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CLINICAL INVESTIGATION

Transcatheter Arterial Chemoembolization (TACE) or Embolization (TAE) for Symptomatic Bone Metastases as a Palliative Treatment

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Abstract
Purpose This study was designed to evaluate the effect of transcatheter arterial chemoembolization (TACE)/embolization (TAE) for symptomatic bone metastases especially in palliation.
Methods Between April 2006 and December 2009, 24 bone metastatic lesions of 18 patients (8 women and 10 men; mean age, 64 years) underwent palliative TACE or TAE. A total of 40 sessions were performed, with 1–4 sessions per lesion. The primary lesions included hepatocellular carcinoma, colorectal cancer, renal cell cancer, ovarian cancer, thyroid cancer, uterine cervical cancer, and esophageal cancer. Symptomatic lesions involved thoracic spine, lumbar spine, pelvis, rib, and femur. The procedures were performed with a coaxial catheter technique to catheterize selectively target arteries. If not possible due to small branches, blood flow alteration by coil was achieved. Gelatin sponge was the initial embolic materials. As anticancer agents, epirubicin, fluorouracil, and mitomycin were mainly used in consideration for primary lesion and past treatment.
Results Sufficient devascularization of targeted lesions was obtained in 18 of 24 (75%) lesions without any serious complication. Pain relief was obtained in 20 lesions (83%), with significantly decrease in the visual analogue scale score ($P < 0.001$). A relationship was found between the devascularization grade and pain relief ($r = 0.49$, $P < 0.05$). Follow-up CT images at 1 month of nine lesions (50%) revealed necrotic change in the tumors.
Conclusions Palliative TACE/TAE for symptomatic bone metastases could be a suitable treatment method because it is minimally invasive, repeatable, effective, and rapid-acting.

Keywords Bone metastases · Transcatheter arterial chemoembolization · Transcatheter arterial embolization · Blood flow alteration · Pain relief · Devascularization

Introduction

Metastatic bone tumors are a major cause of morbidity, resulting in pain, decreased mobility, and pathologic fracture [1–3]. Treatments for bone metastasis include surgery, radiation therapy, radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), transcatheter arterial embolization (TAE), cement augmentation procedures, such as percutaneous vertebroplasty and kyphoplasty, strontium-89, systemic chemotherapy or hormonal therapy as well as bisphosphonates. The choice of the treatment usually depends on the localization, number, and size of the metastatic lesions. In addition, it is likely to change by the condition of the patient, the stage of disease, and the situation of facilities.

TAE of metastatic bone tumors has a broad range of indications, from curative treatment to palliation. Above all, preoperative TAE has been widely accepted to reduce bleeding during surgery [2–4]. However, curative or palliative TACE/TAE has not been established yet. Although a few literatures were published about palliative TAE [5–7], no large series has been investigated the clinical outcomes or described current technical aspects.

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Compared with radiation therapy with dose limitation, TAE is possible for additional treatment when necessary. In addition, compared with surgery, TAE is minimally invasive and can enter the therapeutic choice for multifocal pain due to multiple bone metastases. Thus, if the safety and the effectiveness of TAE are guaranteed, it is necessary to give priority to curative or palliative TAE as choices of the bone metastasis treatment. The purpose of this study was to evaluate the effect of TACE/TAE for symptomatic bone metastases, especially in palliation.

Materials and Methods

This single-center, retrospective study received our institutional ethical review board. All patients gave a written, informed consent. Between April 2006 and December 2009, 24 bone metastatic lesions of 18 patients (8 women and 10 men; mean age, 64 (range, 45–84) years underwent TACE or TAE as a palliative treatment. The primary lesions included hepatocellular carcinoma (HCC) in seven, colorectal cancer in three, renal cell cancer (RCC) in three, ovarian cancer in two, and thyroid cancer, uterine cervical cancer, esophageal cancer in one patient each. In patients with multiple metastatic lesions, not all lesions but only the lesions with analgesic-resistant pain ($n = 24$) and neurologic deficit ($n = 11$) were targeted. Symptomatic lesions involved thoracic spine in 11, lumbar spine in 3, pelvis in 8, and rib and femur in 1 each.

Each lesion showed hypervascular in the preprocedual contrast-enhanced CT images and was a candidate for TACE/TAE. The indications of TAE or TACE were postradiation in 11, emergency because of progressive neurologic deficit in 4, and anticipation of radiation therapy in 9. Of the 11 lesions with postradiation, the period from radiation therapy to TACE was for an average of 19 months (range, 1 month to 9 years). Table 1 summarized the patients' characters.

The procedures were performed from a common femoral approach. A diagnostic arteriogram defined the arterial anatomy of the region. A 4-Fr catheter was used in conjunction with a coaxially placed 2.0- to 2.2-Fr microcatheter to selectively catheterize target arteries supplying metastases. When a portion of the lesion's blood supply originated from small branches that could not be selectively catheterized, to avoid TACE in nontarget region, such as skin and muscles, blood flow alteration was achieved by coil embolization at distal side of the arteries beforehand (Figs. 1, 2).

The target arteries were internal iliac a., intercostal a., lumbar a., iliolumbar a., lateral sacral a., superior gluteal a., median sacral a., inferior epigastric a., internal mammary a., thyrocervical trunk, and lateral and medial circumflex femoral a.

Basically, anti-cancer agents were scheduled to be used for TAE/TACE. As a key drug, epirubicin was chosen for the lesions from HCC and esophageal ca, and both fluorouracil and mitomycin were chosen for the lesions from colorectal ca, ovarian ca, and uterine cervical ca. The total dose divided into the different arteries feeding the metastasis according to the volume of the tumor bed. TAE, just embolized without anti-cancer agent, was performed for the lesions from renal cell carcinoma or thyroid cancer in which there is generally no effective agent. Furthermore, anti-cancer agent was not used in the case that had the bone-marrow suppression.

As the initial embolic materials, gelatin sponge particles with sizes of 1-mm sliced by hand were used in each case. Additional coil embolization was performed in 11 lesions that seemed to be difficult to repeat TACE/TAE because of the poor general condition. N-butyl cyanoacrylate (NBCA) was used secondarily in three procedures of two cases in state with coagulation abnormality. The goal of embolization was the disappearance of tumor stain or stagnation of the target artery's flow.

TAE or TACE was repeated on an as-needed basis. A total of 40 sessions were performed, with 1–4 sessions per lesion.

Evaluate items in this study were as follows: technical success, complications, pain relief, improvement of neurological deficits, and early tumor response at 1 month of CT images.

Technical success reflected immediate results and was typically evaluated with completion angiography. Each lesion was angiographically categorized on the basis of devascularization grade, as in previous studies [2, 4]. Grade 1 was >75% reduction of tumor blush; grade 2, 50–75% reduction of tumor blush; and grade 3, <50% reduction of tumor blush. Complications of treatment were categorized on the basis of the Society of Interventional Radiology [8].

The degree of pain was assessed as follows. Fifteen lesions were assessed by the visual analogue scale (VAS) score at 1 day before TACE and at 1–7 days after TACE. The best score of the 7 days was used as the score of postprocedure. Remaining nine lesions in which the VAS scores were not available were assessed by the subjective reports of pain. In addition, the use of analgesics also was assessed. Complete pain relief was defined as the complete freedom from pain without analgesics. Partial relief was defined as the status with improved pain, but still analgesic need. No relief was defined as the status with unchanged pain or progressive pain. The time to pain relief also was recorded.

