess the clinical value of the combined use of fluorescence navigation system (PDE) using indocyanine green and CE-IOUS with Sonazoid, as a novel tool in patients undergoing anatomical liver resection.

## Patients and method

### Patients' backgrounds

From January 2008 to December 2009, 22 consecutive patients (mean age, 73.5 years; SD, 9.8 years; range, 43–82 years of age; 14 males and eight females) were enrolled to undergo an anatomical liver resection for hepatocellular carcinoma (HCC) at Wakayama Medical University Hospital (WMUH). The anatomical resection procedures included a hemihepatectomy (removal of right lobe in four patients, the removal of a left section in four patients), a sectionectomy (removal of the anterior section in three patients, removal of posterior section in five patients), and a segmentectomy (removal of 8 in four patients, segment 6 in two patients) based on Couinaud's classification. The operative procedures conducted in the anatomic resections are shown in Table 1. All patients were fully informed of the study design according to the Ethical Committee on Clinical Investigation of Wakayama Medical University Hospital and consented in writing to participate in this study.

In all patients, multi-detective CT scanning (MDCT) and magnet resonance imaging (MRI) were performed in a standardized preoperative examination within 2 weeks before the hepatic resection. The CT diagnoses were based on a triphasic contrast-enhanced protocol using a 64-row multi-detective CT scanner (Aquilion 64, Toshiba Medical, Japan), and MR imaging was performed using the 1.5 T MRI system (Philips, Achieva, Netherlands) with an 8-channel body phased-array coil. The use of MDCT allows for a three-dimensional image construction of the liver and a preoperative estimation of the resected liver weight using the CT-volumetry software program Virtual Place Advance (AZE Inc., Tokyo, Japan) [9]. We evaluate the consistency of the shape and/or weight of the resected specimen with those estimated based on preoperative 3D-CT using this software program. Preoperative 3D simulation images taken during the resection of segment 8 arranging from the MDCT are shown in Fig. 1.

**Table 1** Operative producers of an anatomic resection using combined PDE and CE-IOUS

| Hepatectomy procedure | No. | No. of cases in which the demarcation line was detected | |
|---|---|---|---|
| | | Only ligated in the portal pedicle | Adding use of PDE |
| Right liver (S5 S6 S7 S8 ) | 4 | 4 | 4 |
| Left liver (S2 S3 S4) | 4 | 3 | 4 |
| Posterior sector (S6 S7) | 5 | 4 | 5 |
| Anterior sector (S5 S8) | 3 | 2 | 3 |
| S8 segment | 4 | 2 | 4 |
| S6 segment | 2 | 2 | 2 |
| Total | 22 | 17 | 22* |

*$p<0.018$ vs. only ligated in the portal pedicle

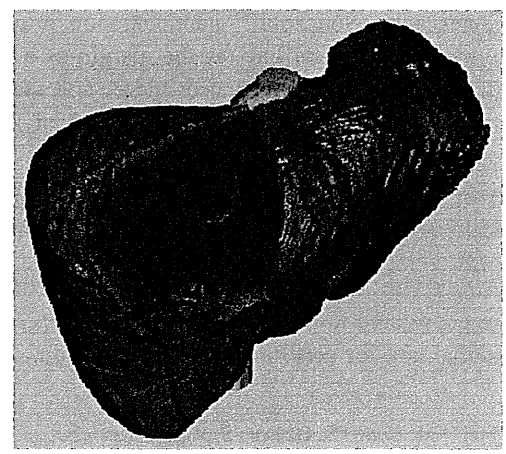

**Fig. 1** Preoperative 3D simulation image during segment 8 resection arranging from the MDCT using the Virtual Place Advance software program. Virtual landmark veins were found in the cutting surface: the right hepatic vein, the middle hepatic vein, and the stump of the Glisson of segment 8

Equipment of PDE and CE-IOUS system

Intra-operative fluorescent techniques using the commercially available near-infrared (NR) fluorescence imaging system (PDE; Hamamatsu Photonics K.K. Hamamatsu, Japan) activates ICG with emitted light at a wavelength of 760 nm and filters out light with wavelengths below 820 nm. The light source was a light-emitting diode (LED), and the detector was a charge-coupled device (CCD) camera. The fluorescence signals were sent to a digital video processor for display on a TV monitor. When ICG binds to human plasma, ICG is detectable as a fluorescent signal using the PDE infrared observation camera system. A contrast-enhanced (CE-IOUS) system with Sonazoid™ was performed on an Aloka ProSound α10 system (Aloka Ltd., Tokyo, Japan) equipped with a micro-convex 3.5 MHz frequency probe. None of the authors or Wakayama Medical University Hospital received any financial benefits by advertising these equipments, and there are no conflicts of interest to declare.

Surgical technique

Following the portal pedicle ligation via the posterior intrahepatic approach for anatomical hepatectomy, 1 min after ICG was injected in the cephalic vein at a dose of 0.5 mg/kg body weight, the negative-brightness area of the liver area without blood flow was clearly detected on the liver surface using the PDE system. At the same time, the contrast agent Sonazoid™ was administered at a dose of 0.0075 ml/kg by a manual bolus injection following a flush with 3.0 ml of normal saline. This contrast agent is characterized by prolonged maintenance of its contrast attributes and allows continuous vascular and postvascular imaging. Microbubbles of the perflubutane-based contrast agent are phagocytosed by reticuloendothelial cells in the liver 10–30 min after injection, enhancing the liver parenchyma. Intravascular Sonazoid administration provides a parenchymal transactional line at the margin with a loss of blood flow, shown on a hypo-enhanced image for a long duration approximately 1 h, and the resectional line of the parenchyma could be confirmed with CE-IOUS at any time during hepatectomy. Following contrast administration, the liver parenchyma enhances uniformly, and the ischemic regions were easily identified appearing as a dark contrast free. We were able to recognize the resection line with the intermittent use of CE-IOUS by sandwiching a piece of gauze between the cutting surfaces of the liver parenchyma. The resection of the liver parenchyma was performed using an ultrasonic dissector under intermittent clamping by means of occlusion of blood inflow, both pedicular or selective, 20 min and then release for 5 min using a rubber tape with a tourniquet.

