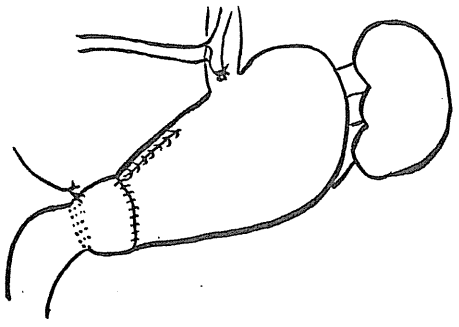

Figure 25.2. Pylorus preserving distal partial gastrectomy.

the incidence of postgastrectomy symptoms. Pylorus preserving gastrectomy is one of these options. This procedure was originally described by Maki as a surgical treatment for benign gastric ulcer [6]. By preserving the pylorus with a small part of the gastric antrum, rapid emptying of the stomach, causing the dumping syndrome, should be reduced. In the 1990s, this technique was introduced in patients with early gastric cancer of the middle part of the stomach [1]. There is now experience with hundreds of patients who have undergone this operation with satisfactory results, in terms of QOL and survival. The original method preserved 1.5 cm of the distal antrum but the preference now is to preserve at least 3 cm of the antrum for better gastric emptying (Figure 25.2).

Concept, Classification and Efficacy of Lymph Node Dissection for Gastric Carcinoma

Concept

The initial description of lymph node dissection for cancer treatment was in breast cancer by Halsted and the work was developed by Haagensen. The primary aim of this procedure is to avoid local failure in axillary lymph nodes. Originally all systemic metastasis was thought to occur via lymphatic spread. In this theory, called the Halstedian cancer model, cancer cells spread initially to the nearest nodes and then to farther nodes step by step, and eventually to various distant sites. Therefore the wider the nodal dissection, the better the survival that should be achieved. Local recurrence should be rare after adequate nodal dissection. However, cancer metastases occur not only via lymph stream but also primarily via the bloodstream and sometimes directly through the pleural or peritoneal cavity. In breast cancer, 20–30% of node-negative patients develop systemic recurrence [7]. Local recurrence sometimes occurs as a part of systemic recurrence in high grade tumours. Prognosis of patients with multiple nodal metastases worsens steeply as the number of metastatic nodes increases [8]. All these facts demonstrate that regional lymph nodes do not form an effective barrier to cancer dissemination. Several clinical trials have shown nodal dissection does not contribute to better survival for breast cancer and nodal metastasis is an indicator of poor prognosis. Nodal disease is indicative of a high risk of the presence of systemic disease (systemic disease model).

Unlike breast cancer, gastric cancer more closely follows the requisites for the original Halstedian model. Those having no or limited spread of nodal metastasis have a good prognosis if peritoneal seeding does not occur. Five-year survival rates of those having 4, 6, 8, 10 nodal metastases are 52.3%, 43.5%, 37.7%, 29.9%, respectively (unpublished data from National Cancer Center Hospital Tokyo). Systemic/distant metastases are quite rare in T1 and T2 tumours, whereas lymph node metastases are already frequent in these stages (Table 25.1) [9]. Thus in gastric cancer, nodal metastasis is the primary site of metastatic spread in most cases and systemic recurrence after curative operation in node-negative patients is rare. The commonest type of recurrence of advanced tumours is peritoneal seeding after formal nodal dissection [10]. However, recurrence after limited surgery occurs most frequently in the gastric bed and, with regional peritoneal seeding, accounts for over 90% of recurrences [11]. These differences between breast and gastric cancers might be explained by the following. First, the stomach is located in the portal venous system, with bloodborne metastases occurring most frequently via the portal vein to the liver rather than through the lympho-venous connection in the neck. Second,

the high intraluminal bacteria count is associated with an abundant lymphatic system including mucosa associated lymphoid tissue.

Most of the reported adjuvant chemotherapy trials have failed to prove any efficacy over surgery alone [12]. Recently a clinical trial comparing surgery plus radiochemotherapy versus surgery alone showed significantly better survival for the radiochemotherapy group [13]. In this study, 90% of the patients underwent either D0 or D1 lymph node dissection. This could be interpreted as showing that adjuvant chemotherapy may be effective when the local regional lymph node metastases are well controlled by radiotherapy. However, the survival results of the radiochemotherapy group in this study could not reach the level of the results achieved by D2 dissection alone. Therefore it is still uncertain whether D0/1 surgery plus radiochemotherapy can replace D2 dissection or not. In fact, retrospective analysis of the patients in this trial suggests that surgical undertreatment undermined survival [14].

Classification

Of the two commonly used classifications for gastric cancer, the Japanese classification [15] and the Union Internacional Contra la Cancrum (UICC) TNM classification, only the former includes a method for classification of the extent of lymph node dissection. The regional lymph nodes are topographically classified from the first to third tier nodes, according to the tumour location in the stomach. In general terms, perigastric nodes are usually classified as the first tier and lymph nodes in the suprapancreatic area with splenic hilum nodes comprise the second tier; nodes in the hepatoduodenal ligament, retropancreatic and para-aortic nodes are the third tier. Nodal dissection is defined as D1, D2 and D3. D0 is defined as excision which fails to remove all of the first tier nodes. D1 includes all first tier stations but not all of the second tier stations. D2 dissection includes all first and second tier stations but not all the third tier nodes. D3 means dissection including all first, second and third tier stations.

Efficacy

Many retrospective comparisons of lymph node dissection, D1 versus D2, have shown better survival for D2 (Table 25.2). The results of D1 have never reached the level of D2 dissection in terms of long-term survival according to stage. When the results of surgery are compared according to TNM stage, stage migration confounds comparisons. The wider the dissection, the more accurate the stage diagnosis, thus resulting in an increase in the number of cases at advanced stages and improvement of the results by stage in each category, stage migration. Therefore, for gastric cancer, the results of two groups who underwent different nodal dissection should be compared by T stage, which is not influenced by type of nodal dissection. Even in such comparisons, D2 always shows better results than D1. However, randomised controlled trials (RCTs) have never proven the superiority of D2 dissection over D1. Table 25.2 shows the results of these RCTs. Furthermore the two large-scale RCTs, the MRC trial [16] and the Dutch trial [17], showed significantly higher postoperative hospital mortality after D2 than D1. Initially these results we interpreted as pointing to an

Table 25.1. Metastases at the time of operation, 5-year survival, and haematogenous recurrence after resection in 4683 patients at National Cancer Center Hospital Tokyo, 1972–1991

Tumour depth	*n*	LN	Liver	Peritoneum	5Y SR (%)	Haematogenous rec.
pT1(m)	1063	3.3	0	0	93.3	2 (0.2%)
pT1(sm)	881	17.4	0.1	0	88.9	9 (1.0%)
pT2(mp)	436	46.7	1.1	0.5	81.3	26 (5.9%)
pT2(ss)	325	63.6	3.4	2.2	65.8	31 (9.5%)
pT3	1232	79.9	6.3	17.8	35.5	149 (12.1%)
pT4	724	89.7	15.5	41.6	10.1	106 (14.6%)
All	4683	47.8	4.5	11.5	60.3	318 (6.8%)

n. number: LN. lymph node: 5Y SR. 5-year survival rate, Rec, recurrence
Reproduced with permission from Mitsuru Sasako, What is reasonable treatment for gastric adenocarcinoma? J Gastroenteroc 2000; 35 [suppl XII]: 117.

inherently greater risk in D2 dissection. However, precise analyses of these trials and other reports elucidated surgical inexperience in those undertaking D2 dissection in these trials. Moreover, the only single arm study to assess the safety and effectiveness of D2 dissection, which was started after the publication of the results of MRC and Dutch trials, has demonstrated the safety of D2 dissection if done in high volume hospitals in the West. These trials provide important lessons around the importance of quality assurance in phase trials in surgery. The issue of timing of trial initiation has been raised, with suggestions that this should be determined on the basis of demonstration that individuals are near to the plateau of their learning curve of a difficult technique. Inexperience can produce large biases when comparing technically demanding surgical procedures.

Survival results of these trials in comparison to other studies are shown in Table 25.3. This table compares exclusively the results of D2 surgery, to avoid the stage migration effect. Sometimes, the results of the Dutch trial and MRC trials are interpreted as real evidence of non-superiority of the D2 dissection for gastric cancer. However, these are not trials set up to show the equality of D1 and D2 and with the factors pointed out above, the question is still unsolved. However, from the experience in these trials, it is obvious that D2 dissection should not be carried out by surgeons with insufficient experience of this technique and inexperienced surgeons should carry out this procedure strictly under the supervision of experienced surgeons.

Indications for Extended lymph Node Dissection (D2 Dissection)

Tumour Factors

This procedure should not be undertaken in incurable patients because of the increased morbidity associated with the technique. For T1

Table 25.2. D1 versus D2 5-year survival rates

Author	5-year survival rate D1	5-year survival rate D2	Reference
Pacelli F, et al	50.1	65.4	Br J Surg 1993;80:1153–6
Onate-Ocana LF, et al	35.1	64.0	Ann Surg Oncol 2000;7:210–17
De Manzoni G, et al	28	63	Br J Surg 1996;83:1604–7
Lee WJ, et al	34.8	41.5	World J Surg 1995;19:707–13
Sue-Ling H	18	45	Eur J Surg Oncol 1994;20:179–82
Gall FP, et al	43.6	51.8	Eur J Surg Oncol 1985;11:219–25

Table 25.3. D2 Surgery: trial results

				5-Year survival rates (%)						
Author	No. of patients	# patients/y/h	PO mortality	Overall	IA	IB	II	IIIA	IIIB	IV
Siewert	803	14	5.0	NM	84	68	57	32	14	13
Pacelli	157	16	3.8	65	86	→	66	49	→	none
Sue-Ling	207	10	6	54	87	→	65	24	→	NM
Cuschieri	200	1	13.0	33	58	→	31	11	→	none
Bonenkamp	331	1	9.7	47	81	61	42	28	13	28
Sasako	2541	254	0.3	66	92	90	76	59	37	8
Jatzko	345	33	4.9	58	98	84	56	49	8	11
Hundahl *	32532	NM	NM	28	78	58	34	20	8	7

* Results of National Data Base, most cases are treated by D0/1, NM, not mentioned; none, no patient included; →, stage IB is included in stage IA and stage IIIB is included in stage IIIA; # patients/y/h, number of patients treated per year per hospital; PO mortality, postoperative mortality.

tumours, the risk of second tier node involvement is 5% and therefore in Western practice where the postoperative mortality is of the order of 5% in experienced centres, a D1 resection would be appropriate. This is dependent on the assumption that preoperative assessment of the depth of invasion is accurate.