Differences in the VAS score of preprocedure and postprocedure were analyzed by two-sided Wilcoxon's

Table 1 Characteristics

Lesion no.	Age (yr)	Sex	Primary lesion	Target site	Neurological deficit	Indication
1	70	F	RCC	Pelvis	Vesicorectal disturbance	Pre-RT
2	70	F	Thyroid cancer	Pelvis		Post-RT, 8 yr
3	70	M	HCC	Pelvis		Pre-RT
4	60	M	HCC	Th3-5		Post-RT, 4 yr
5	60	M	HCC[a]	Pelvis	Right lower numbness	Pre-RT
6	60	M	HCC[a]	5th rib		Pre-RT
7	60	M	HCC[a]	Th1		Pre-RT
8	60	M	HCC[a]	Th12		Pre-RT
9	60	M	HCC[a]	Femur		Pre-RT
10	80	M	HCC	Th1	Left upper numbness	Emergency
11	80	M	HCC[b]	Th1	Left upper numbness	Post-RT, 3 mo
12	40	F	Ovarian cancer	Pelvis		Post-RT, 2 yr
13	50	M	Colon cancer	Th6		Post-RT, 3 mo
14	50	M	Colon cancer[c]	Th5-7	Paralysis, paresthesia	Post-RT, 18 mo
15	60	F	Colon cancer	L2		Post-RT, 3 mo
16	60	M	Esophageal cancer	L1		Post-RT, 4 mo
17	70	F	HCC	Th12-L1		Post-RT, 7 mo
18	50	M	Rectal cancer	Pelvis	Numbness	Post-RT, 6 mo
19	50	F	RCC	Th5	Paralysis, paresthesia	Post-RT, 1 mo
20	60	F	Uterine cancer	Pelvis		Pre-RT
21	60	M	HCC	Pelvis	Numbness	Pre-RT
22	40	F	Ovarian cancer	Th4-L2	Vesicorectal disturbance	Emergency
23	50	M	RCC	Th6/11	Paralysis	Emergency
24	60	M	HCC	Th5	Paralysis, paresthesia	Emergency

[a] Lesions were of the same patient

[b] Lesion was recurrence of the lesion 10

[c] Lesion was recurrence of the lesion 13

Emergency TACE or TAE was performed immediately before radiation therapy, *Pre-RT* TACE or TAE was performed before radiation therapy, *Post-RT* radiation therapy was performed at the region previously, *HCC* hepatocellular carcinoma, *L* lumbar spine, *RCC* renal cell carcinoma, *Th* thoracic spine

signed-rank test. Spearman's rank correlation test was calculated to assess the correlation between the devascularization grade and the pain relief. Differences with $P < 0.05$ were considered significant.

Results

Table 2 summarizes the procedures. Table 3 summarizes clinical response and follow-up.

Technical Success

Initial diagnostic angiograms confirmed the hypervascularity of the bone tumors in all lesions. Sufficient devascularization of targeted lesions as grade 1 was obtained angiographically in 18 lesions (75%). Devascularization was insufficient as grade 2 and 3 in six lesions (25%): because the common blood supply was involved in anterior spinal artery in 5 (lesions 13, 14, 15, 17, and 19), and because of cessation by severe local pain when TACE with mitomycin was performed for the pelvic lesion from rectal cancer in 1 (lesion 18).

Complications

No serious complications, including nerve injury, skin necrosis, muscle abscess, or death, were seen in any case. Local pain was seen as class C in 3 sessions of 2 lesions because of TAE with NBCA (lesion 2, 11), and as class B in 1 session because of TACE with mitomycin C (lesion 18).

Clinical Response

The mean VAS scores of preprocedure and postprocedure were 5.8 and 1.3, respectively. The VAS score was significantly decreased by TACE/TAE ($P < 0.001$). Improvement in VAS score was seen in 13 lesions (87%) and the

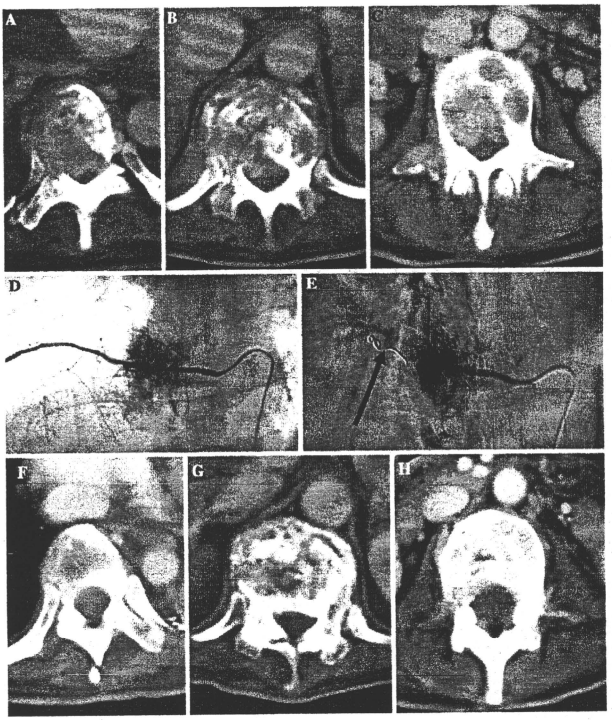

Fig. 1 A 45-year-old woman with the paralysis, paresthesia, and numbness of the lower limbs due to multiple spinal metastases from ovarian cancer (lesion 22). **A–C** CT images revealed a lot of osteolytic changes and invasion into the spinal canal at several levels. **D** In the selective arteriography of the right eighth intercostal artery, tumor stain that corresponds to the spinal metastasis can be seen. **E** The arrowhead pointed microcoils, by which the distal side of the artery was embolized to prevent chemotherapeutic agent perfusion or embolization of the skin and the muscles (blood flow alteration). Then, TACE using cisplatin and the gelatin sponge particles was performed to achieve adequate stasis of the artery (angiography was not performed after TACE). **F–H** CT images after four sessions of TACE revealed the sclerotic changes in the lesions and decrease in size. Paralysis and the paresthesia were improved

change was 4.7 (range, 1–10). The mean time to pain relief was 1.6 (range, 1–5) days. Of the nine lesions in which VAS score was not available, remarkable pain relief was obtained in seven lesions (78%) and the mean time to pain relief was 1.4 (range, 1–3) days. Decrease in analgesic use was seen in 12 lesions (50%). Overall, clinical response was obtained in 20 lesions (83%), and the mean time to pain relief was 1.5 days.

Of the 11 cases with neurologic deficit, a remarkable improvement was seen in 6 (55%). There were at least four cases in which the patients became ambulatory or were able to get into a sitting position again—in other words, had marked improvement of daily activities.

In 18 lesions, CT images at 1 month after TAE were evaluated. Noted necrosis within the tumor or decrease of tumor size was seen in nine lesions (50%).

Table 4 summarizes the devascularization grade as related to the pain relief. A relationship was found between the devascularization grade and the pain relief ($r = 0.49$; $P < 0.05$).

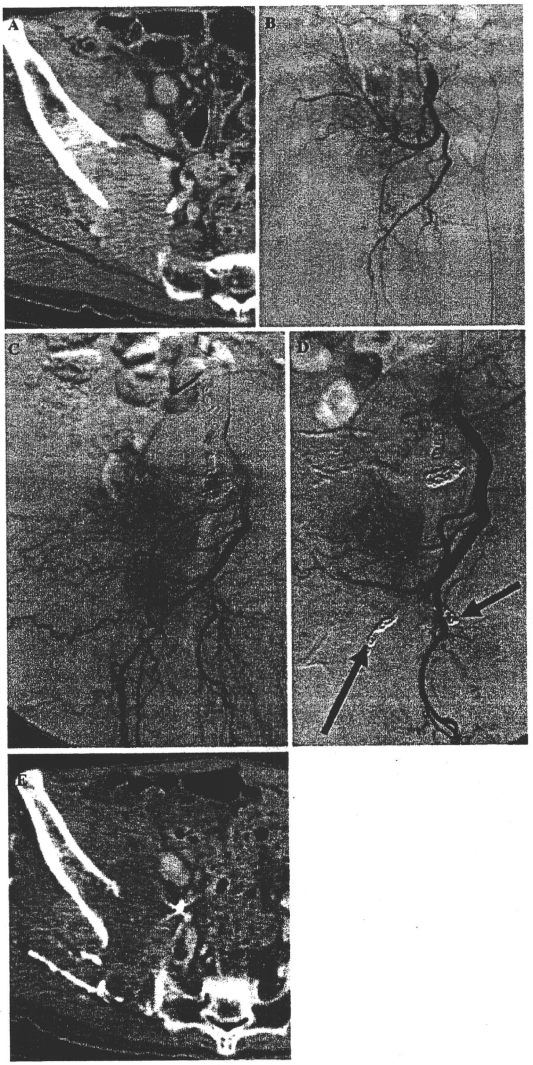

Fig. 2 A 64-year-old man who has pain and paresthesia of the right lower leg due to a pelvic metastasis from HCC (**A**) (lesion 21). Angiography of the right internal iliac artery revealed the stain corresponding to the lesion (**B**). The right superior gluteal artery, the right iliolumbar artery, and right fourth lumbar artery were selectively catheterized respectively and TACE was performed. In addition, the distal sides of branches of right internal iliac artery were embolized using microcoils (**C**, **D**: arrowheads) for blood flow alteration and TACE was performed to achieve adequate stasis of the artery (angiography was not performed after TACE). CT image after two sessions of TACE revealed the necrosis of the lesion (**E**). The pain was relieved, and he became free from the analgesics. Paresthesia of lower limb also was relieved