As for the statistical analyses, the chi-square test was used to evaluate the differences of the number of patients by Stat View program (version 5 Hulinks, Tokyo, Japan). Statistical significance was defined as a $P$ value of $<0.05$.

## Results

The surgical procedures used during the anatomic resections are shown in Table 1. Although the demarcation line of the liver surface after the portal pedicle ligation was apparent in 17 patients, the resection line using PDE was clearly detected in all 22 patients ($p<0.018$). The median blood loss during hepatectomy was 480 ml (range 130 to 1,250 ml) and the median duration of surgery was 280 min (range 140 to 380 min). There were no problems with the PDE and CE-IOUS procedure. No postoperative complications, such as bile leakage, developed as a result of either type of liver resection in this study. The median hospitalization period was 11 days (range 8 to 15 days). The surgical procedures conducted in the anatomic resections are shown in Table 1. After the ligation of the portal pedicle prior to the parenchymal dissection for anatomic resection, 17 of 22 cases (77%) had the demarcation line appear on the liver surface without using ICG-fluorescent imaging, but in all cases, the discolored area indicating the ischemic area of the liver was detected following the use of the PDE system. The demarcation line of the liver segment was visible with the PDE camera system, even 10 s after ICG injection. In our cases, intravenous ICG has not been associated with any adverse effects apart from occasional allergic reactions. For example, Fig. 2 shows the time course of the appearance of the negative-brightness area of segment 8.

Immediately after the administration of Sonazoid, the portal veins, hepatic veins, and the normal liver parenchyma, but not the segment with the loss of blood flow, were uniformly enhanced following portal pedicle ligation. For example, segment 8 was due to be removed and was identified as a filling defect during hepatectomy (Fig. 3). Approximately 60 min after the injection, the remnant liver was identified by contrast enhancement. Our standard views are shown after the anatomic resection of segment 8 (Fig. 4). After performing the liver resection, we confirmed that the positive-brightness area on the remnant liver was clearly detected on the raw liver surface using the ICG-fluorescent images. With regard to the benefit of using both methods after clamping of the pedicle, clear discoloration marks on the liver surface could be confirmed with the PDE system, and the resectional line of the parenchyma could be confirmed with CE-IOUS at any time during hepatectomy.

If the metastatic lesion was in the remnant liver, the filling defects were clearly confirmed with CE-IOUS at any time

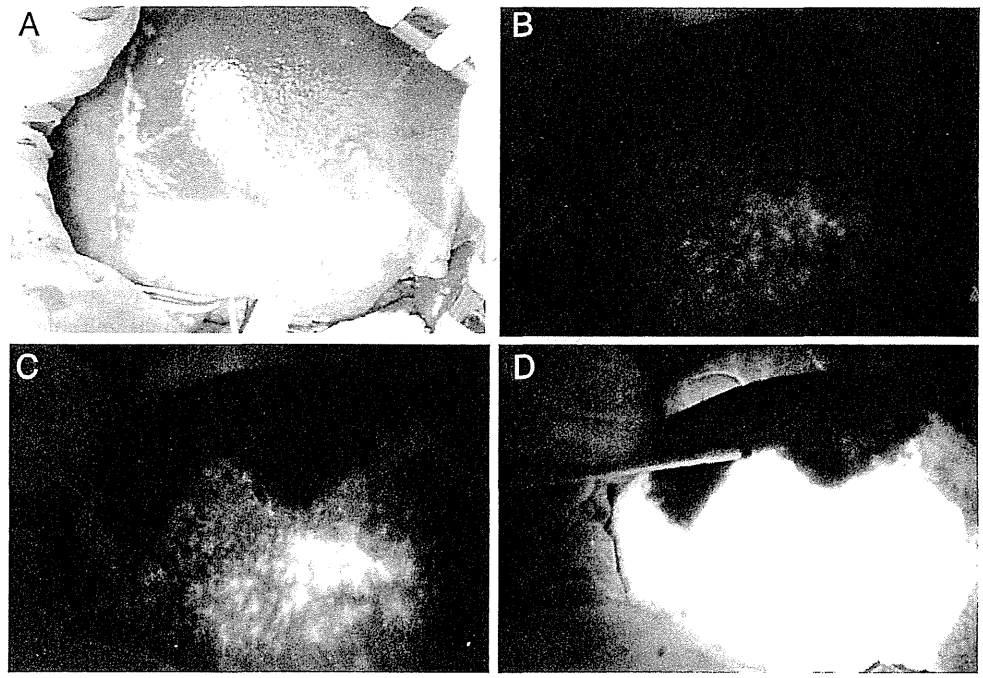


**Fig. 2** The time course of the appearance of the negative-brightness area in segment 8 with the intra-operative PDE image after intravenous ICG injection. **a** Normal view of pre-injection. **b** One minute after injection. **c** Two minutes after injection. **d** Ten minutes after injection

within 30 min after the intravenous injection of Sonazoid. Figure 5 shows IOUS and CE-IOUS images of an HCC metastasis with liver cirrhosis at segment 7. The metastatic lesion was unclearly detected as a slightly hypoechoic mass, which could not be differentiated from fibroid indurations based on the liver cirrhosis with IOUS; however, the CE-IOUS view of the same lesion revealed the metastatic lesion to be a clear hypoechoic mass at the late Kupffer phase.

Two hours after venous ICG injection, its excretion into the bile was monitored by PDE, and when used with bile duct imaging was a better choice for detecting the cutting portion of bile duct (Fig. 6). The PDE system for imaging of the extrahepatic biliary duct can detect the cutting portion of the bile duct to permit real-time monitoring of the resection of liver parenchyma.

We evaluated the correlation of the weight of the resected specimen with that estimated based on preoperative 3D-CT using this software program. Figure 7 shows the correlation diagram between the estimated volume of the resected specimen and the true weight of the removed specimen. The correlation coefficient showed a satisfactory result for the estimate ($R$=0.982).

