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CLINICAL INVESTIGATION

Peripheral Stent Placement in Hemodialysis Grafts

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Abstract The purpose of the present study was to evaluate the clinical outcome of peripheral stent placement after failed balloon angioplasty in patients with grafts who are on hemodialysis. We examined 30 Wallstents that were placed in 26 patients because balloon angioplasty failed or early restenosis (<3 months) occurred within 3 months. We retrospectively reviewed 267 consecutive balloon angioplasties performed in 71 patients with graft access between August 2000 and March 2007. Stent placements accounted for 30 (11.2%) of the 267 balloon angioplasties. The clinical success rate of stent placement was 93.3% (28 of 30 stent placements). The 3-, 6-, and 12-month primary patency rates were 73.3%, 39.3%, and 17.7%, respectively. The 1-, 2-, and 3-year secondary patency rates were 90.2%, 83.8%, and 83.8%, respectively. Primary patency was significantly prolonged by stent placement after early restenosis compared with previous balloon angioplasty alone ($P = 0.0059$). Primary patency after stent placement was significantly lower than after successful balloon angioplasty without indications for stent placement ($P = 0.0279$). Secondary patency rates did not significantly differ between stent placement and balloon angioplasty alone. The mean number of reinterventions required to maintain secondary patency after stent placement was significantly larger than that after balloon angioplasty alone (Mann–Whitney U test, $P = 0.0419$). We concluded that peripheral stent placement for graft access is effective for salvaging vascular access after failed balloon angioplasty and for prolonging patency in early restenosis after balloon angioplasty. However, reinterventions are required to maintain secondary patency after stent placement. Furthermore, peripheral stent placement for graft access cannot achieve the same primary patency as balloon angioplasty alone.

Keywords Stent · Graft · Balloon angioplasty · Stenosis · Vascular access

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Introduction

Percutaneous transluminal angioplasty has become the first choice of treatment for failure of vascular access. The introduction of cutting and ultrahigh pressure balloons appears to have increased the success rate of balloon angioplasty [1–4]. However, stents are still occasionally placed to treat stenosis after failed balloon angioplasty. The guidelines of the Dialysis Outcomes Quality Initiative (DOQI) and of the Society of Interventional Radiology (SIR) state that central and peripheral stent placement is useful in selected instances of failed balloon angioplasty [5, 6]. Stent placement for failed balloon angioplasty has been studied in detail and therapeutic outcomes have been documented [7–17]. The authors of these publications seem to promote stent use for failed balloon angioplasty. However, repeated reinterventions seem to be required after placement of stents, which limits their effectiveness. Thus,

the present study evaluates the clinical results of peripheral stent placement after failed balloon angioplasty and examines whether or not the primary patency of stent placement in this circumstance can equal that of balloon angioplasty alone.

Materials and Methods

Study Design

This study was a retrospective investigation. Our institutional review board approved the study protocol and all patients provided written informed consent before undergoing interventions. We investigated 30 stent placements for graft access in 26 Asian patients (12 women, 14 men; mean age, 64 ± 11 years [standard deviation]) with 30 peripheral stenoses, including 2 at the stented segment. All grafts (Thoratec; Thoratec Laboratories Co., Pleasanton, CA, USA) comprised 5-mm-diameter nontapered polyurethane. Two grafts were straight, and 24 were loops. Fifteen grafts crossed the elbow, and the others were placed at the upper arm. We retrospectively reviewed 267 consecutive balloon angioplasties performed due to access failures in 71 patients (30 women and 41 men; mean age, 64 ± 10 years) between August 2000 and March 2007. We evaluated the clinical success rates, as well as complications, primary patency, and secondary patency. We then compared the patency before and after stent placement in early restenosis and compared stent placement with balloon angioplasty for the primary patency, secondary patency, and number of reinterventions required to maintain secondary patency. All patients underwent hemodialysis at our dialysis center or at our dialysis branches connected on the medical network. Consecutive medical records and radiographic images of all patients were reviewed. The first author (a radiologist with 13 years of experience in interventional procedures as of 2007) performed all procedures at the same institution.

Indications for Balloon Angioplasty and Stent Placement

For all balloon angioplasties and stent placements, we selected interventional or surgical procedures after discussion with an interventional radiologist and access surgeon. According to DOQI guidelines [5], all angioplasties were performed on patients exhibiting >50% stenosis and clinical/physiologic abnormalities. Stents were placed after failed balloon angioplasty defined as follows:

Indication A was failed balloon angioplasty based on insufficient restoration of access flow assessed by fistulography and insufficient conversion of a continuous palpable thrill at the distal (venous) end of grafts.

Indication B was restenosis occurring within 3 months after the last balloon angioplasty for the same lesion. However, when the vascular diameter and access flow after the present balloon angioplasty were more favorable than those after the last balloon angioplasty, stent placement was excluded.

Balloon Angioplasty Procedures

All procedures were accomplished on an outpatient basis at our hospital. Patients were monitored using pulse oximetry, blood pressure measurements, and electrocardiography. An anticoagulant (intravenous heparin, 3,000 U) was administered during thrombolysis only. Fistulography was performed immediately before balloon angioplasty to measure vessel diameter. Thereafter, if a lesion was identified as requiring dilation (>50% stenosis), an appropriately 6- to 7-Fr sheath introducer (Medikit Co., Miyazaki, Japan) was positioned and balloon angioplasty proceeded. The sheath introducer was placed in the graft or outflow vein. Balloon size was determined based on the diameter of the adjacent normal vessel. The balloon catheters ranged in size from that of the normal vessel diameter to 20% larger (6–10 mm in diameter). We used Ultra-thin Diamond (Boston Scientific, Natick, MA, USA; rated burst pressure, 15 atm), Blue Max (Boston Scientific; rated burst pressure, 20 atm), or Peripheral Cutting (Boston Scientific; rated burst pressure, 10 atm) balloons. All balloons were dilated using a pressure inflation device (Everest; Medtronic, Minneapolis, MN, USA) to below the rated burst pressure until the balloon waist disappeared and then were inflated for 1 min (or for 5 min in the event of recoil). We determined whether or not a continuous palpable thrill was converted immediately after each balloon angioplasty. Fistulography was performed after balloon angioplasty to confirm whether sufficient restoration of access flow could be obtained. The entire access circuit from the arterial anastomosis to the superior vena cava was evaluated by digital subtraction angiography during the procedure.

Before balloon angioplasty, patients with thrombosis underwent thrombolysis using the lyse-and-wait technique with 60,000–180,000 U of urokinase (Urokinase; Benesis, Osaka, Japan) admixed with 3,000–5,000 U of heparin as described by Cynamon et al. [18]. Residual thrombus was dislodged using balloon catheters and sheath introducers.

Stent Placement

We positioned self-expanding stents and Wallstents (Easy Wallstent or Wallstent RP; Boston Scientific) of 6- to

10-mm nominal diameter that were adapted to the largest diameter of the segment covered with the stent so that the entire stent could touch the luminal wall. The stent was kept as short as possible but long enough to bridge the entire lesion with a slight overlap at its proximal and distal ends. Stents were dilated after deployment using the original balloon to ensure close contact with the vessel wall. We examined the conversion of a continuous palpable thrill at the distal (venous) end of grafts immediately after stent placement. Fistulography was performed to visualize access flow after stent placement. No patients underwent anticoagulation treatment for stent placement after the procedure.

Study Definitions and Follow-Up

Percentage stenosis was defined as the minimal luminal diameter determined by fistulography in the single view or the multiple view if necessary. The percentage stenosis was defined by NASCET criteria (1 − MLD/reference vessel × 100). The reference vessels were defined as graft in graft-to-vein anastomotic stenosis, graft in artery-to-graft anastomotic stenosis, adjacent normal vein in autogenous venous stenosis, and adjacent normal vein in in-stent restenosis. Clinical success after an interventional procedure was defined as the resumption of normal dialysis for at least one session, in accordance with published SIR guidelines [6]. Clinical follow-up of all patients included a physical examination, venous dialysis pressure measurements at each hemodialysis session, and monthly evaluations of dialysis dose and urea recirculation. Ultrasonography was performed when results were abnormal during clinical follow up. Follow-up findings were determined via access meetings with staff in the dialysis units. Follow-up continued until the patient died, surgical revision excluded the stent-implanted segment, or the graft was abandoned. We defined "postintervention primary patency" and "postintervention secondary patency," described in the published SIR guidelines [7], as primary and secondary patency, respectively. Loss of patency was defined as treatment of a lesion anywhere within the access circuit, from the arterial inflow to the superior vena cava-right atrial junction, according to published SIR guidelines [7].

Comparison of Primary Patency

When stent placement was successful, primary and secondary patencies were calculated after the first stent placement. We also calculated primary patency for indications A and B, as well as nonthrombotic and thrombotic access. Primary and secondary patencies were also calculated when balloon angioplasty alone was sufficient to treat stenosis. Primary and secondary patencies after successful stent placement due to failed balloon angioplasty were then compared with those after successful balloon angioplasty alone.

We compared the primary patency for stent placement with that of previous balloon angioplasty alone in the indication B group. We compared the mean number of reinterventions required to maintain the secondary patency of stent placement with that for balloon angioplasty alone.

Statistical Analysis

Primary and secondary patencies were calculated using the Kaplan–Meier method and patency rates were compared using the Breslow–Gehan–Wilcoxon test. To compare the mean primary patency periods of stent placement with those of previous balloon angioplasty alone, we used the Wilcoxon signed-rank test as a matched pair test for comparisons of the same lesions at different times. We compared the number of reinterventions required to maintain secondary patency of stent placement with that for balloon angioplasty alone using the chi-square test. Values of $P < 0.05$ were considered statistically significant.