Table 2 Procedure, technical success and complications

Lesion no.	No. of sessions	Blood flow alteration	Anticancer agent	NBCA	Coil	Devascularization grade	Complication, grade
1	1	+	5-FU 1000 mg, MMC 20 mg			1	
2	3	+	None	+	+	1	Pain, C
3	1	+	EPIR 50 mg			1	
4	2		EPIR 40 mg			1	
5	1	+	EPIR 40 mg		+	1	
6	2		EPIR 60 mg		+	1	
7	1		None		+	1	
8	2	+	CDDP 50 mg		+	1	
9	1	+	None			1	
10	1		None		+	1	
11	1		None		+	1	
12	3	+	5-FU 1000 mg, MMC 10 mg			1	
13	1		5-FU 1000 mg, MMC 20 mg			2	
14	1		MMC 8 mg, EPIR 20 mg		+	2	
15	1	+	EPIR 40 mg		+	2	
16	1	+	EPIR 40 mg		+	1	
17	1	+	EPIR 30 mg, 5FU 750 mg		+	2	
18	1	+	5-FU 1000 mg, MMC 15 mg			2	Pain, B
19	1		None			3	
20	4	+	5-FU 1000 mg, CDDP 70 mg, MMC 10 mg		+	1	
21	2	+	EPIR 40 mg	+	+	1	Pain, C
22	4	+	5-FU 1500 mg, CDDP 120 mg			1	
23	3	+	None			1	
24	1	+	EPIR 40 mg			1	

CDDP cisplatin, *EPIR* epirubicin, *MMC* mitomycin C, *5-FU* 5-fluorouracil, *Coil* additional coil embolization, *NBCA N*-butyl cyanoacrylate

Follow-up

The mean follow-up period was 7.5 (range, 1–29) months. Six lesions underwent subsequent radiation therapy. Three lesions of pelvis underwent subsequent percutaneous cement injection to increase bone strength. During the follow-up period, two cases (lesions 10 and 13) suffered a relapse of symptom at 3 months and 14 months and performed subsequent TACE, which achieved pain relief and improvement of neurological deficit (lesions 11 and 14).

Discussion

Some studies have been reported in the literature about palliative TAE for metastatic hypervascular tumor, such as HCC, RCC, and thyroid tumor. Actually, we sometimes encounter symptomatic bone metastases from malignant tumors and try to perform TACE/TAE for hypervascular lesions. However, the indication mainly includes recurrence or relapse of symptoms after radiation therapy, resistance to systemic chemotherapy or hormonal therapy, and intolerance to surgical stress. That is, TACE/TAE for symptomatic bone metastases is considered as an alternative method if there was no therapeutic choice. No large series has investigated the clinical efficacy of palliative TACE or TAE. As a current state, palliative TACE/TAE rarely rise to choices of treatment for bone metastases.

In this study, we reported the outcome of palliative TACE or TAE for hypervascular bone metastases from various tumors. Pain relief was obtained for 83% of lesions, including those in postradiation. It also is expected that TACE or TAE provides improvement of neurological deficit. Furthermore, TACE has as much rapid acting as radiation therapy, which often can produce pain relief within 48 h of the start of therapy. Thus, TACE can be of value in progressive pain due to hypervascular bone metastatic lesion.

By interrupting the blood supply to the hypervascular metastatic tumor, tumor growth is reduced and subsequent distention or destruction of richly innerved periosteum is slowed or stopped altogether, as suggested by Chuang et al.

Table 3 Clinical response and follow-up

Lesion no.	VAS pre/post	Analgesics	Pain relief	Time to pain relief	Neurological deficit	Improvement of daily activity	Follow-up CT	Additional treatment	Follow-up time (mo)
1	NA	Grade down	PR	1	NC		NA	BSC	1
2	5/1	Grade down	PR	2		Walking again	Necrosis	Cement	12
3	4/1	NC	PR	5			NA	Cement	1
4	NA	NC	NR	–			Increase	BSC	1
5	NA	Grade down	CR	2	Improve		Decrease	RT	23
6	NA	Grade down	CR	1			Decrease		29
7	6/0	NC	CR	1			Decrease	RT	7
8	10/2	NC	PR	1			Decrease		11
9	NA	NC	PR	1			NC	BSC	4
10	10/0	Grade down	CR	1	Improve		NC	RT	3#
11	3/1	NC	PR	1	Improve		NC		4
12	NA	NC	PR	3			NC	BSC	2
13	2/0	Dose down	PR	1			NC		14#
14	3/2	NC	PR	1	Improve		NC		4
15	10/1	NC	PR	2			NC		11
16	5/1	Dose down	PR	1			Increase		9
17	6/0	Grade down	CR	1			Decrease		1
18	2/2	NC	NR	–	NC		NC	BSC	1
19	9/9	NC	NR	–	NC		NA	BSC	1
20	8/0	Grade down	CR	1		Walking again	Decrease	RT	15
21	8/0	Grade down	CR	3	Improve	Walking again	Decrease	Cement, RT	6
22	NA	Grade down	PR	1	Improve		Decrease	RT	14
23	NA	Grade down	PR	1	Improve	Sitting again	NC	BSC	6
24	NA	NC	NR	–	Improve		NA	BSC	1

BSC best supportive care, *CR* complete pain relief, *NA* not available, *NC* no change, *NR* no relief, *PR* partial pain relief, *RT* radiation therapy, *VAS* visual analogue scale, *cement* cement injection by percutaneous bone plasty, # recurrence of symptoms

[9]. Additional benefits may result from decreased blood flow and reduction of edema, which may cause direct pressure effects on adjacent structures and nerves in the surrounding tissues.

In general, painful bone metastases often have treated by radiation therapy. However, recurrence of the tumor and relapse of symptoms after irradiation can happen. For such a case as a major target, further spread of this treatment is expected. In addition, we experienced two cases that underwent repeat TACE for relapse of symptoms after initial TACE, which demonstrates that TACE for bone metastases is repeatable when necessary.

Although sufficient reduction of tumor blush is important for the clinical response, scrupulous technique will be required to avoid complications due to embolization of nontarget region.

Unfortunately, for the lesions associated with anterior spinal artery, it is unable to treat by embolization. As treatment option for such a lesion, radiation and radiofrequency ablation should be considered.

Past literature reports have revealed that embolization of the intercostal artery, intermammary artery, and internal iliac artery may induce dermal or muscle necrosis, and sciatic paralysis [5, 6, 10–16]. In our series, there was no case of dermal or muscle necrosis and nerve injury. It is expected that blood flow alteration contribute to prevent TACE of nontarget regions. Although the technique is a little costly and has risks, such as coil migrations or arterial injury, it should be performed aggressively depending on the situation. In addition, in this limited study, there was no case in which symptoms neurologically worsened, as the risk of spinal cord compression due to ischemic edema of the embolized tumor had been reported [11]. Nevertheless, it is not always easy to detect nontarget small arteries and the reflux of the gelatin sponge particles in the angiography. Thus, the technique requires scrupulous attention to avoid embolization for the nontarget region.

As an embolic material, the gelatin sponge was mainly used. It is a temporary vascular occluder, most popular in Japan and has a potential of recanalization. To prevent

Table 4 Relationship between devascularization grade and pain relief

Devascularization grade	Complete relief	Partial relief	No relief
I	6	10	2
II	1	3	1
III	0	0	1

A relationship was found between the devascularization grade and the pain relief ($r = 0.49$, $P < 0.05$)

recanalization, additional embolization by microcoils was performed in some cases. Controversy exists as to whether the additional embolization by microcoils is necessary because the blood supply of residual or recurrent tumor consists of not only recanalization but also neovascularization and collateral pathway. However, people terminally ill with cancer were mainly targeted in this study. Therefore, there were a lot of cases in which it seemed to be difficult to repeat TACE/TAE because of the poor general condition. For such a case, the additional coil embolization was performed after ordinary TACE to improve the embolic certainty even a little. Nevertheless, the advantage of TACE is repeatable. Therefore, in the case that has some life expectancy, it might not be preferable to use coils.

NBCA is permanent occluder and effective even in the state of coagulation abnormality. However, it often induces more severe local pain than gelatin sponge particles. For palliation, procedural pain should be minimized. Thus, we recommend gelatin sponge as first line of an embolic material. Furthermore, trial of embolization for bone metastatic tumors with polyvinyl alcohol (PVA) particles and microspheres should be performed.

In the present study, we basically used chemotherapy in consideration for primary lesion and past treatment. Although confusion remains concerning the efficacy of chemotherapy added to TAE, such as embolization for other lesions, previous literature showed that TACE for bone metastases appeared to be more effective and reliable than TAE to provide pain relief [17]. Therefore, anti-cancer agents should be used if it seems to be effective without any contraindication.

The indication of TACE or TAE of bone metastases should be discussed. The vascularity is very important to identify the lesion and to determine the endpoint of the treatment. Therefore, the vascularity of the lesion is essential for TACE/TAE.

Because they are effective even in postradiation, we believe that they should be performed if there is no therapeutic choice for the patient. Even in the patient who has a chance of radiation therapy, when the lesions are hypervascular and/or at multiple sites, TACE/TAE can be a feasible option.

There are several limitations to this study. First, it was a retrospective study with small number of patients at a single institute. Second, it is difficult to compare our results with those of other therapies because there are no established criteria for evaluating the imaging response of bone metastatic tumors. Third, there were only short follow-up period because patients with metastases often were likely to have not enough life expectancy due to underlying disease and changing hospitals. Fourth, it is difficult to assess the efficacy of any single treatment modality because additional therapy, including radiation therapy, bisphosphonates, and steroids often is required in the clinical course of patients with symptomatic bone metastatic tumors. Nonetheless, the VAS score was significantly decreased by TACE/TAE. In addition, CT images revealed the efficacy of TACE/TAE as necrotic change in the metastatic tumor. Thus, it is expected that TACE/TAE is effective for pain relief and the local control of the osseous metastasis.

In conclusion, palliative TACE/TAE for symptomatic bone metastases could be a suitable treatment method because it is the minimally invasive, repeatable, effective, and rapid-acting.

Conflict of interest The authors declare that they have no conflict of interest.

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Phase I/II Multiinstitutional Study of Uterine Artery Embolization with Gelatin Sponge for Symptomatic Uterine Leiomyomata: Japan Interventional Radiology in Oncology Study Group Study

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PURPOSE: This multicenter prospective study was conducted to evaluate the safety and the efficacy of uterine artery embolization (UAE) with gelatin sponge for symptomatic leiomyomas.

MATERIALS AND METHODS: Patients with symptomatic uterine leiomyomas were enrolled and treated with UAE. In phase I, nine patients were evaluated for safety. In phase II, 24 patients were accrued, and an intent-to-treat analysis was performed on all 33 patients. The primary endpoint was safety. Secondary endpoints included technical success, hospital stay, change in symptoms, leiomyoma volume on magnetic resonance (MR) imaging, and incidence of treatment failure.

RESULTS: UAE procedures were performed for all 33 patients. Two patients were lost to follow-up at 3 and 12 months. The median follow-up period was 33.4 months. Minor adverse events (AEs) occurred in 10 patients (33%); major AEs of permanent amenorrhea and leiomyoma expulsion occurred in two (6%). The most common AE was transient amenorrhea. Technical success was achieved in all patients. The median hospital stay was 5 days. At 12 months after UAE, menorrhagia had improved in 90% of patients, pelvic pain in 78%, and bulk-related symptoms in 97%. The mean reduction in leiomyoma volume on MR imaging at 12 months was 61%. Treatment failure occurred in one patient, who underwent hysterectomy for recurrent menorrhagia at 21 months.

CONCLUSIONS: UAE with gelatin sponge is safe, with efficacy comparable to other embolic agents based on published data. Gelatin sponge should be an option for UAE, but a prospective comparison versus other standard UAE embolic agents may be warranted.

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Abbreviations: AE = adverse event, FSH = follicle-stimulating hormone, PVA = polyvinyl alcohol, QOL = quality of life, SIR = Society of Interventional Radiology, TAGM = tris-acryl gelatin microsphere, UAE = uterine artery embolization

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VARIOUS embolic agents have been used for uterine artery embolization (UAE); however, no definitive consensus exists regarding the choice of embolic agent. From previous reports, the choice of embolic agent seems to depend not only on its safety and efficacy, but also on its availability in each country.

Since the introduction of UAE in 1995, nonspherical polyvinyl alcohol (PVA) has been most widely used (1–4). Spherical agents such as tris-acryl gelatin microspheres (TAGMs) and

spherical PVA particles were developed in the past decade, and recently, the use of TAGMs has been expanding. In the United States, European countries, and some other countries, several types of embolic agents are available for UAE. In contrast, no embolic agent is approved for UAE in Japan, and only gelatin sponge is available.

Gelatin sponge has been used for embolization in various fields for more than 30 years. In gynecology, it has been used as part of the standard interventional procedure to control the bleeding of obstetric hemorrhage or malignant tumors (5). In the early years of UAE, gelatin sponge was used, and favorable mid- and long-term outcomes were reported in retrospective and single-institutional studies (6,7). However, no clinical trial has yet prospectively investigated gelatin sponge for UAE. Therefore, we undertook a phase I/II multiinstitutional prospective clinical trial of UAE with gelatin sponge (Japan Interventional Radiology in Oncology Study Group trial 0302). In this study, we evaluated the safety and the efficacy of UAE with gelatin sponge for patients with symptomatic uterine leiomyomata.

MATERIALS AND METHODS

Patient Eligibility

Premenopausal women with symptomatic uterine leiomyomas confirmed by imaging studies were eligible. Symptoms uncontrolled with medical therapies, adequate organ function, and an Eastern Cooperative Oncology Group performance status of 0 to 1 were required.

Exclusion criteria included pregnancy, nursing, or desire for future pregnancy; active inflammatory disease; pelvic malignancy; hormonal therapy within 12 weeks; contraindication to magnetic resonance (MR) imaging; contraindication to iodized contrast material; uncontrolled comorbid disease; and adenomyosis confirmed with MR imaging.

This study was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of the participating institutions. All patients provided written informed consent.

Study Endpoints

The primary endpoint was safety, and the secondary endpoints were clinical outcomes and the incidence and grade of adverse events (AEs).

Study Design

This was a multiinstitutional, single-arm, open-label, noncomparative trial. In phase I, nine patients were enrolled and evaluated for safety according the three-by-three method of the Japan Interventional Radiology in Oncology Study Group. This method has been described in detail elsewhere (8), and, briefly, consists of three phases with intervals of 4 weeks between phases. With three patients entered per phase, a total of nine patients were evaluated. This method was developed to assure the safety of a new treatment with a meticulous, step-by-step approach.

In phase II, an additional 24 patients were enrolled, and the study was completed with a total of 33 patients. All enrolled patients were included in the intent-to-treat analysis for the primary and secondary endpoints. A total of 10 institutions participated in this study. Patient accrual started in May 2004 and terminated in April 2006.

Embolic Material

We used gelatin sponge in this study. Gelatin sponge is absorbable embolic material that dissolves within several days to several weeks. At present, a number of types of gelatin sponge are on the market worldwide. In Japan, three products—Spongel (Astellas, Tokyo, Japan), Gelfoam (Pfizer Japan, Tokyo, Japan), and Gelpart (Nippon Kayaku, Tokyo, Japan)—are commercially available; however, Gelpart was not available at the time of the present study. The products are supplied in various forms: Spongel in blocks of two sizes (2.5 × 5 × 1 cm and 7 × 10 × 1 cm), Gelfoam in sheets of two sizes (8 × 12.5 × 1 cm and 2 × 6 × 0.7 cm), and Gelpart in 1-mm or 2-mm particles in bottles. We used a 2.5 × 5 × 1 cm Spongel block, which weighs approximately 235 mg. A block was cut into 1-mm cubes with a scalpel and scissors according to the previously reported procedure (6) and sterilized by ethylene oxide. This preparation was performed by the principal investigator, and the particles were distributed to coinvestigators.

UAE Procedure

The UAE was performed as follows. Bilateral uterine artery catheterization was performed under local anesthesia, and a vascular sheath was inserted from the unilateral or bilateral femoral arteries. A 4-F or 5-F angiography catheter was advanced into the internal iliac arteries and a coaxial microcatheter system was used to select the uterine arteries. Embolization of both uterine arteries was performed with 1-mm^3 gelatin sponge particles. The gelatin sponge was diluted with approximately 10 mL of nonionic contrast material and aspirated in 1-mL or 2.5-mL syringes. The embolic material was injected under fluoroscopy and saline solution was injected to avoid aggregation of the gelatin sponge in a microcatheter. The embolization endpoint was stasis of blood flow in the ascending branch of the uterine artery, as confirmed by injection of contrast material under fluoroscopy. Embolization of the ovarian artery was not allowed even if the supply from this artery to the leiomyomas was observed on angiography. Evaluation of pelvic arterial anatomy was performed with aortography during UAE or MR angiography before UAE in all patients. Pain management was administered according to local practice.

The size and type of microcatheter systems, use of prophylactic antibiotics, total amount of gelatin sponge used, and pain control procedures were reported. These data were collected with dedicated case report forms.

Outcome Measures

The primary endpoint was the incidence and type of AEs. AEs and their causality and severity were evaluated based on the Society of Interventional Radiology (SIR) classification (9).

Secondary endpoints were clinical outcomes, which included technical success; linear analog pain scale score at 6, 12, 18, and 24 hours and 2 and 7 days after UAE; hospital stay; change in symptom score ranging from 0 (marked worsening) to +10 (marked improvement) on a scale on which +5

represented no change; change in volume of dominant leiomyomas on MR imaging; ovarian function measured by follicle-stimulating hormone (FSH) and presence or absence of menstruation; and treatment failure, defined as the need for subsequent intervention for symptom control, including hysterectomy and repeated embolization. According to the SIR guidelines, the UAE was considered successful when bilateral UAE was confirmed (10). Unilateral UAE was considered successful if only single-sided uterine arterial flow was present.

Baseline clinical symptoms were scored before the UAE on a scale of 0 (no interference with daily life) to 10 (marked interference with daily life). Baseline imaging was obtained by MR imaging according to the standardized protocol at each hospital with or without contrast enhancement.

Symptom change was assessed by patients with a score divided into three levels: marked improvement (score 8–10), moderate improvement (score 5–8), and none (score 5 or lower).

We assessed outcome measures at 1, 3, 6, 9, and 12 months and annually thereafter, except for the postprocedural pain score. We present 12-month results, with the exceptions of major AEs and treatment failure, which were reported through the final analysis in September 2007.

All data were collected with case report forms. Adverse events were to be reported with other items on the schedule. Severe adverse events were to be reported immediately after the events.

Statistical Analysis

In phase I, a cohort of nine patients was considered to be adequate for quick termination when the incidence of severe AEs associated with UAE with gelatin sponge exceeded one third of the population. Throughout phase I and phase II, the study was designed to detect the incidence of AEs set at 10% for the least, 10% for the predicted, and 30% for the unacceptable, with a power of 80%. Therefore, the target number of patients to be accrued was calculated to be 33, including an anticipated dropout rate of 10%.

Demographic and baseline variables were summarized by descriptive statistics. Comparisons with baseline data were performed for the FSH level with paired *t* tests. The statistical significance level was set at .05. All statistical analyses were performed with SPSS software (version 11.01; SPSS, Chicago, Illinois).

RESULTS

Patients

A total of 33 patients were enrolled. All received UAE and were assessable for study endpoints. Patient characteristics are shown in **Table 1**. Two patients were lost to follow-up at 3 and 12 months. In one patient, MR imaging was not performed at 12 months. The median follow-up period was 33.4 months (range, 13.6–41.2 months).

Table 1
Baseline Characteristics of the Patients (N = 33)

Variable	Value
Age (y)	
Median	43
Range	37–54
Previous treatment	
Myomectomy	5 (15)
Hormonal therapy	11 (33)
Other medication	19 (58)
Dominant leiomyoma location	
Intramural	26 (79)
Submucosal	5 (15)
Subserosal	2 (6)
No. of leiomyomas	
1	9 (27)
2–5	14 (42)
> 5	10 (30)
Dominant leiomyoma volume (mL)	
Median	321
Range	64–1,922
Presenting symptom	
Menorrhagia	32 (97)
Severity score	6.9 ± 2.6
Pelvic pain	29 (88)
Severity score	4.6 ± 3.0
Bulk-related symptoms	32 (97)
Severity score	6.7 ± 2.5

Note.—Values in parentheses are percentages. Values expressed as mean ± SD, where appropriate.

Primary Outcome

During phase I, major AEs were not encountered; therefore, the study proceeded to phase II. Among all enrolled patients, minor AEs were reported in 10 patients (33%) and major AEs were reported in two patients (6%; **Table 2**). The most common AE was transient amenorrhea. Other AEs were observed in one patient each. Permanent amenorrhea occurred in one patient who was 46 years of age whose menstruation stopped 6 months after UAE. Leiomyoma expulsion occurred at 2 months in one patient with a submucosal leiomyoma, and the leiomyoma was removed successfully without hospitalization. Complications of angiography were not encountered, and no deaths occurred. Pelvic infection, postembolization syndrome requiring prolonged admission or readmission, radiation injury, adverse drug reactions, and pulmonary embolism were not encountered.

Secondary Outcomes

UAE procedures.—Technical success was achieved in all 33 patients. Dominant ovarian arterial supply to leiomyomas was not encountered. The median procedural time was 55 minutes (range, 29–120 min), and the median fluoroscopic time was 18 minutes (range, 6–44 min). The median mass of gelatin sponge used was 168 mg (range, 80–320 mg). The sizes of the microcatheters used were 2.3 F (Microferret [Cook, Bloomington, Indiana] or Tracker-18 [Boston Scientific, Natick, Massachusetts]; n = 7); 2.4 F (On-the-Road [Solution, Yokohama, Japan], n = 2); 2.5 F (FasTracker-18 [Boston Scientific]; n = 3); 2.6 F (Shirabe High Flow [Piolax, Yokohama, Japan]; n = 3); 2.7 F (Renegade Hi-Flo [Boston Scientific]; n = 17); and 2.8 F (Progreat Omega [Terumo, Tokyo, Japan]; n = 1). Thirty-two patients underwent UAE under local anesthesia and one underwent UAE under conscious sedation. Primary pain control methods were epidural analgesic agents in 17 patients, intravenous or subcutaneous opioid agents in 14 patients, and intramuscular pentazocine in two patients. Oral or suppository nonsteroidal antiinflammatory drugs were administered in combination with primary analgesic agents. A prophylactic antibiotic was used for 1–4 days in all patients. The type of antibiotics were cephazolin (n = 22), piperacillin (n = 7), fosfomycin (n = 2), flomoxef (n = 1), and faropenem (n = 1).

Pain score.—The mean and SD vi-

Table 2
Summary of AEs

Event	SIR Class	At ≤ 1 Month	At 1–12 Months
Major			
Leiomyoma expulsion	C	1 (3)	0
Permanent amenorrhea	E	NE	1 (3)
Minor			
Transient amenorrhea	A	NE	6 (18)
Anemia	B	0	1 (3)
Elevated ALP	A	1 (3)	0
Elevated ALT	A	1 (3)	0
Elevated bilirubin	A	0	1 (3)

Note.—Values in parentheses are percentages. ALP = alkaline phosphatase; ALT = alanine aminotransferase; NE = not evaluable.

Table 3
Changes in Symptom Scores

Symptom/Improvement	1 Month	3 Months	6 Months	12 Months
Menorrhagia	*n* = 32	*n* = 31	*n* = 31	*n* = 30
Marked	16 (50)	21 (68)	23 (74)	23 (77)
Moderate	10 (31)	6 (19)	5 (16)	4 (13)
None	6 (19)	4 (14)	3 (10)	3 (10)
Pelvic pain	*n* = 29	*n* = 28	*n* = 28	*n* = 27
Marked	14 (48)	14 (50)	16 (57)	17 (63)
Moderate	7 (24)	7 (25)	8 (29)	4 (15)
None	8 (28)	7 (25)	4 (14)	6 (22)
Bulk-related symptoms	*n* = 32	*n* = 31	*n* = 31	*n* = 30
Marked	15 (47)	26 (84)	22 (71)	26 (87)
Moderate	13 (40)	4 (13)	8 (26)	3 (10)
None	4 (13)	1 (3)	1 (3)	1 (3)

Note.—Values in parentheses are percentages.

sual analog scale score for pain was as follows: baseline, 0.5 ± 1.8; 6 hours, 5.8 ± 3.7; 12 hours, 4.8 ± 3.7; 18 hours, 3.7 ± 2.8; 24 hours, 2.7 ± 2.6; 2 days, 2.4 ± 2.3; and 7 days, 0.2 ± 0.2.

Length of hospital stay.—The median hospital stay was 5 days (range, 2–10 d). Readmission was not observed in any case.

Clinical outcome.—Symptomatic changes are summarized in **Table 3**. At 12 months after UAE, moderate to marked improvement was observed in terms of menorrhagia in 90% of patients, in pelvic pain in 78% of patients, and in bulk-related symptoms in 97% of patients.

Imaging outcome.—Dominant leiomyoma volume on MR imaging is presented in **Table 4**. At 12 months after UAE, the volume reduction was 61.4% (95% CI, 52.9%– 69.9%).

Ovarian function.—No statistically significant increase in FSH level was demonstrated (**Table 5**). In six patients with transient amenorrhea, the median baseline FSH level was 9.2 mIU/mL. In one patient with permanent amenorrhea, the FSH level showed an increase from a baseline of 11.4 mIU/mL to 152.5 mIU/mL at 12 months.

Treatment failures.—In one patient, hormonal therapy was performed for recurrent bleeding and anemia at 12 months; however, these symptoms were not controlled. This patient underwent hysterectomy at 21 months. No patients underwent repeat UAE. Therefore, the rate of treatment failure was 3% (ie, one of 33).

DISCUSSION

Data regarding UAE with nonspherical PVA, spherical PVA, and TAGMs have been published worldwide, but there have been few studies of gelatin sponge for UAE except for single-institution experiences from Japan (6,7). Follow-up procedures or intervals vary among studies; however, there are few differences in major clinical outcomes between studies that used gelatin sponge and studies that used other embolic agents. Therefore, UAE with gelatin sponge shows safety and efficacy similar to UAE with other widely distributed embolic agents.

Several studies comparing embolic materials for UAE have been reported. Spies and colleagues (11) conducted a randomized controlled trial comparing TAGMs with nonspherical PVA by measuring the recovery after UAE and the 3-month clinical outcome. No significant difference was noted between the two embolic materials in peri- and postprocedural symptoms, tumor infarction, patient satisfaction, symptom improvement, and quality of life (QOL). A difference was observed only in the incidence of microcatheter occlusion, which was more common with PVA. Subsequently, the investigators performed a similar randomized controlled trial (12) comparing TAGMs and spherical PVA. Although no significant differences were observed in symptom control, QOL, and AEs, 500–700-μm PVA spheres were associated with a significantly higher rate of failed tumor infarction, which resulted in the early termination of the trial. In response to these results, Rasuli and coworkers (13) performed a historical comparison of spherical versus nonspherical PVA particles for UAE; UAE with spherical PVA particles resulted in less leiomyoma shrinkage and less improvement in clinical symptoms than UAE with nonspherical PVA, which supported the results of the previous trials (11,12). In terms of the degree of tumor infarction after UAE, Siskin and colleagues (25) undertook a randomized study comparing TAGM with spherical PVA. They evaluated the degree of tumor infarction using contrast-enhanced MR imaging. UAE with TAGMs showed a significantly greater degree of tumor infarction than UAE with spherical PVA, and the authors concluded that TAGMs should be the preferred embolic material for UAE. Conceptually, the spherical shape of spherical PVA particles could improve the tendency of the material to clump in the catheter; however, previous clinical trials have demonstrated the clinical and

Table 4
Changes in Dominant Leiomyoma Volume

Value	Baseline	3 Months	6 Months	12 Months
No. of Pts.	33	32	32	30
Mean volume (mL)	298 (171–426)	180 (83–277)	157 (64–251)	138 (52–224)
Mean reduction (%)	NA	43.7 (36.6–50.8)	53.6 (45.7–61.4)	61.4 (52.9–69.9)

Note.—Values in parentheses are 95% CIs. NA = not applicable.

Table 5
Changes in FSH Levels

Interval	No. of Pts.	Mean FSH (mIU/mL)	*P* Value
Baseline	33	10.3 (6.8–13.5)	NA
3 Months	32	16.7 (7.5–25.9)	.065
6 Months	32	15.3 (8.6–21.9)	.056
12 Months	31	20.7 (5.9–35.4)	.708

Note.—Values in parentheses are 95% CIs. *P* values comparing data at baseline and each month were calculated with paired *t* tests. NA = not applicable.

imaging failure of spherical PVA (12,13). To our knowledge, no study has compared gelatin sponge versus another embolic material.

The incidence of severe AEs in the present study was 6%, which was similar to those of previous reports (0%–11%; **Table 6**) (2–4,6,7,11,14–17). Minor AEs occurred at a rate of 33% in the present study, which was also similar to those of the other studies (20%–53%). Transient amenorrhea, which was seen in 18% of patients, was the most frequent AE, although no significant elevation in FSH levels was observed. Hovsepian and colleagues (18) reported that, within a 6-month follow-up period, no significant difference in FSH levels or new-onset menopausal symptoms was observed among patients undergoing UAE, hysterectomy, or myomectomy in their prospective comparison. In the present study, one case of permanent amenorrhea occurred in a patient who was 46 years of age. Of the six patients who experienced the complication of transient amenorrhea, three were 45 years of age or older. The incidence of amenorrhea after UAE is highly age-dependent, and the reported occurrence in women 45 years of age or older is 26%–58% (18,19).

The technical success rate of 100% in the present study is comparable to those of previous reports (Table 6). No periprocedural complications were observed. We did not experience any case of aggregation of gelatin sponge particles in the microcatheters. Not only nonspherical PVA particles, but also spherical PVA particles, are known to have a tendency to aggregate in microcatheters and vessels (11,20). Gelatin sponge particles are also quoted to have the same tendency; however, the use of gelatin sponge differs depending on the gelatin sponge product, institute, or country. Our procedure of preparing the gelatin sponge (Spongel) was similar to that of Katsumori and coworkers (6) and consisted of manual shaving and cutting of a block into 500–1,000-μm particles. With gelatin sponge prepared by this technique, no microcatheter occlusion or proximal arterial occlusion was experienced in the present study.

In the present study, the average maximum visual analog scale score for subjective pain after UAE was 5.8. In previous randomized and nonrandomized comparison studies (11,12,21), the maximum score ranged from 3.0 to 5.9 after UAE, which was similar to that observed in the present study. In addition, there was no significant difference between nonspherical PVA particles and TAGMs.

Direct comparison of the cost of each embolic material in UAE practice is difficult because the availability varies greatly among countries. Dembek and colleagues (22) reported that the UAE procedure costs were significantly lower than those of myomectomy or hysterectomy in the United States, although no significant difference was noted in 12-month payer costs, mainly because of the high cost of follow-up imaging. In the present study, the UAE procedure costs were reported as a lump sum. The type and quantity of the embolic materials were not evaluated; therefore, the influence of the embolic materials on the total UAE cost was not determined. The price of embolic materials may vary depending on the country; however, the approximate price of one vial of TAGMs (Embosphere) is $240, whereas that of a block of gelatin sponge (Spongel) is $2. Given the variable use of each embolic material, the cost per procedure would be approximately $960 for TAGMs and $5 for gelatin sponge, approximately a 200-fold difference. Differences in local practices such as the length of hospital stay or the type of pain control may affect the total cost of UAE. Also, we did not perform a cost analysis in the present study; however, the low cost of gelatin sponge may have an impact on the medical cost of UAE. As long as the safety and efficacy are demonstrated in an evidence-based manner, the use of low-cost embolic materials is important to reduce the escalating health care cost of UAE.

Several weaknesses of the present trial should be acknowledged. First, this trial was not a randomized controlled trial, and therefore a direct comparison with other embolic materials was not possible. Spies (23) pointed out the importance of properly designed randomized controlled trial comparing the new embolic agents versus the established ones to answer the key question of symptom relief and tumor infarction predicting symptom recurrence. Nevertheless, our data are of value as a baseline for future randomized controlled trials of

Table 6
Comparison of Clinical Outcome of Embolic Agents in Symptomatic Leiomyomas (2–4,6,7,11,12,14–17)

Study, Year	Embolic Particle Size (μm)	Study Design	No. of Pts.	Technical Success (%)	AEs (%)	Symptom Improvement (%)	Leiomyoma Volume Reduction (%)
Nonspherical PVA							
Pelage et al (2), 2000	150–300	Prospective	76	95	Transient amenorrhea; 3; permanent amenorrhea, 5; prolonged postembolization syndrome, 9	95 (2 y)	52 (6 mo, US)
Spies et al (3), 2002	500–710	Prospective	291	99	Minor, 7; major, 4.3	NA	NA
Walker and Pelage (4), 2002	150–500	Prospective	395	99	Infection (hysterectomy), 1; leiomyoma passage, 2; permanent amenorrhea, 7; transient amenorrhea, 2	Menorrhagia, 84; pain, 79; bulk, 82	67 (6 mo)
Spies et al, (11) 2004	355–710	RCT*	46	99	17	Scores equivalent to TAGM (3 mo)	NA
Volkers (15), 2006	355–500	RCT†	88	82.7	Minor, 25.9; major, 4.9 (in-hospital); minor, 53.1; major, 11.1 (discharge 6 weeks)	Menorrhagia, 96.3 (2 y)	60.5 (2 y)
Spherical PVA							
Spies et al (12), 2005	500–900	RCT*	17	100	NA	QOL and symptom scores inferior to TAGM	NA
Siskin et al (25), 2006	500–1,200	Cohort	77	NA	26	88.3 (6 mo)	43.7 (6 mo)
TAGMs							
Spies et al (16), 2001	500–900	Prospective	30	100	Minor, 33; major, 0	Menorrhagia, 100 (6 mo)	—
Spies et al (11), 2004	500–900	RCT*	54	99	Minor, 20; major, 0	Scores equivalent to TAGM (3 mo)	NA
Spies et al (12), 2005	500–900	RCT*	19	95	NA	QOL and symptom scores superior to spherical PVA	NA
Lohle et al (17), 2006	500–1,200	Prospective	158		Permanent amenorrhea, 11; transient amenorrhea, 13; leiomyoma expulsion, 10	Menorrhagia, 91; pain, 92; bulk, 92 (12 mo)	66
Gelatin sponge							
Katsumori et al (6), 2002	500–1,000	Case series	60	98	Leiomyoma expulsion, 3; permanent amenorrhea, 2	Menorrhagia, 100; bulk, 100 (12 mo)	70
Katsumori et al (7), 2005	500–1,000	Prospective	96	NA	Minor, 23; major, 3	96 (1 y), 94.5 (2 y), 89.5 (3 y), 89.5 (4 y), 89.5 (5 y)	—
Present study, 2009	500–1,000	Prospective phase I/II	33	100	Permanent amenorrhea, 3; transient amenorrhea, 18; leiomyoma expulsion, 3	Menorrhagia, 90; bulk, 76; pain, 96 (12 mo)	61

Note.—NA = not available; RCT = randomized controlled trial.
* RCT comparing embolic agents in UAE.
† RCT comparing UAE versus other treatments.

embolic materials including gelatin sponge. Second, we did not measure QOL with preexisting QOL instruments. Although subjective symptom reports like those in the present study are essential for evaluation of the efficacy of UAE, QOL scores on instruments such as the Uterine Fibroid Symptom QOL questionnaire, Short Form–12, Short Form–36, or EuroQol have a positive meaning in the setting of the endpoints for UAE trials. Third, we did not evaluate contrast-enhanced MR imaging for follow-up imaging after UAE. Recently, this issue has been amplified with an increase in data with spherical PVA showing an unacceptably high rate of failed tumor infarction, and with data suggesting a relationship between incomplete tumor infarction and long-term clinical failure (20,24,25). As for UAE with gelatin sponge, Katsumori and coworkers (7,26) evaluated the association of tumor infarction on contrast-enhanced MR imaging with long-term clinical outcome. Of 221 cases, 100% infarction

was achieved in 142 (group A), 90%–99% in 74 (group B), and less than 90% in 5 (group C). The cumulative rates of symptom control at 5 years were 93%, 71%, and 60% in groups A, B, and C, respectively. According to these results, a high rate of tumor infarction was achieved with gelatin sponge in conjunction with a favorable long-term clinical outcome (7,26).

In conclusion, UAE with gelatin sponge is safe, with efficacy equivalent to previous data for other widely used embolic materials. Gelatin sponge should be an option for UAE, but randomized controlled trials including cost analysis will be needed to determine the impact of gelatin sponge on UAE clinical practice.

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CLINICAL INVESTIGATION

Ultrasound-Guided Radiological Placement of Central Venous Port via the Subclavian Vein: A Retrospective Analysis of 500 Cases at a Single Institute

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Abstract The purpose of this study was to assess the technical success rate and adverse events (AEs) associated with ultrasound (US)-guided radiological placement (RP) of a central venous port (CVP) via the subclavian vein (SCV). Between April 2006 and May 2007, a total of 500 US-guided RPs of a CVP via the SCV were scheduled in 486 cancer patients (mean age ± SD, 54.1 ± 18.1 years) at our institute. Referring to the interventional radiology report database and patients' records, technical success rate and AEs relevant to CVP placement were evaluated retrospectively. The technical success rate was 98.6% (493/500). AEs occurred in 26 cases (5.2%) during follow-up (range, 1–1080 days; mean ± SD, 304.0 ± 292.1 days). AEs within 24 h postprocedure occurred in five patients: pneumothorax ($n = 2$), arterial puncture ($n = 1$), hematoma formation at the pocket site ($n = 2$), and catheter tip migration into the internal mammary vein ($n = 1$). There were seven early AEs: hematoma formation at the pocket site ($n = 2$), fibrin sheath formation around the indwelling catheter ($n = 2$), and catheter-related infections ($n = 3$). There were 13 delayed AEs: catheter-related infections ($n = 7$), catheter detachments ($n = 3$), catheter occlusion ($n = 1$), symptomatic thrombus in the SCV ($n = 1$), and catheter migration ($n = 1$). No major AEs, such as procedure-related death, air embolism, or events requiring surgical intervention, were observed. In conclusion, US-guided RP of a CVP via the SCV is highly appropriate, based on its high technical success rate and the limited number of AEs.

Keywords Central venous port · Ultrasound · Subclavian vein · Venous access · Indwelling catheter

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Introduction

Central venous catheter placement is generally required for repeated continuous infusion of anticancer agents or total parenteral nutrition (TPN). To reduce problems caused by central venous catheter placement and to improve the quality of life of patients, a central venous port (CVP) is widely used [1–14]. Thus, the placement of a CVP is an indispensable procedure in the management of cancer patients, especially outpatients receiving repeated intravenous chemotherapy or TPN [15]. Since the report by Morris et al. in 1992 [1], radiological placement (RP) of a CVP has become a widely accepted interventional radiology procedure, although ultrasound (US)-guided RP via the internal jugular vein (IJV) is the most commonly used method [12, 13]. One possible reason for this preference is the higher rate of pneumothorax complications associated with RP of a CVP via the subclavian vein (SCV) [11, 12, 16].

