



Universiteit  
Leiden  
The Netherlands

## Experimental therapeutic strategies in restenosis and critical limb ischemia

Tongeren, B. van

### Citation

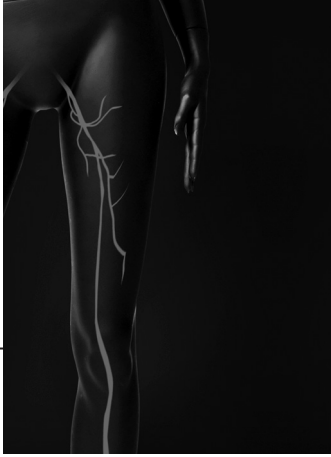
Tongeren, B. van. (2010, April 22). *Experimental therapeutic strategies in restenosis and critical limb ischemia*. Retrieved from <https://hdl.handle.net/1887/15290>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/15290>

**Note:** To cite this publication please use the final published version (if applicable).



**Chapter**

# 02

# Radiotherapy for peripheral vascular disease: an overview

---

*Adapted from: J Cardiovasc Surg. 2000;41:891-895*

M.R.H.M. van Sambeek

T. Hagens

R.B.M. van Tongeren

L.C. van Dijk

J.M. Hendriks

V.L.M.A. Coen

## Abstract

26

The response of cells to ionising radiation has been extensively studied for the past 30 years. When radiation is absorbed in biological material, it can directly ionise a critical site (direct effect) or interact with other molecules to produce reactive free radicals, which can subsequently damage critical biological molecules (indirect effect). DNA is considered the critical target damaged by ionising radiation by both direct and indirect processes. Since radiotherapy had proven to be effective in the treatment of non-malignant proliferative processes, it was assumed that this adjunctive treatment would also inhibit vascular restenosis. The major difference between external and intravascular radiation is dose distribution. Intravascular delivery results in extremely high doses to the lumen with a fall-off in dose as a function of distance from the source; whereas, external beam would deliver a uniform dose over the entire volume of tissue treated. Unlike in the coronary circulation most of the peripheral vessels treated are greater than 3 mm in diameter; in fact many are 7 to 10 mm in diameter. Since beta radiation is related to lower penetration properties and more heterogeneous distribution of radiation in comparison to gamma radiation, it was therefore necessary to use a gamma radiation source because it would be difficult to irradiate the sub-intimal tissue with a beta source centered in a large vessel. Radiation can and does have the potential to destroy blood vessels. The challenge in vascular brachytherapy was to treat blood vessels to a point where restenosis is inhibited; yet the vessel is not irreparably damaged.

## Introduction

Restenosis remains the major problem after endovascular interventions for obstructive disease. After an intervention there are three components that influence the mechanism of restenosis. First, elastic recoil immediately after (over)stretching an artery.

This is an immediate effect and over time there is only minimal further progression of this elastic recoil. Second, restenosis caused by intimal hyperplasia. Most likely, this process starts after a few days and may continue for months to years. The third mechanism is elucidated as constrictive fibrosis. The entire artery may become contracted, resulting in a smaller lumen.<sup>1-3</sup>

Vascular injury causes a cascade of events leading to platelet aggregation and therefore thrombus formation, inflammation, and activation of monocyte-derived macrophages and smooth muscle cells. The smooth muscle cells are stimulated to rapid division by Transforming Growth Factor-(TGF- $\beta$ ) and/or Platelet Derived Growth Factor (PDGF), activated in response to damage to the endothelium. The cause of intimal hyperplasia appears to be the rapid proliferation of smooth muscle cells after migration from the media to the intimal layer. Besides that, a lesion of the vessel wall stimulates adventitial myofibroblasts proliferation and thereby  $\alpha$  smooth muscle actin, leading to a fibrotic response in the adventitia.

Over the last 20 years the focus of restenosis treatment has been through application of pharmacologically active agents, mechanical devices and prosthetic technologies. Unfortunately most of these methods have proven to be of limited success in the battle against restenosis.

Since the discovery of radium by Madame Curie in 1898, ionizing radiation has been well known as an antiproliferative agent. Since radiotherapy had prove to be effective in the treatment of non-malignant proliferative processes such as the fibroblastic activity of keloid scar formation and ocular pterygia, it was assumed that this adjunctive treatment would also inhibit vascular restenosis. This was the beginning of a new field in medicine called vascular brachytherapy.