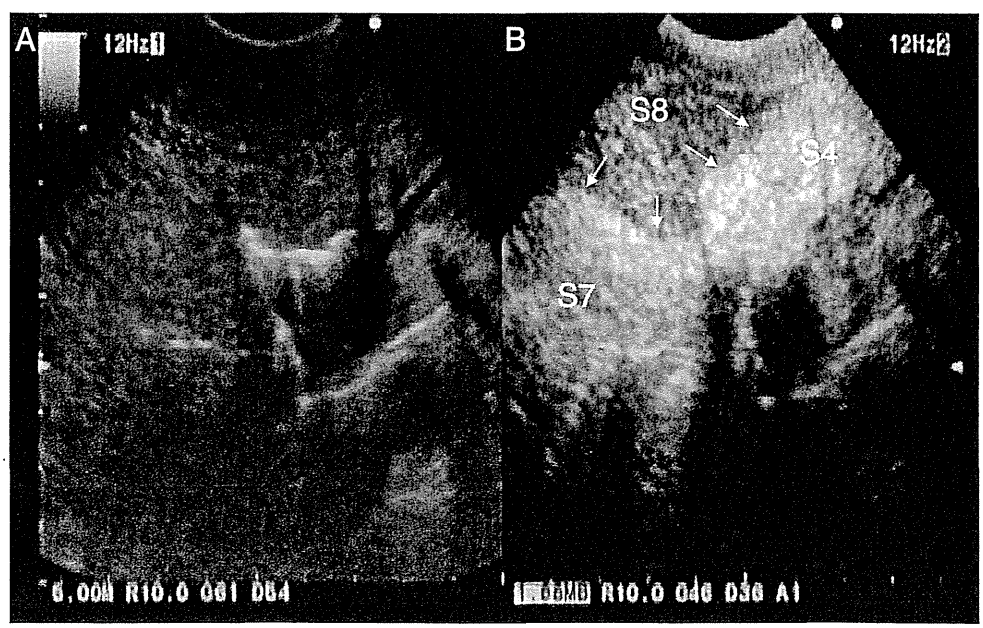


**Fig. 3** IOUS image and CE-IOUS image of the Kupffer phase using Sonazoid after the ligation of the segment 8 pedicle. **a** Non-enhanced IOUS cannot provide a parenchymal transactional line. **b** Sonazoid administration provides a clear parenchymal transactional line as the margin with loss of blood flow, as shown on the hypo-enhanced image

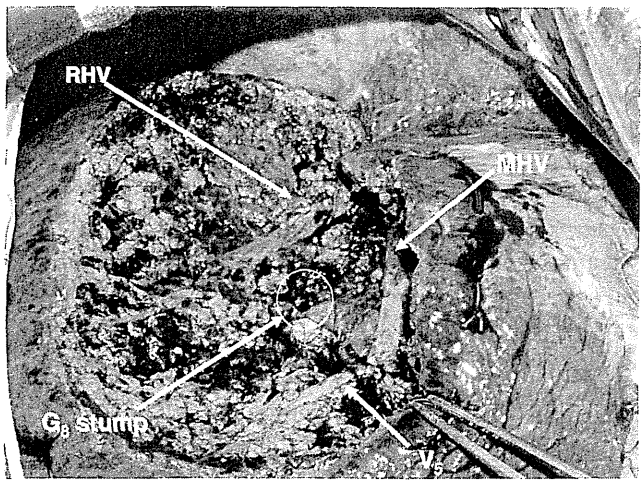


**Fig. 4** Standard view after the anatomical resection of segment 8. The landmark veins were longitudinally exposed in the cutting surface; the right hepatic vein (RHV), the middle hepatic vein (MHV), and drainage vein of segment 5 (V5). The stumps of the branch of Glisson's triad in segment 8 are seen

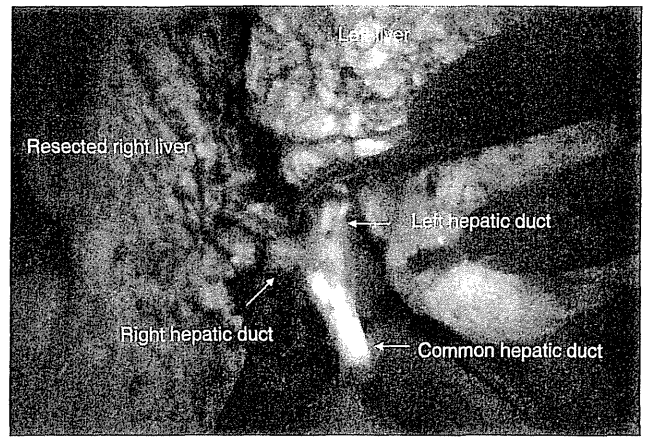


**Fig. 6** The PDE view during right hepatectomy 2 h after venous ICG injection. ICG excretion into the bile from the parenchyma was monitored by PDE; the cutting delineation for the right hepatic duct was clearly visible

## Discussion

Several studies on hepatocellular carcinoma (HCC) have demonstrated a survival benefit for anatomical liver resection [10, 11] because it usually arises within one segment of the liver and the entire functional liver unit can be easily removed. The development of segment-based resection using intrahepatic glissonian access enabled the development of techniques that identify and isolate the right and left segmental glissonian pedicles. These techniques permit a tailored liver resection by removing only the involved liver segments. This technique for performing an anatomic resection of the liver segments using the CEUS and ICG-fluorescent navigation system has been described in a previous report [10]. Careful avoidance of the anatomical landmarks of the liver segments during resection prevents impaired vascularization of the remaining parenchyma and excessive bleeding [10, 11]. The anatomic resection technique, based on specific anatomical landmarks following a control of a Glissonian pedicle with hilar dissection, is important, and fluorescence navigation with ICG and contrast-enhanced intra-operative ultrasound with Sonazoid is thus considered to be a useful tool for safe and systematic hepatic resection.