For T4 tumours, a D2 dissection should be applied only when the entire tumour can be resected by the resection of neighbouring organs involved by the primary tumour. It remains unclear whether D2 dissection is of value in linitis plastica because of the frequency of recurrence in the peritoneal cavity despite an even higher incidence of nodal metastases in the second tiers than in other types. Indeed some authors claim that surgery is not indicated for this type of tumour. However, about 20% of cases of linitis plastica can be cured by D2 dissection combined with adjuvant chemotherapy when an R0 resection can be achieved. Although the recurrence rate in the peritoneum is high, cure without resection is not realistic and therefore D2 dissection remains an option in curable linitis plastica. As most tumours involve the greater curvature of the body and often the gastrosplenic ligament, splenectomy is usually required in addition.

Patient Factors

Postoperative hospital mortality after D2 dissection is over three times greater in aged patients and mortality after total gastrectomy is over five times greater in patients over 80 years old compared with those under 70. The results of the Dutch trial showed much higher mortality after D2 in aged patients. D2 total gastrectomy for aged patients should be carried out only in high volume hospitals by experienced surgeons.

As D2 dissection includes the meticulous dissection of lymph nodes in the suprapancreatic area, in obese patients the risks are increased as the pancreas is embedded in thick adipose tissue, hindering recognition of the border of the organ and increasing the risk of injury to either the parenchyma or the vessels to the pancreas.

Patients with impaired liver function are regarded as high risk for D2 dissection, especially cirrhotic patients. The development of massive and often uncontrollable ascites after D2 dissection occurs frequently and is often fatal. These patients have increased lymphatic flow surrounding the liver and D2 dissection disturbs the lymph circulation of these patients enormously.

After D2 dissection, fluid retention in both the abdominal and the retroperitoneal space is very great and maintenance of fluid balance following surgery can be difficult. Thus pneumonia or cardiac failure during the resorptive phase can occur and this phase requires intensive management. D2 should be undertaken with caution in those with impaired respiratory and cardiac function.

Combined Organ Resection for Lymphadenectomy

In the history of radical resection of cancers, combined resection of organs surrounding the primary tumour is based on the idea of en-bloc resection, which means complete resection of all the tissues through which draining lymph vessels pass. In gastric cancer surgery, complete bursectomy and omentectomy, pancreaticosplenectomy were based on the same idea. In en-bloc resection of the gastric bed with vascular pedicle, Appleby's operation, three-quarters of the pancreas distal to the portal vein, spleen, coeliac artery with its branches are resected en bloc [18]. Until 1980, pancreaticosplenectomy was a standard part of the D2 radical total gastrectomy. However, comparison of the survival benefit against the increased morbidity and mortality and the high incidence of diabetes mellitus led many surgeons to abandon pancreas resection. As a result, pancreas-preserving total gastrectomy became the standard in Japan during the 1990s [19]. It is now recognised that good survival rates can be achieved in node-positive patients without en-bloc resection of these neighbouring organs.

Two large clinical trials comparing D1 versus D2 showed that combined resection of spleen and pancreas largely accounted for the increased morbidity and mortality in a D2 dissection [16,17]. The remaining question is whether splenectomy alone increases the risk of operative mortality and whether it contributes to improved survival. Although in these trials splenectomy was associated with a worse prognosis, the close correlation with tumour site and histology (more proximal tumour and more

diffuse type) confounds unbiased comparison. Therefore, this can be answered only by an RCT comparing D2 TG with or without splenectomy. The Japanese Clinical Oncology Group started such a trial in 2002 aiming to accrue 500 patients to demonstrate non-inferiority of splenic preservation.

Combined resection of the entire or a part of organs invaded by the primary tumour is accepted as the only way to achieve R0 resection for some cases. For these T4 tumours, radiotherapy has not yet been proven to be as effective as surgical resection.

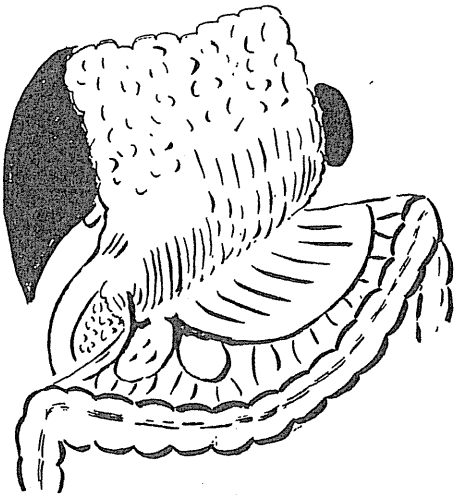

Figure 25.3. Elevation of greater omentum with anterior leaf of transverse mesocolon.

Techniques of D2 Dissection

Standard D2 TG: Pancreas Preserving TG

First an extensive mobilisation of the duodenum and the head of the pancreas is carried out to observe and palpate the para-aortic area. If there are nodes which are suspicious, sampling for frozen section should be carried out. If they are negative for cancer, radical D2 dissection is started. Complete omentectomy with resection of the anterior sheet of mesocolon is carried out (Figure 25.3). Many T3 tumours have lymphatic spread in the omentum, complete omentectomy remains a part of the standard D2 dissection. Similarly, T3 tumours adhering to the anterior sheet of the mesocolon and/or the pancreatic capsule may necessitate the resection of these structures and frequently turn out to be invading them. Complete bursectomy avoids tumour exposure in such cases. By carrying out this procedure, the accessory right colic vein is identified and followed proximally. It joins with the right gastroepiploic vein, forming Henle's surgical trunk which flows into the superior mesenteric vein (Figure 25.4). The right gastroepiploic vein is ligated and divided at its origin. For antral tumours, nodes on the superior mesenteric vein are also dissected. As the layer exposed by the bursectomy continues to the posterior aspect of the pancreas, the layer of the dissection should be changed to the anterior surface of the pancreas. Several vessels coming from behind the pancreas towards the anterior

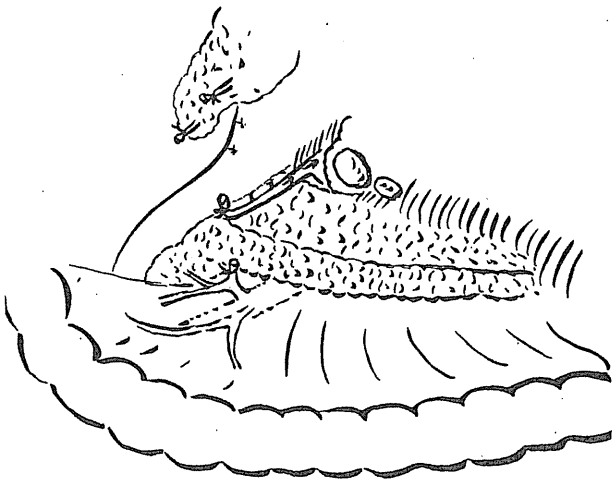

Figure 25.4. Division of right gastro-epiploic vein at Henley's trunk.

sheet of the mesocolon should be ligated at the inferior border of the pancreas.

The capsule of the pancreas is now dissected from the parenchyma in the middle part of the organ first, then toward the tail and the head, until the gastroduodenal artery is recognised. Following this artery, the root of the right gastroepiploic artery is found. After ligation and division of this artery at its origin, the stomach is lifted up to divide the back surface of the proximal duodenum from the pancreas and the gastroduodenal artery is followed cranially until the bifurcation of the common hepatic artery is recognized (Fig ure 25.4). The stomach

is laid back to the natural position and the lesser omentum is divided near the lateral segment of the liver from the left edge of the hepatoduodenal ligament to the oesophageal hiatus (Figure 25.5). This line is extended on the hepatoduodenal ligament to the left side of the common bile duct, where this incision is turned caudally towards the duodenum. Then the supraduodenal vessels, usually three or four in total, are ligated and divided close to the duodenal wall (Figure 25.6). This procedure makes a window above the duodenum, through which the gastroduodenal artery can be clearly seen. The connective tissue containing the lymph nodes in the hepatoduodenal ligament left of the common bile duct is dissected from right to left, from the duodenum towards the hepatic hilum along the gastroduodenal and then the hepatic artery. By doing so, the origin of the right gastric artery is easily identified, ligated and divided (Figure 25.6). Now the duodenum is divided a couple of centimetres from the pylorus by a linear type stapler. Pulling up the stomach from right to left and/or cranially, the suprapancreatic lymph nodes, common hepatic, coeliac, left gastric and splenic artery nodes are dissected, starting from the lymph nodes on the left side of the portal vein towards the nodes along the splenic artery. Downward traction of the pancreas by an assistant is extremely useful (Figure 25.7). During this procedure, the left gastric vein is encoun-

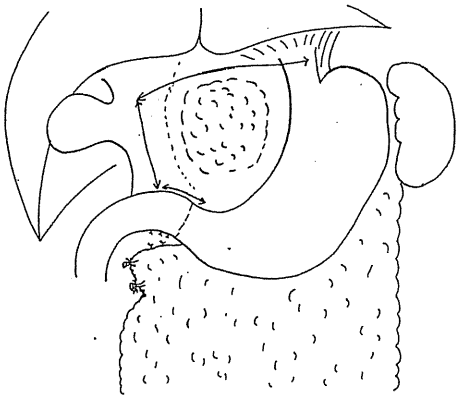

Figure 25.5. Line of division of the lesser omentum and duodenal clearance.

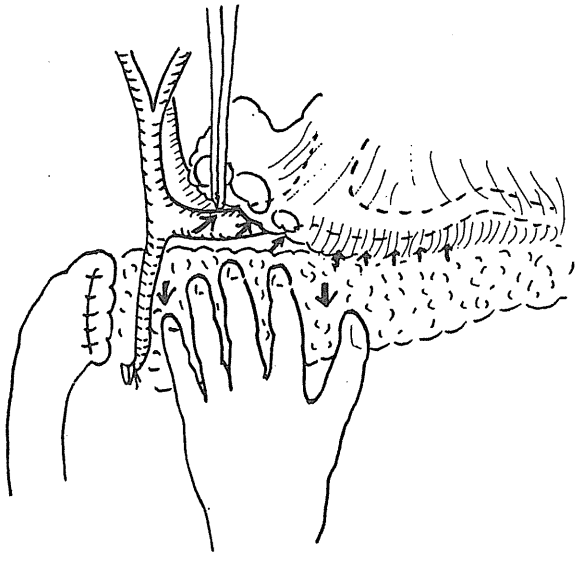

Figure 25.7. Clearance of suprapancreatic nodes along hepatic artery, celiac axis and splenic artery and peritoneum over pancreas. Note downward tension provided by assistant.

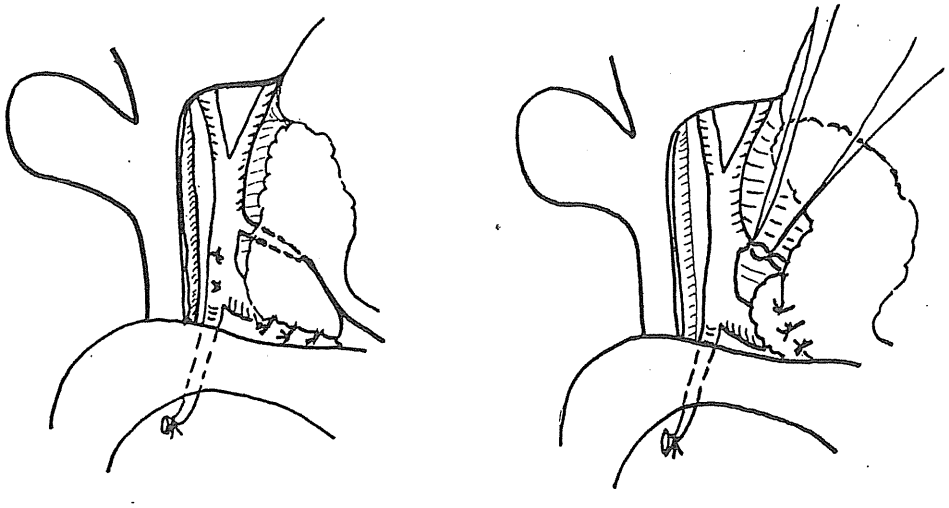

Figure 25.6. Identification and ligation of right gastric artery.

tered, most commonly behind the common hepatic artery (Figure 25.8). As a second frequent variation, this vein crosses over the common hepatic or splenic artery, flowing into the splenic vein. This vein is carefully found and then ligated and divided near its origin. The adipose tissue and thick nerve structures on the crus surrounding the oesophageal hiatus are divided from the crus, thus skeletonising the right side of coeliac artery and the origin of the left gastric artery. When the left hepatic artery is a branch of the left gastric artery, it should be preserved up to the origin of the hepatic artery in poor risk patients, to avoid necrosis of the lateral segment. Otherwise it should be ligated and divided at its origin.

The splenic artery nodes are dissected from the splenic artery around the origin of the posterior gastric artery (Figure 25.9). Near the origin of the posterior gastric artery, the great pancreatic artery branches off and comes into the pancreatic parenchyma. The splenic artery is now ligated and divided distal to the origin of the great pancreatic artery. In most cases, one of the large branches of the splenic vein appears on the anterior surface of the pancreatic tail. Then the pancreatic tail is mobilised completely from the retroperitoneum along Toldt's retropancreatic fascia. Traditionally the mobilisation started lateral to the spleen and the spleen is mobilised medially, pulling the spleen up with the operator's left hand. In this technique, the dissection on the left adrenal gland is carried out blindly, sometimes injuring the gland. To avoid this and the loss of the plane of dissection, it is better to mobilise the pancreatic body along Toldt's fascia at the upper border of the organ and continue towards the spleen. The lateral retroperitoneum is incised last (Fig 25.10). When the pancreas left of the coeliac artery is completely mobilised, the lymph nodes on the posterior surface of the pancreatic tail are dissected carefully, preserving the branches of splenic vein to the pancreas (Figure 25.11). All the branches from splenic vein to the stomach are carefully ligated and divided. After the pancreatic tail vein is preserved, the trunk of the splenic vein is ligated and divided. The vein commonly divides before the tip of the pancreatic tail and the branches are ligated separately. Now the pancreatic tail is naked and separated completely from the stomach and the spleen (Figure 25.12). The last step of the procedure is to dissect the left side of the oesophageal hiatus

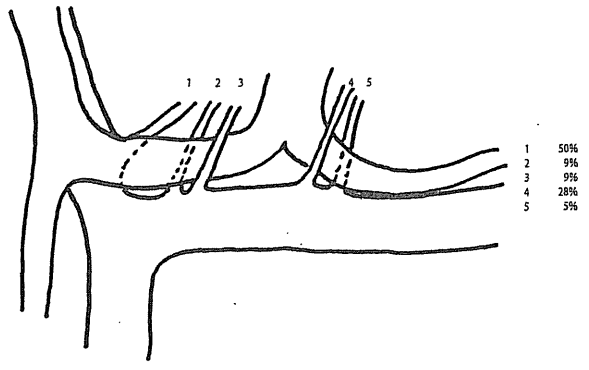

Figure 25.8. Variations in anatomy of left gastric vein.

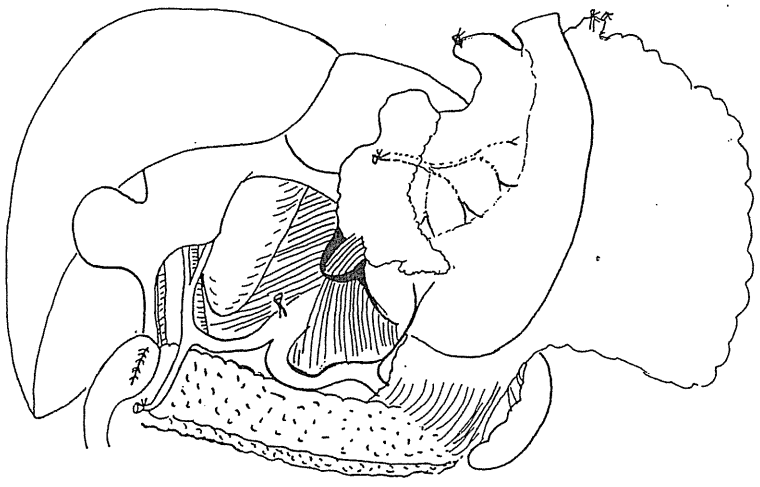

Figure 25.9. Origin of posterior gastric artery, defining point of division of splenic artery.

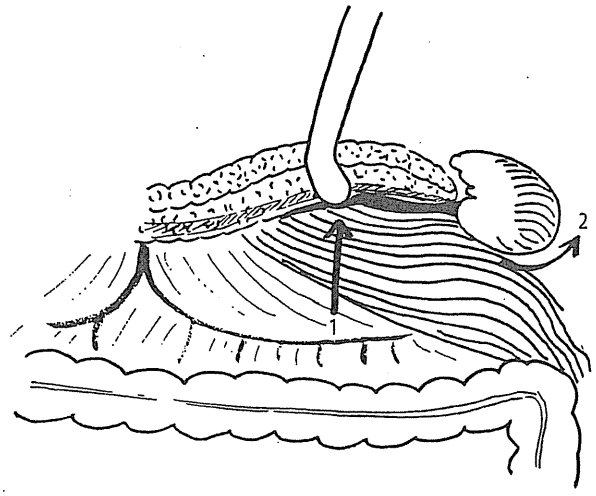

Figure 25.10. Mobilisation of the pancreatic tail along Todt's fascia.

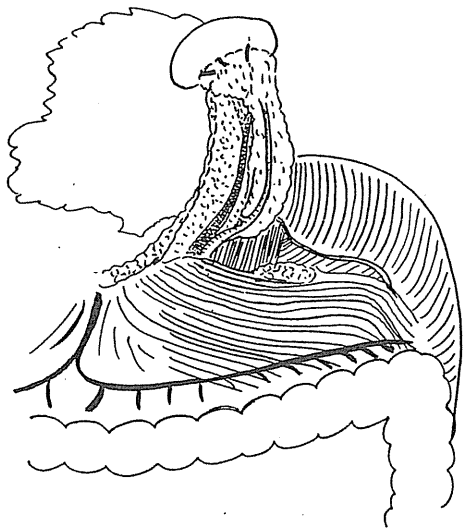

Figure 25.11. Dissection of pancreas to region of celiac axis preserving venous drainage to pancreas.

by ligating the oesophagocardiac branch of the inferior phrenic vessels. Both vagal nerves are divided 2–3 cm proximal to the cardia and the abdominal oesophagus is transected. An alternative technique is to divide the oesophagus as the primary step and the splenic artery nodes are dissected by pulling the entire specimen downward.

There are several methods of reconstruction of the digestive tract after total gastrectomy. The commonest and simplest method is Roux-en-Y reconstruction. Another commonly used

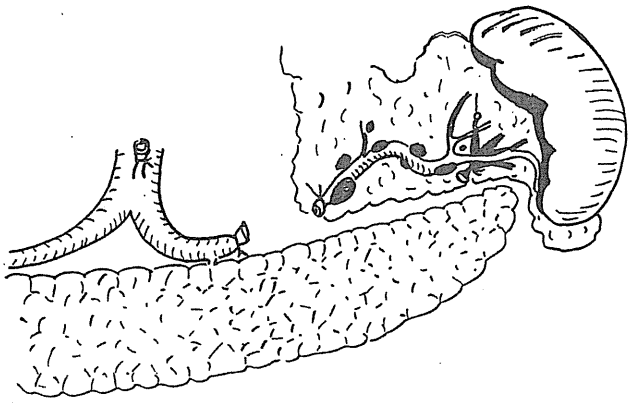

Figure 25.12. Separation of distal splenic artery and spleen following division of branches from splenic vein to spleen and stomach.

method is jejunal interposition. Reconstruction using a pouch in conjunction with either method has been trialled but the advantage of these techniques over simple reconstruction is not clear. The oeophagojejunal anastomosis should be end to side and can be carried out using a circular stapler, with a leakage rate of 1–2% [20]. In cases where the anastomosis lies in the mediastinum, it may be necessary to divide one or two jejunal arteries from their trunk, keeping the peripheral arcade intact, to allow the jejunum to reach the anastomotic site without tension.

TG with PS

In a conventional D2 total gastrectomy with pancreaticosplenectomy, the pancreas is transected near the coeliac artery. The indications for a combined resection are a T4 tumour invading the pancreas, bulky nodal metastases in the suprapancreatic area or metastatic nodes invading the pancreas. In these cases, the pancreas is transected adjacent to the portal vein. When the pancreas is resected, the splenic artery is ligated and divided at its origin, preserving the common hepatic artery, and then the splenic vein is divided at the resection line of the pancreatic parenchyma or its origin from the portal vein. The remainder of the procedure is the same as pancreas preserving total gastrectomy.

Standard Distal Gastrectomy

Most of the procedure is as described for total gastrectomy. A crucial issue in the procedure of

distal subtotal gastrectomy is splenectomy. In the MRC and the Dutch trials, some surgeons carried out splenectomy in distal gastrectomy. In D2 dissection, where the left gastric artery is ligated and divided at its origin, the blood supply to the remnant stomach is provided by the short gastric vessels, posterior gastric vessels and cardio-oesophageal branch from the inferior phrenic vessels. As the latter two are sometimes absent, the short gastric vessels are crucial to the viability of the remnant. Splenectomy should be avoided in distal gastrectomy, despite many textbooks of surgical technique showing all short gastric vessels ligated in distal subtotal gastrectomy. Mortality after D2 distal gastrectomy with splenectomy was 50% in the Dutch trial.

Another technical point is the dissection of right cardiac nodes in distal gastrectomy. These nodes are embedded in adipose tissue loosely attached to the gastric wall and easily divided from the wall without breaking the membrane enveloping the adipose tissue. All small branches to the gastric wall are divided, anterior and posterior branches separately (Figure 25.13) together with numerous small vagal fibres. The last technical point is how to dissect the greater curvature nodes along the left gastroepiploic vessels. These vessels are most commonly the last branch of the splenic vessels.

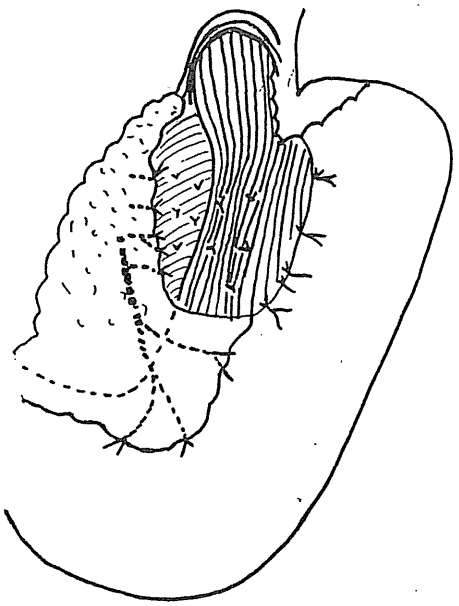

Figure 25.13. Clearance of right cardia nodes in distal gastric resection.

At the tip of the pancreas, near the splenic hilum, they arise from the inferior border of the organ running toward the stomach in the splenogastric ligament (Fig 25.14). Unlike the right gastroepiploic artery and vein, these vessels do not have a main trunk but three or four long branches in a palm-like shape. Sometimes, the inferior polar branch of the splenic artery comes from the gastroepiploic artery. In such cases, ligation of the left gastroepiploic artery renders a small part of the spleen ischemic but rarely causes any serious problems.

PPG

PPG was originally advocated by Maki [6] as surgical treatment for benign gastric ulcer, to avoid dumping syndrome, the most important long-term sequela of distal gastrectomy. As a result of the remarkable increase in early gastric cancer in Japan, this technique was introduced in the 1990s for early gastric cancers located near the incisura. A 3 cm antral remnant is preserved and anastomosed to the proximal gastric remnant close to the greater curvature. By preserving the hepatic branch of the anterior vagal trunk and subsequently the pyloric branch, gastric emptying function is well preserved. As a result, the suprapyloric nodes are not systematically dissected in this operation as early gastric cancers in the middle part of the stomach have a less than 1% risk of these nodes being involved. Other nodal stations in D2 distal gastrectomy can be dissected as usual. Precise evaluation of this technique in terms of both

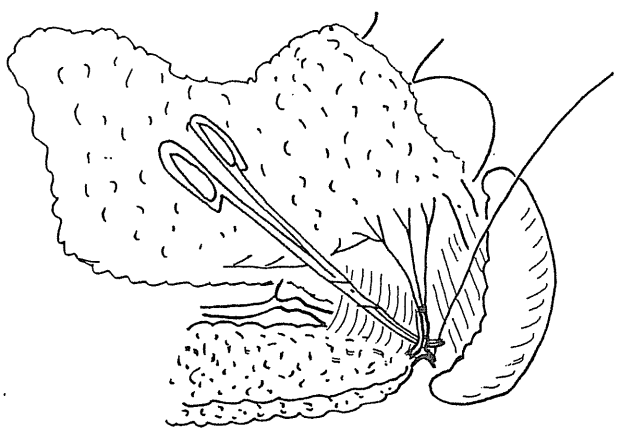

Figure 25.14. Identification of left gastro-epiploic vessels, usually last branch of splenic vessels.

survival and quality of life after gastrectomy should be available in the near future.

Para-aortic Nodal Dissection

In patients with advanced gastric cancer, the incidence of metastases in the para-aortic lymph nodes is reported in as many as 30% of cases. While there are reports of long-term survivors in this group the value of routine dissection remains unproven. Therefore, a randomized controlled trial was carried out by the Japanese Clinical Oncology Group (JCOG), recruiting 523 patients with curable advanced gastric cancer. Four out of 523 patients died in hospital postoperatively; thus the overall postoperative mortality rate was 0.8%, in contrast with the MRC and Dutch trials. Long-term survival evaluation will be carried out in 2006.

Postoperative Care after D2 Dissection

Morbidity after D2 dissection in the Dutch trial and after D2 or D4 in JCOG trial is shown in Table 25.4. The most important complications after D2 or more extended gastrectomy are those related to pancreatic resection or nodal dissection around the pancreas, including splenectomy. Therefore, prophylactic use of drainage tubes and careful drain handling is recommended. The management of pancreatic leakage is complex with outcome dependent on skilled management. This includes high volume continuous irrigation or continuous suctioning together with somatostatin analogues [21]. In low volume hospitals learning how to treat pancreatic complications after D2 dissection is difficult and, in the Dutch D2 study, many patients who developed such complications died. Anastomotic leakage used to be the most important and frequent complication after a total gastrectomy but the availability of staple guns has been instrumental in reducing this to very low levels [20]. One remarkable difference between the results of the Dutch and JCOG trials is the low mortality after major complications. All participating hospitals in the JCOG trial are high volume hospitals, whereas many of those in the Dutch trial were not. In the publication of the results, it was concluded that D2 dissection should not be carried out as the standard treatment in low volume hospitals and that gastric cancer patients should be treated in specialist centres in low incidence countries.

Table 25.4. Postoperative complications

Type of complication	Incidence (%)	
	Dutch (D2)	JCOG (D2/4)
Surgical		
Haemorrhage	5	0.6
Wound infection	9	1
Anastomotic leak	9	2
Intra-abdominal infection	17	5
Pancreatic leak	3	4
Non-surgical		
Cardiac	5	0.1
Pulmonary	15	4
Urinary tract	2	0.4
Thromboembolic	2	0.4

Questions

1. What are the indications for choosing the extent of gastric resection?
2. What are the consequences of splenic resection in partial gastrectomy?
3. What are the patient factors which determine whether extended nodal dissection is feasible?

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ORIGINAL REPORT

First-Line Single Agent Treatment With Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer: A Phase II Study

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ABSTRACT

Purpose
We conducted a phase II study of single agent treatment with gefitinib in chemotherapy-naïve patients with advanced non–small-cell lung cancer (NSCLC) to assess its efficacy and toxicity.

Patients and Methods
Patients received 250 mg doses of gefitinib daily. Administration of gefitinib was terminated if partial response (PR) was not achieved within 8 weeks or if tumor reduction was not observed within 4 weeks. In these cases, platinum-based doublet chemotherapy was given as a salvage treatment. We evaluated mutation status of the epidermal growth factor receptor (EGFR) gene in cases with available tumor samples.

Results
Forty-two patients were enrolled between March and November 2003, with 40 of these patients being eligible. The response rate was 30% (95% CI, 17% to 47%). The most common toxicity included grade 1 or 2 acne-like rash (50%) and grade 1 diarrhea (18%). Grade 2 or 3 hepatic toxicity was observed in 8% of patients. Four patients developed grade 5 interstitial lung disease (ILD). Thirty patients received second-line chemotherapy. Median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55%. Tumor samples were available in 13 patients, including four cases of PR, six cases of stable disease, and three cases of progressive disease. *EGFR* mutations (deletions in exon 19 or point mutations [L858R or E746V]) were detected in four tumor tissues. All four patients with *EGFR* mutation achieved PR with gefitinib treatment.

Conclusion
Single agent treatment with gefitinib is active in chemotherapy-naïve patients with advanced NSCLC, but produces unacceptably frequent ILD in the Japanese population.

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INTRODUCTION

Previous meta-analysis demonstrated that cisplatin-based chemotherapy yielded a modest but significant survival benefit over best supportive care in advanced non–small-cell lung cancer (NSCLC).[1-4] In the 1990s, new agents, including vinorelbine, gemcitabine, paclitaxel, docetaxel, and irinotecan became available for the treatment of NSCLC. Several phase III trials comparing doublet platinum-based chemotherapies demonstrated no significant difference with respect to response rate, survival, or quality of life.[5,6] Nonplatinum or triplet platinum-based combination chemotherapies have been investigated, but none of these produced longer survival than standard doublet platinum-based chemotherapy.[7-9]

Recently, molecular-targeted agents have been introduced for the treatment of NSCLC. Gefitinib is an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, which displays activity against recurrent NSCLC after platinum-based chemotherapy. Two international, randomized phase II trials in patients with advanced or metastatic NSCLC after platinum-based chemotherapy demonstrated response rates of 12% to 18% (28% in the Japanese population).[10,11] Two international, randomized, double-blinded, placebo-controlled phase III trials investigated the role of gefitinib combined with platinum-based chemotherapy regimens, including carboplatin and paclitaxel, or cisplatin and gemcitabine in chemotherapy-naïve patients with advanced NSCLC.[12,13] Surprisingly, there were no improvements in overall survival,

time to progression, or response rate. There are no data available regarding first-line treatment with single agent gefitinib against NSCLC in the Japanese population. Here, we conducted a phase II study of single agent treatment with gefitinib in chemotherapy-naïve patients with advanced NSCLC. If a failure with gefitinib treatment was perceived, standard platinum-based doublet chemotherapy was performed as salvage. The primary end point of this phase II trial was response rate, and the secondary end points were toxicity, survival, and response rate of salvage chemotherapy.

PATIENTS AND METHODS

Patient Population

Patients were required to have histologically or cytologically confirmed stage IIIB (malignant pleural or pericardial effusion and/or metastasis in the same lobe) or stage IV NSCLC. Recurrences after surgical resection were permitted. Other criteria included: (1) age 20 years or older, but younger than 75 years; (2) Eastern Cooperative Oncology Group performance status (PS) 0 or 1; (3) measurable disease; (4) PaO2 $\geq$ 60 mmHg; (5) adequate organ function (ie, total bilirubin $\leq$ 2.0, AST and ALT $\leq$ 100 U/L, serum creatinine $\leq$ 1.5 mg/dL, leukocyte count 4,000 to 12,000/mm^3, neutrophil count $\geq$ 2,000/mm^3, hemoglobin $\geq$ 9.5 g/dL, and platelets $\geq$ 100,000/mm^3); (6) no prior chemotherapy or thoracic radiotherapy; (7) no interstitial pneumonia or pulmonary fibrosis, as determined by chest x-ray; (8) no paralytic ileus or vomiting, (9) no symptomatic brain metastases, (10) no active infection; (11) no active concomitant malignancy; (12) no pregnancy or breast-feeding; (13) no severe allergy to drugs. Patients with PaO2 less than 60 mmHg were excluded, because those patients might have pulmonary fibrosis, which is a risk factor of interstitial lung disease (ILD).[14] All patients were required to provide written informed consent and the institutional review board at the National Cancer Center approved the protocol.

Treatment Plan

Treatment was started within a week after enrollment in the study. Patients received 250 mg of gefitinib orally daily. In the event of grade 3 or more and/or unacceptable toxicities, gefitinib was postponed until these toxicities were improved to grade 2 or less. Dose reduction was not performed. If treatment was postponed four times or more, the treatment was terminated. Therapy was continued unless the patient experienced unacceptable toxicity or progressive disease, partial response (PR) was not achieved within 8 weeks, or the sum of the longest diameters of the target lesions decreased less than 10% within 4 weeks. If the gefitinib treatment failed according to these criteria, platinum-based doublet chemotherapy was performed as a salvage regimen.

Previous trials of gefitinib for pretreated patients with NSCLC reported that most responding patients showed rapid tumor regression within 4 or 8 weeks.[11] Furthermore, most responses by gefitinib were extreme shrinkage of the tumor. Minor response, as frequently seen by the treatment with cytotoxic agents, was seldom experienced. Stable disease with gefitinib corresponded to no tumor reduction or slight progression. If patients with stable disease continued the treatment with gefitinib until progressive disease became obvious, those patients might not be able to receive platinum-based salvage chemotherapy because of poor PS due to progressive disease. Platinum-based combination chemotherapy is the standard care for patients with advanced NSCLC and good PS. Platinum-based chemotherapy was thought to be essential for patients with no response from the first-line single agent treatment with gefitinib. Therefore, we implemented these early stopping criteria for treatment with gefitinib.

Study Evaluations

Pretreatment evaluations consisted of a complete medical history, determination of performance status, physical examination, hematologic and biochemical profiles, arterial blood gas examination, ECG, chest x-ray, bone scan, and computed tomography (CT) scan of the chest, ultrasound or CT scan of the abdomen, and magnetic resonance imaging or CT scan of the whole brain. Evaluations performed included a weekly chest x-ray for 4 weeks, and once every 2 weeks for biochemistry, complete blood cell, platelet, leukocyte differential counts, physical examination, determination of performance status, and toxicity assessment. Imaging studies were scheduled to assess objective response every month.

Response and Toxicity Criteria

Response evaluation criteria in solid tumors (RECIST) guidelines were used for evaluation of antitumor activity.[15] The target lesions were defined as $\geq$ 2 cm in the longest diameter on CT scans. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A PR was defined as an at least 30% decrease in the sum of the longest diameters of the target lesions for more than 4 weeks with no new area of malignant disease. Progressive disease (PD) indicated at least a 20% increase in the sum of the longest diameter of the target lesions or a new malignant lesion. Stable disease was defined as insufficient shrinkage to qualify for PR and insufficient increase to qualify for PD. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Mutation Analysis of the EGFR Gene

Tumor specimens were obtained during diagnostic or surgical procedures. Biopsied or surgically resected specimens were fixed with formalin or 100% methanol, respectively. Tumor genomic DNA was prepared from paraffin-embedded sections using laser capture microdissection in biopsied specimens or macrodissection in surgically resected specimens at Mitsubishi Chemical Safety Institute LTD. Exons 18, 19, and 21 of the *EGFR* gene were amplified and sequenced as previously described.[16]

Statistical Analysis

In accordance with the minimax two-stage phase II study design by Simon,[17] the treatment program was designed to refuse response rates of 10% (P_0) and to provide a significance level of .05 with a statistical power of 80% in assessing the activity of the regimen as a 25% response rate (P_1). The upper limit for first-stage drug rejection was two responses in the 22 assessable patients; the upper limit of second-stage rejection was seven responses within the cohort of 40 assessable patients. Overall survival was defined as the interval between enrollment in this study and death or the final follow-up visit. Median overall survival was estimated by the Kaplan-Meier analysis method.[18] Fisher's exact test was used in a contingency table.

RESULTS

Patient Population

A total of 42 patients were enrolled in this study between March and November, 2003, with 40 of these patients being eligible. One patient was found ineligible due to anemia, the other because spinal magnetic resonance imaging could not confirm a positive bone scan. Patient characteristics are listed in Table 1. Sixty percent of patients were male; median age was 61 years. The most common histologic subtype was adenocarcinoma (75%). Most patients (93%) had stage IV disease or recurrence after surgical resection. Eighty percent of patients were current or former smokers.

Efficacy

One patient (3%) has been receiving gefitinib after 22 months. Four patients suspended gefitinib for 11, 14, 27, or 29 days, because of liver dysfunction (n = 3) and fever due to urinary tract infection (n = 1). Thirty-nine patients terminated gefitinib because of progressive disease (n = 20), no tumor reduction within 4 weeks (n = 12), not achieving PR within 8 weeks (n = 1), toxicities including pulmonary (n = 3), nausea and vomiting (n = 1), rash (n = 1), or hepatic dysfunction (n = 1).

There were 12 PRs in 40 eligible patients, and the objective response rate was 30% (95% CI, 17% to 47%; Table 2). All but one

Table 1. Patient Characteristics

Characteristic	No. of Patients
Patients enrolled	42
Patients eligible	40
Sex	
Male	24
Female	16
Age, years	
Median	61
Range	44-74
Performance status	
0	14
1	26
Stage	
IIIB	3
IV	34
Recurrence after surgery	3
Histologic type	
Adenocarcinoma	30
Squamous cell carcinoma	3
Large cell carcinoma	7
Smoking history	
Current	27
Former	5
Never	8

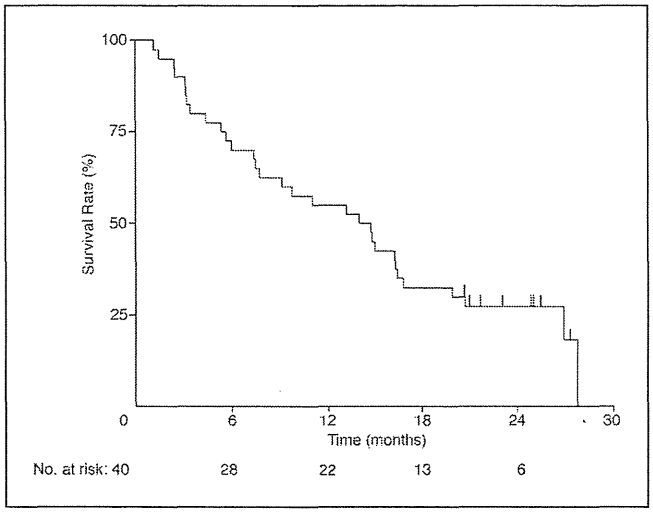

Fig 1. Overall survival of all eligible patients (n = 40) was calculated according to the Kaplan-Meier method. The median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55%.

patient from this subgroup achieved PR within 4 weeks, with the remaining patient achieving PR within 8 weeks. The background of the 12 responding patients was as follows: nine females, three males; 11 adenocarcinomas, one large-cell carcinoma; six individuals who never smoked, five current smokers, and one former smoker. Response rates based on patient characteristics were as follows: three of 24 (13%) males, nine of 16 (56%) females ($P = .0050$); 11 of 30 (37%) individuals with adenocarcinoma, one of 10 (10%) individuals with squamous or large-cell carcinoma ($P = .0048$); six of 32 (19%) current or former smokers, and six of eight (75%) individuals who never smoked ($P = .0048$).

The median follow-up time was 23 months, and nine patients were still alive at the most recent follow-up. The median survival time was 13.9 months (95% CI, 9.1 to 18.7 months), and the 1-year survival rate was 55% (Fig 1).

Safety and Toxicity

Toxicity was evaluated in all eligible patients. The most common toxicity was rash (Table 3). Thirty-eight percent and 13% of patients experienced grade 1 or 2 rash, respectively. One patient experienced grade 3 nausea and vomiting, leading to gefitinib treatment being terminated. Grade 3 hepatic toxicity was observed in one patient, also causing termination of gefitinib treatment.

The most problematic toxicity was ILD. We reviewed the medical records, chest x-rays, and CT films of all the cases, which were suspected as ILD by the physician in charge. ILD was diagnosed on the basis of standard or high-resolution CT findings of the chest (diffuse ground-glass opacity, consolidation, or infiltrate) and no response to antibiotics. We diagnosed that four patients experienced grade 5 ILD during or after first-line treatment with gefitinib. The first patient was a 61-year-old man. He developed dyspnea and fever elevation (38.1°C) on day 23 of the treatment with gefitinib and administration of gefitinib was terminated. Chest CT demonstrated bilateral diffuse ground-glass opacity, and PaO2 was 43.7mmHg in the room air. KL-6 antigen, a serum marker of interstitial pneumonia, was not elevated

Table 2. Efficacy of Single Agent Treatment With Gefitinib in Patients With Stage IIIb or IV Non–Small-Cell Lung Cancer

Type of Response	No. of Patients	% of Patients
Complete	0	0
Partial	12	30
CR + PR	12	30
95% CI	17 to 47	
Stable disease	16	40
Progression	12	30

Abbreviations: CR, complete response; PR, partial response.

Table 3. Maximum Toxicity Grades Associated With Single Agent Treatment With Gefitinib in 40 Patients With Non–Small-Cell Lung Cancer

	Toxicity Grade									
	1		2		3		4		5	
Toxicity	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Rash	15	38	5	13	0	0	0	0	0	0
Dry skin	4	10	0	0	0	0	0	0	0	0
Diarrhea	7	18	0	0	0	0	0	0	0	0
Nausea	3	8	0	0	1	3	0	0	0	0
Mucositis	6	15	0	0	0	0	0	0	0	0
Alopecia	4	10	0	0	0	0	0	0	0	0
Hyponatremia	24	60	0	0	3	8	0	0	0	0
Hypokalemia	12	30	0	0	0	0	0	0	0	0
Hepatic	11	28	2	5	1	3	0	0	0	0
Renal	4	10	1	3	0	0	0	0	0	0
ILD	0	0	0	0	0	0	0	0	4	10

Abbreviation: ILD; interstitial lung disease.

(351 U/mL) on day 24, but elevated on day 31 (1,400 U/mL). Beta-D-glucan, a serum marker of fungal infection and *Pneumocystis carinii* pneumonia, was also negative. Methylprednisolone and antibiotics were administered, with temporal improvement of ILD. However, subsequently, pulmonary function gradually deteriorated, leading to death. Autopsy revealed alveolar damage with organization around the bronchus and vessels in both neoplastic and non-neoplastic lesions, compatible with drug-induced ILD. The second patient was a 64-year-old man. Chest CT on day 27 showed stable disease, but administration of gefitinib was continued (protocol violation). Periodic chest x-ray film on day 45 showed abnormal shadow in the left lung field. High-resolution CT of the chest on the same day revealed reticular shadow on bilateral upper lobe. The treatment with gefitinib was terminated on day 45. KL-6 antigen was not elevated on day 49 (276 U/mL). Methylprednisolone and antibiotics were administered, but were not effective, leading to death. The third patient was a 67-year-old man. Chest CT on day 30 demonstrated enlargement of primary lesion and bilateral reticular shadow in subpleural lesions. Gefitinib was terminated on day 30. The patient developed dyspnea without fever elevation on day 37. Pao2 in the room air fell to 61.0 mmHg from 82.4 mmHg at pretreatment. Chest x-ray showed that the bilateral diffuse reticular shadow deteriorated. Methylprednisolone and antibiotics were administered, but were not effective, leading to death. Autopsy revealed severe fibrotic thickness of alveolar septum, compatible with severe interstitial pneumonia. There was no pathological evidence of carcinomatous lymphangiosis. The fourth patient was a 59-year-old woman. Chest x-ray showed consolidation in the left lung on day 21. Slight fever (37.9°C) developed on day 22. Blood culture was negative. Antibiotics were administered, but consolidation deteriorated and spread to both lungs on day 25. Gefitinib was terminated on day 25. KL-6 antigen was elevated to 3,590 U/mL. Methylprednisolone was administered, but was not effective, leading to death (Table 4). Four other patients experienced ILD after second-line or third-line chemotherapy. Two patients received second-line treatment with cisplatin plus vinorelbine (one and four courses), one patient received treatment with cisplatin plus gemcitabine (one course), and one patient received third-line treatment with docetaxel (four courses). Three of four patients received steroids, with temporal improvement of ILD being observed in two patients. However, ILD deteriorated during tapering of steroid treatment, with three patients subsequently dying. One patient stopped the third-line treatment with docetaxel, with the associated ILD showing improvement in this case without steroid treatment (Table 4).

We retrospectively reviewed the pretreatment chest x-rays and CT films of all patients. Interstitial shadow was not detected on pretreatment chest x-ray films in any patients. However, six patients showed evidence of interstitial shadow on pretreatment chest CT films. Three of the six patients with interstitial shadow, as determined by pretreatment chest CT, experienced ILD either during or following administration of gefitinib or second-line chemotherapy. None of the six patients responded to gefitinib treatment. On the other hand, four of 34 patients who showed no interstitial shadow on pretreatment chest CT films experienced ILD. Interstitial shadow as determined by pretreatment chest CT was not a statistically significant risk factor of ILD ($P = .0819$; Table 5).

Second-Line Chemotherapy

A total of 30 patients received second-line chemotherapy. Twenty-seven patients received platinum-based chemotherapy (cisplatin plus vinorelbine; n = 17), carboplatin plus paclitaxel (n = 5), cisplatin plus gemcitabine (n = 3), cisplatin plus docetaxel (n = 1), and cisplatin plus irinotecan (n = 1). The remaining three patients received vinorelbine plus gemcitabine or vinorelbine alone. Nine of 30 patients achieved PR with these second-line chemotherapies. The objective response rate of second-line chemotherapy was 30% (95% CI, 15% to 50%).

Mutation Status of the EGFR Gene

Out of 42 enrolled patients, 16 patients were diagnosed pathologically, 22 were diagnosed cytologically, and four patients recurred after surgical resection. Biopsied specimens were available in nine patients. Therefore, tissue samples were available in a total of 13 patients. These 13 patients included four PRs, six with stable disease, and three PDs. *EGFR* mutations were detected in four tumor tissues, including the in-frame nucleotide deletions in exon 19 (n = 3) and an L858R mutation in exon 21 (n = 1). One tumor had an in-frame deletion and

Table 4. Four Patients Developed Interstitial Lung Disease During First-Line Chemotherapy With Gefitinib, With Another Four Patients Showing ILD During Either Second- or Third-Line Chemotherapy

Age (years)	Sex	Smoking Index	Pathology	Onset of ILD	Response to Gefitinib	Death From Chemotherapy
61	M	1,520	AD	Day 23*	PD	Day 74
64	M	880	AD	Day 45*	SD	Day 51
67	M	1,880	SQ	Day 37†	PD	Day 45
59	F	0	AD	Day 21*	PD	Day 35
61	M	820	AD	Day 131‡	SD	Day 154
68	M	2,000	LA	Day 37‡	PD	Day 106
68	M	705	AD	Day 22§	PR	Day 87
59	M	1,170	AD	Day 108‖	SD	Alive

Abbreviations: ILD, interstitial lung disease; M, male; F, female; AD, adenocarcinoma; SQ, squamous cell carcinoma; LA, large-cell carcinoma; PD, progressive disease; SD, stable disease; PR, partial response.
*During gefitinib administration.
†One week after discontinuation of gefitinib.
‡ After 2nd-line chemotherapy of cisplatin and vinorelbine.
§ After 2nd-line chemotherapy of cisplatin and gemcitabine.
‖ After 3rd-line chemotherapy of docetaxel.

Table 5. Interstitial Shadow on Pretreatment Chest Computed Tomography Films and ILD

Interstitial Shadow on Pretreatment Chest Computed Tomography Scans	No ILD	ILD
No existence	29	5
Existence	3	3

NOTE. $P = .0819$.
Abbreviation: ILD interstitial lung disease.

an E746V mutation in exon 19. All four PR patients had *EGFR* mutations (Table 6).

DISCUSSION

This phase II study was designed to evaluate the efficacy and safety of first-line single agent treatment with gefitinib in patients with advanced NSCLC. There is no other paper that evaluates single agent treatment with gefitinib prospectively in patients with advanced NSCLC. The observed response rate of 30% (95% CI, 17% to 47%), median survival of 13.9 months and 1-year survival of 55% are promising. However, grade 5 ILD occurred in 10% (95% CI, 3% to 24%) of patients. This high rate of ILD was not acceptable. The incidence of ILD was seen to be less than 1% in two randomized controlled studies comparing gefitinib with placebo in combination with gemcitabine and cisplatin or paclitaxel and carboplatin.[12,13] The reason for the high incidence of ILD observed in our study is unknown. The West Japan Thoracic Oncology Group analyzed 1,976 patients receiving gefitinib retrospectively. In this case, the incidence of ILD was 3.2% (95% CI, 2.5% to 4.6%) and the death rate due to ILD was 1.3% (95% CI, 0.8% to1.9%). Multivariate analyses found that risk factors included being male, individuals who smoked, and complication of interstitial pneumonia.[14] Our retrospective analyses revealed that three of six patients with interstitial shadow on pretreatment chest CT films, but not detected on chest x-ray films developed ILD; on the other hand, five of 34 patients without interstitial shadow developed ILD. Interstitial shadow on pretreatment chest CT was a marginally significant risk factor of ILD ($P = .0819$). It might be suggested that patients with interstitial shadow on pretreatment chest CT films be excluded from administration of gefitinib; however, our analyses were biased because we analyzed retrospectively and did not blind patient clinical information. Prospective analysis is needed to evaluate interstitial shadow by chest CT before treatment with gefitinib.

The Southwest Oncology Group conducted a phase II trial to evaluate gefitinib in patients with advanced bronchioloalveolar carcinoma (SWOG 0126). Previously untreated (n = 102) and treated (n = 36) patients were entered and eligible in SWOG 0126. The response rate was 19% and the median survival time was 12 months in the untreated population.[19] These subset analyses were comparable to our results.

Recently, mutations in the tyrosine kinase domain of EGFR were found to be associated with gefitinib sensitivity in patients with NSCLC.[16,20,21] Our retrospective analyses demonstrated that *EGFR* mutations were detected in four of 13 patients, and those four patients achieved PR in the single agent treatment of gefitinib. These results were compatible with previous reports.[16,20,21]

Thirty patients received second-line chemotherapy, including platinum-based (n = 27) and nonplatinum-based (n = 3) regimens; the response rate was 30%. Pretreatment with gefitinib does not seem to adversely affect the response of second-line chemotherapy. However, our small-scale study does not suggest the best second-line regimen. Platinum combined with any third-generation agents including paclitaxel, docetaxel, vinorelbine,

Table 6. Mutation Status of the *EGFR* Gene

Sex	Age (years)	Pathologic Type	Smoking Status	Overall Survival (months)	*EGFR* Gene	Effect of Mutation	Response to Gefitinib	Response to Second Line Chemotherapy
M	68	AD	Current	14.9	Deletion of 15 nucleotides (2236-2250)	In-frame deletion (E746-A750)	PR	PD
F	67	AD	Current	16.2	Deletion of 15 nucleotides (2236-2250)	In-frame deletion (E746-A750)	PR	PD
F	54	AD	Current	5.6	Deletion of 18 nucleotides (2238-2255) and substitution of T for A at nucleotides 2237	In-frame deletion (L747-S752) and amino acid substitution (F746V)	PR	NR
F	57	AD	Never	25.4	Substitution of G for T at nucleotide 2573	Amino acid substitution (L858R)	PR	SD
M	61	AD	Current	7.5	Wild	—	SD	SD
M	54	AD	Current	9.7	Wild	—	SD	SD
M	45	AD	Current	16.2	Wild	—	SD	PR
M	59	AD	Current	14.7	Wild	—	SD	PR
M	67	SQ	Current	2.4	Wild	—	SD	NR
M	59	AD	Current	24.9	Wild	—	SD	PR
M	61	AD	Current	2.4	Wild	—	PD	NR
F	61	SQ	Current	3.4	Wild	—	PD	PD
F	61	AD	Current	16.3	Wild	—	PD	PR

Abbreviations: EGFR, epidermal growth factor receptor; M, male; F, female; AD, adenocarcinoma; SQ, squamous cell carcinoma; PR, partial response; SD, stable disease; PD, progressive disease; NR, not received.

gemcitabine, or irinotecan is probably acceptable as the current standard first-line chemotherapy.

First-line single agent with gefitinib is active, but produces unacceptably frequent ILD in the Japanese population. Being female, as well as adenocarcinoma, those who never smoked, and *EGFR* mutation were associated with response to gefitinib. Patients who responded to gefitinib did not experience ILD during gefitinib chemotherapy. Further research via genetics and image analysis is needed to avoid ILD and identify a subgroup of patients that benefit from gefitinib treatment. If this is realized, single agent treatment with gefitinib could be an option as first-line chemotherapy in selected patients with advanced NSCLC. Furthermore, randomized trials are warranted to compare first-line single agent treatment with gefitinib followed by second-line platinum-based chemotherapy with first-line platinum-based chemotherapy followed by second- or third-line gefitinib treatment.

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Randomised phase II study of docetaxel/cisplatin *vs* docetaxel/irinotecan in advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group Study (WJTOG9803)

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Docetaxel plus cisplatin and docetaxel plus irinotecan are active and well-tolerated chemotherapy regimens for advanced non-small-cell lung cancer (NSCLC). A randomised phase II study compared their efficacy and toxicity in 108 patients with stage IIIb/IV NSCLC, who were randomised to receive docetaxel 60 mg m^{-2} and cisplatin 80 mg m^{-2} on day 1 (DC; $n=51$), or docetaxel 60 mg m^{-2} on day 8 and irinotecan 60 mg m^{-2} on day 1 and 8 (DI; $n=57$) every 3 weeks. Response rates were 37% for DC and 32% for DI patients. Median survival times and 1- and 2-year survival rates were 50 weeks (95% confidence interval: 34–78 weeks), 47 and 25% for DC, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18% for DI, respectively. The progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) with DC and 18 (95% confidence interval: 12–22 weeks) with DI. Significantly more DI than DC patients had grade 4 leucopenia and neutropenia ($P<0.01$); more DC patients had grade $\geqslant 2$ thrombocytopenia ($P<0.01$). Nausea and vomiting was more pronounced with DC ($P<0.01$); diarrhoea was more common with DI ($P=0.01$). Three treatment-related deaths occurred in DC patients. In conclusion, although the DI and DC regimens had different toxicity profiles, there was no significant difference in survival.
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Keywords: combination chemotherapy; doublets; irinotecan; cisplatin; docetaxel; non-small-cell lung cancer; carboplatin

Unfortunately, non-small-cell lung cancer (NSCLC) is a member of the group of neoplastic diseases that is relatively chemoresistant. Recent meta-analyses show that cisplatin-based chemotherapy improves survival (Non-Small Cell Lung Cancer Collaborative Group, 1995), and it is considered a standard treatment for NSCLC, Most cisplatin-based regimens have substantial toxicities that require close monitoring and supportive care. Thus, there is a need to develop active and less toxic chemotherapy regimens that include new active compounds with novel mechanisms of action.

In the 1990s, several new, active therapies with single-agent response rates of 15–30% became available for NSCLC, including irinotecan, docetaxel, paclitaxel, vinorelbine, and gemcitabine. Because irinotecan and docetaxel were approved for NSCLC earlier than the other drugs in Japan, development of regimens containing irinotecan or docetaxel is more advanced. Docetaxel 60 mg m^{-2} showed good antitumour activity against advanced NSCLC (Kunitoh *et al*, 1996), and the combination of docetaxel plus cisplatin (DC) is one of the most effective regimens for advanced NSCLC (Rodriguez *et al*, 2001; Schiller *et al*, 2002). Studies in Japan included a phase II study in which DC yielded a response rate of 42% (Okamoto *et al*, 2002), and a phase III study in which DC was associated with better survival than the vindesine and cisplatin (VC) combination (Kubota *et al*, 2002).

Irinotecan demonstrated activity similar to that of VC in stage IIIb/IV NSCLC (Negoro *et al*, 2003), and significant longer overall survival time than VC in stage IV NSCLC (Fukuoka *et al*, 2000). We reported a phase I study of docetaxel plus irinotecan (DI) in patients with advanced NSCLC, in which a promising response rate of 48% and the median survival time of 48 weeks were achieved with acceptable toxicities (Masuda *et al*, 2000). Thus, DI appeared to be a promising non-cisplatin-containing regimen.

Based on the above findings, we conducted a randomised trial of DC *vs* DI in patients with advanced NSCLC to compare the respective response rates, survival data, and toxicity profiles of the two regimens. This was a multicentred phase II study.

PATIENTS AND METHODS

Patients

Patients enrolled in this trial had histologically or cytologically confirmed stage IIIb or IV NSCLC. Patients with stage IIIb disease who were not candidates for thoracic radiation and patients with stage IV disease were eligible if they had not received previous therapy, had measurable disease, and had a life expectancy of at least 3 months. Additional entry criteria were age $\geqslant 20$ years, performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, adequate bone marrow function (leucocyte

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count 4000–12 000 μl^{-1}, haemoglobin concentration $\geqslant 9.5\,g\,dl^{-1}$ platelet count $\geqslant 100\,000\,\mu l^{-1}$), kidney function (creatinine $\leqslant$ upper limit of normal, 24-h creatinine clearance $\geqslant 60\,ml\,min^{-1}$), liver function (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leqslant 2.0$ times the upper limit of normal, total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$), and pulmonary function ($PaO_2 \geqslant 60$ torr). Patients with active concomitant or a recent (<3 years) history of any malignancy, symptomatic brain metastases, past history of drug allergy reactions, complication by interstitial pneumonia, watery diarrhoea, ileus, treatment with nonsteroidal anti-inflammatory drugs, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, massive pleural effusion or ascites, or serious active infection were excluded. All patients gave written informed consent, and the institutional review board for human experimentation approved the protocol.

Study evaluations

Pretreatment studies included a complete medical history and physical examination, chest X-ray, electrocardiography, computed tomography (CT) scan of the brain and chest, CT or ultrasound examination of the abdomen, and bone scintigraphy. Blood and blood chemistry studies included complete blood cell count, liver function test, serum electrolytes, serum creatinine, and blood urea nitrogen. Chest X-ray, blood and blood chemistry analyses, and urinalysis were repeated weekly.

Randomisation and treatment schedule

Patients were randomly assigned to receive the DC regimen or the DI regimen by a minimisation method using stage (IIIB/IV) and treatment institution. The DC regimen was consisting of docetaxel $60\,mg\,m^{-2}$ on day 1 and cisplatin $80\,mg\,m^{-2}$ on day 1, and the DI regimen was consisting of docetaxel $60\,mg\,m^{-2}$ as a 60-min intravenous infusion on day 8 and irinotecan $60\,mg\,m^{-2}$ as a 90-min intravenous infusion on days 1 and 8 (Figure 1). Both regimens were repeated every 3 weeks. Participating researchers at each institution decided the amount of fluid replacement and the type of antiemetic therapy to administer. Standard antiemetic treatment in the DC arm consisted of 5-HT_3 receptor antagonist plus 16 mg dexamethasone intravenously on day 1, before cisplatin administration. In the DI arm, standard antiemetic treatment consisted of 5-HT_3 receptor antagonist intravenously before chemotherapy administration on days 1 and 8. Patients received at least two treatment cycles, and those with a complete or partial response after two cycles had treatment continued until there was evidence of disease progression, intolerable toxicity, or patient refusal.