In 1994 it was Liermann *et al.* who performed and published the first cases of vascular brachytherapy in patients who had undergone a PTA of the femoropopliteal artery.<sup>6</sup> After these first clinical applications a lot of experimental work was performed by Wiedermann, Waksman and Mazur.<sup>7-9</sup>

Radiation can and does have the potential to destroy blood vessels (e.g. radiation for Hodgkin's disease and radiation for arteriovenous malformation). The challenge is to treat blood vessels to a point where restenosis is inhibited; yet the vessel should not be irreparably damaged.

## Radiation biology

When radiation is absorbed in biological material, it can directly ionize a critical site (direct effect) or interact with other molecules to produce reactive free radicals, which can subsequently damage critical biological molecules (indirect effect). DNA is considered the critical target damaged by ionizing radiation (by both direct and indirect processes) by formation of exchange-type aberrations.

There is a dose-response linear-quadratic relation between the fraction of cells surviving and the dose. At low doses, the linear component dominates, but at higher doses, the term that is quadratic in dose starts to dominate.<sup>10</sup>

One of the most important consequences of exposure of biological tissue to ionizing radiation is the loss of the cell's ability to reproduce, which ultimately results in the death of the cell. Cell death should be distinguished from the intuitive concept we have of death: that is, complete and irreversible loss of all functions. While it is true that super-high dose of radiation (in the region of several hundred Gray) will certainly cause such an effect, lower radiation doses will not give such an effect. In fact, the vast majority of such irradiated cells appears morphologically normal and continues to perform complex biological functions including protein and DNA synthesis. However, in terms of continued health of that biological tissue, a proportion of these cells will lose their ability to sustain reproduction and will die at the next mitosis.<sup>11</sup>

Cells proliferate and multiply, therefore, individual cells traverse through a distinct cell cycle containing: mitosis, G1, S and G2 phase. Since the 60's it is already known that the cell radiosensitivity varies as a function of cell cycle position.<sup>12</sup> Cells in G2 and mitosis are the most radiosensitive, while cells in the late S phase are the most resistant to a given dose of radiation.

Taking the *in vitro* cell survival data of smooth muscles cell in to account it appears that a dose of 12 to 20 Gray is efficacious in preventing restenosis. From experimental systems it is documented that the biological effect of a given dose rate is decreases when the dose is delivered at a low dose over a longer period of time.<sup>13</sup>

A number of radionuclides have been under investigation for vascular brachytherapy. Some of the most commonly used are shown in Table I.

**Table I.** Radionuclides under investigation for vascular brachytherapy.

Radionuclide	Emission	Half-life
<sup>32</sup> P	β	14 day
<sup>90</sup> Y	β	2.7 day
<sup>90</sup> SR/ <sup>90</sup> Y	β	29 year/2.7 day
<sup>103</sup> Pd	X	17 day
<sup>188</sup> RE	β	17 hr
<sup>188</sup> W	β	60 day
<sup>102</sup> Ir	γ	74 day

### External beam radiation versus endovascular radiation

Ionizing radiation, to prevent restenosis after an intervention, can be administered in 2 fashions: by external beam irradiation or endovascular brachytherapy (therapy from a short distance). The main advantage of external beam radiotherapy is the homogeneity of dose distribution at the target field, with no overdose to specific layers. Another advantage is that this technique is noninvasive and therefore can be delayed for hours or days, at a time when more cells are proliferating. It also can be more efficiently fractionated in several doses. The major drawback of external beam radiation is the possible long-term effect on the irradiated vessels and the adjacent structures. In theory, these drawbacks could be eliminated with the use of stereotactic radiotherapy. There has been considerable controversy regarding the use of external beam radiation treatment to prevent restenosis. External beam irradiation is mainly used when a superficial location is involved such as the anastomotic sites of an AV dialysis shunt.<sup>14</sup>

The major difference between external and endovascular radiation is dose distribution. Endovascular delivery results in extremely high doses to the lumen with a fall-off in dose as a function of distance from the source (Table II); whereas, external beam would deliver a uniform dose over the entire volume of tissue treated. Therefore, endovascular irradiation is more suitable for blood vessels at a deeper location.

Endovascular irradiation can be delivered by catheter-based systems immediately after an endovascular intervention (or by radioactive stents). Usually endovascular irradiation is delivered by an afterloader system. "Unloaded" tubes are positioned at the target site to be irradiated. Subsequently they are loaded with the radioactive source (hence the term "afterloader"). In the early days this afterloading was performed manually, but in the currently used "remote afterloaders" the radioactive source is stored in a shielded container and inserted into the tubes via a remote controlled afterloading device.<sup>15</sup> High-activity  $\beta$  or  $\gamma$  seeds, pellets, capsules and wires can be used for this purpose. To provide a homogenous intramural radiation dose delivery, a special centering balloon was developed to assure optimal centering. