

# Prevention of Recurrent Central Venous Stenosis Using Endovascular Irradiation Following Stent Placement in Hemodialysis Patients

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## Abstract

This study was done to evaluate the outcome after brachytherapy (BT) given to prevent restenosis after stent insertion for central venous stenosis in patients with ipsilateral hemodialysis arteriovenous fistulas (AVF). Angioplasty and stenting were performed on 9 primary central venous stenoses in 8 patients with AVF followed by BT, delivering Iridium-192 radiation using an afterloading technique. BT was also administered to three patients with five recurrent stenoses at the stent margins. There was no residual stenosis after angioplasty and stenting. Venographic follow-up (77–644 days, mean 272 days) showed no restenosis in seven primary stenoses. New strictures (45%–100%) developed at the stent margin in six veins (five patients). Angioplasty or stenting was performed for five margin stenoses in three patients, followed by a second BT. Residual stenosis before BT was 0–30%. In our venographic follow-up (140–329 days, mean 215 days), three restenoses occurred (35%–100%). All progressed to complete occlusion on later venographic follow-up irrespective of whether BT was given to the stent margin or not. The mean primary and assisted primary patency of the central veins were 359 days and 639 days, respectively. Endovascular irradiation with a noncentering source does not prolong the patency after angioplasty and stenting of central venous stenosis in hemodialysis patients.

**Key words:** Radiations—Dialysis—Stents and prostheses—Veins, innominate

Central venous stenosis is a major problem for patients depending on hemodialysis via an upper extremity arteriovenous fistula (AVF) or graft [1]. These patients usually present with swelling of the arm bearing the AVF, and adequate hemodialysis is not feasible. Central venous stenosis may be due to a variety of causes, but previous subclavian vein catheter placements for hemodialysis play an important role [2]. To relieve the upper limb swelling, the AVF may need to be ligated. Angioplasty of the obstruction may preserve the AVF, but may require repeated angioplasty and stent placements. The long-term results are poor due to restenosis from intimal hyperplasia [3–8]. Recently, endovascular irradiation or brachytherapy (BT) after angioplasty has been reported to prevent in-stent intimal hyperplasia in peripheral arteries [9, 10] and in coronary arteries [11, 12]. We applied this technique to eight patients with nine central venous stenoses.

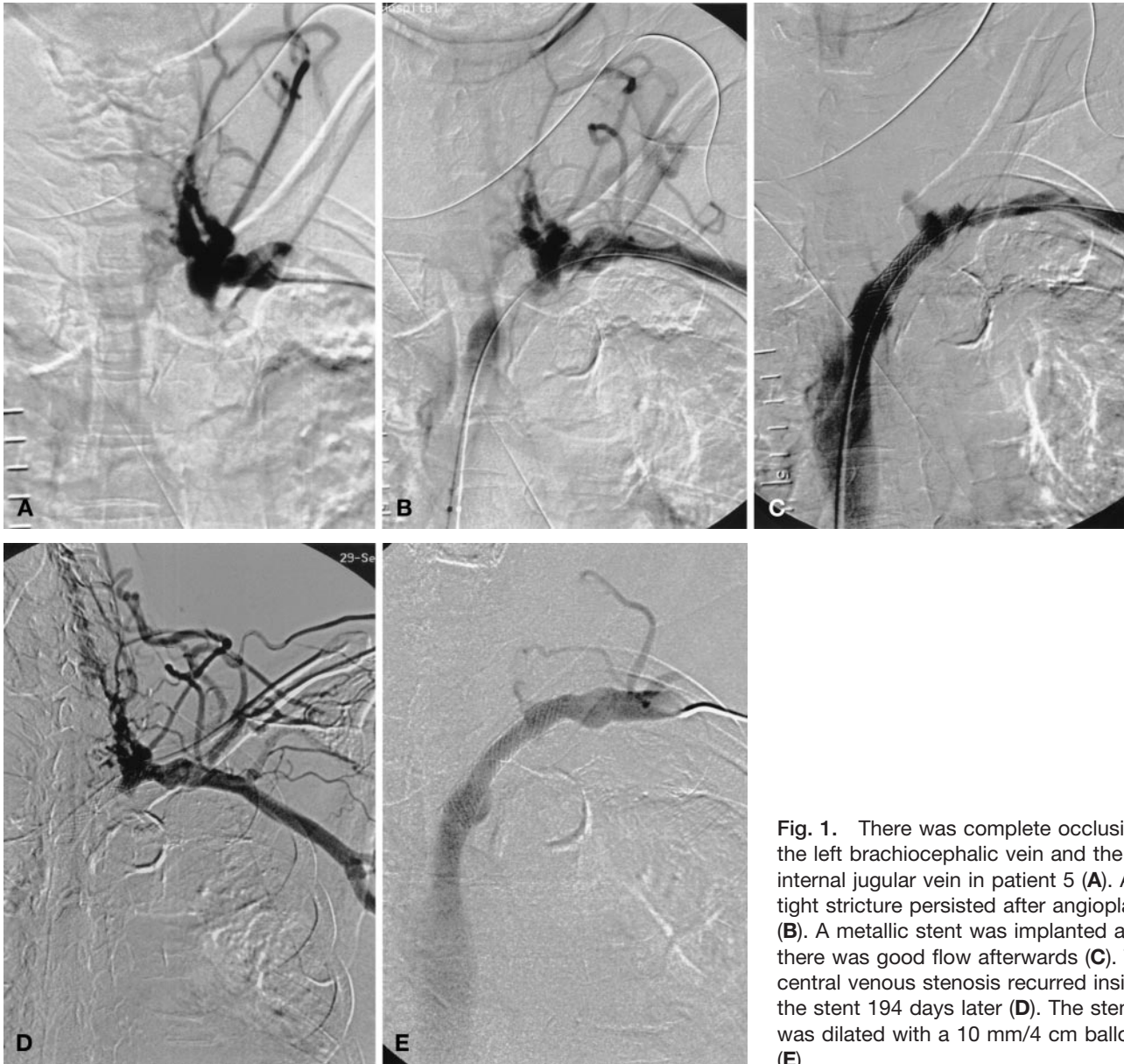
## Materials and Methods

From November 1996 to September 1999 we treated 8 hemodialysis patients (three males, five females) with a mean age of 52 years (range: 36–66 years) (Table 1). There was no control group. The data were reviewed retrospectively. All eight patients presented with central venous stenosis of more than 90% and swelling of the arm bearing the AVF. Thrombotic occlusion was present in two

**Table 1.** Venous stenoses: outcome after angioplasty, stenting, and brachytherapy

Patient no. Sex/Age (years)	Site, Original length and degree of stenosis	Vascular intervention	Dose and extent of BT	Confirmatory venogram after 1 <sup>st</sup> BT when stenosis was discovered (days)	Venographic % Restenosis of the original stenosis	Venographic % secondary stenosis at stent margin	Final outcome
1 (left arm) F/36	Previously implanted Gianturco Z-stent and Memotherm stent at junction of left BCV and SVC Recurrence focal stenosis ( $<1$ cm) with thrombosis 100% stenosis	Thrombolysis + PTA + 10-mm/3-cm Palmaz stent	12 Gy; part of the stent covering the stenosis	181	0%	45%, distal	Thrombosis of SV 639 days after 1 <sup>st</sup> BT
1 (right arm)	Right SV Focal stenosis $< 1$ cm 90% stenosis	PTA + 12-mm/3.9-cm Wallstent	12 Gy, whole stent + 1 cm margin outside stent	77	0%	60% stenosis inside distal 1/4 stent	Complete occlusion at distal stent margin 217 days after 1 <sup>st</sup> BT, AVF function through collaterals
2 M/47	Left BCV Focal stenosis $< 1$ cm Stenosis $> 90\%$	PTA + 20-mm/8.4-cm Wallstent	12 Gy, part of the stent covering the stenosis	393	5%	50% proximal, 65% distal	Renal transplant done 1 month after 2 <sup>nd</sup> BT, died of CMV infection 250 days later, no clinical evidence of venous occlusion
3 F/55	Left BCV with thrombosis Focal stenosis $< 1$ cm 100% stenosis	Thrombolysis + PTA + 14-mm/7-cm Wallstent	12 Gy, part of the stent covering the stenosis	644	0%	65% distal	Complete obstruction at distal stent margin 973 days after 1 <sup>st</sup> BT, good AVF function through collaterals
4 M/65	Right BCV 1 cm stenosis 90% stenosis	PTA + 14-mm/6-cm Memotherm stent	12 Gy, whole stent	166	0%	0%	Died of septicemia 226 days after BT, no evidence of restenosis
5 F/566	Inside previously implanted Wallstent in left BCV Focal stenosis $< 1$ cm 100% stenosis	PTA	12 Gy, whole stent	359	0%	90% distal	Thrombosis of the AVF with successful thrombectomy 150 days after 2 <sup>nd</sup> BT. Died of chest infection 7 months after 2 <sup>nd</sup> BT.
6 F/55	Right SV Focal stenosis $< 1$ cm 90% stenosis	PTA + 12-mm/4-cm Wallstent	12 Gy, whole stent	170	0%	0%	Refuse venogram all along, arm swelling and occlusion of distal stent margin noted 979 days after BT
7 F/44	Left BCV 2 cm stenosis 90% stenosis	PTA + 14-mm/4-cm Symphony stent	12 Gy, whole stent + 1 cm margin outside stent	169	Not known	100% distal	Good AVF all along, thrombosis of AVF 7 days after venogram
8 M/48	Left BCV 1 cm stenosis 90% stenosis	PTA + 20-mm/8.4-cm Wallstent dilated to 12 mm	12 Gy, whole stent + 1 cm margin outside stent	287	Complete occlusion		Stent slipped proximally, stricture not stented; AVF function through collaterals

AVF = arteriovenous fistula; BCV = brachiocephalic vein; BT = brachytherapy; PTA = percutaneous transluminal balloon angioplasty; SV = subclavian vein; SVC = superior vena cava



**Fig. 1.** There was complete occlusion of the left brachiocephalic vein and the internal jugular vein in patient 5 (A). A tight stricture persisted after angioplasty (B). A metallic stent was implanted and there was good flow afterwards (C). The central venous stenosis recurred inside the stent 194 days later (D). The stenosis was dilated with a 10 mm/4 cm balloon (E).

patients. Seven patients had *de novo* stenoses and two had recurrent stenosis inside previously placed metallic stents (Fig. 1a-d). One patient had a *de novo* stenosis of the right subclavian vein after the occlusion of a previously stented and irradiated left brachiocephalic vein and abandonment of the left AVF. Informed written consent for the treatment was obtained from all patients after full explanation of the experimental nature of the treatment by a nephrologist, an interventional radiologist, and a clinical oncologist.

The strictures were approached from the ipsilateral brachial vein (six central venous stenosis in five patients) or right common femoral vein (three patients). Thrombolysis was performed in two patients with urokinase, first using a pulse spray technique through a multihole catheter (Angiodynamics, Queensbury, NY, USA) and then continuous infusion for 24 hr before the procedure. Angioplasty was performed with balloons of 8–20 mm in diameter, depending on the diameter of the central vein Fig. 1e. This was followed by insertion of metallic stents if the response to angio-

plasty was unsatisfactory. The size of the stents ranged from 10 to 20 mm in diameter, including one Palmaz stent (Johnson & Johnson, Warren, NJ, USA), one Memotherm stent (Angiomed, Karlsruhe, Germany), five Wallstents (Schneider, Bulach, Switzerland), and one Symphony stent (Boston Scientific Corporation, Watertown, MA, USA). Only one stent was used for each stenosis.

For BT, a 90-cm long, 10 Fr guiding catheter (Daig, Minnetonka, MN, USA) was introduced beyond the stenotic venous segment. A 6 Fr, 100 cm, end-occluded barrier catheter (Lumen-cath, Nucletron, Veenendaal, The Netherlands) was introduced inside the guiding catheter to prevent physical contact between the radioactive source and the patient's blood. A dummy marker wire with radioopaque markers at 1 cm intervals was then passed into the barrier catheter to calculate the distance between the radiation source and the stent. (Fig. 2). As no centering catheter was available, we tried to improve the catheter centering and thus radiation homogeneity by varying the arm position if possible. The patient





**Fig. 2.** A 10 Fr guiding sheath was placed through the central vein and stent. The dummy guidewire and the blinded-ended brachytherapy catheter passed through the sheath. The markers in the dummy guidewire served to measure the irradiation length and radius. The brachytherapy wire was not exactly in the central lumen due to the curvature of the vein and stent.

was then transferred to the radiation suite of the department of oncology with the catheters left *in situ*. The position of the catheters was checked with a mobile C-arm.

The radiation delivery system was a high-dose rate (HDR) remote after-loader (MicroSelectron, Nucletron Engineering BV, Veenendaal, The Netherlands) employing Iridium-192 (Ir-192) as gamma source. The source length and diameter (including capsule) were 5 mm and 1.1 mm, respectively. As the delivery catheter was not in the central position, the radiation dose was calculated so that 12 Gy was delivered to the farthest luminal surface of the vessel wall seen in the AP projection. The nearer luminal surface would thus receive a greater dose. In the first three patients, the length of the stricture as well as an additional 10 mm at both ends were irradiated. In the next six patients, the entire length of the stent was irradiated. After the procedure, all catheters were removed. The patients were given intravenous heparin for 24 hr, and then switched to oral aspirin 80 mg daily for 6 months.

A follow-up venogram was performed 6–8 months after BT to detect asymptomatic stenosis, or when there were clinical signs of venous obstruction, which included arm swelling or increased ve-

nous pressure during hemodialysis. In three of the five patients who developed restenosis at the stent margin, angioplasty and/or stenting were performed again to relieve the obstruction, followed by a second BT. The cumulative patency of the central vein, the mean patency, and the 95% confidence interval after intervention were analyzed by the Kaplan-Meier method. Primary patency was defined as less than 45% stenosis on follow-up in this series, because we had performed angioplasty in one patient, and assisted primary patency as restoration of patency after intervention. We had no result on secondary patency as we did not reintervene once the vein was occluded. The statistical calculation was done with SPSS statistical software version 8.0 (SPSS, Inc., USA).

## Results

There were nine primary central venous stenoses in eight patients with AVF. The interventional procedures are listed in Table 1. After angioplasty and stenting, there was no immediate residual stenosis in all strictures. Venographic follow-up at 77–644 days (mean 272 days) showed no restenosis in seven original strictures. The status of two original strictures was not known. One had complete occlusion of the distal subclavian vein on follow-up venogram and the other had slipped stent resulting in venous thrombosis.

The first three patients in which BT was delivered only to the stricture plus an additional 10 mm developed restenosis at the distal stent margins, with one patient also having stricture at the proximal stent margin (patient 2). We subsequently irradiated the entire length of the stent in the last six patients.

In total, seven new strictures developed at the stent margin in six veins (five patients). Six of these were in the distal margin (45%–100%) (Fig. 3) and one was in the proximal margin (50%). Angioplasty or stenting was performed for five margin stenoses in four veins (three patients) followed by a second BT (Table 2). There was 0–30% immediate residual stenosis after intervention. Venographic follow-up of three stenoses at 140–242 days (mean 177 days) showed 30%–100% restenosis.

Three patients died of unrelated causes before a longer venographic follow-up was performed. The remaining six veins (in five patients) progressed to complete occlusion irrespective of whether BT was given to the stent margin (169–979 days after first BT, mean 525 days) (Table 1). Five patients are still alive at the time of the review. The AVF in these patients is still functioning through venous collaterals. The mean primary patency was 359 days (range: 215–502 days); the mean assisted primary patency was 639 days (range: 375–902 days), both at the 95% confidence level. The primary patency rates at 6, 12, 18, and 24 months were 67%, 40%, 27%, and 0%, respectively. The assisted primary patency rates were 89%, 65%, 65%, and 43%, respectively. The patency curves are shown in Figures 4 and 5. Neither pseudoaneurysm formation of the irradiated veins nor brachial plexus injury were encountered.



**Fig. 3.** There was recurrence of stricture at the stent margin 359 days after brachytherapy. There was no stenosis in the original stricture inside the stent.

## Discussion

Central venous stenosis has been a difficult problem in hemodialysis patients since it leads to a swollen arm and may progress to thrombosis in the AVF, which renders hemodialysis unfeasible. The amount of collaterals is usually not adequate for venous return. Repeated angioplasty and metallic stents are the usual treatment but unfortunately the result is not satisfactory. We used BT in two stenoses inside previously placed stents, which were adequately dilated with angioplasty. In the other seven *de novo* stenoses, angioplasty alone was insufficient to dilate the strictures and we stented these as adjunct procedures.

With the use of metallic stents, Shoenfeld et al. [3] showed only a primary patency of 68% and secondary patency of 93% at 17 months; Vesely et al. [5] showed a 1-year primary patency of 25% and secondary patency of 56%. As the etiology of in-stent restenosis is intimal hyperplasia, and BT in peripheral arteries and coronary arteries is proven to be useful in preventing intimal hyperplasia, we applied the technique to central vein stenosis, hoping it would act similarly to prevent intimal hyperplasia. Our 1-year and 18-month primary patency rate were 40% and 27%,

respectively, and assisted primary patency rate were 65% and 65%, respectively. They were better than in Vesely's series, but worse than in Shoenfeld's series. In intracoronary radiation using gamma ray [11], the rate of angiographic restenosis (>50% diameter stenosis of stent and/or stent margin) at 6 months was 17% in the irradiated group and 54% in the placebo group; the 3-year restenosis rate was 33% and 64%, respectively; our result with irradiation of central veins was also worse.

Although the patency rates were not improved with the addition of BT, the mechanism of occlusion has changed. In the central venous stenoses treated with angioplasty and stents, the restenosis usually appeared at the original sites. After BT the original strictures did not seem to recur, but new strictures developed at the stent margin, which progressed to complete occlusion irrespective of whether BT was given here. In intracoronary irradiation there was a similar trend; the reduction in restenosis was significant inside the stent whereas the reduction in restenosis at the margin was insignificant [13].

Liermann et al. [9] gave BT to the stenoses only when they recurred after intervention and we followed this same principle in the first patient. However, since it is well known that central venous stenosis will recur even after angioplasty and stenting, we decided to apply BT immediately after angioplasty or stenting, hoping to prevent its recurrence and thus avoid further complicated interventional procedures. A stented endothelial surface was also smoother and the irradiation dose might be more homogeneous.

There are several other uncertain factors when we applied angioplasty, stents, and BT to central venous stenosis, which may affect the final result. First, when the stents are deployed, they inadvertently cause injury to the adjacent venous wall by angioplasty balloon, catheters, and guidewires; the exact length of injury is usually not known. Though we failed to suppress the restenosis by reirradiation in several patients, this might be due to inadequate coverage of the vascular injury.

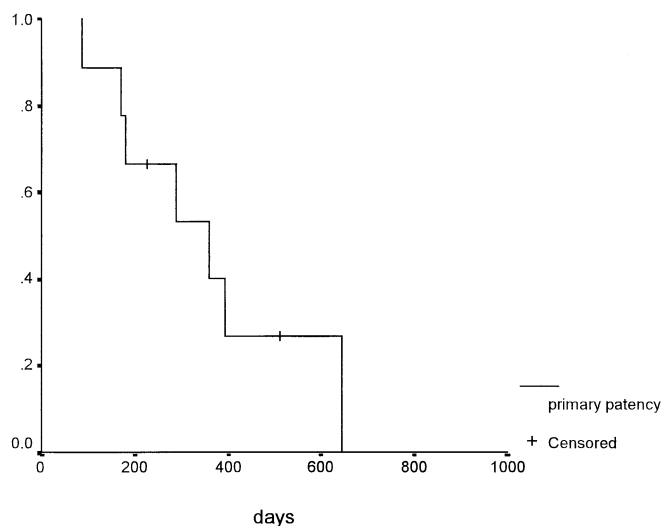
Secondly, we do not know whether the effect of irradiation is the same in artery and vein. The effectiveness of BT has been shown in peripheral arteries and coronary arteries; however, its effect in veins had not been documented when we started our study. It has been shown that there are physiological difference between arteries and veins [14]; the effect of angioplasty and stent is also different in arteries and veins. Thus, the effect of BT may also be different. We have used 12 Gy to the farthest luminal surface, a dose that has been used successful in arteries but whether this dose is useful in veins is uncertain.

Thirdly, the venous side of the av fistula and the central vein is subjected to a continuous turbulent high flow, which is unphysiological to the native vein [15–18]. This probably contributes to the formation of intimal hyperplasia. This is different from a stent in the coronary artery and peripheral artery, where BT can effectively prevent the formation of intimal hyperplasia. In our series, it seems that the effect of

**Table 2.** Secondary, postbrachytherapy stenosis: outcome after second brachytherapy

(right arm) Sex/Age (years)	Site and degree of stenosis	Coverage of stenotic site by 1 <sup>st</sup> BT	Additional vascular intervention	Immediate residual stenosis after PTA	Dose of 2 <sup>nd</sup> BT	Time after 1 <sup>st</sup> BT (days)	Confirmatory venogram after 2 <sup>nd</sup> BT (days)	Venographic % restenosis
1 F/36 (left arm)	Distal margin of Palmaz stent 45%	No	PTA	0%	12 Gy	181	242	45%
1 (right arm)	Inside distal part of Wallstent 60%	Yes	PTA	10%	12 Gy	77	140	100%
2 M/47	proximal margin of Wallstent 50%	No	PTA+	30%	12 Gy	393	Nil	Not available
	Distal margin of Wallstent 65%	No	PTA + 14-mm, 7.6-cm Wallstent	20%	12 Gy	393	Nil	Not available
3 F/55	Distal margin of Wallstent 65%	No	Nil	Not applicable	Nil	644	Nil	Not applicable
5 F66	Distal margin of Wallstent 90%	Yes	PTA	10%	12 Gy	359	148	35%

AVF = arteriovenous fistula; BCV = brachiocephalic vein; BT = brachytherapy; PTA = percutaneous transluminal angioplasty; SV = subclavian vein; SVC = superior vena cava

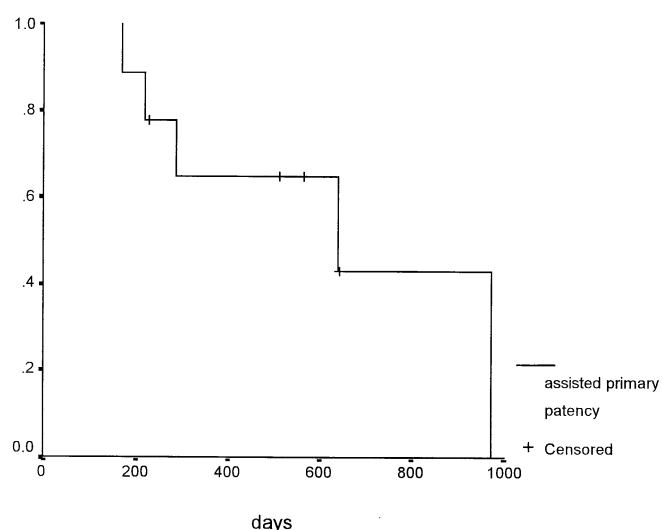


**Fig. 4.** The cumulative primary patency curve. The mean primary patency was 359 days.

irradiation is also different in the original stricture inside the stent and at the stent margin where the native vein meets a stent. Here, there is a change in flow parameters, change in radial force applied to the native vein, and difference in pulsatile motion between the native and the stented segments. All these factors may contribute to the apparent ineffectiveness of BT.

Fourthly, we do not have a catheter for source centering. In small coronary and superficial femoral arteries (3–4 mm diameter), the need for centering is arguable and the eccentricity of the plaque is the reason centering is not useful. However, in large central veins (10–20 mm diameter) and without plaque formation, the dose variation of noncentering may be big, and the result of such a big variation is not known [19].

Our result is also limited by its retrospective nature and there is no control group for comparison. There were several



**Fig. 5.** The cumulative assisted primary patency curve. The mean assisted primary patency was 639 days.

treatment protocols in this small series and the treatment result is bound to be heterogeneous. Nevertheless, one can still get an idea of the effect of BT on this disease.

More recently, there have been other publications on the ineffectiveness of BT in the prevention of peripheral av graft stenosis [20, 21]. Though the site of treatment is not exactly the same as ours, the reason for failure may be similar.

In conclusion, endovascular irradiation with a noncentering source cannot prolong the patency after angioplasty and stenting of central venous stenosis in hemodialysis patients. The suppression of restenosis in the original stricture indicates that further evaluation of this treatment is worthwhile. Future studies may need to examine the effect of centering catheters and the dose and range of irradiation after angioplasty and stenting.

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