Treating In-Stent Restenosis with Brachytherapy: Does it Actually Work?

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PACIFIC NORTHWEST ENDOVASCULAR CONFERENCE

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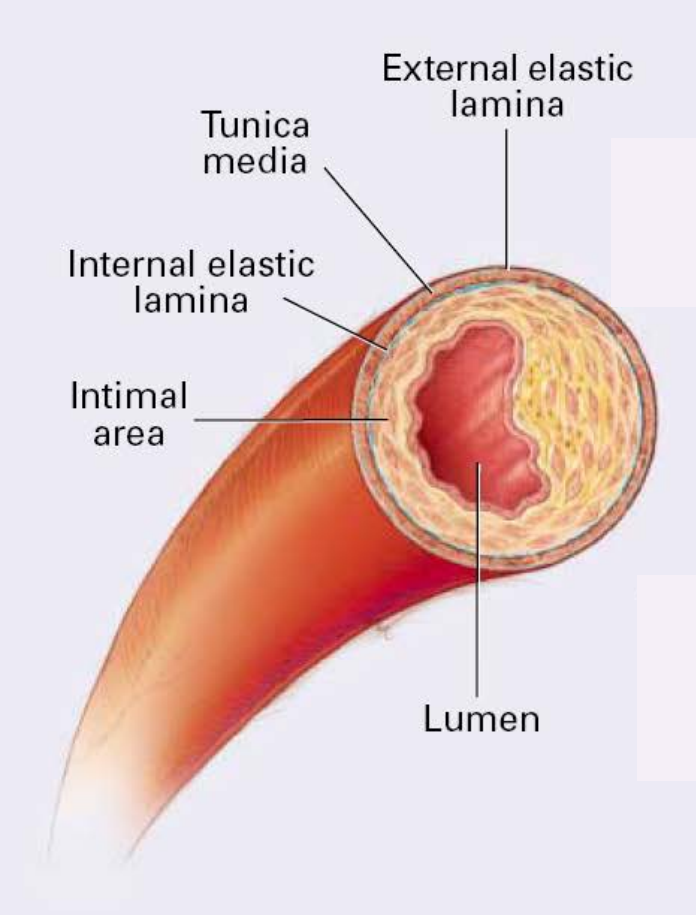
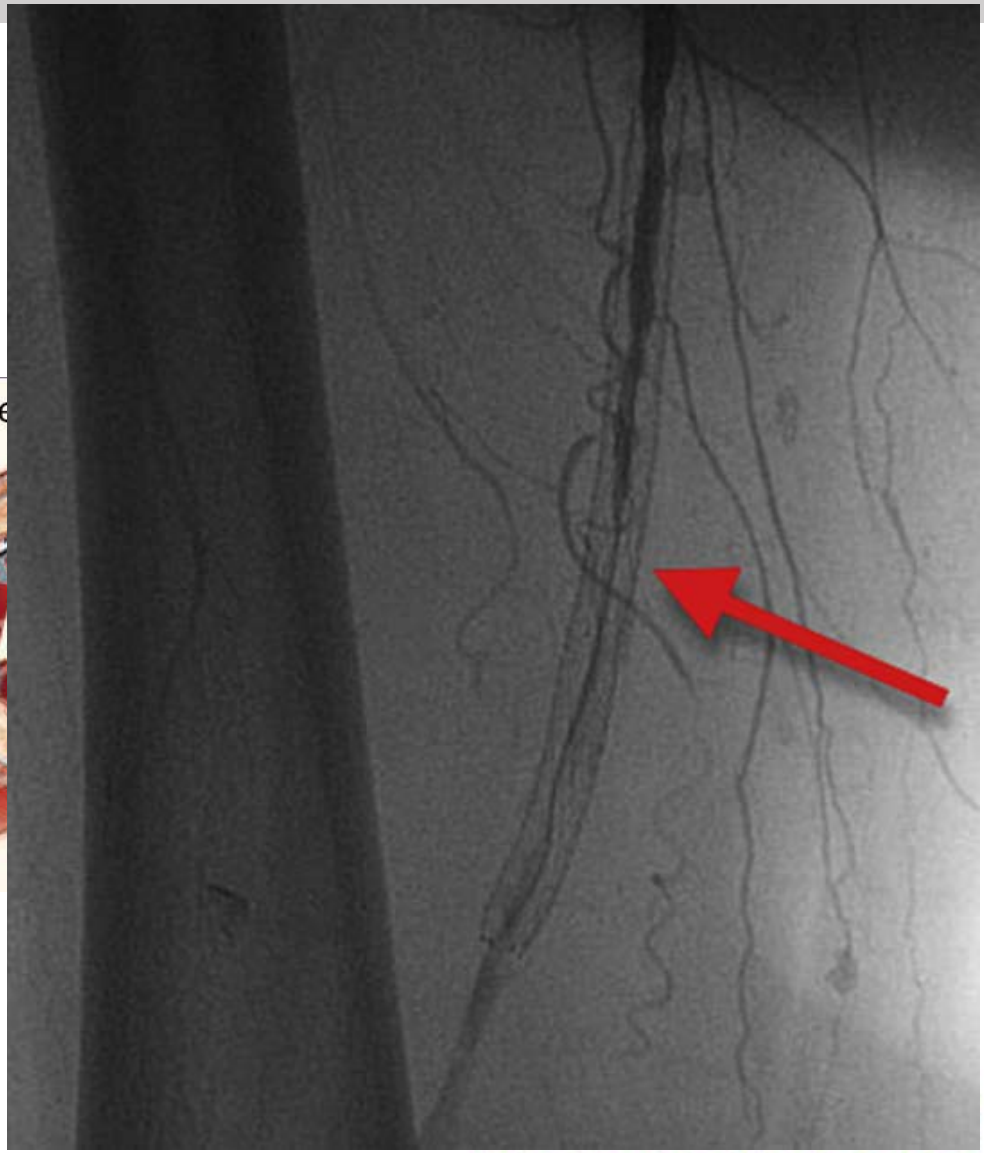
DISCLOSURE

Matthew Menard, MD

- **Advisory Board: Janssen**

In-stent restenosis (ISR)





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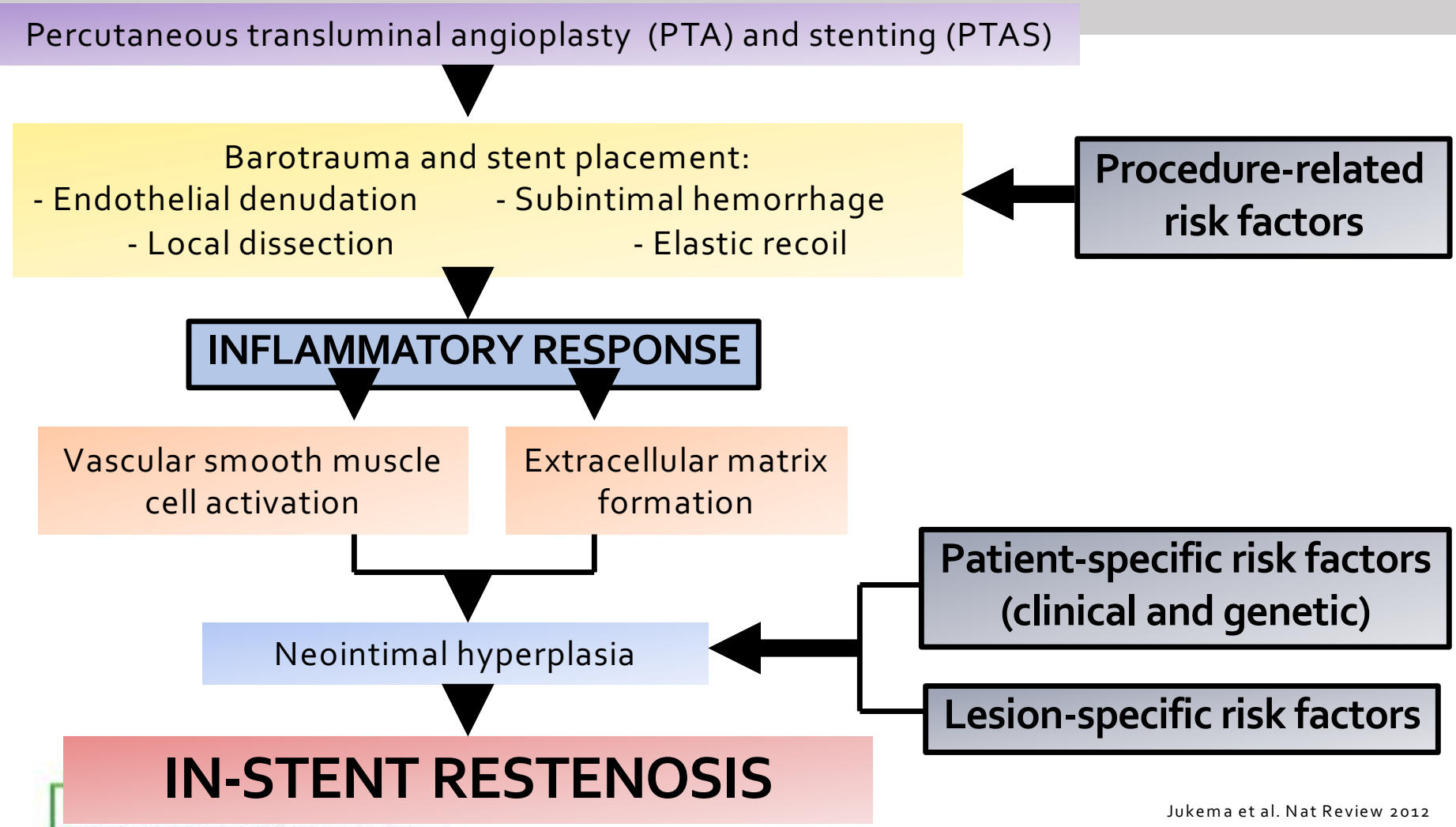
Bittl. NEJM 1996

Pathophysiology of ISR



Jukema et al. Nat Review 2012

Radioactivity

- Radioactive isotopes are made with neutron bombardment of stable elements in a reactor or accelerator
- Large unstable nucleus yearning for peace
- As nucleus decays emanations occur – conservation of mass, energy
  - Alpha, beta, gamma, neutrinos, bosons, …

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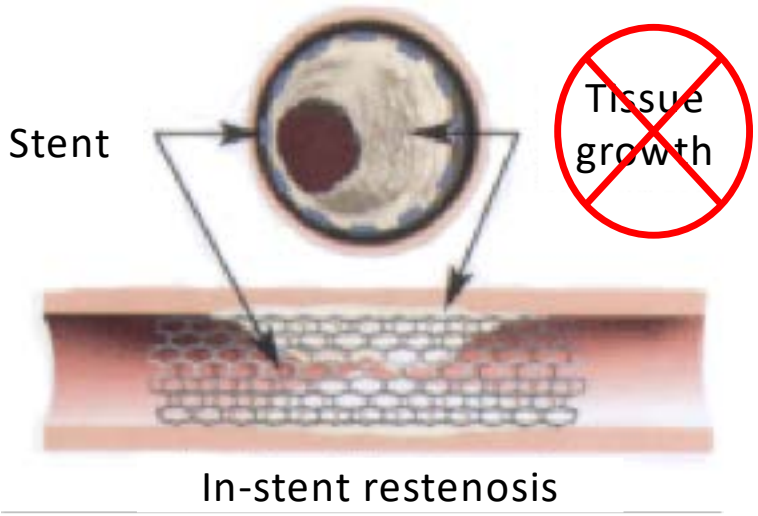
What is brachytherapy?