Results

Stent Placement

Stent placements accounted for 11.2% (30 of 267 procedures), 19.2% (16 of 83), 8.8% (9 of 102), and 6.0% (5 of 82) of all procedures during the period of review, as well as between 2000 and 2003, between 2004 and 2005, and after 2006, respectively. Table 1 reports the characteristics of access and stenosis with stent placement. The insertion of one stent was sufficient to cover the entire lesion in 26 procedures, and two were required for coverage in 4 others. Thirty-four stents were placed over the course of the present study. The lyse-and-wait technique was performed for nine patients with thrombosis before angioplasty with 30 stent placements.

Clinical Success

The clinical success rate of stent placement was 93.3% (28 of 30 procedures) for all procedures, 85.7% (12 of 14 procedures) for indication A, and 100% (16 procedures) for indication B. Table 2 reports the number of stent placements and clinical successes. One unsuccessful patient underwent first stent placement for graft-to-vein anastomotic stenosis and second stent placement for artery-to-graft anastomotic stenosis. The second stent placement was not clinically successful because arterial stenosis occurred immediately after deployment and access flow was insufficient. Another

Table 1 Number of accesses and stenoses among patients with stent placement

No. of accesses[a]	
All graft accesses with stent placement	30 (100%)
Thrombotic access	9 (30%)
Nonthrombotic access	21 (70%)
Indication A[b]	14 (47%)
Indication B[c]	16 (53%)
No. of stenoses[d]	
All stenoses with stent placement	30 (100%)
Graft-to-vein anastomosis	28 (93%)
Artery-to-graft anastomosis	1 (3%)
Autogenous vein	1 (3%)
Upper arm	26 (87%)
Lower arm	4 (13%)
Stenosis without stent	28 (93%)
Stenosis at stented segment	2 (7%)

[a] Data are numbers of accesses with stent placements that were retrospectively reviewed

[b] Failed balloon angioplasty based on insufficient access flow and insufficient conversion of continuous palpable thrill

[c] Restenosis within 3 months of previous balloon angioplasty for same lesion

[d] Data are numbers of retrospectively reviewed stenoses with stent placements

unsuccessful patient underwent first stent placement for graft-to-vein anastomotic stenosis and thrombosis occurred in the graft within 24 h of stent placement. The mean minimal diameter of the placed stent and mean residual percentage diameter stenosis were 4.2 ± 0.7 mm and 14.6 ± 14.2%, respectively.

Successful stent placement was not associated with any complications.

Primary Patency

Table 3 reports the mean primary patency periods, the primary patency rates for successful stent placement, and the subgroups. During the 79 months that we retrospectively reviewed, 45 patients were treated using balloon angioplasty alone without indication for stent placement, and 44 were clinically successful. Table 3 lists the mean primary patency periods and the primary patency rates for successful balloon angioplasty alone. The mean period of primary patency after successful stent placement was significantly shorter than that after successful balloon angioplasty for stenosis without indications for stent placement (Breslow–Gehan–Wilcoxon test, $P = 0.0279$) (Fig. 1).

Table 4 reports a comparison of the access patency in indication B after stent placement and previous balloon angioplasty for the same lesions. Primary patency persisted significantly longer after stent placement than after previous balloon angioplasty alone (Breslow–Gehan–Wilcoxon test, $P = 0.0468$; Wilcoxon sign-rank test, $P = 0.0059$).

Secondary Patency and Reintervention

Table 5 reports the secondary patency rates, mean number of reinterventions required to maintain secondary patency, and mean follow-up periods for stent placement and balloon angioplasty alone. Secondary patency rates did not significantly differ between stent placement and balloon angioplasty alone. The number of reinterventions per 1,000 patency days required to maintain secondary patency after stent placement was significantly larger than that after balloon angioplasty alone (χ^2 test, $P < 0.0001$).

Seventy reinterventions for 96 lesions including stenosis at stented segments (67.7%) and stenosis without stents (32.2%) were required to maintain secondary patency after stent placement. The mean percentage stenosis was 74.5 ± 12.6% at the stented segment. Stenosis at the stented segment occurred in 78.6% of cases (22 of 28 successful stent placements) during the study periods.

Stenosis caused by delayed shortening occurred in 3.5% (1 of 28) of successful stent placements and another stent placement was required for treatment of the stenosis.

Discussion

The SIR guidelines do not recommend the routine use of stents to prevent restenosis and state that the role of stents has yet to be fully defined [6]. Three prospective randomized studies have found that stent placement does not confer an advantage over successful angioplasty [19–21]. Thereafter, some studies have described the placement of metallic stents for peripheral lesions after failed balloon angioplasty, which seems to have been effective [9–11, 16, 17]. Thus, the present study evaluates the clinical outcomes of peripheral stent placement after failed balloon angioplasty and examines whether or not the primary patency of stent placement in this circumstance equals that of balloon angioplasty alone.

We defined the indication for peripheral stent placement as failed balloon angioplasty. Stent placement has been indicated by many investigators to treat severe residual stenosis (≥30–50%) after balloon angioplasty [9, 10, 19]. The ratio (%) of stenosis in enlarged irregular veins or at the anastomosis of two very different vessels may be difficult to ascertain. Furthermore, vessel diameters cannot be accurately determined by fistulography because of unidirectional imaging. We also have occasionally observed that intimal flap and dissection immediately after balloon dilation do not improve the visualization of access flow assessed by

Table 2 Number of stent placements and clinical successes

Case no.	1st stent placement		2nd stent placement for stenosed stented segment		2nd stent placement for stenosis without stent		3rd stent placement for stenosis without stent		Total no. of stent placements	
	Success	Failure	Success	Failure	Success	Failure	Success	Failure	Success	Failure
1[a]	+		+						2	
2[b]	+					+			1	1
3[c]	+		+				+		3	
4[d]		+								1
5–26[e]	+								22	
Total	25[f]	1	2			1	1		28[g]	2
	26		2		1		1		30	

[a] Case 1 required second stent placement for stenosis at the stented segment

[b] Case 2 required first stent placement for graft-to-vein anastomotic stenosis and second stent placement for artery-to-graft anastomotic stenosis. The second stent placement was not clinically successful

[c] Case 3 required the first stent placement for graft-to-vein anastomotic stenosis, the second for stenosis at the stented segment, and the third for outflow venous stenosis without stent at the cephalic arch

[d] First stent placement was not clinically successful in case 4

[e] Cases 5–26 required only first stent placement

[f] Primary and secondary patency rates calculated for these 25 patients

[g] Clinical success rate of stent placement was 93.3% (28 of 30 procedures) for all procedures

Table 3 Primary patency of stent placements compared with balloon angioplasty alone

Category	No. of patients	Primary patency period (months)[a]	Primary patency rate (%)[b]			*P*-value
			3 months	6 months	12 months	
Stent placement	25	7.0 ± 9.8	73.3 ± 9.4 (16)	39.3 ± 10.7 (8)	17.7 ± 8.8 (3)	0.0279[c]
Subgroup						
Indication A[d]	10	6.5 ± 3.8	80.0 ± 12.6 (8)	57.1 ± 16.4 (5)	17.1 ± 14.5 (1)	
Indication B[e]	15	7.3 ± 12.5	68.4 ± 13.2 (8)	25.7 ± 12.7 (3)	17.1 ± 11.0 (2)	
Nonthromboticaccess	18	7.2 ± 11.0	81.4 ± 9.8 (12)	44.8 ± 13.3 (6)	18.6 ± 11.4 (2)	
Thrombotic access	7	6.6 ± 6.7	57.1 ± 18.7 (4)	28.6 ± 17.1 (2)	–	
Balloon angioplasty alone	44	12.7 ± 12.9	80.9 ± 6.1 (32)	72.8 ± 7.0 (27)	44.1 ± 8.4 (13)	

[a] Data are mean ± standard deviation

[b] Data are primary patency rate ± standard error. Numbers in parentheses are numbers at risk at start interval

[c] Determined by Breslow–Gehan–Wilcoxon test. $P = 0.0279$ vs. balloon angioplasty alone

[d] Technical failure of balloon angioplasty based on insufficient access flow and insufficient conversion of continuous palpable thrill

[e] Restenosis within 3 months after previous balloon angioplasty for the same lesion

fistulography and also do not achieve conversion of a continuous palpable thrill. Residual stenosis rates in these types of lesions are difficult to assess by fistulography. Therefore, for indication A, we based our judgment on restoration of access flow assessed by fistulography and the conversion of a continuous palpable thrill at the distal (venous) end of grafts immediately after balloon angioplasty. Trerotola et al. have advocated using thrill as the procedural endpoint and we support this recommendation [22].

The SIR guidelines recommend stent placement for lesions in central, but not peripheral, veins within 3 months of initially successful balloon angioplasty [6]. Some investigators have placed stents to treat restenosis within 3 months [9–11], and we have likewise done so within 3 months of balloon angioplasty. However, we have not placed stents if dilation was more favorable compared with the previous balloon angioplasty (indication B), unlike other investigators. Prolonged inflation of a larger balloon or the use of a cutting balloon achieved better dilation in some of our patients.

According to our study, the prevalence of stent placement has decreased annually, reaching 6.0% after 2006. The reasons for this appear to be recent technical improvements in angioplasty. The 85.7% clinical success rate of stent

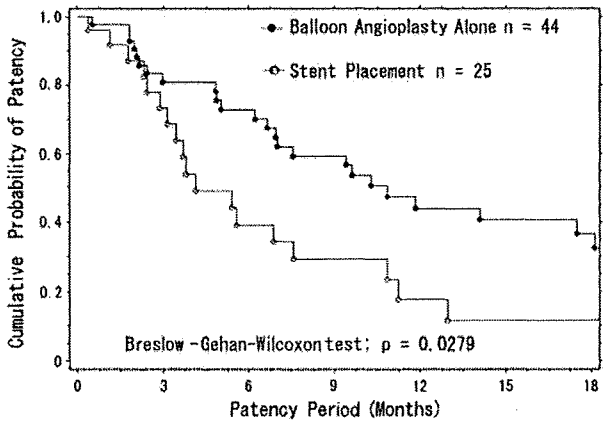

Fig. 1 Kaplan–Meier analysis of primary patency rates after stent placement ($n = 25$) and after balloon angioplasty alone ($n = 44$). *Open circles* indicate stent placement. *Filled circles* indicate balloon angioplasty alone. Primary patency after successful stent placement was significantly shorter than that after successful balloon angioplasty alone for stenosis without stent placement (Breslow–Gehan–Wilcoxon test, $P = 0.0279$)

placement for indication A in the present study indicates that peripheral stent placement is effective for salvaging hemodialysis access after failed balloon angioplasty.

We found delayed stent shortening in 3.5% of successful stent placements. Haage et al. reported that stent shortening was delayed in 6% of central Wallstent placements (3 of 50) and that angioplasty and additional stents were placed to treat uncovered segments with restenosis [14]. Delayed stent shortening should be acknowledged as a limitation of Wallstents. Vogel et al. placed Nitinol stents for graft access after failed balloon angioplasty and our indications were compatible with theirs, although they used different stents [10]. They reported 3-, 6-, and 12-month primary patency rates of 77%, 51%, and 20%, respectively, while in our study the primary patency rates for graft access were 73.3%, 39.3%, and 17.7%, respectively. These findings indicate that the Nitinol stent seems to be superior to the Wallstent, although the two stents are difficult to compare.

If early restenosis occurs, stent placement can be a useful option because the present study found that primary patency was prolonged significantly by stent placement for peripheral stenoses recurring within 3 months. However, the duration of primary patency after stent placement following failed balloon angioplasty was significantly shorter than that for successful balloon angioplasty alone for stenosis without stent placement. Even when stents were placed for stenosis after failed balloon angioplasty, the primary patency was never the same as that for successful balloon angioplasty alone. Thus, we suggest improving the success rate of balloon angioplasty and reducing the use of stents. Our results are different from those of Maya et al., who found that the primary patency rate of 14 stents placed to treat thrombosed grafts was higher than that of balloon angioplasty alone [12].

Table 4 Comparison of primary patency between previous balloon angioplasty (BA) alone and stent placement in indication B group: restenosis within 3 months after previous BA for the same lesion ($N = 15$)

Intervention	Primary patency period (month)[a]	P-value[b]	Primary patency rate (%)[c]					P-value[d]
			1 month	2 months	3 months	6 months	12 months	
Previous BA	1.9 ± 0.7	0.0468	86.7 ± 8.8 (13)	53.3 ± 12.9 (8)	0 (0)	–	–	0.0059
Stent placed	7.3 ± 12.5		93.3 ± 6.4 (13)	85.6 ± 9.5 (10)	68.4 ± 13.2 (3)	25.7 ± 12.7 (3)	17.1 ± 11.0 (2)	

[a] Data are mean ± standard deviation

[b] Determined by Wilcoxon signed-rank test. Primary patency periods after stent placement were compared with those after previous BA alone

[c] Primary patency rate ± standard error. Numbers in parentheses are those at risk at start interval

[d] Determined by Breslow–Gehan–Wilcoxon test. Comparison of primary patency rates after stent placement with those after previous BA alone

Table 5 Comparison of secondary patency and number of required reinterventions to maintain secondary patency between previous balloon angioplasty (BA) alone and stent placement

Category	No. of patients	Mean follow-up period[a]	No. of reinterventions per 1,000 patency days[b]	P-value[c]	Secondary patency rate (%)[d]			P-value[e]
					1 year	2 years	3 years	
Stent placed	25	22 ± 19	4.5	<0.0001	90.2 ± 6. (16)	83.8 ± 8. (9)	83.8 ± 8. (6)	0.0891
BA alone	44	23 ± 19	1.9		97.1 ± 2. (28)	97.1 ± 2. (14)	97.1 ± 2. (9)	

[a] Data are mean ± standard deviation

[b] Number of required reinterventions to maintain secondary patency. Data are mean ± standard deviation

[c] Determined by Mann–Whitney U test between stent placement and BA alone

[d] Data are secondary patency rate ± standard error. Numbers in parentheses are those at risk at start interval

[e] Determined by Breslow–Gehan–Wilcoxon test between stent placement and BA alone

Published secondary patency rates in peripheral graft access after stent placement at 1 year range from 60% to 90% [10–12, 19]. Our results for secondary patency rates are comparable with these. Although peripheral stents allow long-term secondary patency, multiple reinterventions are required to maintain it. Furthermore, more reinterventions may be needed to maintain secondary patency compared with balloon angioplasty alone. Our data indicate that although stent patency was sometimes quite long, stenosis at the stented segment is predictable (78.6%).

The present study had some study limitations. The present study was limited by the small patient population, particularly in the subgroups, and by its retrospective design. There was bias because all patients were Asian with 5-mm-diameter polyurethane grafts. The use of stents might decrease annually due to recent technical improvements in angioplasty. Therefore, the stent usage rate in our study might be higher. The subset analyses were thus weak. Occurrence of indication A was not quantitative because it was decided by visualized restoration of access flow in fistulography and by palpable thrill. Our procedures included angioplasty using cutting balloons, which might not be similar to that using regular balloons. To more accurately determine the effectiveness of stent placement to treat failed balloon angioplasty, stent placement with balloon angioplasty alone after failed balloon angioplasty should be examined in a randomized study.

In conclusion, peripheral stent placement is effective for salvaging hemodialysis access after failed balloon angioplasty. Peripheral stent placement for early (<3 months) recurring stenosis significantly improves primary patency compared with previous angioplasty alone. However, reinterventions were required to maintain secondary patency after stent placement. We emphasize that peripheral stent placement cannot achieve the same primary patency as successful balloon angioplasty without stent placement. We recommend that although peripheral stent placement is effective for failed balloon angioplasty, the success rate of balloon angioplasty needs to be improved to reduce the use of stents.

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Surgical Results After Preoperative Chemoradiation Therapy for Patients With Pancreatic Cancer

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Objectives: The results of surgical therapy alone for pancreatic cancer are disappointing. We explored surgical results after neoadjuvant chemoradiation therapy (NACRT) for patients with pancreatic cancer that extended beyond the pancreas.

Methods: Sixty-eight consecutive patients with pancreatic cancer who underwent pancreatic resection were included. Twenty-seven patients underwent surgical resection after NACRT (NACRT group). The other 41 patients were classified as surgery-alone group. Surgical results were compared in patients who underwent curative resection (R0/1) who were followed up for at least 25 months and underwent no adjuvant therapy.

Results: A lower frequency of lymph node metastasis was observed in the NACRT group ($P < 0.05$). The frequency of residual tumor grading in the NACRT group was significantly different from that in surgery-alone (R0/1/2%, 52/15/33 vs 22/51/27; $P = 0.0040$). In R0/1 cases, overall survival and disease-free survival rates in the NACRT group (n = 18) were significantly longer than in surgery-alone (n = 30, $P < 0.05$). The rate of local recurrence in the NACRT group was significantly less than in surgery-alone (11% vs 47%, $P = 0.0024$).

Conclusions: This single-institution experience indicates that NACRT is able to increase the resectability rate with clear margins and to decrease the rate of metastatic lymph nodes, resulting in improved prognosis of curative cases with pancreatic cancer that extended beyond the pancreas.

Key Words: curative resection, retrospective analysis, gemcitabine, 5-FU, CDDP, survival analysis

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The results of surgical therapy alone for pancreatic ductal cancer are still disappointing. Surgical resection for patients with pancreatic cancer at an early stage, which corresponds to cancer growth within pancreatic parenchyma, is the only curative treatment option; however, both distant and local/regional patterns of relapse are common within a year, even after curative resection.[1] In approximately 50% of resected pancreatic tumors, the surgical margins contain tumor cells.[2] The aggressive features of pancreatic cancer can lead to a dismal prognosis, and surgery alone is not optimal for achieving locoregional control of pancreatic cancer.[3,4]

To achieve 5-year survival exceeding 50% in patients with pancreatic cancer, Traverso LW advocated appropriate patient selection for curative resection by accurate staging, balanced resection, centralized treatment in high-volume centers, and the use of an effective adjuvant or neoadjuvant therapy.[4] Neoadjuvant (preoperative) chemoradiation therapy (NACRT) has several possibilities such as improved patient selection after the restaging evaluation, increased resectability rate with clear margins (R0 resection),[5] decreased rate of metastatic lymph nodes, and decreased rate of local relapse.[6] We previously reported that preoperative chemoradiation (5-fluorouracil [5-FU] or gemcitabine + 40 Gy) enabled the selection of 24 of 32 patients for surgery and resulted in acceptable toxicity.[7]

The objectives of this retrospective study were to compare the pathological results, overall survival (OS) and disease-free survival (DFS) rates, and type of recurrence in pancreatic cancer patients who underwent surgical resection after NACRT with those of patients who underwent surgery alone.

