radiation oncologists. However, it could not be determined in our study, because we did not encounter any severe toxicity.

Verification is a very important process, especially in hypofractionated stereotactic radiotherapy. Negoro *et al.* previously reported the details of our verification method and the results of setup error (10). We used A-P and lateral verification films obtained by a X-ray simulator after CT scan, to compare linacography (A-P and lateral port films) immediately before irradiation. X-ray simulation films have a higher resolution than digital reconstructed radiography, especially in the C-C direction. X-ray simulation films can be easily taken using our integrated system, in which the CT simulator and the X-ray simulator are employed on the same couch. Therefore, we used X-ray simulation films to verify patient setup.

Dose correction for lung inhomogeneity is still a controversial issue. The application of the Monte Carlo calculation method to routine clinics in the future is one of the solutions. In the present situation, we consider that dose correction using a method such as the generalized Batho method should be performed to deliver the true prescribed dose.

Target delineation and definition are other important issues in SRT for lung tumors. Interobserver variation in target delineation is not negligible in some cases. There has been no universal target definition for small solitary lung tumor in SRT. Although the only concept is proposed by International Commission on Radiation Units and Measurements Report 62, details of target definition depend on the treatment methods, such as the way to scan the CT of the tumor and the verification method. Further discussions on these issues are necessary.

In conclusion, the use of multiple noncoplanar static ports achieved homogeneous target dose distribution and avoided high dose to normal tissues, despite the limitation of the beam arrangement from the use of the body frame and couch structure. Tolerance doses to the normal tissues are yet unknown when using single high-dose irradiation. Therefore, we should continue to make treatment plans carefully. In addition, further follow-ups of clinical cases are required to know the tolerance dose to the normal tissues in stereotactic radiotherapy.

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Breast Cancer The Journal of the Japanese Breast Cancer Society
Vol. 12 No. 2 April 2005

Breast Cancer
Vol. 12 No. 2 April 2005

Original Article

Bilateral Breast-Conserving Therapy for Bilateral Breast Cancer: Results and Consideration of Radiation Technique

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Background: Although breast-conserving surgery followed by definitive irradiation is an established treatment for patients with early breast cancer, the role of breast-conserving therapy (BCT) for patients with bilateral breast cancer has not been well studied and the radiation therapy technique is still under investigation. We examined the feasibility of breast-conserving therapy for bilateral breast cancer and present here our radiation therapy technique with CT simulator.

Methods: Between July 1990 and December 1998, we treated 17 patients with bilateral breast cancer who underwent bilateral breast-conserving surgery followed by definitive irradiation. Seven patients had synchronous bilateral breast cancer and ten had metachronous bilateral breast cancer. Radiation therapy consisted of 50 Gy to the bilateral whole breast in all patients but one. A CT simulator was used to plan a tangential radiation field to the breast in all patients. Boost irradiation of 10 Gy was administered to 8 tumors with close or positive margins.

Results: With a median follow-up periods of 95 months from each operation, no patients showed locoregional recurrence on either side, and none suffered distant metastasis. Furthermore no serious late adverse effects were observed.

Conclusion: This study demonstrated that BCT is feasible for bilateral breast cancer and the CT simulator is useful for determining the radiation field, especialy when lesions are metachronous.

Breast Cancer 12:135-139, 2005.

Key words: Bilateral breast cancer, Breast-conserving therapy, BCT, Breast-conserving surgery, Radiation therapy

The incidence of clinically observed bilateral breast cancer is reported to range from 1.4 to 11.8%[1-3], small but significant. Although breast-conserving surgery followed by irradiation is an established treatment for patients with early breast cancer, the frequency of patients receiving bilateral breast irradiation ranges from 0.4% to 5.5%[4-6]. The role of breast-conserving therapy for patients with bilateral breast cancer has not been well studied and scant attention has been devoted to the techniques for radiation therapy. We herein present our technique, which utilizes a CT simulator, and analyze the outcome of treatment for patients with bilateral breast cancer treated with breast-conserving therapy (BCT).

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Abbreviations:
BCT, Breast -conserving therapy

Received June 1, 2004; accepted November 24, 2004

Materials and Methods

Between July 1990 and December 1998, a total of 1036 patients with breast cancer were treated with BCT, defined as breast-conserving surgery and axillary lymph node dissection followed by definitive radiation therapy at the Department of Radiology at Kyoto University Hospital. Among them, 35 patients (3.4%) had bilateral breast cancer, and 17 of them were treated with bilateral BCT (Fig 1). Therefore, 17 patients treated with bilateral BCT were analyzed in the present study.

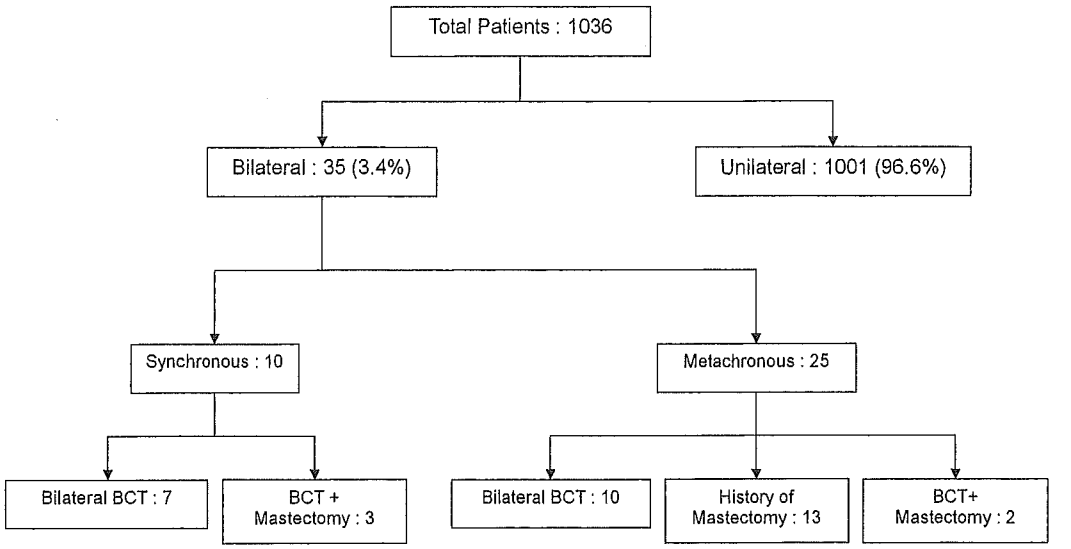

Fig 1. Total patients treated between July 1990 and December 1998.

Table 1. Patient Characteristics

	Synchronous (7 Pt.)	Metachronous (10 Pt.)
Age at diagnosis	Median 53 (43-68)	Median 45 (28-54)*
Family history		
1st degree	0	3
2nd degree	1	0
Menstrual status		
Premenopausal	2	8
Perimenopausal	0	0
Postmenopausal	2	2
Unknown	1	

* age at the diagnosis of the 1st tumor

Table 2. Tumor Characteristics of the 34 Treated Breasts

	Number	%
Pathology		
DCIS	1	
Invasive ductal	32	94
Invasive lobular	1	
Clinical T Stage		
T0	1	3
T1	22	65
T2	11	32
Clinical UICC Stage		
I	22	65
IIA	9	26
IIB	3	9
Pathologic N stage		
N0	31	91
N1	3	9
Estrogen receptor status		
Negative	11	32
Positive	13	38
Not done/unknown	10	30

Seven patients had synchronous bilateral breast cancer and 10 patients had metachronous bilateral breast cancer. They developed the newly diagnosed contralateral breast cancer 4 to 70 months after the first BCT with a median interval of 29 months. Synchronous breast cancer was defined as the diagnosis of both tumors within 1 month. The patients' characteristics and the characteristics of the 34 breast cancers are summarized in Tables 1 and 2.

As regards conservative surgery, 14 tumors were treated by quadrantectomy, while 20 tumors were treated by wide excision. All patients underwent axillary dissection bilaterally. Twenty-six tumors had negative margins of resection, 6 had close margins of resection, that is, within 5 mm from the resected margin, and 1 had positive margins of resection, defined as microscopic involvement at the resected margin on the histological examination.

Following breast conserving surgery, a total dose of 50 Gy in daily fractions of 2 Gy was delivered over 5 weeks to the whole breast via opposing tangential fields. We used a CT simulator (Shimadzu Corp. CT-S, Kyoto) to plan the tangential

fields. We selected the beam energy for the tangential fields according to the breast size: twenty-seven unilateral breasts were treated with cobalt-60 gamma rays, 1 with 4-MV photons, and 5 with 6-MV photons for the tangential fields. One breast was irradiated with an en-face electron beam. Seven patients with simultaneous breast cancer were treated by matched midline technique with bilateral tangential fields using the CT simulator (Fig 2). On the other hand, we referred to the CT simulation images of the first tumors to avoid field overlapping when we determined the tangential fields for the second tumors in the patients with metachronous breast cancers (Fig 3). The primary site was boosted in the 7 patients with close or positive surgical margins. This boost irradiation comprised to a total dose of 10 Gy in 5 fractions of electron beams through a field 6 to 8 cm in diameter, including the tumor bed. The ipsilateral supraclavicular and ipsilateral internal mammary nodal areas were not included in the target volume.

All patients received oral 5-fluorouracil (5-FU) or its derivatives, and also received tamoxifen for 2 years after the operation, regardless of the axillary node status or estrogen receptor (ER) status.

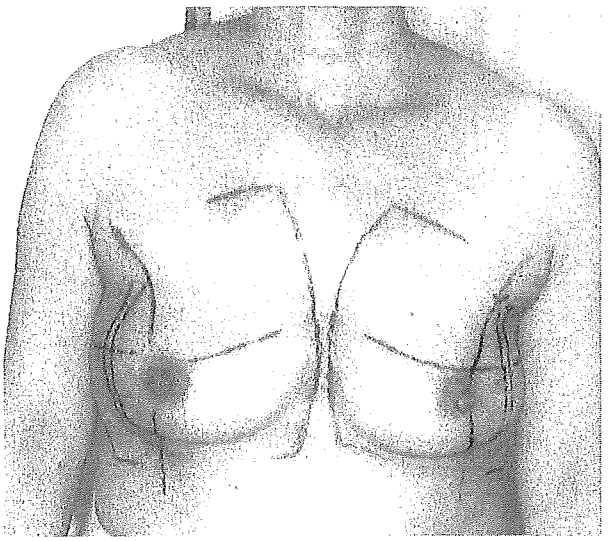

Fig 2. A case of simultaneous breast cancer: It is confirmed that there is no overlap by the skin markings.

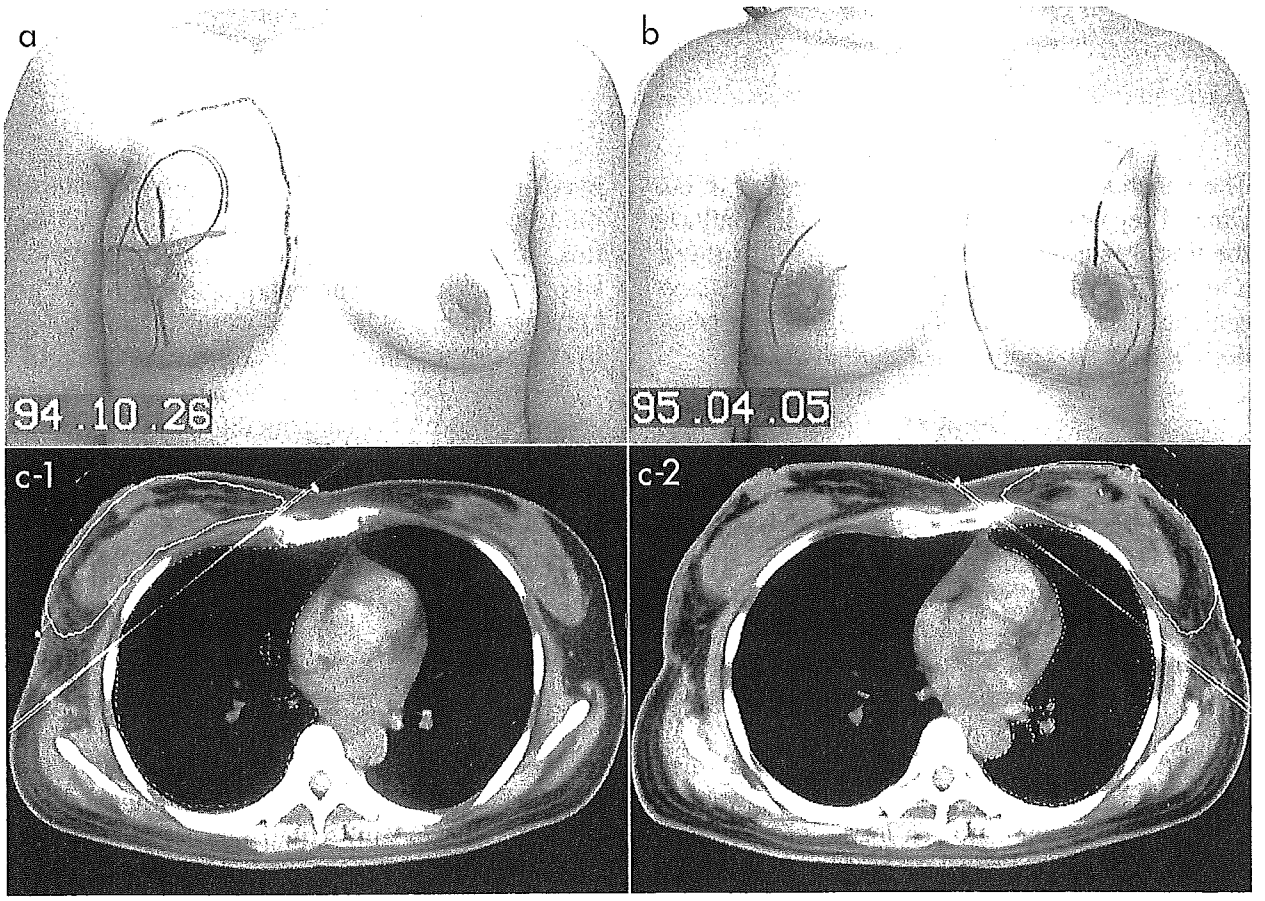

Fig 3. A case of metachronous breast cancer. (a) Radiation field for the first treatment. (b) Radiation field for the second treatment. Identifying the first field by the skin reaction is impossible. (c) We could recognize the first field accurately with the use of images from the previous CT simulation.

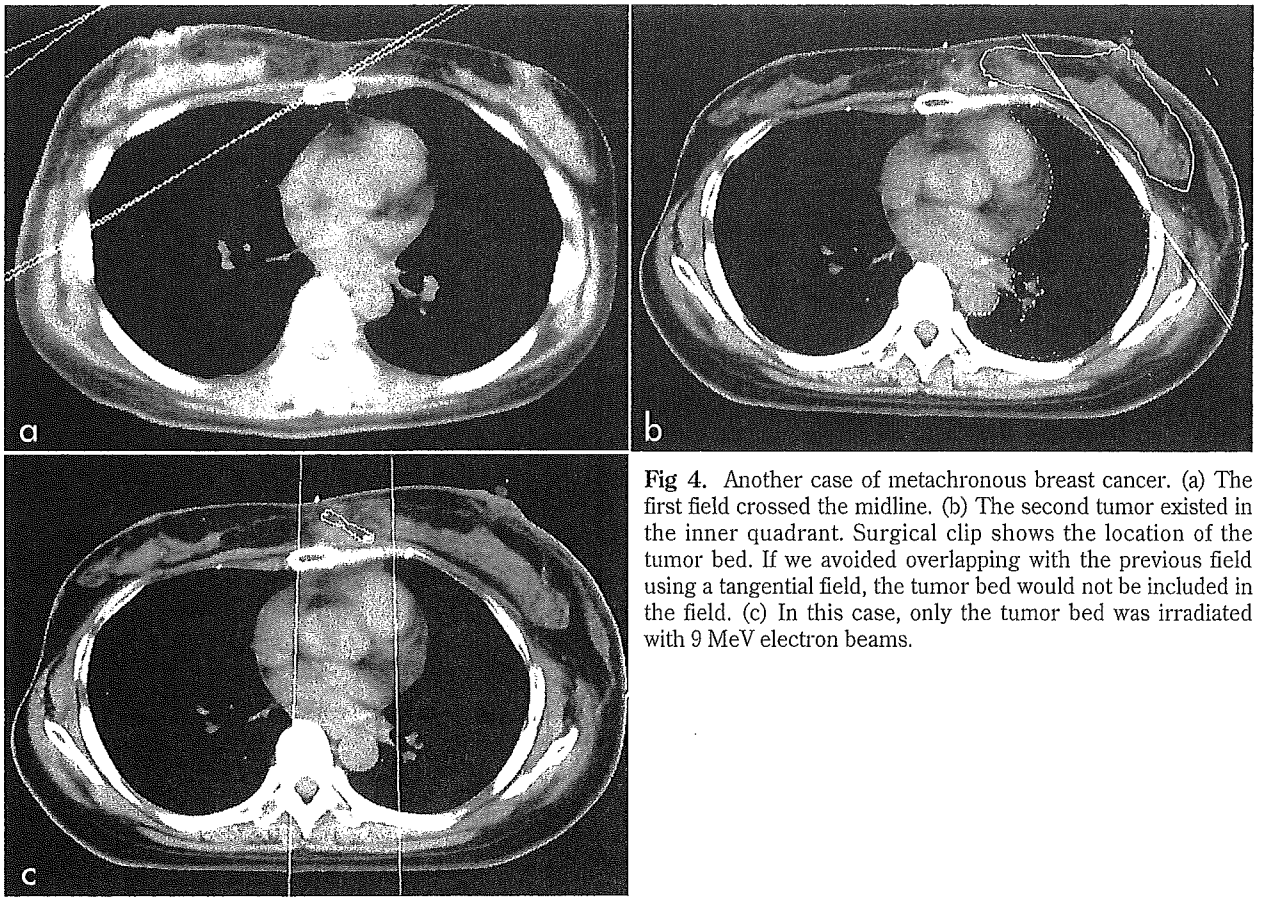

Fig 4. Another case of metachronous breast cancer. (a) The first field crossed the midline. (b) The second tumor existed in the inner quadrant. Surgical clip shows the location of the tumor bed. If we avoided overlapping with the previous field using a tangential field, the tumor bed would not be included in the field. (c) In this case, only the tumor bed was irradiated with 9 MeV electron beams.

The patients were periodically followed-up at our clinic. They were examined every 3 to 6 months in the first 2 years, and every 6 to 12 months thereafter according their pathological status. Loco-regional recurrence, distant metastasis, complications and cosmetic outcomes were evaluated.

Results

Of 17 patients, 15 patients were irradiated with matched tangential fields without overlapping, 1 patient was irradiated iwith matched tangential fields with overlapping of 1.2 cm, and 1 patient with a medially located metachronous tumor received en-face electron beam alone because overlapping with the previous field could not be avoided with tangential field (Fig 4).

No patients were lost to follow-up. The median follow-up period after each operation was 95 months. No patients showed loco-regional recurrence on either side or distant metastasis.

Regarding complications associated with treatment, severe arm edema was observed in one patient whose upper arms showed a 4 cm difference in circumference. One patient developed moderate fibrosis at the site of overlapping, but this did not affect cosmetic outcome. The patient who was irradiated with overlapping of 1.2 cm did not develop any skin or soft tissue complications. In other cases, complications were none or slight.

We also evaluated cosmetic outcome using the cosmetic score[7]. Six patients (35%) were scored as excellent and 10 (59%) were scored as good. Only one patient (6%) was graded fair because of unilateral breast contracture.

Discussion

Although as many as 10% of the patients with breast cancer may develop bilateral cancer[1-3] and radiation therapy is essential to breast conserving therapy, there is scant information on the technical aspects of such irradiation[8,9]. To minimize late damage to skin and soft tissue, overlapping of bilateral tangential fields should be avoided. On the other hand, maintaining good coverage of breast tissue is important to minimize the risk of intra-breast recurrence. In the patients with meta-

chronous breast cancer patients, which account for 2/3 of all bilateral cases, it is necessary to reproduce the previous tangential field before planning the contralateral tangential beam. In a conventional X-ray simulator, it is almost impossible to reproduce the medial margin accurately. Tattooing, which is commonly used in Western countries and might be useful in such situations, is seldom used in Japan. CT-simulation is quite useful because the overlapping of bilateral tangential fields can be evaluated much more accurately than conventional simulation, although there are some limitations derived from the change of the patient's figure and the difference in positioning. In patients with thick subcutaneous tissue at the midline, or those with tumors located very near to the midline, overlapping may be unavoidable despite the use of a CT simulator. However, it is still possible to explore the use of a CT for planning tangential fields for irradiation of metachronous breast cancer patients.

Conclusion

This study demonstrated that BCT is feasible for bilateral breast cancer and the CT simulator is useful for determining the radiation field, especially when they are metachronous. It is helpful in minimizing overlap of the radiation fields and provides the best possible treatment plan.

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Gastric Cancer (2005) 8: 1–5
DOI 10.1007/s10120-004-0298-z

Original article

Pancreaticoduodenectomy for advanced gastric cancer

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Abstract

Background. **Although pancreaticoduodenectomy has been rarely performed for gastric caner because of frequent morbidity and mortality, some favorable results after this procedure have been reported recently. Our objective was to present our data that might aid in the selection of patients to undergo this procedure.**

Methods. **Between 1970 and 2001, 23 patients who had pancreaticoduodenectomy for gastric cancer with tumor invading the pancreatic head were identified, and they were the subjects of this study. Clinical, operative, and pathological data, and morbidity and mortality rates were collected and analyzed. Survival outcome was also calculated and analyzed.**

Results. **Five patients underwent this procedure for disease in the gastric remnant, 18 undergoing the procedure for primary tumors. Median operating time was 8 h (range, 6–13 h), and median blood loss was 1600 ml (range, 700–16 000 ml). Regarding extent of gastrectomy, all patients with primary cancer ($n = 18$) underwent a distal gastrectomy and patients with disease in the gastric remnant ($n = 5$) underwent a completion gastrectomy. Incurable factors, including paraaortic lymph node metastasis, positive lavage cytology, or peritoneal dissemination were found in 8 patients. The postoperative morbidity rate was 73.9%; however, operation-related death was zero. The overall 5-year survival rate was 34.3%. The 5-year survival rate of the 8 patients with incurable factors was 0%, while that of the 15 patients without incurable factors was 47.4%.**

Conclusion. **If an R0 resection can be achieved by pancreaticoduodenectomy, this procedure should be performed for patients with tumor invading the pancreatic head. Patients with incurable factors should not be considered for pancreaticoduodenectomy.**

Key words Gastric cancer · Pancreaticoduodenectomy · Combined resection of adjacent organs

Offprint requests to: H. Katai
Received: April 8, 2004 / Accepted: September 1, 2004

Introduction

Complete removal of all evaluable disease, i.e., R0 resection, is vital to a successful outcome in gastric cancer treatment. Extended surgery is occasionally required for advanced gastric cancer with infiltration of adjacent organs to achieve complete tumor clearance. For locally advanced gastric cancer with infiltration of the pancreatic head or duodenum, pancreaticoduodenectomy (PD) is required. However, this procedure has been rarely performed because of substantial morbidity and mortality [1]. Prior to the 1990s, few reports regarding PD for gastric cancer had been published [2]. Only Kishimoto et al. [3] and Scott et al. [4] referred to a long survivor after this procedure in their reports about gastrectomy with combined resection. Recently, with current advances in operative techniques and in nutritional support, some favorable results of the patients undergoing this procedure have been reported [5–7]. However, only a few reports with a large number of cases have been published so far. In the current study, we present our data that might aid in the selection of patients to consider who should undergo this procedure.

Subjects and methods

A retrospective review of our prospective database, spanning from 1970 to 2001 and containing 9349 patients, identified 195 (2.1%) who had locally advanced cancer with macroscopically suspected infiltration of the pancreatic head. We included patients with pancreatic head invasion from metastatic lymph nodes, and excluded type 4, linitis plastica cancer. Of the 195 patients identified, 23 underwent PD with presumed curative intent, and they were the subjects of this study.

In these 23 patients, clinical data, including age, sex, symptoms, and primary tumor or tumor in the gastric remnant, were collected and analyzed, using the appro-

Table 1. Patients undergoing pancreaticoduodenectomy

		Disease	Stage	pT	pN	P	CY	Adjuvant Chemo.	Combined resection	Recurrence	FUT (months)	Status
1	63/F	Primary	IV	4	1	0	0	−	Liver	N	13	DOD
2	42/M	Primary	IIIB	3	1	0	ND	−		—	157	DOC
3	64/M	Primary	IIIB	2	2	0	0	−		—	182	NED
4	67/M	Primary	IV	3	2	0	ND	−		—	87	DOC
5	76/M	Primary	IV	4	3	0	0	−	Colon	Unclear	4	DOD
6	67/M	Primary	IIIB	4	0	0	0	+		—	26	DOC
7	65/M	Primary	IV	4	3	0	1	+		N	6	DOD
8	74/F	Primary	IV	2	3	0	0	−	Colon	H	34	AWD
9	70/M	Primary	IV	4	2	0	0	−	Colon	N, H	14	DOD
10	62/M	Primary	II	2	0	0	0	−	Colon	—	52	NED
11	65/M	Primary	IV	4	2	0	0	−		N	36	AWD
12	65/F	Primary	IV	4	2	0	0	−		N, H, spleen	12	DOD
13	58/M	Primary	IV	4	3	0	0	−	Colon	N	6	DOD
14	60/M	Primary	IIIB	2	2	0	0	−	Colon	—	12	NED
15	64/M	Primary	IV	4	2	1	1	−	Colon	Unclear	19	DOD
16	51/F	Primary	IIIB	2	2	0	0	−		H	11	DOD
17	61/M	Primary	IV	4	1	0	ND	−		H	4	DOD
18	70/M	Primary	IV	4	3	0	1	−		N, lung	4	DOD
19	60/M	Remnant	IV	4	2	1	1	−		N	13	DOD
20	57/M	Remnant	IV	4	1	0	0	−	Liver, colon	N, H	26	DOD
21	64/F	Remnant	IIIB	4	0	0	0	−		N	64	DOD
22	47/M	Remnant	IV	4	3	0	0	−		N	17	DOD
23	60/M	Remnant	IIIB	4	0	0	0	−	Colon	P	4	AWD

Primary, Primary tumor; remnant, tumor of the gastric remnant; P, peritoneal dissemination; CY, lavage cytology; ND, not done; N, lymph node; H, liver; FUT, follow-up time; NED, no evidence of disease; AWD, alive with disease; DOC, dead of other cause; DOD, dead of disease; unclear, site of recurrence unclear

priate nonparametric tests. Operative data, including operating time, blood loss, hospital stay, extent of gastrectomy, extent of lymphadenectomy, and combined resection with PD, were also evaluated. Pathological data, including pT, pN stage, site of tumor, and incurable factors, such as paraaortic lymph node metastasis (pN3), peritoneal dissemination, and positive lavage cytology, were analyzed according to the Japanese classification. Perioperative morbidity and mortality were also investigated.

The survival data of the 195 patients with tumors invading the pancreatic head, including the 23 PD patients, were calculated by the Kaplan-Meier method and analyzed by the log-rank method.

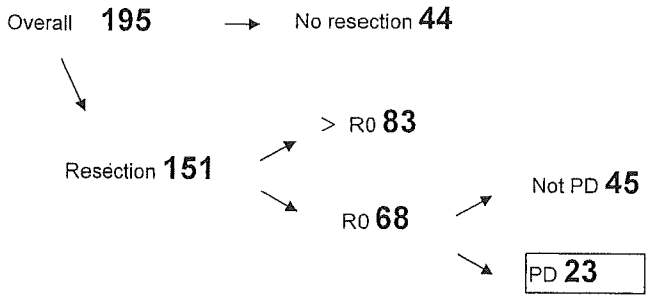

Fig. 1. Patients with tumors invading the pancreatic head. *No resection*, patients undergoing only exploration or bypass operation. *Not PD*, patients undergoing R0 resection, but with a lesser pancreatic resection than pancreaticoduodenectomy (*PD*)

Results

Demographics

Of the 195 patients with tumors invading the pancreatic head, 151 (77%) underwent resection, and the remaining 44 underwent only an exploration or a bypass surgery. In 68 patients, an R0 resection was carried out. In 45 patients with R0 resections, a lesser pancreatic resection (not PD) was performed because of a slight degree of tumor infiltration. The remaining 23 patients (12%) underwent PD (Fig. 1).

In the 23 patients undergoing PD, the median age at the time of resection was 64 years (range, 42–76 years), with a male-to-female ratio of 18:5 (Table 1). Twenty-one patients (91.3%) were symptomatic, most commonly with abdominal pain (n = 13) and symptoms due to obstruction, including fullness and vomiting (n = 11).

Eighteen patients underwent the PD procedure for primary cancer and 5 for gastric remnant cancer following previous Billroth I gastrectomy. Of the 5 patients with gastric remnant cancer, 4 had undergone distal partial gastrectomy for gastric cancer. Two of these

patients had early cancers, and the other 2 had advanced disease. The disease-free intervals were 1.5 and 6 years for those with advanced cancers and 8 and 10 years in those with early cancers. The fifth patient had had a partial gastrectomy for a benign gastric ulcer 30 years previously.

Operative data

The median operating time for PD was 8h (range, 6–13h), with a blood loss of 1600ml (700–16000ml). The median length of postoperative hospital stay was 37 days (range, 25–92 days). Regarding extent of gastrectomy, patients with primary cancer ($n = 18$) underwent a distal gastrectomy and those with gastric remnant cancer ($n = 5$) underwent a completion gastrectomy. As to extent of lymph node dissection, 14 patients underwent D2 lymphadenectomy and 9 underwent D3. In 9 patients, a combined resection of the colon was performed because of direct infiltration of the mesocolon (Table 1). Two patients underwent a partial hepatectomy because of a direct invasion of the liver. Modified Child's method was selected for a reconstruction for all patients. Two patients received postoperative adjuvant chemotherapy of 5-fluoruracil (5-FU) after surgery.

Pathology

Resection specimens from all patients revealed adenocarcinoma of gastric origin. In 7 patients, infiltration of the pancreatic head could not be confirmed histopathologically. Regarding site of tumor, 18 primary tumors involved the antrum, and 11 of these tumors extended into the duodenum.

Incurable factors, including pN3, peritoneal dissemination, and positive lavage cytology were found in eight patients (Table 1). No patient in this series had a visceral metastasis. In 6 patients, pN3 was found. These patients had been considered as negative for pN3 intraoperatively, but the finding was changed to positive by pathological examination postoperatively. Of these 6 patients, 2 also had positive lavage cytology. Two patients had positive lavage cytology and peritoneal dissemination synchronously; the peritoneal dissemination was a single nodule that was removed easily at operation.

Seventeen patients developed recurrences. The most common recurrence sites were nodal, in 11 patients, followed by liver, in 6; peritoneum in 1; lung in 1, spleen in 1, and unclear, in 2.

Morbidity and mortality

Postoperative complications were seen in 17 patients (73.9%; Table 2). Pancreatic fistula was the most common. All patients who developed this complication recovered, after receiving drainage and continuous irrigation, using double-lumen drainage tubes. No operation-related death occurred in this series.

Regarding the long-term postoperative morbidity, body weight at 12 months was maintained within 10% of the preoperative weight in all patients who lived for more than 1 year. Serum albumin levels were not decreased. However, two patients who underwent PD with completion gastrectomy required total parenteral nutrition (TPN) at home, for 1 and 3 years, respectively, after discharge from hospital, because of malnutrition. Postoperative pancreatic endocrine function was adequate in all patients, but three patients required pancreatic exocrine enzyme support postoperatively.

Table 2. Postoperative morbidity

	n
Postoperative morbidity	17 (73.9%)
Pancreatic fistula	10 (43.5%)
Abdominal abscess	3 (13.0%)
Anastomotic or jejunal stenosis	3 (13.0%)
Cholangitic infection	3 (13.0%)
Anastomotic leakage	2 (8.7%)

Table 3. Survival of patients with tumor invading the pancreatic head

	n	Median survival (months)	5-Year survival rate (%)
Overall	195	10	13.6
No resection	44	7	0
Resection	151	12	17.7
>R0	83	8	7.9
R0	68	21	29.3
Not PD	45	22	28.1
PD	23	17	34.3

No resection, Patients who underwent only exploration or bypass operation; not PD, patients who underwent R0 resection but received a lesser pancreatic resection than PD

Survival

In the 195 patients with tumors invading the pancreatic head, the 5-year survival rate was 13.6%. Of these 195 patients, the 68 patients who underwent an R0 resection showed a better survival outcome, with a 5-year survival of 29.3%. In patients who had R0 resections, there was no significant difference in survival between patients who underwent PD and those not receiving PD (Table 3).

In the 23 PD patients, the median follow-up time was 13 months (range, 4–182 months). The status of the

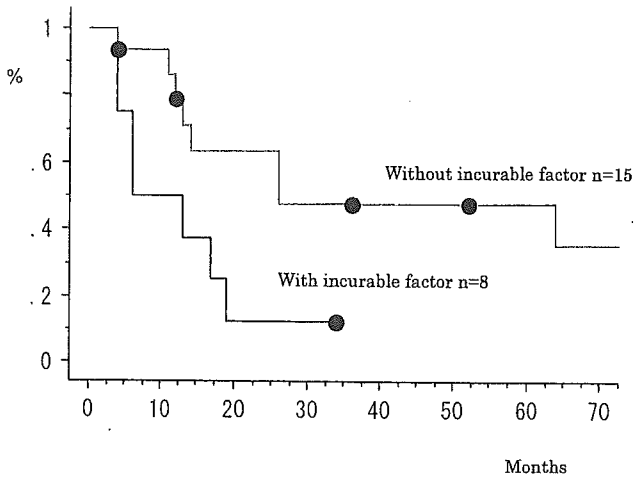

Fig. 2. Survival curves of patients undergoing pancreaticoduodenectomy (*PD*). The overall 5-year survival rate and the median survival of the 8 patients with incurable factors were 0% and 6 months, respectively, and these values in the 15 patients without incurable factors were 47.4% and 26 months ($P = 0.035$)

patients was as follows: no evidence of disease, 3; alive with disease, 3; dead of other causes, 3; and dead of disease, 14. The overall 5-year survival rate was 34.3%. The 5-year survival rate and the median survival of the 8 patients with incurable factors (pN3, positive lavage cytology, and peritoneal dissemination) were 0% and 6 months respectively, while these values in the 15 patients without incurable factors were 47.4% and 26 months (Fig. 2). Four patients have survived for more than 5 years.

Discussion

In our data, of 195 patients with tumors invading the pancreatic head, 23 (12%) underwent PD. This procedure has been rarely performed because of high morbidity and mortality rates. Prior to the 1990s, there had been only a few reports about this procedure [2–4]. Recently, with current advances in operative techniques, nutritional support, and antibiotics, some favorable results have been reported [5–11]. Ohashi [9] reported a large number of patients (145) undergoing this procedure. The 5-year survival rate of patients undergoing PD in that study was 6%, and it was approximately equal to the result for patients undergoing more than R0 resection in our data. Thus, it is inferred that Ohashi's subjects included patients with far-advanced tumors that could not be removed by this procedure. With proper indications, PD could account for 10% of surgeries for tumors invading the pancreatic head, and the number of patients who would have this procedure would be around 30, even at a large institution.

In our study, tumor infiltration of the pancreatic head could not be confirmed in 7 patients (30%) histopathologically. Such patients, theoretically, could have avoided this procedure; however, inconsistency between macroscopic and microscopic findings of infiltration has been reported to be 30%–50%, often because of inflammatory reactions surrounding the tumor [8,12]. Even if the latest diagnostic modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) are used, it is very difficult to distinguish between inflammatory reactions and tumor infiltration before operation. Intraoperative ultrasound could be more helpful than these modalities, but it was not used in any patients in the present series. It seems that inconsistency at a level of around 30% is unavoidable at present.

Morbidity after PD was in Ohashi's study [9] 51.6% and 37.8% in that of Shchepotin et al. [11]. Regarding mortality, these authors reported rates of 6.3%, and 10.8%, respectively. Buchholtz et al. [1] recommended that PD should not be performed for gastric cancer because of an unacceptable risk, with no greater degree of palliation. The morbidity rate in our series (73.9%) was higher than the rates in these previous reports [9,11], to be sure. However, the operative mortality rate was 0% and all surviving patients could resume a regular life. Pancreatic fistula was the most common complication in this series. This is critical, as it may lead to intraabdominal abscess and rupture of arterial aneurysm. This complication was diagnosed by the detection of infectious drain discharge with a high concentration of amylase (>10000IU/l). For the early detection of pancreatic fistula, the concentration of amylase in the drain discharge is checked routinely after PD. When pancreatic fistula has developed, continuous drainage is performed, initially. If there is infection, continuous irrigation, using double-lumen drainage tubes, is done. To achieve better control of this complication, the medical staff including not only the surgeon but also nursing staff, have to be skilled at careful drain management. Therefore, this procedure should be performed only at institutions where PD for pancreatic cancer is frequently performed.

No patient in our series developed diabetes mellitus after PD, and only three required pancreatic exocrine enzyme support postoperatively. However, after PD with completion gastrectomy, two patients required TPN at home for a long period because of malnutrition. Total gastrectomy combined with PD should be considered very carefully, as nutritional problems may be severe.

The overall prognosis of patients with tumors invading the pancreatic head was poor; however the 5-year survival rate of patients undergoing R0 resection was about 30% in this series. In the patients with R0 resec-

tions, there was no significant difference in survival between those requiring PD and those not requiring PD. Thus, to achieve R0 resection is an important objective, irrespective of whether or not PD is performed.

Ajisaka et al. [5] and Shchepotin et al. [11] reported that the 5-year survival rates of patients undergoing PD were 35% and 17%, respectively. In a study of 26 patients undergoing PD combined with right hemicolectomy, Yonemura et al. [10] reported that the 5-year survival rate of 13 patients with tumors infiltrating the pancreatic head was 55%. In our series, the 5-year survival rate for such patients was 34.3%. In PD patients without incurable factors, the 5-year survival rate was higher, at 47%, and 4 patients have survived for more than 5 years. Careful application of the PD procedure can achieve improved survival outcome. Kodama et al. [13] and Habu et al. [14] mentioned that a small amount of peritoneal dissemination and limited liver metastasis, respectively, were not contraindications for PD. However, most patients in the present series who had incurable factors died of the disease soon after operation. Incurable factors, such as pN3, positive lavage cytology, peritoneal dissemination, and visceral metastasis, should be regarded as a contraindication for PD.

In summary, the results after PD for patients with advanced gastric cancer with tumors invading the pancreatic head were acceptable from the aspects of morbidity, mortality, and survival benefit. If an R0 resection can be achieved by PD in such patients, this procedure should be performed. Patients with incurable factors should not be considered for PD. The combination of PD and total gastrectomy should be considered with caution.

Acknowledgments Dr. S. S. Mudan was supported by a grant from The Japanese Foundation for Cancer Research.

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Int J Clin Oncol (2005) 10:165–170
DOI 10.1007/s10147-005-0486-9

FROM THE ASCO-JSCO JOINT SYMPOSIUM

Mitsuru Sasako

Clinical trials of surgical treatment of malignant diseases

Received: March 14, 2005

Abstract The Dutch Gastric Cancer Study Group Trial was the first clinical phase III trial to be carried out in the field of cancer surgery. In spite of the excellent quality of the trial, it was heavily criticized for the poor quality of the treatment itself. Actually, the hospital mortality after the new surgical treatment (D2 lymph node dissection for gastric cancer) was unacceptably high. In surgical trials, special attention should be paid to quality issues specific to surgery. The first and the most important issue is the quality of treatment given. Reproducibility, homogeneity, and verifiability are the greatest problems in surgical trials. There are also some patient factors. If the patient is old, or fragile, or obese, the results of the surgical treatment can easily be affected by these factors. The surgeon can also be a prognostic factor, especially in complicated procedures or those requiring experience and training. Experience, including postoperative care, and dexterity affect the results. If surgeons do not know how to manage complications, mortality becomes very high. Because blinding is impossible in surgical trials, the treatment may easily be affected by personal preference or prejudice. To minimize the influence of these hampering factors, the procedures should be defined in as detailed a way as possible. If pretrial training or a feasibility study (phase II) is needed, it should be carried out properly for the patients' sake. An excellent design and excellent statistical analysis cannot lead to meaningful results if the quality of treatment is poor. Nonsense in, nonsense out.

Key words Clinical trials of surgical treatment · Quality assurance of treatment · Gastric cancer · Lymph node dissection

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The ASCO-JSCO Joint Symposium was held in Kyoto, Japan, on October 29, 2004.

Quality control in the Dutch Gastric Cancer trial

The Dutch Gastric Cancer Study Group Trial was the first well-designed, large-sized, randomized clinical trial (RCT) comparing the surgical procedures in cancer treatment (Fig. 1). In this trial, randomization was carried out before surgery, because the quality controller of the surgery, who usually came from outside the hospital, should be in the operation theater at every D2 dissection. So the group randomized patients before operation, based on the clinical staging, but they expected that some of these patients, about 30% of them, might have peritoneal seeding, and the operation would turn out to be non-curative in such patients. The estimated survival rates of the D1 and D2 surgery arms were 20% and 32%, respectively, but with these non-curative cases, the rates were 14% and 21% for D1 and D2, respectively in all randomised patients. The projected sample size was 531 in each arm.[1]

Not following the principles of phase III clinical trials, even the first patient in this RCT was randomized. When this trial started, only one Dutch surgeon knew what a D2 dissection was and had some experience of carrying out D2 gastrectomy. Although none of the other surgeons involved had ever had experience of D2 gastrectomy, they did not plan any feasibility study before starting a phase III study. Instead, they invited the author (M.S.) to carry out D2 dissections and to teach them how to do it. Therefore, they could randomize the first patient in whom he carried out a D2 dissection for the Dutch surgeons. Inviting a surgeon who knows well the new treatment seemed to be a good option and was much better than letting surgeons do a new treatment after just looking at a videotape of the procedure. However, the tutor could not stay there to participate in all D2 surgery during the entire period of the trial. Therefore, in just 4 months he had to teach them how to carry out the procedure. Surgery of this type is not easy to learn without doing it oneself. It was obvious that he could not teach all the participating surgeons of about 80 hospitals. This length of time was not sufficient to teach even the 12 quality controllers of the D2 surgery.[2] A feasibility study or intensive

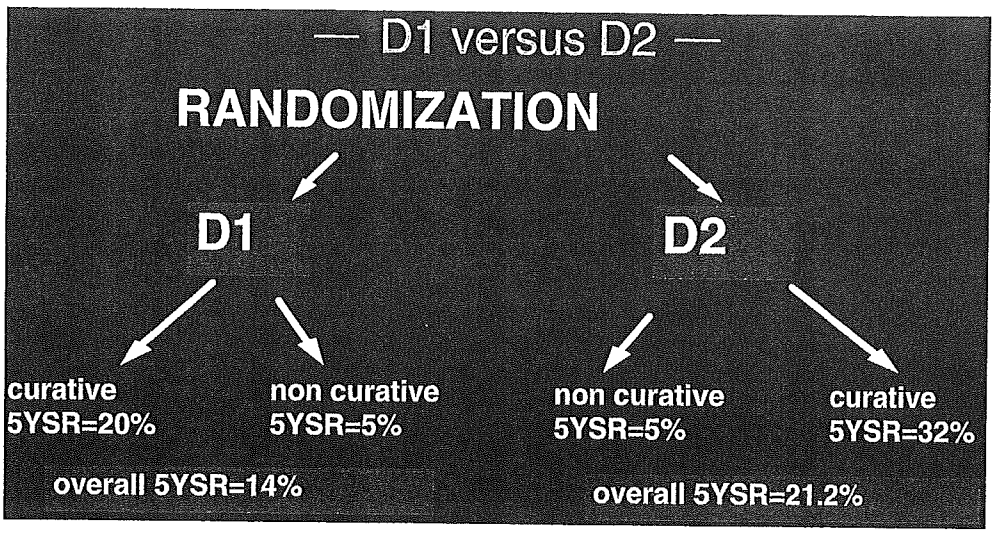


Fig. 1. Dutch trial on lymphadenectomy for gastric cancer.[1] Alpha = 0.05, power = 0.90, 531 patients in each arm requested; *5YSR*, 5-year survival rate

Table 1. Morbidity and mortality after D2 dissection for gastric cancer

Trial	Type	Number of patients	Number of patients per hospital/year	Mortality	Morbidity
Hong Kong[4]	RCT	30	7.5	3%	57%
MRC[5]	RCT	200	1.5	13%	46%
Dutch[1]	RCT	331	1.0	10%	43%
Italian[6]	P-II	191	8.0	3%	21%
Sue-Ling et al.[7]	Retro	142	14.2	5%	17%
Pacelli et al.[8]	Retro	157	15.7	4%	22%

pretrial training should have been carried out. From the scientific and ethical points of view, this kind of setting for a phase III trial of a new surgical technique is not allowed anymore.

The author's major task in this surgical trial was to teach the surgeons how to do a D2 gastrectomy. He himself did 27 operations and instructed the Dutch surgeons as the first assistant in operations for six patients. He also gave many lectures, using videotapes of this operation; the organizers distributed a videotape of the D2 operation on a Dutch patient, which was filmed during this period of the trial, and also distributed a booklet with detailed color photographs showing the anatomy and the technique. This is all that we did for teaching. However, this was not good enough for many of the quality controllers to master the technique sufficiently. Actually, in spite of all the efforts, the morbidity and mortality of this trial was shockingly high for the organizers. Postoperative hospital deaths reached nearly 10% in the D2 arm, much higher than in the D1 arm. This was something unexpected by them before they started this trial. Retrospectively, they should have stopped this trial much earlier and gone back to the feasibility study for the sake of the patients.

Causes of mortality and hospital volume

Theoretically, factors which may influence the morbidity and mortality after this type of surgery are patient factors, tumor factors, operative procedures, and hospital and surgeon factors. Obviously, older patients and obese patients may have more morbidities. But, unexpectedly, sex actually influenced the mortality in this trial very much. And, of course, so did tumor location and histology, the procedures, lymph node dissection, the type of gastrectomy (total or distal), and combined organ resection. Postoperative hospital mortality after D2 in women was as low as that for D1 dissection, but that in male patients reached 14%, or three times higher than that for D1.[3]

Table 1 shows the postoperative hospital mortalities after D2 dissection in various reports.[1,4–8] In the Dutch trial and the MRC (Medical Research Council) trial (British trial), each hospital had very small numbers of cases annually (hospital volume). These two trials had smaller hospital volumes and much higher hospital mortality than in other reports. With such a limited case load, learning how to manage these complications was almost impossible. Actually, the mortality after major surgical complications in the Dutch trial was significantly higher than that experienced at the National Cancer Center Hospital Tokyo (NCCH). The mortality after anastomotic leak and after intraabdominal abscess or pancreatic juice leakage was 41% and 20%, respectively, in the Dutch trial. But, in the same period, the 1980s, the corresponding figures at the NCCH showed much lower 14% after anastomotic leak, and only 3% after intraabdominal abscess.[3] This suggests that experience is needed to manage these major adverse effects to avoid treatment-related deaths. Even in patients with medical treatment, we should know how to manage febrile neu-

tropenia. If not, the patient may die. Greater effort and more experience are needed in the treatment of complications after surgical treatment.

High treatment-related death (TRD) rate offsets treatment effect

Figure 2 shows the survival curves of the Dutch trial.[9] The curve of the D2 arm started at 10% below the D1 arm but caught up with the D1 curve at about 4 years after surgery. However, the difference between the two arms did not become statistically significant at any time. As expected from this, the hazard ratio between the two treatments changed with time; at the beginning, three to four times higher risk for D2 was observed, but the hazard ratio of D2/D1 became less than 1 after 3 years, even with the upper limit of the 95% confidence interval below 1. So, after 3 years, patients who underwent D2 had a significantly lower risk of death than those who underwent D1. These hazard ratio curves by time were completely different for men and women. The curve for women showed a more or less constant hazard ratio, suggesting the applicability of statistical methods based on the hypothesis of a constant hazard ratio. The most common method used to evaluate two survival curves is the log rank test, which is based on the assumption that the hazard ratio is roughly constant. This means that the above statistical methods cannot be properly applied to survival analyses in male patients.

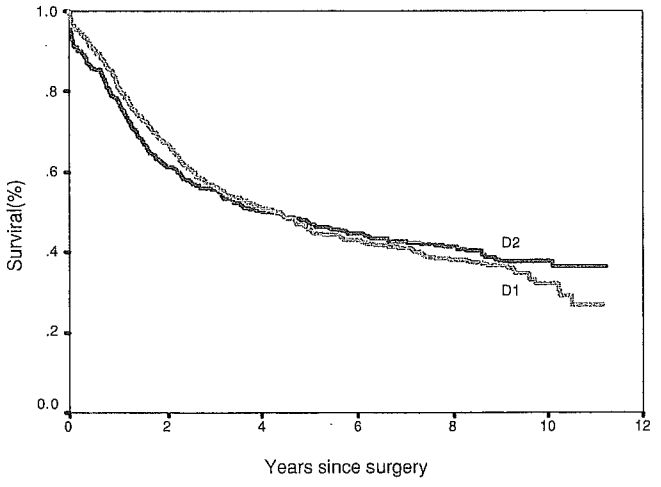
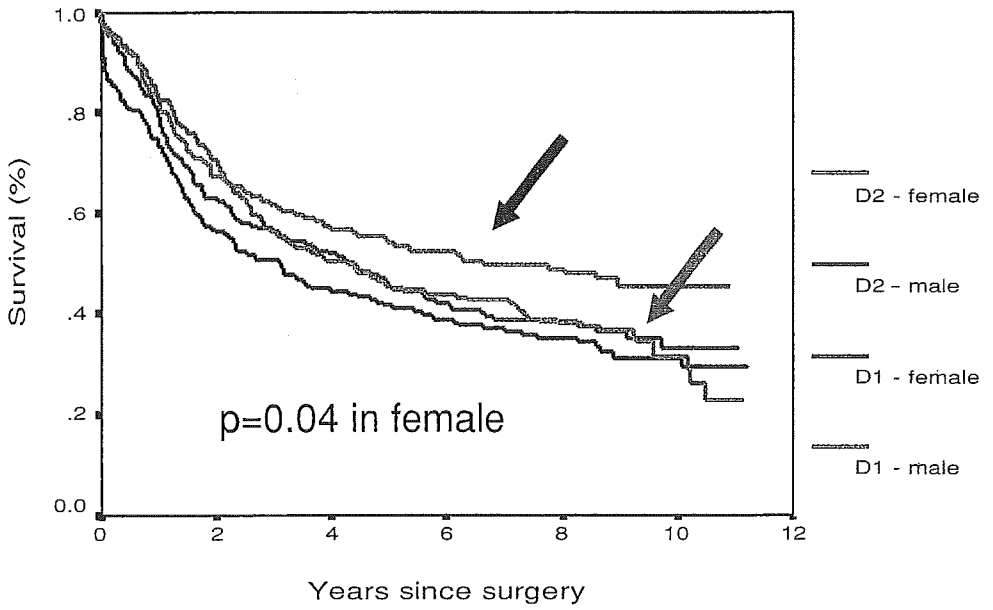


Fig. 2. Survival curves in the Dutch trial[9]

Figure 3 shows the survival curves by treatment by sex in the Dutch trial.[3] The survival curve for the female patients in the D2 arm shows clearly better survival than that for the female patients in the D1 arm. Although the *P* value of the difference by log rank test was 0.04, this cannot be regarded as statistically significant because of the multiplicity of the analysis.

In summary, the conclusion which should be drawn at the moment is that all the RCTs of lymphadenectomy for curable gastric cancer failed to prove the effect of D2 dissection.[10] As discussed already, however, the quality of D2 dissection in these trials was questionable, especially that in the MRC trial. With quite small hospital volumes, each of these trials had treatment-related death (TRD) rates after D2 as high as 10%. The quality of postoperative care to avoid TRD was very poor, and the high TRD rate offset the long-term effect of treatment. This was also confirmed in the French and German studies of squamous cell cancer, reported at Americal Society of Clinical Oncology (ASCO) meetings in 2002[11] and 2003, respectively.[12] Proper D2 dissection is a technically demanding procedure, requiring experience in postoperative care, and should be carried out at specialized centers, at least in low-volume areas.

Fig. 3. Survival curves by treatment (D1 or D2) by sex in the Dutch trial.[3]



Surgical trials with low TRD rate

The results of a Japanese trial, Japan Clinical Oncology Group (JCOG) 9501, a study comparing standard D2 gastrectomy with D2 plus paraaortic lymph node dissection (D3), made a clear contrast to these trials.[13] Unlike the Dutch trial, it was possible to randomize the patients during surgery after confirming the absence of the peritoneal seeding and negative cytology of the peritoneal washing fluid, because every participating surgeon knew the technique and therefore a quality controller from outside the hospital was not needed. This randomization during surgery was done at the central data center by telephone. The primary endpoint was survival and morbidity/mortality, and the projected sample size was 412 at the beginning. But the sample size was amended in June 2000, to increase the statistical power, and we can now evaluate an 8% difference between the two treatment arms. Five hundred twenty-three patients were enrolled, and the results of the survival analysis in 2006 are awaited. The postoperative morbidity and mortality of this trial is shown in Table 2. The D2 arm showed 20% morbidity, including all complications and although slightly more complications were observed in the D3 arm, there was no difference in mortality, at 0.8%, in the two arms. No differences were observed in major surgical complications such as anastomotic leak or pancreatic juice fistula, but an increased of diarrhea juice and ileus was observed after D3.

Table 2. Morbidity and mortality: JCOG 9501 (523 patients)

	D2	D3	All
Morbidity (any*)	20.9%	28.1%	24.5%
Anastomotic leak	2.3%	1.9%	2.1%
Pancreatic fistula	5.3%	6.2%	4.0%
Abdominal abscess	5.3%	5.8%	5.5%
Pneumonia**	4.6%	1.5%	3.2%
Miscellaneous***	9.1%	20.0%	14.5%
Reoperation	1.9%	2.7%	2.3%
Mortality (in hospital)	0.8%	0.8%	0.8%

* $P = 0.067$; ** $P = 0.0724$; *** $P = 0.0005$ (ileus, lymphorrhea, diarrhea)

Figure 4 shows the survival curve for all the patients in JCOG 9501. The investigators do not know yet how are the survival curves for the two treatment arms, but the survival curve for all the patients is quite good, considering the T stage of the patients. So far, from this result, it can be said that morbidity and mortality after extended surgery did not increase much, if the surgery was done by experienced surgeons in countries of high incidence. The incidence of the major complications was the same in both arms, with a slight increase of minor complications in the D3 arm. D3 increased the operation time by 60 min and the blood loss by 230 ml. Unlike the two trials in Europe (Dutch trial[1] and MRC trial[5]), postoperative mortality will not affect the results in the long term.

The only clinical phase II trial of D2 dissection was carried out by the Italian Gastric Cancer Study Group in Turin.[6] This was carried out to confirm the feasibility of D2 carried out by Italian surgeons after the reports of the Dutch[1] and MRC[5] trials. The Italian group achieved 3% mortality. In the Dutch trial, the number of participating hospitals was 80 and the number of D2 dissections per year per hospital was just 1, while in the Italian trial, the number of hospitals was 9 and the number of D2 dissections per year was 7. The hospital volume differred enormously between these two trials. Another important difference that may have affected the morbidity and mortality was the indication for pancreas tail resection. In the Dutch trial, a total gastrectomy was always combined with pancreaticosplenectomy, but in the Italian trial, the pancreas was preserved in principle.

After achieving this 3% mortality, the Italian group started a phase III trial, comparing D1 versus D2 dissection. However, they have actually had much difficulty in enrolling patients. As there was no difference between the mortality rates of D1 and D2, some surgeons had refrained from enrolling patients with a preference for D2. The feeling was, why should they go back to D1 when there

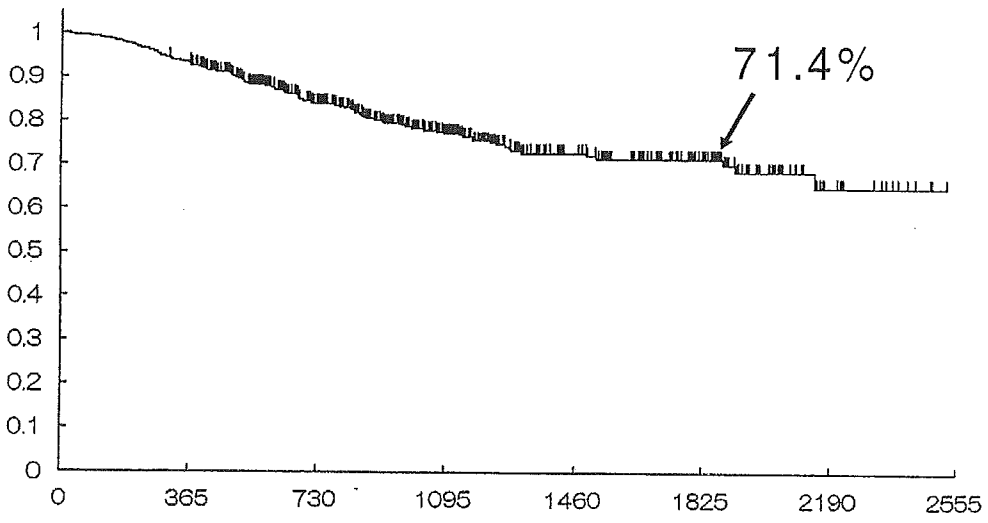


Fig. 4. Survival curve in all patients in the Japan Clinical Oncology Group (JCOG) 9501 trial. Actual proportion of 5 year survivors = 71.4%

is a low mortality for D2 in their hands. If they do enroll patients, it is questionable whether D1 performed by such surgeons can be real D1. If the mortality rates after pancreatico-duodenectomy or three-field dissection for esophageal cancer (major surgery) at specialist institutes in Japan, and in Western countries are compared, they are less than 5%.