- Clinical use of radioactive sources to deliver highly **therapeutic** and **palliative** radiation therapy to a range of targets
  - gynecological, urological, pulmonary, head and neck, gastrointestinal, sarcoma, vascular, dermatological, endocrine disease

- Animal models showed that radiation inhibits the effects of vascular smooth muscle proliferation in blood vessels undergoing angioplasty

Endovascular brachytherapy (EVBT)

- EVBT: intraluminal delivery of radiation



γ-emitter
(^{192}Iridium)

- attenuation of collagen synthesis
- suppression of monocyte/macrophage activity
- decrement or delay of smooth muscle cell proliferation

- **approved by FDA for treatment of ISR in 2000**

Historical background

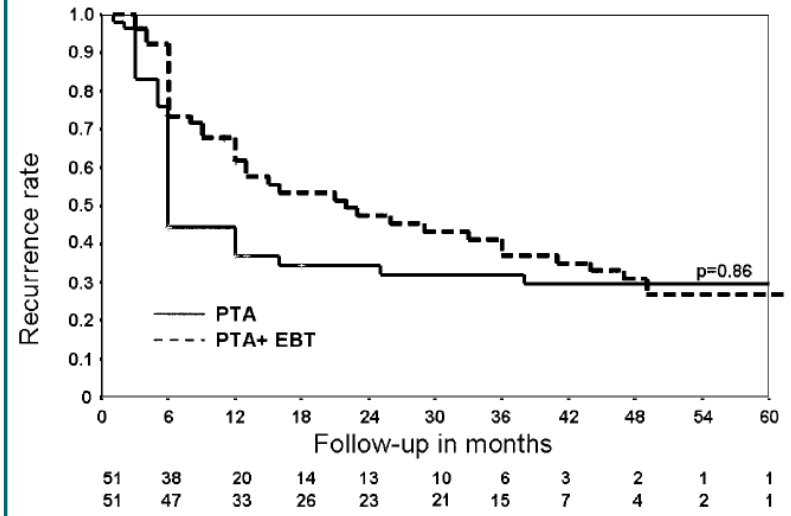
- Initial clinical benefit of brachytherapy for ISR of coronary stents was shown in several trials
  - Gamma 1, Wrist, Long Wrist, Inhibit
- Further application was studied in de novo lesions in the peripheral circulation
  - Vienna and Paris studies

Brachytherapy in the lower extremity: *Vienna-2*

- 102 patients, de novo or restenotic femoropopliteal lesions.
- Randomized to angioplasty and Gamma brachytherapy, or angioplasty alone.
- **No stenting in this trial**

- 6 month restenosis rate:
  - 30% angioplasty and brachytherapy vs
  - 57% for the angioplasty alone group.

- Brachytherapy delayed restenosis recurrence:
  - 17.5 months brachytherapy group vs.
  - 7.4 months in the angioplasty alone group



Kaplan-Meier plot of cumulative recurrence rate after femoropopliteal PTA, according to assigned treatment. Numbers at bottom of figure indicate number of patients at risk. There was no significant difference in patients treated with PTA versus those treated with PTA plus EBT regarding recurrence rate ($P = .86$, log-rank test) during observation period.

Radiology 2006 240(3) 878-844

Effectiveness of treatments for ISR in femoropopliteal artery

Treatment type	Primary patency		Reference
	6 months	1 year	
Repeat balloon angioplasty	27%	--	Dick et al. Radiology 2008
Cutting balloon angioplasty	35%	--	Dick et al. Radiology 2008
Cryoplasty	50% --	0% 28%	Karthik et al. EJVES 2007 Schmieder et al. JVS 2010
Directional atherectomy	--	54%	Zeller et al. JACC 2010
Excimer laser and stent-graft	--	48%	Laird et al. Card Cath Int 2012
PTA, laser, or excisional atherectomy	55%	47.6%	Yeo et al. Card Cath Int 2011
PTA+EVBT	(70%) (67%) 95.2%	-- (57%) 79.8%	Vienna 4 (2001) Vienna 5 (2005) Leipzig 2012

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2012;19:467–475

◆ CLINICAL INVESTIGATION ◆

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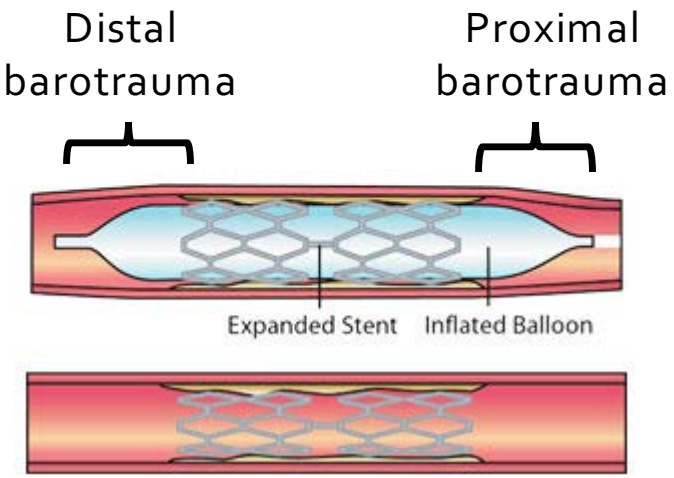
- 90 patients, symptomatic ISR
- > 50% re-restenotic lesions
- Beta-emitting isotope, 13 gray
- 25 cm average lesion length
- Patency: < 50% restenosis by duplex
- 80% 1 year patency

beta-emitting rhenium-188 (Re-188) in patients with long-segment in-stent stenosis in the

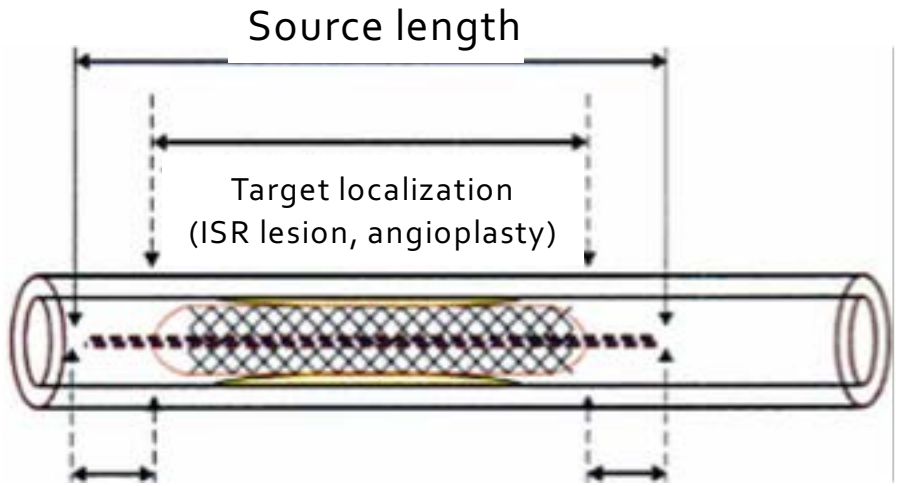
Failure points of prior EVBT studies

EDGE RESTENOSIS

- Restenosis adjacent to the proximal and distal edges of the implanted stent ("edge effect" or "candy wrapper" phenomenon)



Updated protocol for PTA and adjunctive EVBT for ISR



distal
"safety margin"

proximal
"safety margin"

γ-emitter
(^{192}Iridium)

Key features:

- **Higher radiation dose (20 gray)**
- **2 cm"safety margins" of radiation coverage proximal and distal to angioplastied/stented area**
- **Customized treatment depth: 0.5mm + radius of largest PTA balloon**

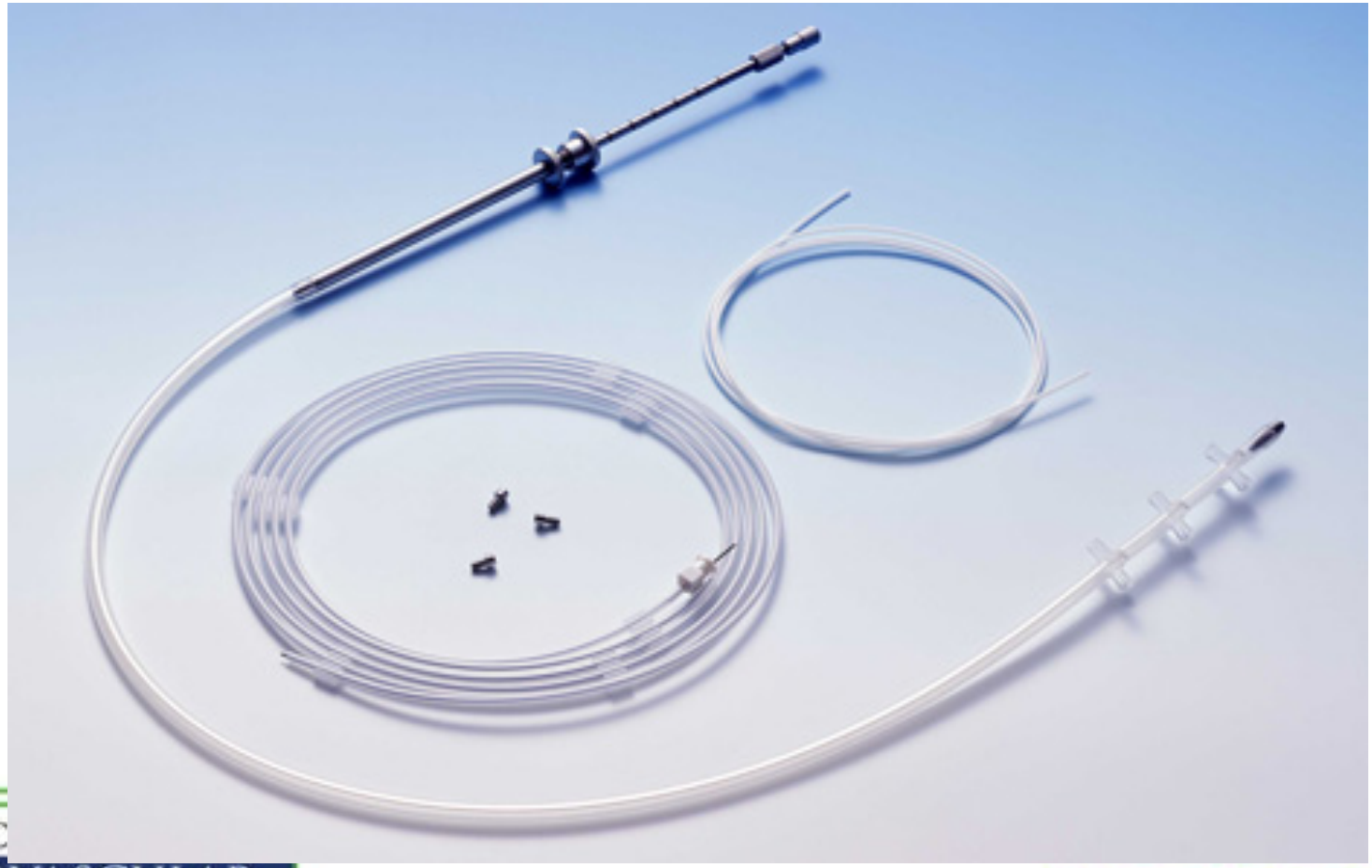
Methods

- Retrospective, single-center review of 43 cases of EVBT for lower extremity ISR at Brigham and Women's Hospital between 2004-2012
- Aspirin and clopidogrel indefinitely
- Stents undergo duplex ultrasound surveillance for recurrent ISR at 1, 3, 6, 9, 12, and 18 months and then yearly
- Primary endpoint: stent patency (primary, primary-assisted, and secondary) at 1 and 2 years
    - Stent patency: freedom from ≥ 50% recurrent stenosis by duplex ultrasound

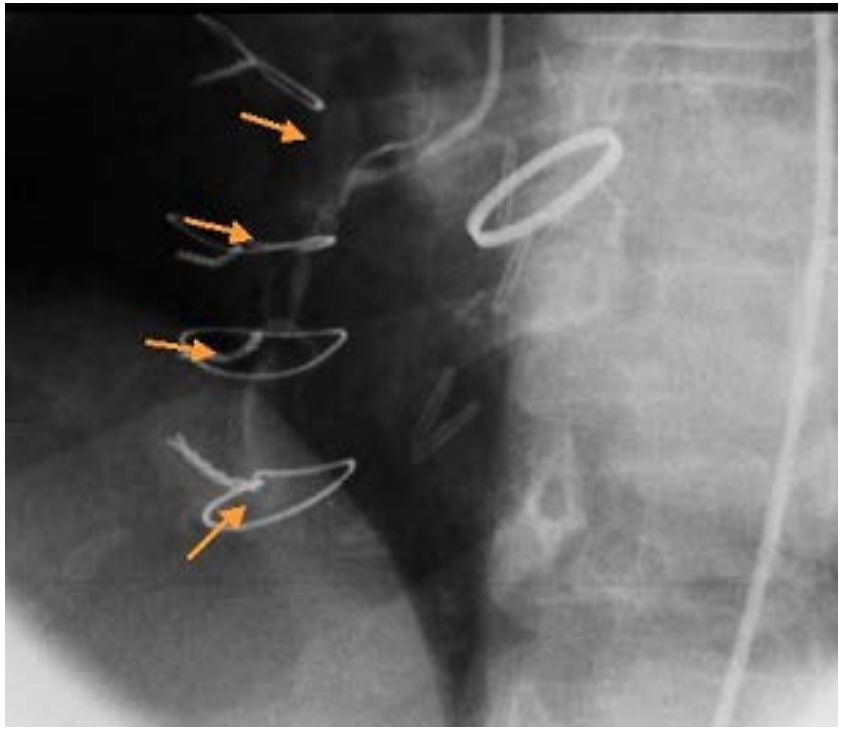
Patient cohort

Stent location	
Iliac artery	9 (21%)
Superficial femoral artery	26 (62%)
Popliteal artery	3 (5%)
Combined SFA and popliteal segments	5 (12%)

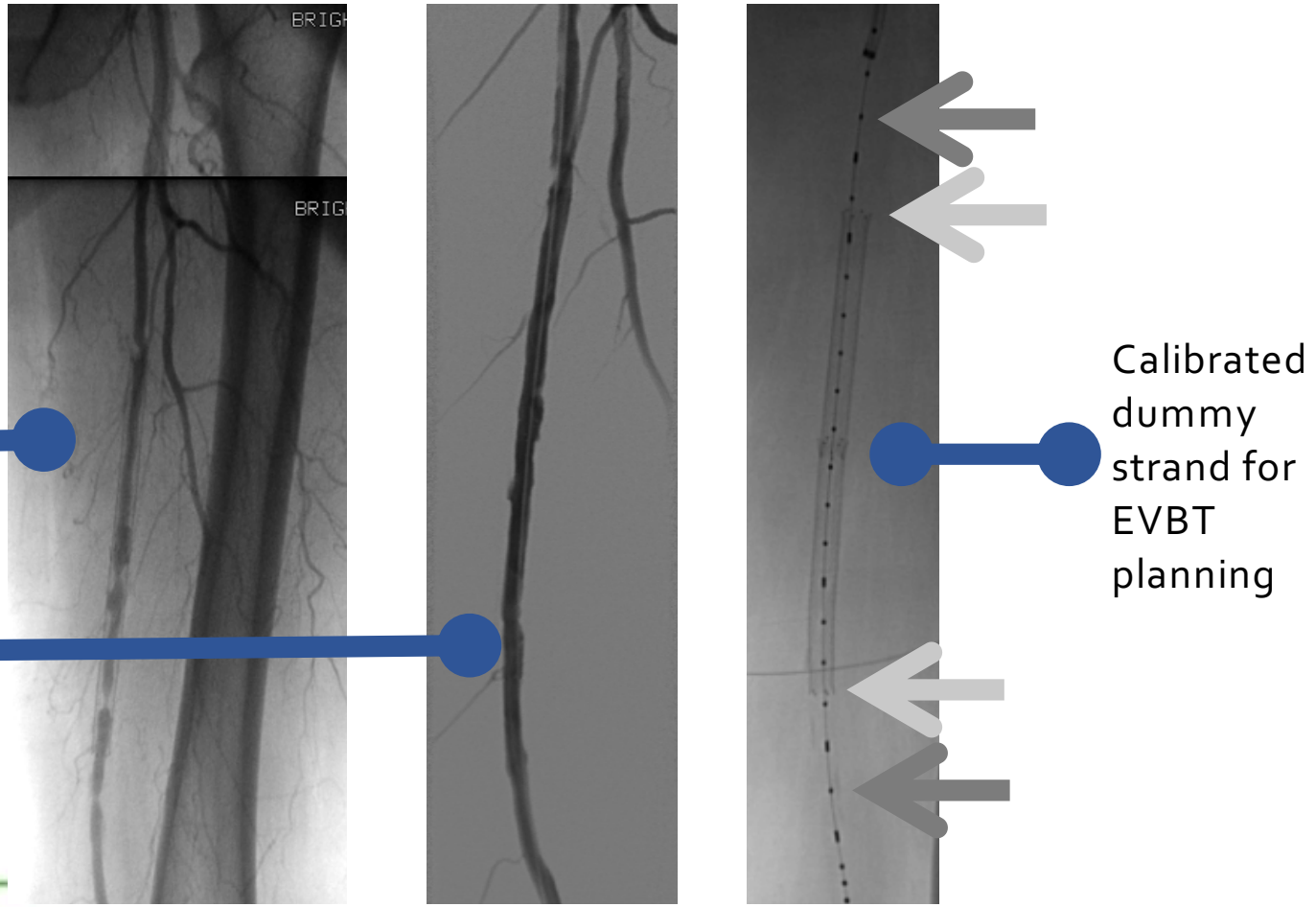
Brachytherapy Catheter



Coronary Artery Brachytherapy



Catheter placement



Indications for Brachytherapy

Claudication Critical stenosis on duplex Critical limb ischemia	16 (50%) 13 (41%) 3 (9%)
At least 1 prior re-intervention for in-stent restenosis	11 (34%)

Technical details

Mean EVBT treated length	24 ±13 cm

Additional stent placement	10 (31%)

Outcomes

- Technical success: 42/43 (98%)
- Follow-up time: 706.3 ± 543.7 days

- Symptom status:
  - Claudicants:
    - Resolved in 18/20 (85%)
    - Improved and then recurred in 2/20

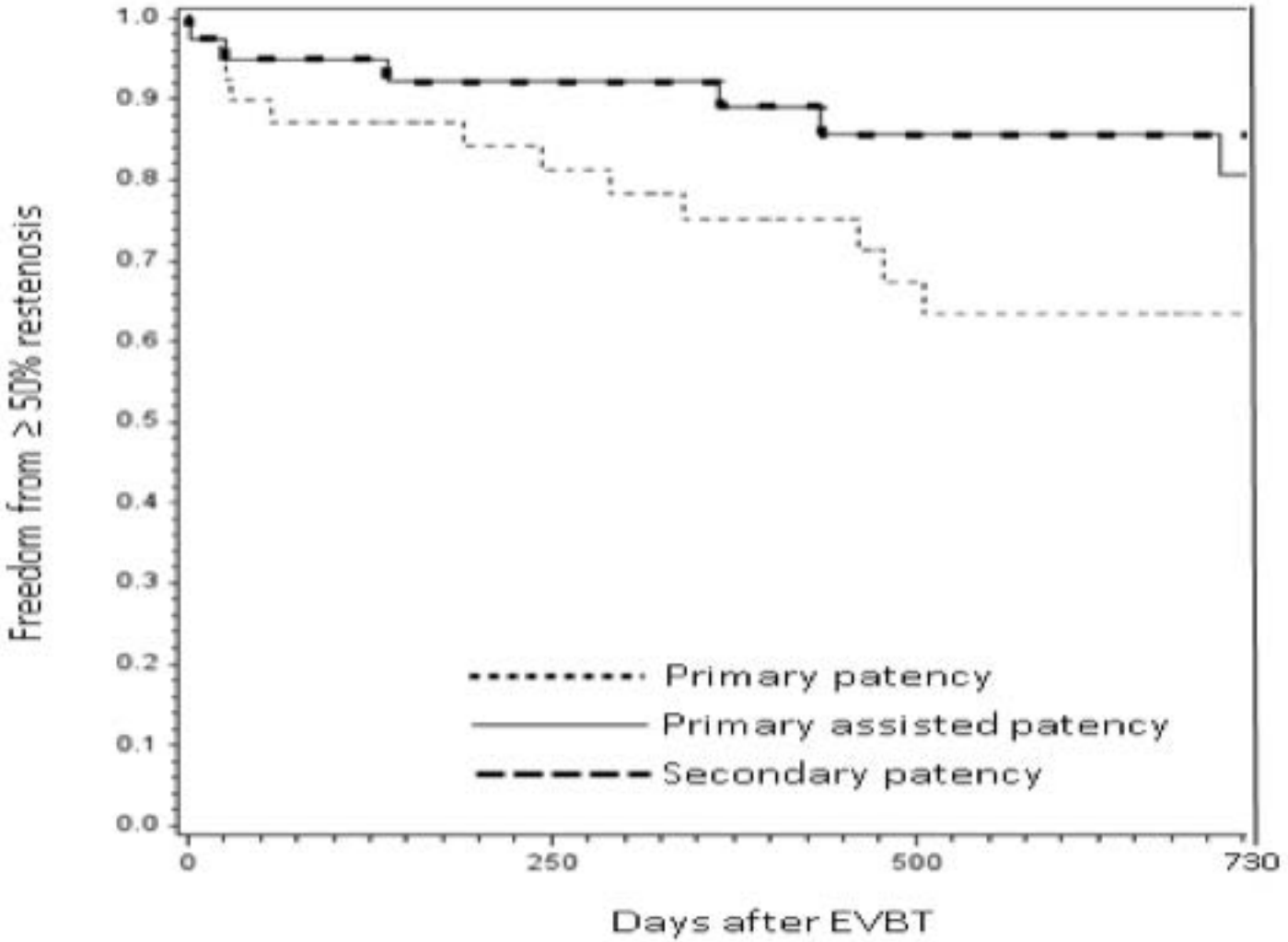
Outcomes

- Recurrent ISR (50-99%) stenosis: 8/42 (19%)
  - Mean time to recurrent ISR: 505 ± 348 days
  - In-stent recurrence: 4/8
  - In-segment recurrence: 4/8
- Early thrombotic occlusion: 2/42 (5%)
  - Time to occlusion: 1 day, 26 days
- Death: 1 (acute coronary syndrome)

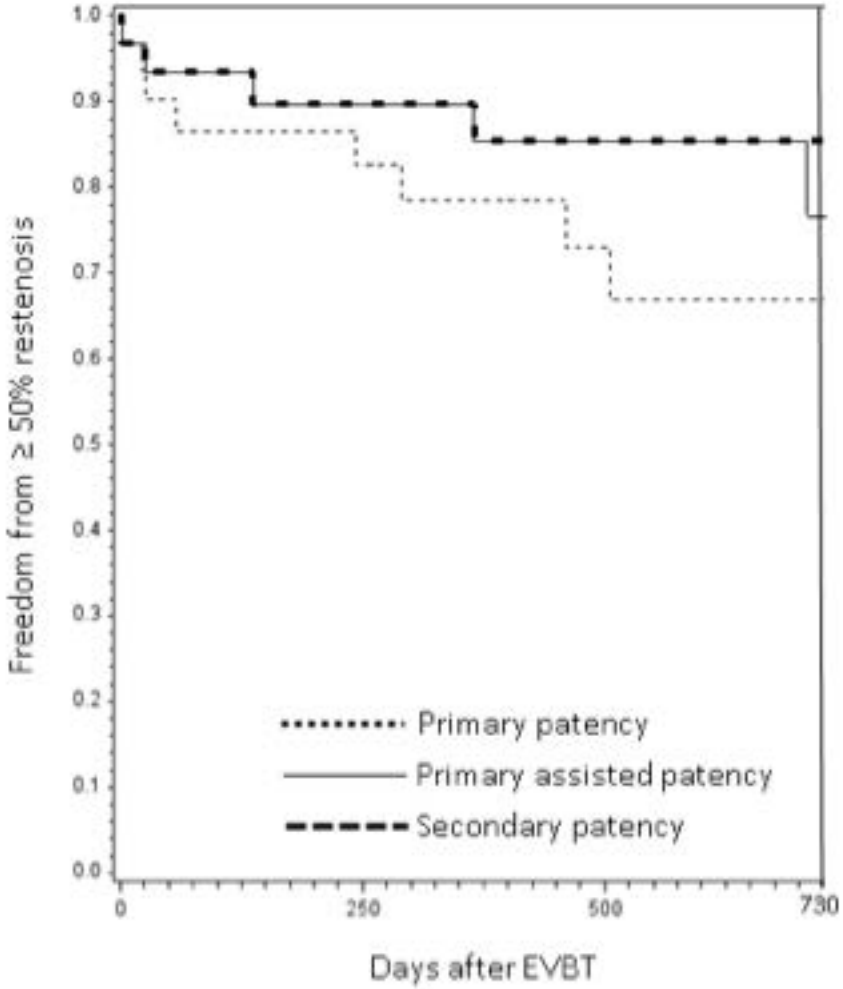
Patency

Time after EVBT	6 months	1 year	2 years
Primary patency	88%	75%	64%
Primary assisted patency	92%	89%	81%
Secondary patency	92%	89%	86%

2-year Patency



Patency after EVBT for femoropopliteal cohort

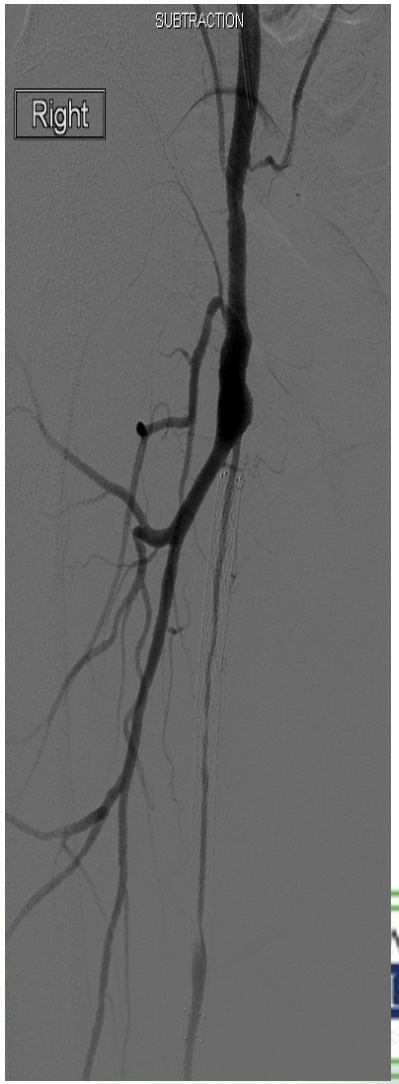


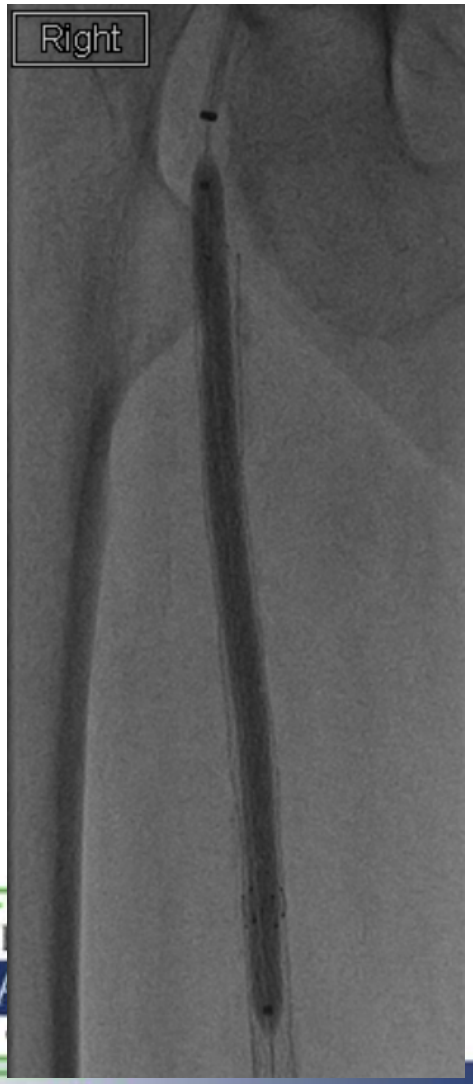
Time after EVBT	6 months (180 days)	1 year (365 days)	2 years (730 days)
Primary patency	86.6% (NAR=22)	78.5% (NAR=17)	66.8% (NAR=7)
Primary assisted patency	89.7% (NAR=23)	85.4% (NAR=19)	76.9% (NAR=8)
Secondary patency	66.8% (NAR=7)	85.4% (NAR=19)	85.4% (NAR=9)

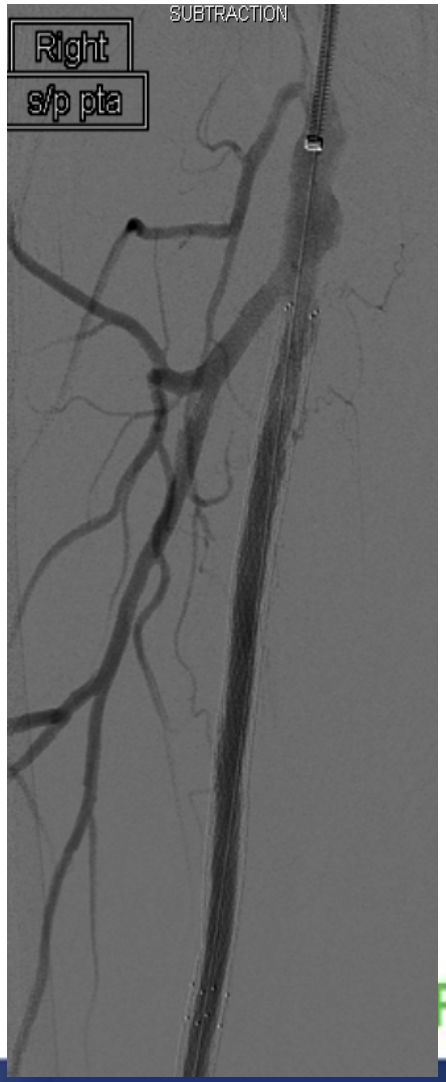
Methods

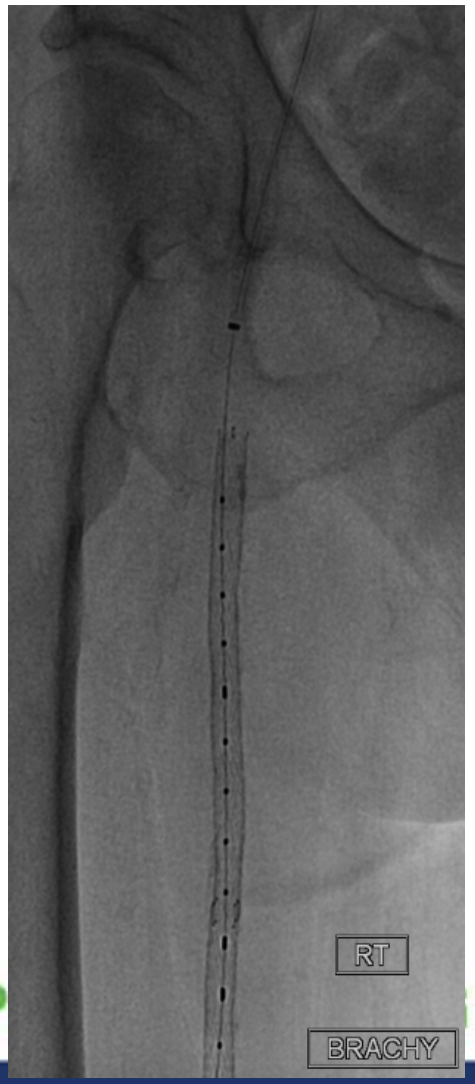
- Retrospective review of consecutive patients who underwent brachytherapy for angiographically proven in-stent restenosis, thrombosis, or occlusion
- 2003 to 2010, Brigham and Women's Hospital
- 42 lower extremities lesions in 32 patients
- Dose 20 gray
- Patient follow-up duration of 5 years