In a randomized trial concerning the insertion of a central venous catheter via the SCV, Mansfield et al. reported that US guidance was not superior to landmark guidance [17]. Other reports have concluded that US guidance is safe and efficient [14, 16, 18–20]. Thus, the clinical efficacy of US-guided RP of a CVP remains controversial, and more data regarding this procedure are needed to enable better clinical decisions. Based on these background factors, we retrospectively assessed the technical success rate and adverse events (AEs) associated with US-guided RP of a CVP via the SCV.

Materials and Methods

Between April 2006 and May 2007, a total of 505 CVPs were implanted at our institute. After excluding 5 cases in which the central venous catheter was inserted via the femoral vein because of neuralgic pain or a bulky tumor of the chest wall, we analyzed the remaining 500 CVPs implanted in the chests of 486 patients by referring to the interventional radiology report database and the patients' records. Institutional Review Board approval was obtained for this study. Among the 486 patients, 265 were male and 221 were female, and the age range was 3–85 years (mean ± SD, 54 ± 18.1 years). Their primary diseases are listed in Table 1. CVP implantation was indicated for chemotherapy in 375 patients (75%), for TPN in 64 patients (12.8%), and for other reasons in 61 patients (12.2%).

Procedure

All procedures were performed by interventional radiologists on X-ray fluoroscopy tables equipped with a portable US device. Antibiotic prophylaxis was used in 334 procedures but was not used in 166 procedures. The reason for this difference is that some referring physicians do not agree with the use of antibiotic prophylaxis despite our recommendation, because the clinical significance of prophylaxis has not been fully established. Local anesthesia was used for all patients, but conscious sedation was not routinely employed except in 34 children (6.8%), with a pediatrician's assistance. None of the procedures was attended by an anesthesiologist.

The CVP was routinely implanted on the side opposite to the patient's dominant hand to enable them to use their dominant hand to easily remove the needle from the port after the completion of infusion. However, if the conditions were unsuitable for implantation on this side, in the case of postmastectomy or radiation therapy areas, the port was placed on the same side as the dominant hand.

The patient was placed in a supine position on the table, and the selected side of the upper anterior chest walls was widely prepared using 10% Popiyodon (Yoshida Pharmaceutical Co. Ltd., Tokyo) and draped. A US probe covered with a sterile disposable vinyl bag was placed at the infraclavicular position and a longitudinal image of the SCV was obtained (Fig. 1). The SCV was distinguished from the subclavian artery by the following characteristics: no pulsations, diameter changes with respiration, and distension with the Valsalva maneuver [20]. A 7.5-MHz linear array probe with a real-time, portable, battery-operated ultrasound device (Site Rite; Dymax Corp., Pittsburgh, PA, USA) was utilized for all cases.

Table 1 Distribution of patients (number) according to primary disease

Diagnosis	
Brain tumor	8 (1.6%)
Lung cancer	6 (1.2%)
Breast cancer	23 (4.7%)
Gastrointestinal system malignancies	310 (63.8%)
Hematological malignancies	18 (3.7%)
Urinary system malignancies	11 (2.3%)
Gynecological malignancies	13 (2.7%)
Unknown primary disease	2 (0.4%)
Other	95 (19.6%)
Total	486 (100%)

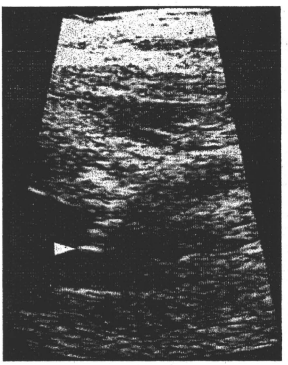

Fig. 1 US imaging of left subclavian vein access. The needle is advanced with visualization of both the needle tip (*arrowhead*) and the subclavian vein (*longitudinal view*). Note that the left side of the figure is proximal

Under US guidance, a 23-G needle was then inserted through the skin directly anterior to the vessel, and subcutaneous 1% lidocaine was injected to spread along the pathway of the catheter. The most proximal possible portion of the SCV (near the subclavian bone) was punctured using an 18-G indwelling needle under real-time US guidance, with the patient breathing quietly. No needle attachment was used, and a freehand procedure was utilized in all cases (Fig. 2). Successful puncture of the SCV was confirmed when blood was drawn back using a 0.035-in., J-shaped guidewire (GW) inserted via the needle. It is important to confirm successful puncture in this manner before inserting the GW because the outer cannula sometimes does not extend right into the vein lumen due to the difference in length between the inner metal needle and the outer cannula, regardless of the appearance on US. An indwelling catheter was then inserted coaxially using an appropriate peel-away sheath. When a Groshong catheter was used, the GW was removed and the catheter was inserted through the sheath. The tip of the indwelling catheter was placed at the level of the atriocaval junction using radiological landmarks.

A subcutaneous pocket for port placement on the anterior upper chest wall was made using a 4-cm-long skin incision in a blunt dissection manner. The proximal side of the indwelling catheter was passed through a subcutaneous tunnel to the pocket, cut to an adequate length, and connected to the port. After confirming that 10 ml of saline could be injected into the port without any problems, all systems were implanted and the skin incision was sutured. After completion of the entire procedure, a chest X-ray was obtained while the patient was lying on the table, to confirm the position of the catheter and port (Fig. 3). Twelve interventional radiologists, including seven rotating residents from other departments performed the procedures. Five of the interventional radiologists had experience with more than 200 CVP placements. The rotating residents performed RP of a CVP under the direction of an interventional radiologist, after sufficient experience with freehand US-guided venous access (more than 20 catheter insertions via the SCV). These residents were already experienced in the landmark method of CVC placement.

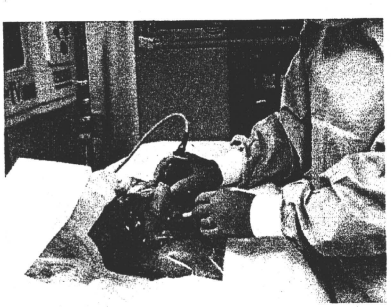

Fig. 2 Setup for the procedure. During each procedure, the interventional radiologist wears a cap, mask, and disposable sterilized gown. The venous puncture is performed freehand

Devices

The following three types of CVP kits, approved for use in Japan, were used in this study: 8-Fr Groshong catheters and MRI ports (Bard Inc., Salt Lake City, UT, USA) in 442 cases; 6-Fr Anthron PU catheters (Toray Medical Co., Tokyo) and CELSITE ports (B. Braun Medical Inc., Bethlehem, PA, USA) in 36 cases; and 5-Fr IV catheters and Septum ports from Orca CV kits (Sumitomo Bakelite Co., Tokyo) in 22 cases.

Maintenance

In most patients, the CVP was used on the day following implantation, from the viewpoint of safety in the administration of chemotherapy. A 24- or 22-G Huber point needle was used for infusion. Saline (10 ml) was injected into the port after each infusion. If the CVP was not used for a long period, 10 ml of saline was injected at least

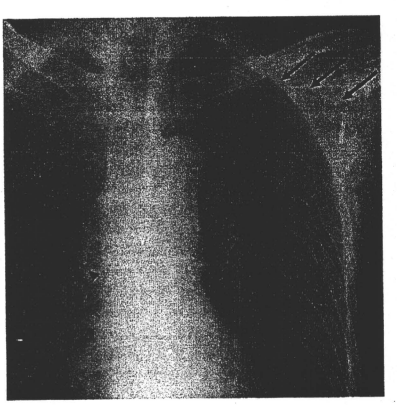

Fig. 3 Chest X-ray of an ideally placed central venous port. The curve of the catheter is gentle, and the catheter tip (*arrowhead*) is adjusted to the level of the atriocaval junction. Note the short subcutaneous tunnel (*arrows*) between the venous access site and the implanted port