Why did the Dutch and the MRC trials have higher mortality than pancreatico-duodenectomy or three-field dissection? Radical pancreatico-duodenectomy is usually more aggressive than D2 gastrectomy. The only difference was that the patients with esophageal or pancreatic cancer were treated at specialist centers, while those with gastric cancer were treated at general hospitals. In both the MRC and the Dutch trials, many hospitals had very low hospital volumes. On the other hand, in the Japanese JCOG trial, both procedures (i.e., D2 and D3 gastrectomy) have commonly been carried out, and all participants had high hospital volumes. Besides, in this trial, together with strict patient selection and quality assurance, according to the number of dissected nodes, each participant showed their operative procedure on videotapes in regular group meetings.

Factors hampering surgical trials

There are several factors which make clinical trials in surgery difficult.[14,15] First of all, skill and experience affect the results. In this aspect, all surgeons cannot be the same. So inter-surgeon variation is unavoidable; some are dexterous and some are "all thumbs" by nature, and techniques suitable only for dexterous surgeons exist. Experience is also a very important factor – knowledge, familiarity, and knacks included. There is a learning curve for most surgical techniques. Surgery is usually followed by sequelae, and, therefore, quality-of-life evaluation is essential in surgical trials when comparing surgical techniques. However, there is no well-established measurement to assess these sequelae. Unlike medical treatment, masking of the allocated arm is impossible, and auditing the treatment given is very difficult in surgical trials.

In the past, we surgeons have experienced the introduction of laparoscopic cholecystectomy, and in this procedure, we heard for the first time, the term, "learning curve". Many articles state that at least 30 cases are needed to reach the plateau of the curve, while some argue that 250 cases are needed. We also observed expansions of indications of this procedure. At the beginning, this technique was not indicated for gallstone disease with acute cholecystitis, or for patients with previous operations in the upper abdomen, or during pregnancy. But actually, many surgeons are now doing laparoscopic cholecystectomy, even in patients with these conditions. Finally, in regard to laparoscopic cholecystectomy, RCTs were carried out, but they were only small trials and the results were reported only after an NIH consensus meeting, and, actually, these RCTs did not have any impact on clinical practice.[16]

Quality of surgical trials

The quality of surgical trials can be summarized in two categories. One category is quality issues that are common to all clinical trials. Indicators of the quality of a trial are, for example, the randomizing of patients (either by the envelope method or by a central computer system), the blinding of the arms, the proportion of excluded cases or protocol violations, sample size projection, the quality and independence of the data center and respect for multiplicity in the analysis, the prospective setting of the interim analysis, and the existence of an independent monitoring committee. If all these factors are fulfilled, the quality of the trial itself should be regarded as excellent. The South West Oncology Group (SWOG), the East Clinical Oncology Group (ECOG), the European Organization for Reseach and Treatment of Cancer (EORTC) and the JCOG are good examples of organizations which support various subgroups of different specialties and can carry out high-quality clinical trials.

The second category is specific to surgical trials. First, and most important, is the quality of treatment given. Reproducibility, homogeneity and verifiability are the greatest problems in surgical trials. There are also some patient factors. If the patient is old, or fragile, or obese, the results of the surgical treatment can easily be affected by these patient factors. Some surgery in obese patients is much more difficult than in slim patients. The surgeon can also be a prognostic factor, especially in complicated procedures or those requiring experience and training.

In surgical trials, quality control should include postoperative care as well. If surgeons do not know how to manage complications, mortality becomes very high, especially in intra-abdominal or intra-thoracic surgery. Therefore, experience and hospital volume are very important factors in surgical trials. Because blinding is impossible in surgical trials, the treatment may easily be affected by personal preference or prejudice. When surgical trials are planned, details of each procedure in each arm should be defined carefully after discussion among the participants to avoid unacceptable heterogeneity. For example, the Gastric Surgery Division of the JCOG now is carrying out an RCT of total gastrectomy with or without splenectomy, and there are several possible techniques in each procedure to be decided among the participants. They had to decide whether or not mobilization of the spleen was allowed for dissection of lymph nodes along the distal pancreas, whether or not a frozen section for splenic hilum node was acceptable, and where the splenic artery and vein should be divided, and also the indications for splenectomy in the spleen-preserving arm. This is because the spleen occasionally has to be taken out if it is injured, to control bleeding, even if the patient is allocated to the spleen-preserving arm. When these details are decided, leading surgeons should demonstrate to all participants, the procedures in detail on a videotape and each step of the procedures should be decided as precisely as possible. Even after starting the trial, it is recommended that the participating surgeons should

visit reciprocally to see others' operations. At each regular meeting among the participants, some of them, perhaps three or four, demonstrate their operation on videotape and discuss the technical details, repeatedly. Each participating center should demonstrate the technique at least once in the course of a trial, and any technical issue should be reevaluated, if needed, even after starting the trial, which may lead to protocol revision. Another difficult issue in surgical trials is how to audit the treatment given. Videotape recording for every patient is the best way. But, as this is not realistic, an onsite visit by referees is also another good way of auditing, but this is also very difficult to perform. Checking a close-up photograph of the operation field after dissection is one of the possible options. Actually, the Colorectal Surgery Division of the JCOG is adopting this method for an ongoing trial of rectal surgery. Close and intensive assessment of resected material, including lymph nodes, is a feasible technique if collaboration of pathologists is available, and was adopted in the Dutch trial on rectal surgery. All these methods to evaluate the quality of surgery become effective when proper feedback of the results to the operators is given regularly.

How to set up clinical trials in surgery

When surgical trials are set up, the following points should be considered. First, when to start phase III trial should be decided. For some surgical techniques that are complicated and surgically demanding, a feasibility study is absolutely needed, because there is usually a learning curve. Assessment of the experience of each participant is also important. Even if the procedures in each arm of a study are familiar to the surgeons, each participant's experience of each technique has to be assessed. A phase III trial should be started after sufficient experience of the procedures. In this regard, a phase III trial comparing two commonly performed operations is much easier than a comparison of old and new techniques. Open colon surgery versus laparoscopic colon surgery for colon cancer is a good example of a difficult trial, because the learning curve is a serious issue for laparoscopic colectomy. Selection of participants is also very important. The more institutes are involved, the faster is the accrual. On the other hand, the more institutes are involved, the more difficult is the quality control of surgery. Careful selection of participating hospitals which have acceptable quality of surgery is essential. The two procedures compared in a trial should be defined in every detail and in each technical point. Some method to verify the treatment given should be included, and the maximum effort should be made to avoid personal preferences affecting the results. Quality-of-life evaluation (i.e., a quality-of-life score or symptom score) should be included in most surgical trials.

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Gastric Cancer (2005) 8: 137–141
DOI 10.1007/s10120-005-0317-8

Original article

Risk factors for pancreas-related abscess after total gastrectomy

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Abstract
Background. **European clinical trials of gastrectomy have shown that pancreas-related complications are the major cause of mortality. The aim of this study was to determine the risk factors for pancreas-related abscess after gastrectomy and to evaluate the effects of the abscess on postoperative mortality.**
Methods. **Between 1992 and 1999, 663 consecutive patients with gastric carcinoma underwent total gastrectomy. Data from these patients were analyzed, to identify the predictors of pancreas-related abscess caused by pancreatic juice leakage, by a multiple logistic regression model.**
Results. **On multivariate analysis, increasing age ($P = 0.018$) and body mass index ($P = 0.006$) were independent preoperative risk factors. Dissection along the distal splenic artery was an intraoperative risk factor. The hazard ratios were increased 9.13-fold ($P = 0.000$) with a pancreas-preserving operation and 16.72-fold ($P = 0.000$) by distal pancreatectomy. Patients with the abscess had a higher postoperative mortality rate ($P = 0.008$), and a higher re-operation rate ($P < 0.001$) than patients without the abscess.**
Conclusion. **Pancreas-related abscess is more likely to occur in older, obese patients undergoing node dissection along the distal splenic artery. Abscess formation is associated with a higher mortality and re-operation rate. Spleen preservation should be evaluated in Japan.**

Key words Gastric cancer · Morbidity

Introduction

The most frequent major complication after gastrectomy with extended dissection is pancreatic juice leakage [1], because recently, the incidence of anastomotic leakage has decreased remarkably [2]. Pancreatic juice leakage is often followed by contamination, resulting in a peripancreatic abscess. Secondary hemorrhage from major arteries damaged by contamination can be fatal. European clinical trials of gastrectomy have shown that pancreas-related complications are a major cause of mortality [3,4].

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

Patients and methods

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

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

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

Offprint requests to: H. Katai
Received: August 9, 2004 / Accepted: January 20, 2005

Operative techniques

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

Statistical methods

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

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

Results

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

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

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

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

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

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

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

Discussion

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

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

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