Superficial Femoral Artery Brachytherapy









Index lesion characteristics

Index intervention	N
Iliac	24%
SFA	76%
Popliteal	2%

Index Lesion	N
Lesion length (mean, range)	266, 40-480 mm

Brachytherapy characteristics

Brachytherapy Indication	N
Claudication	95%
Critical limb ischemia	2.5%
Ultrasound (high grade stenosis, no symptoms)	2.5%

Adjunctive treatment

Adjunctive treatment	N
Angioplasty	42/42 (100%)
Stenting	10/42
Atherectomy	4/42
Laser therapy	2/42
Cutting balloon	2/42
Thrombolytics	2/42

Results

- Average improvement in ABIs: 0.35 (.03 to 0.8)

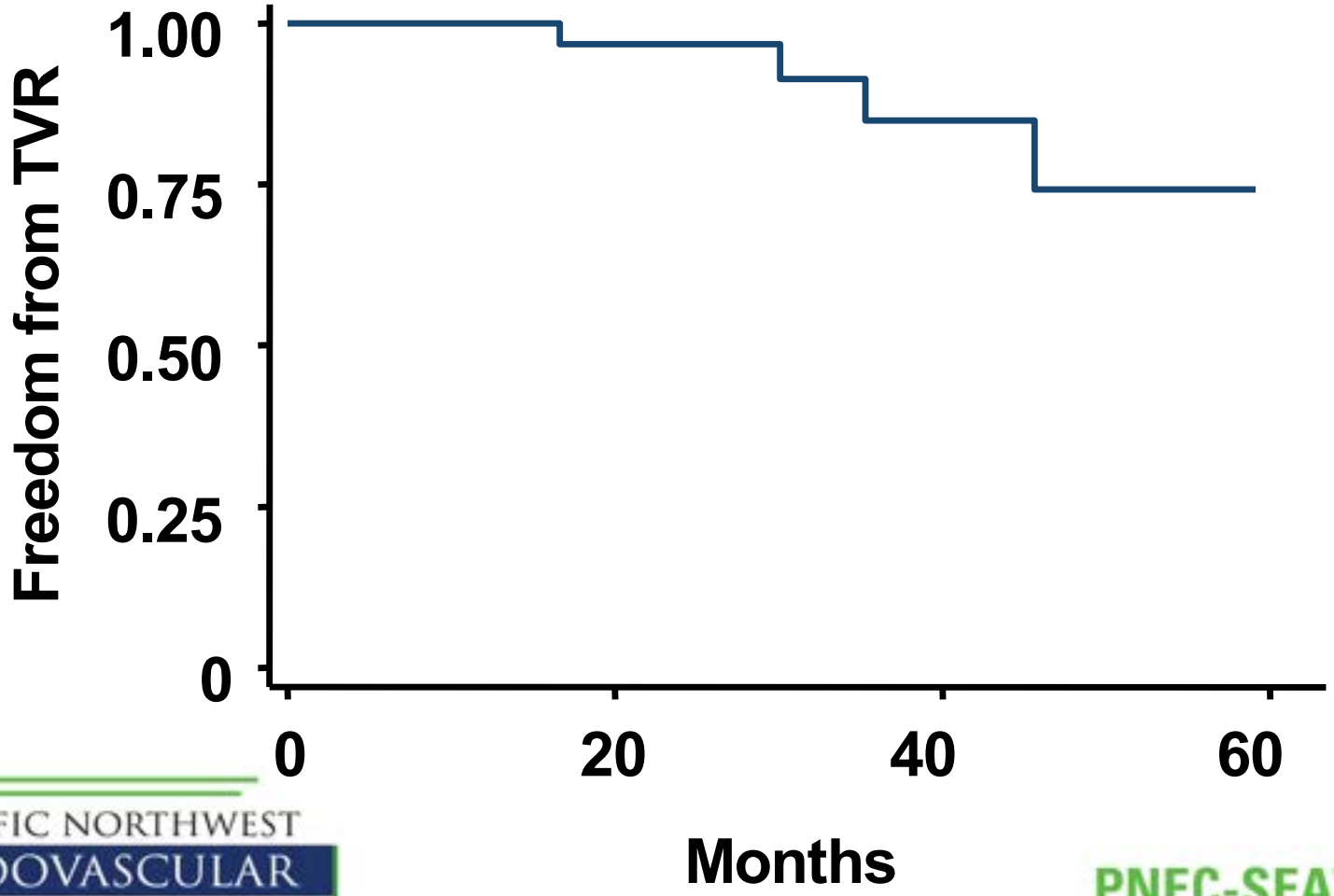
- Overall freedom from Target Vessel Re-intervention by Kaplan-Meier estimates:
  - 100% at 1 year
  - 97% at 2 years
  - 74% at 5 years

Target vessel revascularization

Total cases	5/42 (12%)
Late stent thrombosis	2/5
Restenosis	1/5
Pseudoaneurysm	1/5
Total occlusion	1/5

Note: All cases presented with claudication

5-year Freedom from TVR



Limitations

- Small, single-center, retrospective cohort study
- Logistic challenges to general applicability
  - Need close collaboration between **endotherapist** and **dedicated radiation oncologist**
  - Significant procedural planning
  - Trained staff

Conclusion

Endovascular brachytherapy is an effective and safe adjunctive option in patients with symptomatic lower extremity in-stent restenosis.