ICG is a fluorescent dye administered by intravenous injection for optical arteriography and the visualization of superficial vessels [4]. Recently, experimental and preliminary clinical studies have suggested that ICG can

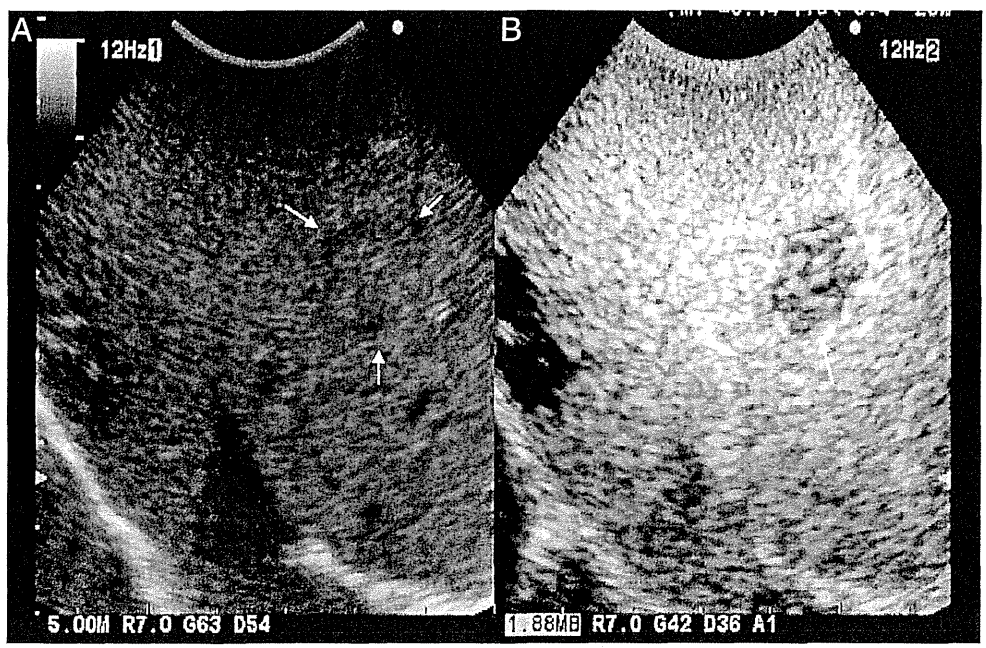


**Fig. 5** IOUS and CE-IOUS images of HCC metastasis with liver cirrhosis at segment 7. **a** A metastatic lesion was detected as a slightly hypoechoic mass which could not be differentiated from the surrounding fibroid indurations based on the liver cirrhosis. **b** The CE-IOUS view of the same lesion shows a clear hypoechoic mass at the late Kupffer phase

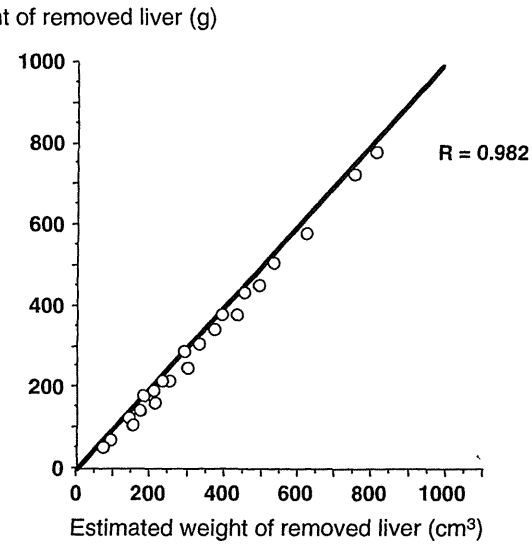


**Fig. 7** The correlation diagram between the weight of the removed specimen and the estimated volume of the resected specimens based on preoperative 3D-CT using this software program

be used for near-infrared (NR) fluorescence imaging for identifying liver metastasis, especially lesions located on the liver surface [12]. Using a PDE system with an ICG flow, the authors transcutaneously observed the liver in real time. In our study, after ligation of the portal pedicle, the demarcation line could not be easily detected as a slightly dark line in five patients (23%), which prevented its differentiated from the non-ischemic area due to liver cirrhosis with type B or C hepatitis. The reason about showing the visible unclear demarcation line in cirrhotic patients may be owing to the decrease of whole blood flow in liver with fibrosis. However, when viewed with the PDE system, the same lesion revealed the ischemic area to be a negative-brightness area. There were no complications resulting from the PDE and CE-IOUS procedure, even in the patients with cirrhosis. The present study confirmed that intra-vascular injection of ICG following a control Glissonian pedicle can be used to identify landmarks of the liver surface in patients for anatomical liver resection, and that this fluorescence ICG navigation system is a safe and highly sensitive method for assessing the regions of liver demarcation. ICG is cleared rapidly from the liver after venous injection, with an extremely short half-life in the blood (<3.4 min) [13]. The high levels of liver uptake require almost 2 h before ICG fluorescence in bile begins to exceed that in the liver, and results in a statistical correlation between NR fluorescence in the liver and subsequent ICG excretion into the bile [14]. ICG is a better choice for bile duct imaging because there is adequate time for clearance (i.e., at least 2 h) during the resection of liver parenchyma for detecting the cutting portion of bile duct. The NR fluorescent system for imaging both the liver parenchyma and the extrahepatic biliary duct can thus be applied during surgery to permit real-time, image-guided assessment of the anatomy and function of the extrahepatic bile ducts. Similar results from the fluorescent imaging of liver segments [15] and the extrahepatic bile ducts utilizing biliary excretion of ICG [16] were recently reported. Aoki et al. [13] previously reported that the fluorescence imaging technique for identification of segments and subsegments of the liver described herein has the advantages of safety and reproducibility, and that this technique provided insights into the imaging system for either subsegmentectomy or segmentectomy in patients with malignant hepatic neoplasms. However, the potential difference from the current paper is the point of combining use of PDE and CE-IOUS. With regard to the benefit of using both methods after clamping of the pedicle, clear discoloration marks on the liver surface could be confirmed with the PDE system, and the resectional line of the parenchyma could be confirmed with CE-IOUS at any time during hepatectomy.

Intra-operative ultrasonography (IOUS) is performed in a systematic fashion, particularly for inspecting the liver parenchyma for previously diagnosed and new nodules, identifying any major vascular or biliary involvement and to establish the surgical strategy. Secondly, contrast-enhanced IOUS (CE-IOUS) is carried out for lesion characterization and for the detection of new nodules. To find the sectional or segmental margin in a parenchyma during hepatectomy, CE-IOUS was performed using the new microbubble agent Sonazoid™, which provides a parenchyma-specific contrast image based on its accumulation in Kupffer cells, and is stable enough to allow image acquisition under ultrasound exposure for more than 30 min. Following the portal pedicle ligation via a posterior intrahepatic approach for anatomical hepatectomy, the normal liver parenchymal cells were uniformly enhanced except for the segment with the loss of blood flow, as detected by CE-IOUS. Furthermore, the segment to be removed was identified to be a filling defect during a hepatectomy. CE-IOUS with Sonazoid™ can be applied to anatomical hepatectomy to permit real-time, image-guided assessment of the patient's anatomical features.

The present results suggested that the concomitant use of CE-IOUS with the Sonazoid™ and PDE system may be a safe and more sensitive method that can be used to visualize the liver in addition to the performance of preoperative CT or MRI. In conclusion, the present study may demonstrate the clinical value of the combined use of a fluorescence ICG navigation system and contrast-enhanced intraoperative ultrasonography image using Sonazoid™, which is a novel modality for the detection of liver sections and segments during an anatomical hepatic resection.

**Conflicts of interest** None.

## References


1. Tajima Y, Yamazaki K, Masuda Y, Kato M, Yasuda D, Aoki T, Kato T, Murakami M, Miwa M, Kusano M (2009) Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer. Ann Surg 249:58–62
2. Troyan SL, Kianzad V, Gibbs-Strauss SL, Gioux S, Matsui A, Oketokoun R, Ngo L, Khamene A, Azar F, Frangioni JV (2009) The FLARE intraoperative near-infrared fluorescence imaging system: a first-in-human clinical trial in breast cancer sentinel lymph node mapping. Ann Surg Oncol 16:2943–2952
3. Tralhão JG, Hoti E, Oliveiros B, Abrantes AM, Botelho MF, Castro-Sousa F (2009) Intermittent pringle maneuver and hepatic function: perioperative monitoring by noninvasive ICG-clearance. World J Surg 33:2627–2634
4. Ishizawa T, Fukushima N, Shibahara J, Masuda K, Tamura S, Aoki T, Hasegawa K, Beck Y, Fukayama M, Kokudo N (2009) Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer 115:2491–2504
5. Hashimoto T, Miki K, Imamura H, Sano K, Satou S, Sugawara Y, Kokudo N, Makuuchi M (2008) Sinusoidal perfusion in the veno-occlusive region of living liver donors evaluated by indocyanine green and near-infrared spectroscopy. Liver Transplant 14:872–880
6. Uchiyama K, Ueno M, Ozawa S, Hayami S, Kawai M, Tani M, Mizumoto K, Haba M, Hatano Y, Yamaue H (2009) Half clamping of the infrahepatic inferior vena cava reduces bleeding during a hepatectomy by decreasing the central venous pressure. Langenbecks Arch Surg 394:243–247
7. Luo W, Numata K, Kondo M, Morimoto M, Sugimori K, Hirasawa K, Nozaki A, Zhou X, Tanaka K (2009) Sonazoid-enhanced ultrasonography for evaluation of the enhancement patterns of focal liver tumors in the late phase by intermittent imaging with a high mechanical index. J Ultrasound Med 28:439–448
8. Torzilli G, Palmisano A, Del Fabbro D, Marconi M, Donadon M, Spinelli A, Bianchi PP, Montorsi M (2007) Contrast-enhanced intraoperative ultrasonography during surgery for hepatocellular carcinoma in liver cirrhosis: is it useful or useless? A prospective cohort study of our experience. Ann Surg Oncol 14:1347–1355
9. Uchiyama K, Mori K, Tabuse K, Ueno M, Ozawa S, Nakase T, Kawai M, Tani M, Tanimura H, Yamaue H (2008) Assessment of liver function for successful hepatectomy in patients with hepatocellular carcinoma with impaired hepatic function. J Hepatobiliary Pancreat Surg 15:596–602
10. Makuuchi M, Hasegawa H, Yamazaki S (1985) Ultrasonically guided subsegmentectomy. Surg Gynecol Obstet 161:346–350
11. Wakai T, Shirai Y, Sakata J, Kaneko K, Cruz PV, Akazawa K, Hatakeyama K (2007) Anatomic resection independently improves long-term survival in patients with T1–T2 hepatocellular carcinoma. Ann Surg Oncol 14:1356–1365
12. Gotoh K, Yamada T, Ishikawa O, Takahashi H, Eguchi H, Yano M, Ohigashi H, Tomita Y, Miyamoto Y, Imaoka S (2009) A novel image-guided surgery of hepatocellular carcinoma by indocyanine green fluorescence imaging navigation. J Surg Oncol 100:75–79
13. Aoki T, Yasuda D, Shimizu Y, Odaira M, Niiya T, Kusano T, Mitamura K, Hayashi K, Murai N, Koizumi T, Kato H, Enami Y, Miwa M, Kusano M (2008) Image-guided liver mapping using fluorescence navigation system with indocyanine green for anatomical hepatic resection. World J Surg 32:1763–1767
14. Tanaka E, Choi HS, Humblet V, Ohnishi S, Laurence RG, Frangioni JV (2008) Real-time intraoperative assessment of the extrahepatic bile ducts in rats and pigs using invisible near-infrared fluorescent light. Surgery 144:39–48
15. Harada N, Ishizawa T, Muraoka A, Ijichi M, Kusaka K, Shibasaki M, Yamamoto K, Hasegawa K, Bandai Y, Kokudo N (2010) Fluorescence navigation hepatectomy by visualization of localized cholestasis from bile duct tumor infiltration. J Am Coll Surg 210:e2–e6
16. Ishizawa T, Bandai Y, Ijichi M, Kaneko J, Hasegawa K, Kokudo N (2010) Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg 97:1369–1377

Ann Surg Oncol (2011) 18:3624–3631
DOI 10.1245/s10434-011-1800-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

# Adjuvant Chemolipiodolization Reduces Early Recurrence Derived from Intrahepatic Metastasis of Hepatocellular Carcinoma After Hepatectomy

**Masaki Ueno, MD, Kazuhisa Uchiyama, MD, Satoru Ozawa, MD, Shinya Hayami, MD, Yoshinobu Shigekawa, MD, Masaji Tani, MD, and Hiroki Yamaue, MD, PhD**

Second Department of Surgery, School of Medicine, Wakayama Medical University, Wakayama City, Japan

## ABSTRACT

**Background.** The recurrence of hepatocellular carcinoma is still high even after surgery. Two general recurrence patterns occur: intrahepatic metastasis (IM) and multicentric carcinogenesis (MC). The aim of this study was to investigate the effectiveness of adjuvant chemolipiodolization for reducing IM or MC recurrences after surgery.

**Methods.** A retrospective case-control study was carried out. From April 2005, adjuvant chemolipiodolization was performed in 63 initial hepatocellular carcinoma patients 3 months after surgery. Sixty-four patients who underwent surgery between April 2001 and March 2005 were analyzed as the control group. Recurrence-free and overall survival as well as prognostic factors were analyzed univariately and multivariately.

**Results.** The 2-year recurrence-free survival was 57% in the chemolipiodolization group and 37% in the control group ($P = 0.02$). However, there was no significant difference at 5 years after surgery ($P = 0.09$). The 5-year overall survival rates in the chemolipiodolization and the control groups were 82.4 and 55.7%, respectively ($P = 0.04$). Cox proportional multivariate analysis revealed that adjuvant chemolipiodolization was an independent favorable prognostic factor for 2-year recurrence-free survival, and the odds ratio [95% confidential interval] was 0.55 [0.34–0.90] ($P = 0.02$). However, adjuvant chemolipiodolization was not an independent favorable prognostic factor for 5-year overall survival.

**Conclusions.** Adjuvant chemolipiodolization can reduce the risk of early recurrences, which would be mainly IM derived. However, chemolipiodolization did not reduce late phase recurrences after surgery, which would be mainly MC derived. To prevent late phase recurrences, another novel strategy would be needed.



First Received: 12 January 2011;
Published Online: 26 May 2011

H. Yamaue, MD, PhD
e-mail: yamaue-h@wakayama-med.ac.jp

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world. Although surgical resection is considered to be a potentially curative treatment, the recurrence rates of HCC are still high. The recurrence rates are about 50–60% at 2 years and 80% at 5 years.[1–3]

In HCC, the recurrence pattern is different from other cancers, and two major origins are thought to underlie the pattern of recurrence: microscopic intrahepatic metastases from the primary tumor (IM), and other newly developed HCCs induced by multicentric carcinogenesis (MC).[4,5] As a result of these unique recurrence patterns of HCC, there are two peaks in the incidence of recurrences after surgery.[1] Previous studies have revealed that 2 years after surgery was the inflection point for the disease-free survival curve.[6,7] Early recurrences that occurred within 2 years of surgery were mainly thought to be IM recurrences and were thought to have a worse prognosis. On the other hand, the late recurrences that occurred more than 2 years after surgery were mainly thought to be MC recurrences and were thought to be the result of viral hepatitis or cirrhosis of the remnant liver.

Previous studies identified various risk factors for IM or MC recurrences. Adverse tumor factors such as tumor size, number of tumor, vessel involvement, and serum alfa-fetoprotein (AFP) levels were found to be risk factors.[3,8] Underlying liver status such as serum albumin level, prothrombin time, serum bilirubin level that would be summarized in Child-Pugh status were also found to be risk

factors.[8,9] Others reported that operative blood loss or blood transfusion and anatomical resection would affect the prognosis after surgery.[10–12]

On the basis of the unique recurrence pattern of HCC and identified risk factors for recurrence, previous studies have reported favorable results for various adjuvant therapies such as systemic chemotherapy, locoregional chemotherapy, and adoptive immunotherapy.[13–18] However, most of these articles had small sample sizes or a short duration of observation and did not clearly discuss their preventive effect by distinguishing IM from MC. Moreover, meta-analyses did not show any recommendation for adjuvant anticancer therapy against HCC.[19,20] However, randomized control trials have demonstrated that there are some promising treatments, such as lipiodol injection.[14,17,18]

The benefits of 131-iodine-labeled lipiodol ($^{131}$I-lipiodol) injection into the hepatic artery for reducing intrahepatic recurrences have been reported in various countries.[14,21,22] However, in Japan and other countries where $^{131}$I-lipiodol was not used, injecting an emulsion of lipiodol and chemotherapeutic agents into the hepatic artery (chemolipiodolization) was proposed.[23,24] Considering the results of the previous studies, our institution has decided to propose the use of adjuvant chemolipiodolization as a new protocol for patients undergoing surgical resection for HCC.

In this retrospective case-control study, we examined the validity of adjuvant chemolipiodolization by analyzing a retrospective series of matched patients treated in our institution before and after this treatment was administered, and we estimated whether chemolipiodolization could reduce IM and/or MC.

## METHODS

### *Patients*

This study was designed as a retrospective case-control study and was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies from the Ministry of Health, Labor and Welfare in Japan.

Because previous adjuvant lipiodolization studies demonstrated about 20% improvement of recurrence, we calculated that we would need a sample size of about 120 patients to detect 20% difference in 2-year recurrence-free survival at 5% type I error and 80% power for a one-tailed log-rank test.[14,21]

From April 2005 to March 2008, 64 patients who underwent curative resection with no macroscopic residual tumor for initial HCC at Wakayama Medical University Hospital were intended to receive adjuvant chemolipiodolization 3 months after surgery. Any patient who experienced recurrence within 3 months after surgery would be administered transarterial chemoembolization (TACE) instead of adjuvant chemolipiodolization and they were enrolled in this study in an intention-to-treat analysis fashion. The patients with a Child-Pugh score of C were excluded from this treatment because of insufficient liver function. All of the patients were given information about the adjuvant chemolipiodolization and its probable benefits and risks. During this period, one patient was determined to have a Child-Pugh score of C at 3 months after surgery. Therefore, 63 patients were defined as an adjuvant treatment group and reviewed in this study. Of these patients, 58 patients were R0 resection and 5 were R1 resection. Among them, 6 patients experienced recurrence within 3 months after surgery and underwent TACE instead of adjuvant chemolipiodolization.

The patients who underwent surgery from April 2001 to March 2005 with matched criteria were enrolled as the control group. A total of 64 patients underwent curative resection with no macroscopic residual tumor for initial HCC during that period. There was no patient with a Child-Pugh score of C by 3 months after surgery. Of these patients, 60 patients were R0 resection and 4 were R1 resection. Therefore, 64 patients were defined as the control group in this study. Among them, 5 patients were diagnosed with a recurrence within 3 months after surgery.

### *Adjuvant Chemolipiodolization*

At 3 months after surgery, the patients were examined by computed tomography (CT) during arteriography, and CT during arterial portography to examine the remnant liver. As previously described, the patients diagnosed with recurrences by this examination were administered TACE. Otherwise, adjuvant chemolipiodolization was performed as follows: 40 mg of epirubicin and 6 mg of mitomycin C were dissolved in 5 ml of water-soluble contrast medium (Omnipaque, Daiichisankyo, Japan). The solution was then mixed with 10 ml of lipid contrast medium (Lipiodol Ultra-Fluid, Terumo, Japan) and the prepared mixture emulsions were injected into the proper hepatic artery through a catheter. The dose of the emulsions was 0.1 ml/kg body weight in this study. Adjuvant chemolipiodolization was administered only one time in this study.

### *Surveillance*

All of the patients were followed up at Wakayama Medical University Hospital every 2–3 months for more than 2 years. Blood examinations were performed every 2–3 months. Ultrasonography and abdominal contrast enhanced dynamic

CT was also alternately performed every 2–3 months as the imaging follow-up. If a recurrence was suspected by ultrasonography, contrast enhancement dynamic CT was performed at that time to reconfirm the lesion.

The image findings were reported by blinded radiologists and the presence of an intrahepatic recurrence was determined by the existence of a hypervascular nodule in early phase with a perfusion defect in the portal phase under contrast enhancement dynamic CT. If an extrahepatic recurrence was suspected, lung CT or bone scintigraphy was performed. An extrahepatic recurrence was determined by the existence of a tumor. After detecting any recurrence, appropriate therapeutic modalities were administered, and the same surveillance was performed.

The primary outcome in this study was defined as the recurrence-free survival especially within 2 years after hepatectomy and the secondary outcome in this study was defined as the overall survival.

### *Data Collection*

The following 16 variables were collected for each patient as potent risk factors for recurrence and survival: age, gender, etiology of underlying liver disease (hepatitis C virus [HCV], hepatitis B virus [HBV], and daily alcohol intake), Child-Pugh score (A or B), indocyanine green retention rate at 15 min (ICG $R_{15}$), The Cancer of the Liver Italian Program (CLIP) score (0, 1, 2, or 3), primary tumor size, number of tumors (single or multiple), vascular involvement (negative or positive), serum AFP levels, liver resection procedure (major or minor), resection margin (R0 or R1), tumor differentiation (well, moderate, or poor) and blood loss during the operation.

Tumor size, number and vascular involvement were measured by the resection specimen. Resection margin and tumor differentiation were pathologically defined. More than sectionectomy and lobectomy were defined as major liver resection and the others were defined as minor liver resection.

Additionally continuous variables of age, ICG $R_{15}$, main tumor size, serum AFP levels, blood loss were also categorized by cutoff values of 69 years old, 15%, 5 cm, 400 IU/ml, and 880 ml, respectively.

### *Statistical Analyses*

Continuous variables were expressed as the medians with interquartile ranges and compared by the Mann–Whitney *U*-test. Dichotomous variables were compared by the Chi-square test or Fisher's exact test. Recurrence-free survival and the overall survival rate were analyzed by the Kaplan–Meier method and log rank test.

In order to adjust for confounding variables, chemolipiodolization and 16 collected variables were analyzed univariately by a Cox proportional hazard model for recurrence-free survival and overall survival and then potent significant variables were entered into multivariate analyses. *P* values of <0.05 were considered statistically significant.

## RESULTS

The patient backgrounds between those treated with and without adjuvant chemolipiodolization therapy are

**TABLE 1** Patients backgrounds between those treated with or without chemolipiodolization

| Variable | Chemolipiodolization | | *P* value |
|---|---|---|---|
| | (−) ($n$ = 64) | (+) ($n$ = 63) | |
| Age (year) | 67 (63, 73) | 70 (65, 76) | 0.08 |
| Gender (male/female) | 44/20 | 53/10 | 0.04 |
| HCV antibody (+/−) | 41/23 | 31/32 | 0.09 |
| HBs antigen (+/−) | 8/56 | 7/56 | 0.81 |
| Daily alcohol intake (+/−) | 19/45 | 25/38 | 0.24 |
| Child-Pugh score (A/B) | 58/6 | 60/3 | 0.31 |
| ICG $R_{15}$ (%) | 9.9 (7.6, 14.4) | 15.0 (10.0, 20.0) | <0.001 |
| CLIP score (0/1/2/3) | 30/20/12/2 | 30/19/13/1 | 0.94 |
| Primary tumor size (cm) | 4.1 (2.8, 6.6) | 4.5 (2.9, 6.4) | 0.96 |
| No. of tumors (single/multiple) | 48/16 | 46/17 | 0.79 |
| Vascular involvement (+/−) | 11/53 | 12/51 | 0.78 |
| Serum AFP levels (ng/ml) | 28.6 (6.0, 136.0) | 14.3 (6.1, 162.8) | 0.75 |
| Liver resection (major/minor) | 36/28 | 32/31 | 0.54 |
| Resection margin (R1/R0) | 4/60 | 5/58 | 0.74 |
| Tumor differentiation (well/moderate/poor) | 13/48/3 | 14/38/11 | 0.06 |
| Blood loss (ml) | 978 (513, 1850) | 740 (420, 1335) | 0.09 |

Continuous variables are expressed as the medians (25th, 75th percentile)

*HBs* hepatitis B surface, *CLIP* cancer of the liver Italian program

summarized in Table 1. The distributions of gender and ICG $R_{15}$ were different between the two groups. However, the Child-Pugh score was similar between the two groups. The tumor status, such as tumor size, number of tumors, presence of vascular involvement, serum AFP levels, and tumor pathological differentiation were not statistically significantly different between the two groups. Therefore, the distributions of the CLIP scores were similar between the two groups. The surgical parameters such as operation procedure, resection margin, and blood loss were not different between the two groups.

There were no complications higher than grade 3 in Common Terminology Criteria for Adverse Event among the patients who received adjuvant chemolipiodolization.

The recurrence-free survival curves after surgery for each group are shown in Fig. 1. At 2 years after surgery, recurrences were observed in 40 patients (63%) without chemolipiodolization. On the other hand, 27 patients (43%) with chemolipiodolization experienced recurrence ($P = 0.02$). However, at 5 years after hepatectomy, these curves were no longer significantly different ($P = 0.09$).

The overall survival curves after hepatectomy for each group are shown in Fig. 2. Although the duration of observation was different between the two groups (the median follow-up period was 35 months in the chemolipiodolization-positive group and 53 months in the chemolipiodolization-negative group), the overall survival rates of the chemolipiodolization-positive and -negative groups were 92.1 and 82.8% at 2 years after surgery ($P = 0.12$) and were 82.4 and 55.7% at 5 years after surgery ($P = 0.04$).

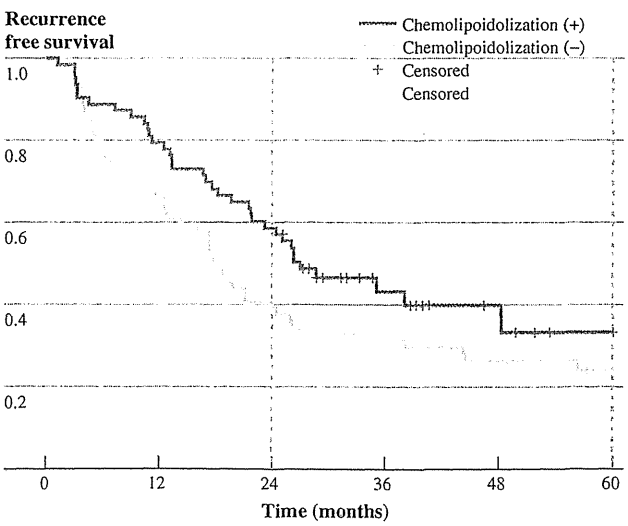


**FIG. 1** Kaplan–Meier recurrence-free survival curves of patients with adjuvant chemolipiodolization and those without. The log rank test was performed at 2 and 5 years after the surgery ($P = 0.02$ and 0.09, respectively)

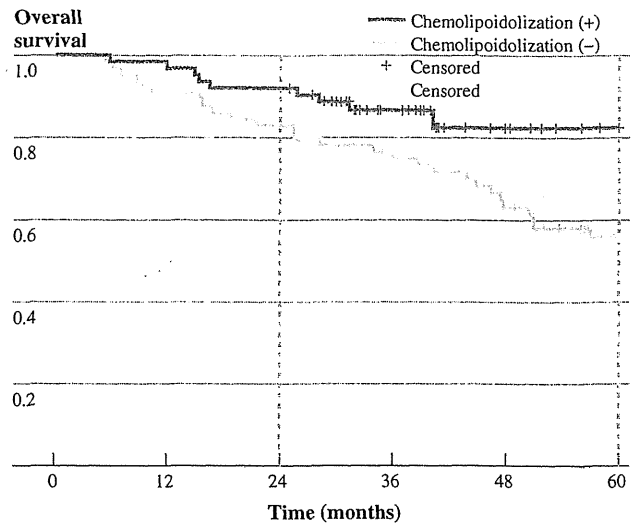


**FIG. 2** Kaplan–Meier overall survival curves of patients with adjuvant chemolipiodolization and those without. The log rank test was performed at 2 and 5 years after the surgery ($P = 0.12$ and 0.04, respectively)

In order to evaluate the independent prognostic factors for 2-year recurrence-free survival after hepatectomy, a Cox proportional hazard model was used (Table 2). In univariate analysis, the number of tumors, blood loss and chemolipiodolization were recognized as potent prognostic factors. The odds ratios [95% confidential interval (CI)] were 2.16 [1.31–3.57], 1.67 [1.03–2.71] and 0.51 [0.29–0.87], respectively. To adjust for confounding factors, these three variables were entered into multivariate analysis. The number of tumors and chemolipiodolization were recognized to be independent factors, and the odds ratios [95% CI] were 1.57 [1.35–3.73] and 0.55 [0.34–0.90], respectively.

A Cox proportional hazard model was also used in order to evaluate the independent prognostic factors for overall survival after hepatectomy (Table 3). In univariate analysis, gender, primary tumor size, number of tumors, poor differentiation, blood loss and chemolipiodolization were recognized as potent prognostic factors. The odds ratios [95% CI] for these factors were 2.22 [1.12–4.40], 2.67 [1.35–5.26], 2.65 [1.31–5.17], 4.14 [1.11–15.5], 2.15 [1.07–4.32] and 0.46 [0.21–0.98], respectively. In this study, there were 35 survival events. In multivariate analysis there need to be 10–15 events per variable; therefore, the top three variables (primary tumor size, number of tumors and blood loss) were entered into multivariate analysis. Only the number of tumors was found to be an independent factor for overall survival, with an odds ratio [95% CI] of 2.18 [1.08–4.37].

The patient outcome in terms of recurrence data at 2 years after surgery is shown in Table 4. The recurrence