MATERIALS AND METHODS

One hundred seventy-five consecutive patients with a clinical diagnosis of pancreatic ductal adenocarcinoma were evaluated for the staging of tumor extension between January 2000 and December 2005 in Kansai Medical University Hospital. Cases involving an endocrine tumor of the pancreas, intraductal papillary mucinous cancer, acinar cell cancer, anaplastic cancer, duodenal cancer, distal common bile duct cancer, or ampullary cancer were excluded. During this period, 68 consecutive patients with pancreatic cancer who underwent pancreatic resection were included in this study. All tissues of the resected patients were pathologically proven ductal adenocarcinoma of the pancreas. Between 2001 and 2004, NACRT was performed in 35 patients who had radiologically diagnosed pancreatic cancer that extended beyond the pancreas (T3/T4 pancreatic cancer by TNM staging), and who were regarded as potentially resectable ([PR] n = 19) and locally advanced ([LA] n = 16), defined by National Comprehensive Cancer Network (NCCN) guideline.[8] Treatment consisted of concurrent radiotherapy (40 Gy within 4 weeks), and chemotherapy with 5-FU and cisplatin (CDDP) ([FP] n = 13) or with gemcitabine ([GEM] n = 22), as described in the previous article.[7] Finally, 27 patients (PR, n = 16; LA, n = 11; FP, n = 8; GEM n = 19) underwent surgical resection (NACRT group). The other 41 patients were classified as the surgery-alone group that consisted of pancreatic cancer patients who had a tumor limited to the pancreas (T1/T2 TNM staging) between 2001 and 2004, and the resected cases from 2000 and from 2005. Forty-eight patients with residual tumor staging of R0/1 were abstracted from 68 resected patients between 2000 and 2005, and the clinical and pathological characteristics, OS rate, DFS rate, and type of relapse were compared (NACRT group, n = 18; surgery-alone group, n = 30). All patients were followed up for at least 25 months and underwent no adjuvant chemotherapy.

As shown in the previous article,[9,10] local tumor unresectability was defined as (1) vascular involvement of a major

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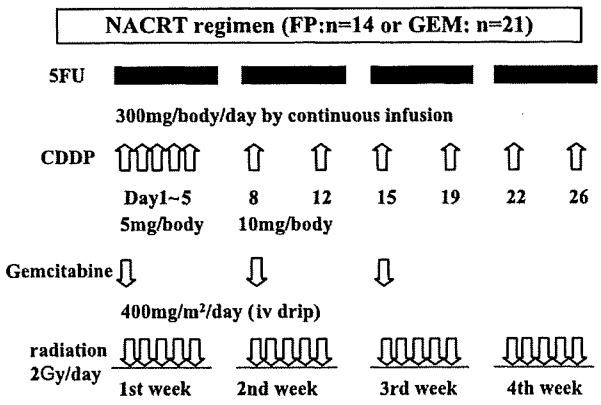

FIGURE 1. The regimen of NACRT.

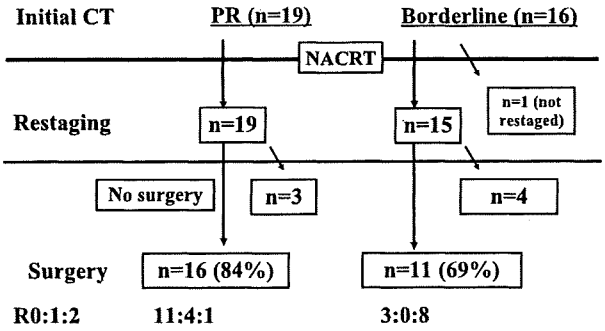

FIGURE 2. Clinical course of the NACRT group. PR indicates potentially resectable; borderline, borderline resectable in the NCCN guidelines.

peripancreatic artery (defined as tumor ingrowth with >50% vessel contiguity in the celiac trunk [CA], common or proper hepatic artery, or superior mesenteric artery); (2) extended obstruction of the portal vein to distal branches of the superior mesenteric vein; or (iii) with cavernous transformation of the porta hepatis. Patients with peritoneal carcinomatosis or distant organ metastasis were also excluded from this study. On the other hand, patients with cancer in the pancreatic body and tail, with CA invasion, and without superior mesenteric artery (SMA) invasion were also classified as candidates for the Appleby operation. All operations were performed by 2 experienced hepatopancreatobiliary surgeons who were in agreement about the extent of surgery to be performed. Preoperative staging was performed using contrast-enhanced computed tomography (CECT), abdominal angiography, CT-assisted hepatic arteriography, and CT during arterial portography before August 2002, and using CE multidetector row CT after September 2002.[9,10]

The detailed eligibility criteria were reported in the previous article.[8] Informed consent was obtained from all patients according to institutional regulations, and this study was approved by the local ethics committee. Patient data were obtained from the prospective database of pancreatic disease at Kansai Medical University Hospital.

Treatment Protocol

Patients received a continuous infusion of 5-FU (200 mg/m^2 5 times per week, 1–4 weeks), accompanied by CDDP (3 mg/m^2 on days 1–5, 6 mg/m^2 on days 9, 12, 14, 19, 23, and 26) in the FP-NACRT arm (Fig. 1). Gemcitabine at a dose of 400 mg/m^{-2} per day was given intravenously over 30 minutes starting 2 hours before radiotherapy 3 times weekly for 4 weeks in the GEM-NACRT arm (Fig. 1). Concomitantly, 10 mg of azasetron was routinely given before chemotherapy administration. Chemoinfusion was started approximately 60 minutes before radiation therapy. The protocol for radiation therapy was as follows. A total of 40 Gy was concurrently delivered in 2-Gy fractions to the tumor bed Monday through Friday for 4 weeks by a linear accelerator using megavoltage photon beams (6 MV). The clinical target volume was delineated slice by slice on the planning CT scan using CT simulation software. It encompassed the gross tumor volume as defined by the preoperative CT scan, plus a margin of 0.8 cm. Also included were retroperitoneal paraaortic lymphatic vessels between the CA and the upper mesenteric artery to the anterior level of the vertebral bodies. The gross tumor volume was defined as the gross tumor mass detected by CT scans. The planning target volume included the clinical target volume, with a 1-cm margin. Usually, a 4-field approach was chosen using anteroposterior and left and right lateral beams.

Surgical resection was performed 3 to 4 weeks after NACRT completion if none of the following were found: disease progression to an unresectable status (as previously mentioned) as determined by repeated abdominal CECT, a prohibitive decline in performance status, or other evidence of metastatic disease. Pancreatectomy was performed with portal vein resection, if portal vein resection was predicted to provide a surgical- or pathological-free margin. For resected patients, curative surgery was performed with extended lymph node dissection including paraaortic lymph nodes. Median time from the last day of NACRT to surgical resection was 28 days (range, 15–60 days). If tumor progression was evident, additional treatment with chemotherapeutic regimens was determined on an individual basis.

TABLE 1. Patient and Operative Factors of the NACRT and Control Groups

	NACRT	Control	P
Total no. patients	27	41	
Age	64 (47–74)	66 (50–83)	n.s.
Gender (male/female)	10:17	23:18	n.s.
CA19-9, U/mL	110 (1–8116)	89.7 (1–9116)	n.s.
Comorbid disease (+/−)	14:13	23:18	n.s.
Site of primary lesion			
Head/body-tail	21:6	28:13	n.s.
Tumor size, mm	30 (16–80)	30 (13–90)	n.s.
CDRS (PR/borderline)	16:11	24:17	n.s.
Type of surgery (PD/TP/DP)	20:1:6	27:1:13	n.s.
PV resection (+/−)	4:23	12:29	n.s.
CA resection (+/−)	2:25	1:40	n.s.
Operative duration, min	560 (325–840)	515 (265–900)	n.s.
Extent of blood loss, mL	1390 (400–6420)	1045 (390–7250)	n.s.

Data are expressed as the median (range).

Borderline indicates borderline resectable; CA19-9, carbohydrate antigen 19-9; CDRS, criteria defining resectability status; DP, distal pancreatectomy; n.s., not significant; PD, pancreaticoduodenectomy; PR, potentially resectable; PV, portal vein; TP, total pancreatectomy.

TABLE 2. Tumor Factors of the NACRT and Control Groups

	NACRT	Control	P
Total no. patients	27	41	
Site of primary lesion			
Head/body-tail	21:6	28:13	n.s.
Tumor size, mm	30 (16–80)	30 (13–90)	n.s.
Pathological differentiation (well/mod/por/other)	6:18:1:2	10:22:5:4	n.s.
Stage I–III : IVa/IVb	10:17	13:28	n.s.
LN mets positive/negative	11:16	28:13	0.0440
INF β/γ	19:8	33:8	n.s.
Ly 0/1:2/3	16:11	13:28	0.0440
V 0/1:2/3	22:5	20:21	0.0102
Ne 0/1:2/3	7:20	6:35	n.s.
Ch positive/negative	12:15	22:19	n.s.
Du positive/negative	14:13	20:21	n.s.
S positive/negative	12:15	16:25	n.s.
Rp positive/negative	16:11	28:13	n.s.
PV positive/negative	8:19	15:26	n.s.
A positive/negative	6:21	7:34	n.s.
PL positive/negative	9:18	19:2	n.s.
R grading 0:1:2 (n)	14:4:9	9:21:11	0.0040
R grading 0:1:2, %	52:15:33	22:51:27	
Radiological response*			
Grade Ia:Ib:II	12:6:9	N/E	

Data are expressed as the median (range).

Mod indicates moderately; por, poorly; other, papillary/adenosquamous cell carcinoma; R0, negative margin; R1, positive microscopic margin; R2, positive gross margin; LN met, lymph node metastasis; INF, mode of histological infiltration; Ly, grade of infiltration of the lymphatic vessels; V, grade of venous infiltration; Ne, grade of perineural invasion; Ch, grade of invasion to intrapancreatic common bile duct; Du, grade of invasion to the duodenum; S, grade of invasion to the anterior capsule; Rp, grade of invasion of the retroperitoneal tissue; Pv, grade of invasion of the portal vein; A, grade of invasion of the large artery; Pl, invasion of the extrapancreatic nerve plexus.

*Radiological response was defined as the amount of degenerated cancer cells.

Ia indicates less than 33% population of degenerated cancer cells; Ib, between 34% and 66%; II, more than 67%.

Follow-Up

After the completion of all treatments, patients were evaluated by physical examination every month, chest radiography, and CECT every 3 months. The development of a new low-density mass in the region of the pancreas bed and root of the mesentery was considered evidence of local recurrence even in the absence of symptoms. Cytological or histological confirmation of recurrent disease was not routinely required. Radiographic evidence of a new low-density region in the liver or lung was considered evidence of distant recurrence; biopsy was rarely performed. Peritoneal recurrence was defined as new ascites on physical examination or on CT and was confirmed by cytological examination of ascites. Sites of recurrent disease were documented at the time of initial recurrence. If the patients had any useful tumor markers at the first admission, these were checked again for confirmation of recurrence. In all patients, the date of first treatment was chosen as the starting point for survival analysis. All patients had a minimum follow-up of 25 months.

End Points and Statistical Analysis

The countable data were expressed as the median and range. The χ test or Fisher exact test was used for comparison of categorical variables when appropriate. The OS and DFS rates were calculated from the start of study treatment until death or the final date of follow-up and determined by the Kaplan-Meier method. Patients alive at the time of the study report were censored. The log-rank test was applied for the comparison of survival rates between different groups. Results were considered significant at $P < 0.05$.

RESULTS

Clinical Course of the NACRT Group

From 2001 to December 2004, 35 patients diagnosed as having pancreatic cancer were treated with NACRT using FP or GEM. Fourteen patients received FP-NACRT, and 21 patients received GEM-NACRT. According to NCCN guidelines, the 35 patients were divided into PR (n = 19) and borderline (n = 16), as shown in Figure 2. After NACRT, 34 patients were restaged using CECT or CE multidetector row CT, and 1 patient refused restaging. Three patients in the PR category (16%) did not undergo surgical resection because of liver metastasis, and 5 patients in the borderline category (31%) who had peritoneal metastasis (n = 2), liver metastasis (n = 1), and progressive disease (n = 1), in addition to 1 patient who refused restaging, did not undergo surgical resection. Finally, 16 patients (84%) in PR and 11 patients (69%) in borderline underwent surgical resection. The frequency of R0/1 in PR was 94%, significantly superior to 27% in borderline ($P < 0.0001$).

When radiological response was defined as the amount of degenerated cancer cells, only 9 patients (33%) in this NACRT regimen had more than 67% population of degenerated cancer cells (Table 1).

TABLE 3. Patient and Operative Factors in R0/1 Cases of the NACRT and Surgery-Alone Groups

	NACRT	Surgery-Alone	P
Total no. patients	18	30	
Age	65 (51–74)	68 (50 – 83)	n.s.
Gender (male/female)	7:11	18:12	n.s.
CA19-9, U/mL	90 (1–8116)	87 (1–9116)	n.s.
Comorbid disease (+/−)	10:8	18:12	n.s.
Site of primary lesion			
Head/body-tail	15:3	18:12	n.s.
Tumor size, mm	29 (16–80)	30 (13–90)	n.s.
PR/borderline	15:3	21:9	n.s.
Type of surgery (PD/TP/DP)	15:0:3	17:1:12	n.s.
PV resection (+/−)	3:15	9:21	n.s.
CA resection (+/−)	1:17	1:29	n.s.
Operative duration, min	557 (330–795)	512 (265–900)	n.s.
Extent of blood loss, mL	1078 (400–6420)	970 (390–5030)	n.s.

Data are expressed as the median (range).

Borderline indicates borderline resectable (NCCN, criteria defining resectability status); DP, distal pancreatectomy; LN, lymph node; PD, pancreaticoduodenectomy; PR potentially resectable; PV, portal vein; TP, total pancreatectomy.

TABLE 4. Tumor Factors in R0/1 Cases of the NACRT and Control Groups

	NACRT	Surgery Alone	P
Total no. patients	18	30	
Pathological differentiation (well:mod:por:other)	5:11:1:1	8:16:2:4	n.s.
Stage I-III/IVa/IVb	10:8	13:17	n.s.
LN met positive:negative	6:12	18:12	n.s.
INF β:γ	12:6	27:3	n.s.
Ly 0/1:2/3	12:6	11:19	n.s.
V 0/1:2/3	15:3	14:16	0.0158
Ne 0/1:2/3	5:13	4:26	n.s.
Ch positive/negative	8:10	13:17	n.s.
Du positive/negative	10:8	12:18	n.s.
S positive/negative	12:15	16:25	n.s.
Rp positive/negative	7:11	18:12	n.s.
PV positive/negative	2:16	8:22	n.s.
A positive/negative	1:17	2:28	n.s.
PL positive/negative	3:15	11:19	n.s.
Radiological response			
Grade Ia:Ib:II	7:4:7	N/E	

Data are expressed as the median (range).

Mod indicates moderately; por, poorly; other, papillary/adenosquamous cell carcinoma; LN met, lymph node metastasis; INF, mode of histological infiltration; Ly, grade of infiltration of the lymphatic vessels; V, grade of venous infiltration; Ne, grade of perineural invasion; Ch, grade of invasion to intrapancreatic common bile duct; Du, grade of invasion to the duodenum; S, grade of invasion to the anterior capsule; Rp, grade of invasion of the retroperitoneal tissue; Pv, grade of invasion of the portal vein; A, grade of invasion of the large artery; PI, invasion of the extrapancreatic nerve plexus.

Comparisons of Surgical Results Between NACRT and Surgery-Alone Groups

The operative and tumor characteristics of all resected patients are listed in Tables 1 and 2. There were no significant differences in patient and operative characteristics between NACRT and surgery-alone groups. On comparison of tumor characteristics, significantly lower frequencies of lymph node metastasis, infiltration of lymphatic vessels, and venous infiltration in the NACRT group were found relative to those in the surgery-alone group ($P < 0.05$). Moreover, the frequency of pathologically curative resection (R0) in the NACRT group was significantly higher that that in the surgery-alone group (R0/1/2%, 52/15/33 vs 22/51/27; $P = 0.0040$). On abstracting R0/1 cases in NACRT and surgery-alone groups (Tables 3 and 4), although there was a tendency of a lower frequency of lymph node metastasis and infiltration of lymphatic vessels in the NACRT group relative to the surgery-alone group, a significant difference was not achieved. A significantly lower frequency of venous infiltration only was found in the NACRT group relative to the surgery-alone group ($P = 0.0158$). There was no difference in the survival curve of R2 cases between them.

Comparisons of OS and DFS Rates

All patients were followed up for at least 25 months without adjuvant chemotherapy. The median follow-up time after NACRT was 20.5 months (range, 3–84 months) for all patients and 56 months (range, 34–84 months) for censored patients. No

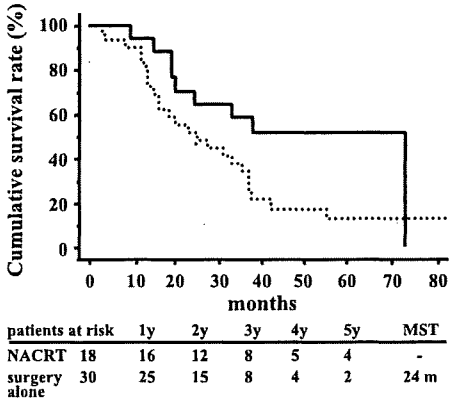

FIGURE 3. Overall survival rates in the NACRT and surgery-alone groups. Solid line indicates NACRT group; broken line, surgery-alone group. MST indicates median survival time.

treatment death occurred. Although the 1-, 3-, and 5-year OS rates in the NACRT group were 85%, 39%, and 34%, superior to 68%, 30%, and 9% in the surgery-alone group ($P = 0.0792$), there was no significant difference. The median survival time in the NACRT and surgery-alone groups was 24.5 and 18.5 months, respectively.

When patients who underwent curative resection (R0/1) were abstracted from all patients, there was a significant difference in the OS curve between the NACRT and surgery-alone groups (OS rates at 1 year, 3 years, and 5 years: 94%, 59%, and 52% in the NACRT group versus 83%, 34%, and 13% in the surgery-alone group; $P = 0.0425$; Fig. 3). The median survival time in the NACRT group was not reached, and in the surgery-alone group was 24 months. At a minimum of 36 months' follow-up, 8 patients in the NACRT group (44%) and 5 patients in the surgery-alone group (17%) were alive. Disease-free survival rates at 1 year, 3 years, and 5 years were 59%, 47%, and 47% in the NACRT group, significantly better than 53%, 12%, and 8% in the surgery-alone group (Fig. 4, $P = 0.0359$). Although the DFS rate at 1 year was similar, the difference in the DFS curve dramatically extended over 1 year after surgical resection. At the minimum follow-up of 25 months, 8 patients (44%) in the NACRT group and only 2 patients (7%) in the surgery-alone group were disease-free, and a significant difference was found between them ($P = 0.0024$). In the

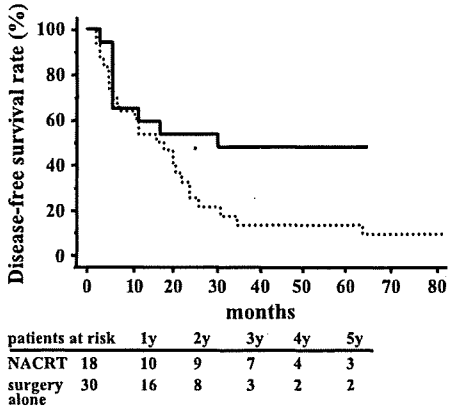

FIGURE 4. Disease-free survival rates in the NACRT and surgery-alone groups. Solid line indicates NACRT group; broken line, surgery-alone group.

NACRT group, all patients disease-free for more than 1 year have survived between 36 and 65 months.

There were no significant differences in OS and DFS rates between the use of GEM- and 5-FU–based chemoradiation. Moreover, there was no significant difference in survival curves between patients with R0 and R1 resection.

Type of Recurrence in Patients Who Underwent Curative Resection (R0/1)

The major pattern of recurrence was distant metastasis such as the liver and peritoneum (39%) in the NACRT and local recurrence (47%) as well as distant metastasis (43%) in the surgery-alone group. The frequency of local recurrence in the NACRT group was 11%, significantly lower than 47% in the surgery-alone group ($P = 0.0024$).

DISCUSSION

Even after curative resection, patients with pancreatic cancer face a 50% to 80% local recurrence rate and a 25% to 50% chance of developing distant metastases at the peritoneum and liver. The dreadful prognosis associated with this disease has mandated studies of combined multimodality therapies with both radiation and chemotherapy.[11,12] Crane et al[13] mentioned that NACRT had its own intrinsic advantages in that it theoretically increased the vulnerability of cancer cells because of intact vasculature, better tumor cell oxygenation, and the probability of sterilizing cells at the resection margin. Neoadjuvant CRT can clinically provide improved patient selection because patients with rapidly progressive systemic disease are identified as part of the restaging evaluation performed after NACRT before the planned surgery. Another advantage is better tolerability, which consecutively allows multimodal treatment in a higher number of patients, and the avoidance of late radiation-related toxicity. Furthermore, NACRT is able to facilitate resectability with free margins and a low frequency of lymph node metastasis. The Duke University group[14] reported that NACRT was associated with a marked reduction in the incidence of pancreatic leak, as well as leak-associated morbidity and mortality. On the other hand, Tse et al[15] referred to the theoretical disadvantages of potential overtreatment for a subset of patients with early-stage disease or with benign disease and of the potential risk of biliary stent–related morbidity.

Our previous study demonstrated that 5-FU/CDDP- or GEM-based CRT could reduce pain at a high rate without affecting Karnofsky performance status and body weight, resulting in acceptable toxicity.[7] Subsequently, we attempted to compare surgical results after NACRT in patients with pancreatic cancer that extended beyond the pancreas with patients who underwent surgery alone in this study. As a result, a lower frequency of lymph node metastasis and a higher frequency of pathologically curative resection were observed in the NACRT group. In patients who underwent curative resection, OS and DFS rates in the NACRT group were significantly longer than in the surgery-alone group. At a minimum follow-up of 25 months, the actual DFS rate in the NACRT group was 44%, significantly better than 7% in the surgery-alone group. Moreover, the frequency of local recurrence in the NACRT group was significantly less than in the surgery-alone group.

Neoadjuvant CRT ultimately leads to patient selection, as patients who show tumor progression during chemoradiation do not undergo surgery. As many as approximately 20% to 40% of patients initially presenting with resectable pancreatic tumors, but which had become unresectable at restaging evaluation, avoided unnecessary laparotomy.[7,16–22] In this article, 16% of PR and 31% of borderline resectable patients in the NACRT group were excluded from the subsequent surgical resection.

In general, the favorable prognostic factors for survival and recurrence in patients with pancreatic cancer have been reported as curative resection and negative lymph node metastasis.[4,5] The quality of surgery and examination of the pathological specimens can vary. Raut et al[23] proposed the term *SMA margin*, which indicates perivascular soft tissue, primarily perineural and mesenteric tissue, adjacent to (and posterior to) the right lateral border of the proximal SMA. In pancreatic cancer, the retroperitoneal margin is very close and often positive. It seems reasonable to conclude that locoregional therapy in pancreatic cancer can be optimized with complete gross tumor resection and treatment of microscopic disease at the SMA margin with chemoradiation. Factors that define resectability include the surgeon's opinion on the necessity of venous or arterial resection and whether high-risk margins for tumor resection are acceptable. In this study, our surgical indication included not only "potentially resectable" but also "borderline resectable," defined by NCCN,[9] and subsequently, we allowed R2 resection in this study. We performed aggressive pancreatectomy with portal vein or CA resection in some cases in which resection had been predicted to generate surgical-free margins. During this study, surgical indication was fixed, and 2 experienced surgeons performed all resections. Two pathologists closely examined pathological specimens of the dependently removed surgical stump of perineural and retroperitoneal fat tissues between the pancreatic parenchyma and the SMA or CA under surgical exposition of the right-sided adventitia of the proximal SMA and CA. Some authors reported that the frequency of pathologically curative resection (R0) after NACRT was 60% to 90%,[7,16,17,19–23] which was similar to our results of 52% (69% in PR and 27% in borderline resectable cases). It has been reported that the frequency of negative lymph node metastasis after NACRT and surgical resection was 40% to 80%, lower than after surgery alone.[7,16,17,19,21,22] In this experience, 59% negative lymph node metastasis in the NACRT group was significantly higher than 32% in the surgery-alone group. Better patient selection and the direct effect of chemoradiation in the NACRT group are able to facilitate resectability with free margins and a low frequency of lymph node metastasis. On the other hand, 20 (29%) of 68 resected patients had R2 residual tumor staging. There were no differences in survival analysis between R2 surgery in the NACRT and surgery-alone groups. Although it is difficult to interpret the results in a small population, surgical results in R2 cases after NACRT were disappointing.

Previous studies have shown that surgery alone yielded local recurrence rates of 50% to 80%, whereas preoperative chemoradiation reduced local failure rates to 5% to 13%.[7,17,20–22,24] The low local recurrence rate (11%) in the NACRT group at a minimum follow-up of 25 months was encouraging and was similar to previous reports.[7,17,21,22] Interestingly, there was a similar DFS rate within 1 year in the NACRT and surgery-alone groups with the absence of adjuvant chemotherapy, but a significant difference of the DFS curve over 1 year was observed among those who underwent curative resection. When all observed patients were followed up for 2 years, 44% of patients in the NACRT group were disease-free, significantly better than 7% in the surgery-alone group. All surviving patients in the NACRT group have been disease-free with a range of follow-up of 36 and 65 months, and the median survival time in the NACRT group was not reached. Over time, the difference in the DFS curve was clearly extended. It is important to note that all patients did not undergo adjuvant

chemotherapy, but patients with recurrent disease underwent weekly GEM administration on recurrence.

The median survival time in 5-FU–based neoadjuvant trials ranged from 15.7 to 45 months, which compares favorably with the survival rate of patients in the observation arms of previous randomized adjuvant trials (range, 11–19 months),[25,26] and is similar to that of the treatment arms of randomized adjuvant trials (range, 20–44 months).[25,27,28] The M.D. Anderson Cancer Center group[29] reported favorable results that the median survival time in GEM-based chemoradiation was 33 months, and most patients were noted to have greater than 50% nonviable tumor cells in the specimen, and 2 pathological complete responses were noted. Moreover, a phase II trial of neoadjuvant GEM (400 mg/m^2) with concurrent radiation of 30 Gy showed that 61 (73%) of 71 patients underwent surgical resection, and the median survival time was 36 months at 2 years' follow-up.[30] A phase II multi-institutional trial of NACRT using full-dose GEM conducted at the University of Michigan[16] demonstrated that 17 of 20 patients underwent surgical resection with 94% R0 grading, and the median survival time and 2-year OS rate were 26 months and 61%, respectively, after a median follow-up of 18 months. Thus, some studies of NACRT have demonstrated favorable outcomes compared with similar series of patients treated with surgery alone; however, the efficacy results must be interpreted with caution because the reports of NACRT for pancreatic cancer are heterogeneous with regard to patient population, treatment methods, modalities, and limited accrual. The University of Liverpool group[27,31] criticized that some studies using NACRT resulted in a median survival time of 9 to 39 months, and the largest comparative study found that neither the survival nor the pattern of disease recurrence was significantly different between neoadjuvant and adjuvant therapy. There have been no randomized controlled trials of neoadjuvant therapy despite the positive outcomes of single-institutional series of neoadjuvant therapy. New trials are being developed to address the neoadjuvant therapy question.[32,33] Brunner et al[32] initiated a multicenter prospectively randomized phase II study that aimed to answer the question of whether NACRT with GEM and CDDP can prolong the OS of patients with ductal adenocarcinoma of the pancreatic head in comparison with primary resected patients.

Chemoradiation therapy followed by curative resection seems to improve survival in patients with pancreatic cancer that extended beyond the pancreas in this study; however, several questions remain controversial: Should therapy be given preoperatively or postoperatively? Which chemoagent with external radiation has the high efficacy to induce tumor cell necrosis? How long is needed? How much radiation and chemotherapy should be used? More effective and less toxic regimens are necessary for neoadjuvant therapy to realize the ultimate goal of maximizing the number of patients who receive curative resection with less frequent metastatic lymph nodes, resulting in 50% or more 5-year survival rates.

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CASE REPORT

Transcatheter coil embolization of an aneurysm of an anomalous splenic artery: Usefulness of double microcatheter method

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Abstract

Transcatheter embolization using two microcatheters of different shapes was performed to treat a 34-mm-diameter aneurysm that was located near the origin of a splenic artery that originated from the superior mesenteric artery (SMA). The procedure resulted in complete packing of the aneurysm and preserving splenic arterial blood flow.

Key words: *Aneurysm, splenic artery, anomaly, embolization, coils*

Introduction

Aneurysms of the splenic artery are the most common splanchnic aneurysms. However, aneurysms of a splenic artery with an anomalous origin from the superior mesenteric artery (SMA) are rare (1–11). Only 14 such cases were identified during a literature search of English-language reports. Of these 14 cases, only two cases were treated with interventional technique (1,2).

Case report

The patient was a 45-year-old male hepatitis B carrier. The patient had annual abdominal ultrasound examinations for the past five years. The most recent ultrasound showed an aneurysm that was located posterior to the pancreatic head. Reconstructed three-dimensional images (Figure 1) based on contrast-medium-enhanced computed tomographic scans obtained by 16-detector CT (Siemens, Erelangen, Germany) showed that the splenic artery had an anomalous origin from the SMA, and that a saccular dilatation of the splenic artery was located 2 mm distal to the origin. A diagnosis of a splenic artery aneurysm was made. The splenic artery aneurysm was 34 mm in diameter and had an aneurysmal neck diameter of 8 mm. No calcification was seen in the wall. Since the patient had been undergoing annual abdominal ultrasound examinations, and this was the first time that an arterial aneurysm had been identified, this implied that the aneurysm had enlarged rapidly. Given this, and that the diameter of the aneurysm was > 30 mm, and that the aneurysmal wall had no calcification, it was concluded that treatment was absolutely indicated. After discussion with a vascular surgeon and an interventional radiologist, percutaneous embolization was selected as the treatment of choice. The procedure was performed after written informed consent was obtained from the patient.

First, a Cobra guiding catheter with an inner diameter of 0.081 inches and an outer diameter of 7 French (Mach 1, Boston Scientific, Watertown, MA, USA) was inserted into the ostium of the SMA via the right femoral artery, and arteriography was performed (Figure 2). Two 2.5 French microcatheters (Renegade-18, Boston Scientific) were then prepared; steam was used to shape one of the microcatheters whose tip was bent to an angle of 60°. The straight microcatheter and the microcatheter bent to an angle of 60° were inserted through the guiding catheter to different sites in the aneurysm (Figure 3). Twenty detachable 30-cm long microcoils (Cook Inc., Bloomington, IN, USA) were

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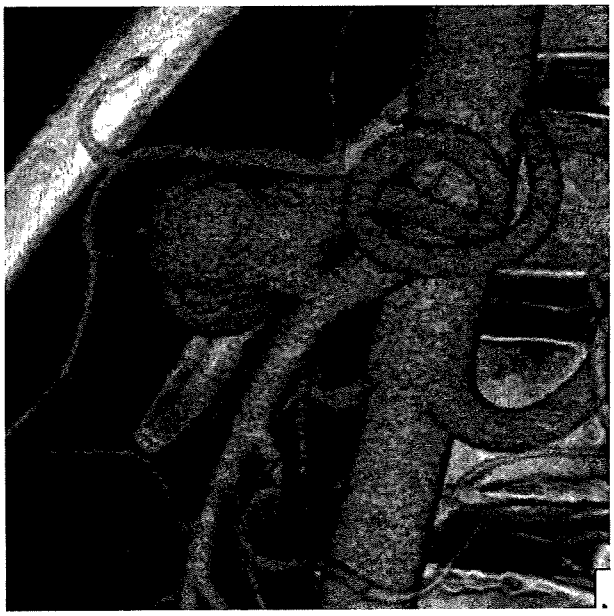

Figure 1. Three-dimensional reconstructed image based on contrast medium-enhanced computed tomographic scans obtained using a 16-detector CT. The splenic artery originating from the SMA and a saccular aneurysm in the splenic artery immediately distal to the origin can be seen.

Figure 2. Left anterior oblique view (45°) obtained during the superior mesenteric arteriogram. A broad-necked arterial aneurysm is seen in the splenic artery, whose origin is the SMA.

inserted using one of the microcatheters. At the time of the insertion of the 21st detachable 30-cm long microcoil, this coil was seen in the main splenic artery. Then the coils were seen in the main splenic artery, the insertion of coils from this microcatheter was stopped, and the detachable coils (6 25-cm-long microcoils; and

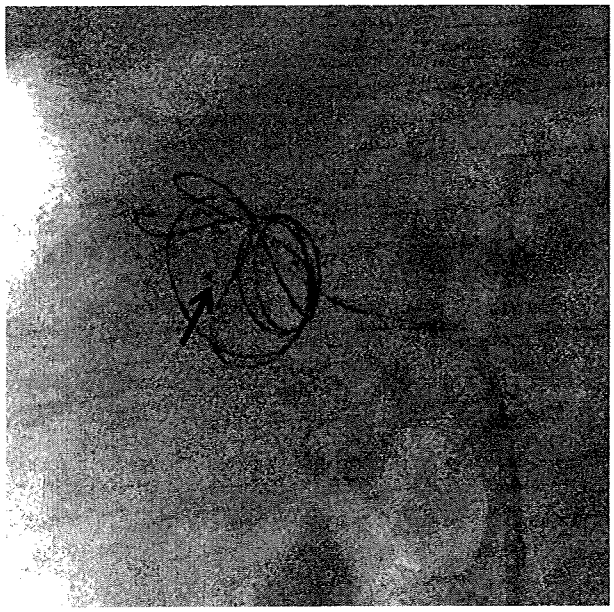

Figure 3. Intraoperative plain X-ray. Two microcatheters have been inserted to different locations in the aneurysm. Detachable coils are being inserted using one of the catheters, while the tip of the other microcatheter can be seen in the aneurysm (→).

10 20-cm long microcoils) were then inserted using the other microcatheter. In this manner, the entire arterial aneurysm was packed. Finally, the two microcatheters were removed, and arteriography was performed using the guiding catheter, which remained in the SMA. On arteriography, no contrast medium flowed into the aneurysm, and the blood flow in the SMA and splenic artery was found to be preserved. Therefore, the procedure was completed (Figure 4). The following microcoils were used: 24 detachable 30-cm long microcoils; six 25-cm-long microcoils; and ten 20-cm long microcoils. The patient had no complications after the procedure, such as pain or fever, and was discharged on the next day. Plain abdominal X-ray examination performed three months after the embolization procedure showed no change in the location of the coils and no coil compaction (Figure 5). Contrast CT performed three months after embolization showed that the main splenic artery was patent; no findings indicative of splenic infarction were noted (Figure 6).

Discussion

Reports of arterial aneurysms occurring in a splenic artery originating from the SMA are very rare (1–11). Only 14 such cases were identified on a literature search of English-language reports. The reported treatment methods used in these 14 cases included:

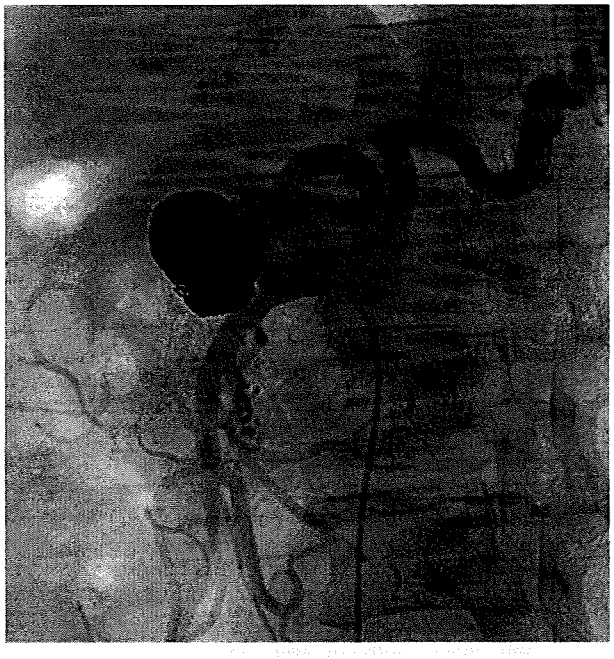

Figure 4. Postoperative superior mesenteric arteriogram. The inside of the aneurysm is completely packed with microcoils; blood flow in the main splenic artery is maintained.

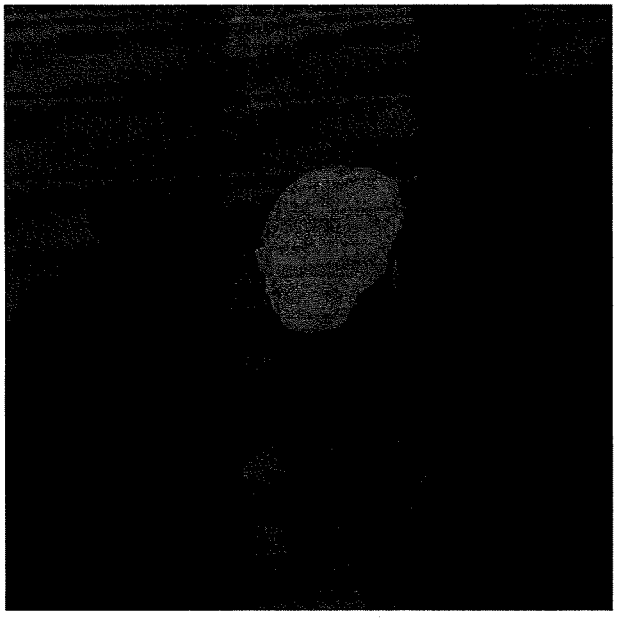

Figure 5. Plain abdominal X-ray, frontal view, obtained three months after embolization. No coil migration or compaction is seen.