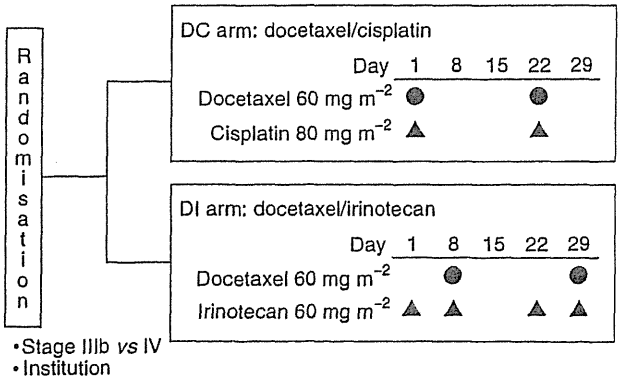

Figure 1 *Treatment schema*: after stratification by stage and institution, enrolled patients were randomly allocated to receive docetaxel plus cisplatin (DC) or docetaxel plus irinotecan (DI).

Dose modifications

Toxicity assessment was based on the National Cancer Institute–Common Toxicity Criteria version 2.0. Dose levels and treatment schedule were modified to avoid severe adverse effects. Patients receiving DI had the day-8 docetaxel and irinotecan doses postponed to day 15 if any of the following toxicities was present on day 8: leucocyte count $<3000\,\mu l^{-1}$, platelet count $<100\,000\,\mu l^{-1}$ diarrhoea consisting of bloody or watery stools, or increased to two or more diarrhoea within 24 h, abdominal pain rated mild or worse, hepatic toxicity $\geqslant$ grade 3, or fever $>38°C$. If these toxicities occurred on day 15 after skipping the day-8 treatment, DI was stopped in that course.

Patients could receive the next treatment course only if the following criteria were met: leucocyte count $\geqslant 4000\,\mu l^{-1}$, platelet count $\geqslant 100\,000\,\mu l^{-1}$ AST/ALT <2.0 times the upper limit of normal, total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$ serum creatinine $\leqslant$ the upper limit of normal, ECOG PS$\leqslant$2, neurotoxicity $\leqslant$grade 1, no diarrhoea or oedema. However, if more than 6 weeks passed before these criteria were satisfied, the patient was removed from the study.

Dose modification criteria for each drug are shown in Table 1. If during the previous course, grade 4 leucopenia, grade 4 neutropenia lasting $\geqslant$3 days, or grade 4 thrombocytopenia had occurred, doses of all drugs were reduced by $10\,mg\,m^{-2}$. Doses of both cisplatin and docetaxel were reduced by $10\,mg\,m^{-2}$ in subsequent cycles if chemotherapy induced grade $\geqslant$2 neurotoxicity. Moreover, dose of docetaxel was reduced by $10\,mg\,m^{-2}$ if grade $\geqslant$2 hepatic toxicity or grade $\geqslant$3 stomatitis had occurred. Dose of cisplatin was reduced by 20/mg/m^2 if grade $\geqslant$2 renal toxicity occurred. Dose of irinotecan was reduced by $5\,mg\,m^{-2}$ if grade $\geqslant$2 hepatic toxicity had occurred and by $10\,mg\,m^{-2}$ if grade $\geqslant$2 diarrhoea or cancellation of day-8 treatment had occurred.

Evaluation of response and survival

Tumour response was classified according to World Health Organization (WHO) criteria (World Health Organization, 1979). Complete response was defined as complete disappearance of all measurable and assessable disease for at least 4 weeks, Partial response was a $\geqslant$50% decrease in the sum of the products of the two IL largest perpendicular diameters of all measurable tumours lasting at least 4 weeks and without appearance of any new lesions. No change was defined as a <50% decrease or a <25% increase of tumor lesions for at least 4 weeks with no new lesions.

Table 1 Dose modification criteria

Toxicities in previous cycle	Decrease in docetaxel dose (mg/m^{-2})	Decrease in cisplatin dose (mg/m^{-2})	Decrease in -irinotecan dose (mg/m^{-2})
Grade 4 neutropenia lasting $\geqslant$3 days, leucopenia or thrombocytopenia	10	10	10
Grade $\geqslant$2 neurotoxicity	10	10	—
Grade $\geqslant$2 renal toxicity	—	20	—
Grade $\geqslant$2 hepatic toxicity	10	—	5
Grade $\geqslant$3 stomatitis	10	—	—
Grade $\geqslant$2 diarrhoea	—	—	10
Cancellation of day-8 treatment	—	—	10

Progressive disease was defined as development of new-lesions or a 25% increase in the sum of the products of the two largest perpendicular diameters of all measurable tumors. Duration of response in patients who achieved complete or partial response was measured from the start of treatment to the date of disease progression.

Statistical methods

Results of this study were evaluated to determine whether the docetaxel plus irinotecan combination warranted further assessment in a phase III trial. Thus, this study was designed to conduct two randomised phase II studies concurrently. We calculated the number of patients required for each of the two studies based on the Fleming's single-stage procedure (Fleming, 1982). In both studies, we set response rates of 40% as target activity level and 20% as the lowest level of interest with a power of 0.9 at a one-sided significance level of 0.05. As a result, a total of 100 qualified patients were to be enrolled, with 50 patients in each treatment arm. The primary objective was to estimate the response rate to both regimens, particularly to irinotecan plus docetaxel.

Overall survival and progression-free survival were analysed by the Kaplan–Meier method. The overall survival was measured from study entry to death. The progression-free survival was measured from study entry until the day of the first evidence of disease progression. If the disease had not progressed by the time of this analysis, progression-free survival was considered censored at the time of the analysis. All comparisons between patient characteristics, response rates, and toxicity incidences were performed by Pearson's χ^2 contingency table analysis.

RESULTS

Patient characteristics

From October 1998 to August 1999, 108 patients were assigned to receive DC ($n=51$) or DI ($n=57$). Baseline patient characteristics according to treatment arm are shown in Table 2. Patients were well balanced between the two treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. There were 23% stage IIIb patients and 74% had adenocarcinoma. All patients were included in the survival evaluation, and all were assessable for antitumor efficacy and toxicity.

Treatment delivery

Patients in both treatment arms received a median of two treatment courses. Two or more courses were delivered to 72.5 and 71.9%, and four courses to 17.6 and 19.1% of patients in the DC and DI arms, respectively. Differences between arms in the number of chemotherapy courses administered were not statistically significant.

Table 2 Baseline patient characteristics

		Docetaxel/ cisplatin	Docetaxel/ irinotecan	χ^2 text
No. of patients		51	57	
Gender	Male/female	37/14	38/19	$P=0.537$
Age (years)	Median	62	60	
	Range	39–74	42–77	
PS	0/1	15/36	15/42	$P=0.830$
Histology	Adenocarcinoma	36	44	$P=0.520$
	Squamous cell carcinoma	13	9	
	Others	2	4	
Disease stage	IIIb/IV	11/40	14/43	$P=0.820$
Brain metastasis	(+)/(−)	4/47	11/46	$P=0.086$

PS = performance status.

Response to treatment and survival

There were no complete responses. In the DC arm, 19 patients had partial responses for an overall response rate of 37% (Table 3). Among DI patients, 18 had partial responses for an overall response rate of 32%. The difference in response rate between arms was not significant ($P=0.55$). Progressive disease was noted in twice as many DI (25%) than DC (12%) patients. Early deaths within 3 months of treatment initiation occurred in 10% ($n=5$) of DC and 5% ($n=3$) of DI patients. The early deaths were treatment-related (three patients, all in the DC arm) or due to disease progression (five patients).

Overall and progression-free survival curves for the two treatment arms are shown in Figures 2 and 3. The median progression-free survival time was 20 weeks (95% confidence interval: 14–25 weeks) in the DC arm *vs* 18 weeks (95% confidence interval: 12–22 weeks) in the DI arm. Median survival times, 1-year survival rates, and 2-year survival rates were 50 weeks (95% confidence interval 34–78 weeks), 47 and 25%, respectively, in the DC arm, and 46 weeks (95% confidence interval: 37–54 weeks), 40 and 18%, respectively, in the DI arm. No significant differences were noted between groups in progression-free survival ($P=0.33$) or overall survival ($P=0.50$), although there were trends toward higher 1-year and 2-year survival rates in the DC.

Table 3 Overall response to docetaxel/cisplatin (DC) or docetaxel/irinotecan (DI) in patients with stages IIIb/IV non-small-cell lung cancer

Response	DC ($n=51$) No. pts	DI ($n=67$) No. pts
Complete response	0	0
Partial response	19	18
No change	23	25
Progressive disease	6	14
NE (TRD)	3	0
Response rate	37.3%*	31.6%*
95% Confidence intervals	24.1–51.9%	19.9–45.2%

pts = patients; NE = not evaluable; TRD = treatment-related death. *$P=0.55$.

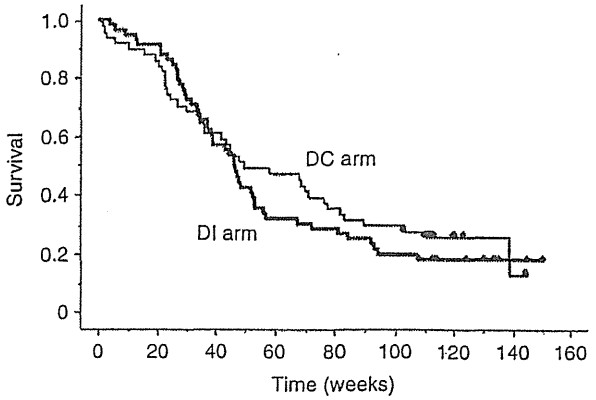

Figure 2 Overall survival according to treatment group, calculated by Kaplan–Meier method. Median survival times were 50 weeks for DC (docetaxel plus cisplatin) and 46 weeks for DI (docetaxel plus irinotecan). $P=0.50$ between treatment groups.