Surgical treatment in 11 cases (2–6, 8–11); transcatheter coil packing of the arterial aneurysm combined with laparoscopic splenic arterial ligation in two cases (7); and coil embolization alone in two cases (1,2). Of the two cases in which coil embolization alone was done, the procedure involved packing alone in one case (1), and packing and isolation in the other case (2). In

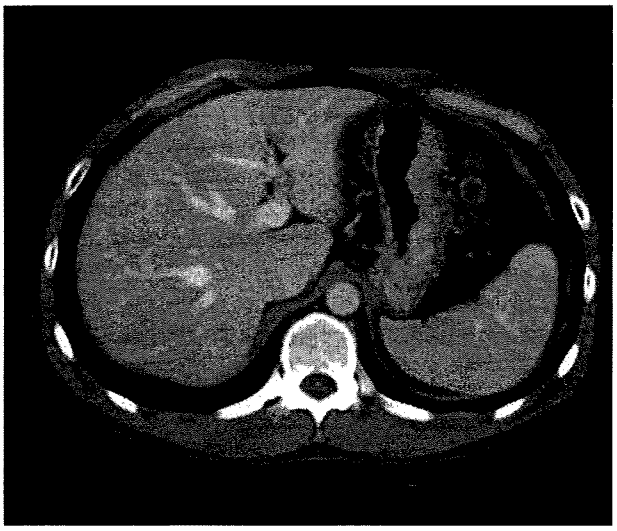

Figure 6. Contrast abdominal CT done three months after embolization. There is no evidence of splenic infarction.

the case reported by Sato, in which packing alone was used, the neck of the aneurysm was narrow, the diameter of the aneurysm was 25 × 23 mm, and the distance from the origin of the artery to the aneurysm was short, as in our case. In the case reported by Migliara et al., in which both packing and isolation were used, the distance from the origin of the splenic artery to the aneurysm was relatively long (25 mm); after packing had been performed within the aneurysm, additional coil embolization was performed in the main splenic artery at the center of the aneurysm and distal to the aneurysm.

In the present case, the distance from the origin of the splenic artery to the aneurysm was short (2 mm), and blood flow through the SMA was preserved. Therefore, it was thought that aneurysm isolation or the placement of a cover stent in the main splenic artery where the aneurysm was located would be difficult. However, since the aneurysm was saccular and had a neck diameter of 8 mm, it was determined that it would be possible to perform coil packing and preserve splenic artery blood flow.

Since the diameter of the aneurysm in the present case was 34 mm, which was larger than the aneurysm diameters in the two cases previously reported and described above, in order to ensure that packing was uniform throughout the entire aneurysm, coil packing was done using two catheters with tips of different shapes. If only a single microcatheter had been used to insert a large number of coils, the coils would have escaped into the parent vessel before aneurysm packing could have been completed. Therefore, two microcatheters with tips of different shapes were inserted through the parent catheter to different aneurysm sites. Then, coils were inserted from one of these

microcatheters. When it appeared that coils were about to escape into the main splenic artery, coil embolization was continued using the other microcatheter. This enabled the aneurysm to be sufficiently packed with coils without coils escaping into the main splenic artery.

In conclusion, coil embolization using two microcatheters with different tip shapes was done to treat a very large, 34-mm-diameter, arterial aneurysm that was located in a splenic artery originating from the SMA. The procedure allowed the aneurysm to be successfully packed while preserving splenic arterial blood flow.

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TECHNICAL NOTE

Development of a New Subclavian Arterial Infusion Chemotherapy Method for Locally or Recurrent Advanced Breast Cancer Using an Implanted Catheter–Port System After Redistribution of Arterial Tumor Supply

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Abstract Locally or recurrent advanced breast cancers can receive arterial blood supply from various arteries, such as the internal thoracic artery (ITA), the lateral thoracic artery, and the other small arterial branches originating from the subclavian artery. Failure to catheterize and subsequent formation of collateral arterial blood supply from various arteries are some of the reasons why the response to conventional selective transarterial infusion chemotherapy is limited and variable. To overcome this problem, we developed a new subclavian arterial infusion chemotherapy method using an implanted catheter–port system after redistribution of arterial tumor blood supply by embolizing the ITA. We named this technique ("redistributed subclavian arterial infusion chemotherapy" (RESAIC)). Using RESAIC, patients can be treated on an outpatient basis for extended periods of time. Eleven patients underwent RESAIC, and the complete remission and partial response rate in 10 evaluable patients was 90%: complete remission [CR] $n = 4$, partial remission $n = 4$, stable disease $n = 1$, and not evaluable $n = 1$. Three of four patients with CR had no distant metastasis, and modified radical mastectomy was performed 1 month after conclusion of RESAIC. The resected specimens showed no residual cancer cells, and pathologically confirmed complete remission was diagnosed in each of these cases. Although temporary grade-3 myelosuppression was seen in three patients who were previously treated by systemic chemotherapy, there was no other drug-induced toxicity or procedure-related complications. RESAIC produced a better response and showed no major complications compared with other studies despite the advanced stage of the cancers.

Keywords Interventional Radiology · Breast cancer · Arterial infusion chemotherapy · Implanted port

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Introduction

Locally or recurrent advanced breast cancers (ABC) are defined as large tumors with extensive regional lymph node involvement or direct invasion of the skin or underlying chest wall [1]. These cancers are considered stages IIIa and IIIb according to the tumor-node-metastasis classification system adopted by the Japanese Breast Cancer Society, which is based on the classification system of the International Union Against Cancer [2]. Inflammatory breast cancer showing extensive histologic infiltration of dermal lymphatics is a distinct subset.

Some previous reports showed that arterial infusion chemotherapy (AIC) was effective for ABC [3–5]. The local response rate was reported to be 70–90%, and rapid tumor regression was seen after the treatment [6–10]. However, problems associated with AIC should be resolved as will be described later. Conventionally in AIC procedures, the chemotherapeutic agents are selectively infused into subclavian and axillary branches supplying the tumor. This procedure is technically complicated and is usually repeated multiple times in each patient. In addition, such repeated infusions cause drug-induced damage to the infused arterial branches, and this promotes the development of collateral arterial blood supply [11, 12]. Therefore, the number of possible repetitions of AIC is limited, and long-term local control is not expected. To overcome this problem, we developed a new subclavian arterial infusion chemotherapy method using an implanted catheter–port system (CPS) after redistribution of the arterial blood supply to the tumor. The arterial redistribution was achieved by embolizing the internal thoracic artery (ITA) using a mixture of N-butyl cyanoacrylate (NBCA; B. Braun, Melsungen, Germany) and iodized oil (LPD) (Lipiodol Ultra-Fluide; Terumo, Tokyo, Japan) [13, 14]. Using this drug-delivery system, patients can be treated on an outpatient basis for extended periods of time. We believe that this new technique, named "redistributed subclavian arterial infusion chemotherapy" (RESAIC), is an epoch-making treatment method that, to the best of our knowledge, has not been reported previously. This study was an initial pilot study evaluating the effectiveness and safety of RESAIC.

Patients and Methods

Patients with ABC whose tumors were resistant to standard systemic chemotherapy or who were physically unable to tolerate systemic chemotherapy were the subjects of this study. In addition, patients >70 years of age with no previous treatment were also included. Eligibility criteria included histologically confirmed carcinoma of the breast, a life expectancy >2 months, World Health Organization performance status <3, adequate bone marrow reserve (white blood cell count >2500/ml, platelet count >50,000/ml), satisfactory renal and liver function (total bilirubin and creatinine <1.25 times the upper normal limits), and normal cardiac function by electrocardiogram (ECG). Any previous systemic chemotherapy except trastuzumab (Herceptin; Chugai, Japan) was discontinued for at least 4 weeks before protocol entry. Trastuzumab was continued to inhibit the development of distant metastases. Eleven patients were entered into this study between April 2006 and December 2007. All patients were female and had diagnosed stage IIIb or IV disease. A 52-year-old woman who had severe anemia (hemoglobin 5.6 g/dl) caused by bleeding from the primary tumor was entered because she was considered unable to tolerate standard systemic chemotherapy. All patients gave informed consent to participate in the trial. Table 1 shows demographics of the participating patients. The patients' ages ranged from 39 to 82 years (median of 61).

All patients were histologically diagnosed as having invasive ductal carcinoma, and one of the patients showed

Table 1 Patient's characteristics

Patient no.	Age	Tumor	Neoadjuvant or resistant	Stage	Distal metastasis	Symptom	Pathology	ER	PgR	Her2
1	58	Primary	Resistant	IV	Lung, liver	Pain	IDC/scirrhous carcinoma	+	+	1+
2	39	Primary	Resistant	IV	Lung, bone	Pain, ulcer, bleeding	IDC/papillo-tubular carcinoma	−	−	−
3	51	Recurrence	Resistant	IV	Lung, bone	Pain, ulcer, bleeding	IDC/scirrhous carcinoma	+	+	2+
4	52	Primary	Neoadjuvant	IIIb	−	Pain, bleeding, effusion	IDC	−	−	2+
5	72	Primary	Resistant	IIIb	−	Pain, ulcer, effusion	IDC	+	+	−
6	61	Recurrence	Resistant	IV	Liver	Pain, ulcer, effusion, arm edema	IDC/solid-tubular carcinoma	+	−	−
7	81	Primary	Neoadjuvant	IIIb	−	Pain, ulcer, effusion, arm edema	IDC	−	−	2+
8	78	Recurrence	Resistant	IIIb	−	Pain, erosion, induration	IDC (inflammatory breast cancer)	−	−	2+
9	70	Primary	Neoadjuvant	IV	Lung, bone	Pain, ulcer, bleeding, arm edema	IDC/scirrhous carcinoma	+	+	2+
10	82	Recurrence	Resistant	IV	Lung, liver	Pain, bleeding	IDC/solid-tubular carcinoma	+	−	−
11	52	Primary	Resistant	IV	Lung, liver, brain	Pain, bleeding, abscess formation	IDC/solid-tubular carcinoma	−	−	3+

IDC invasive ductal carcinoma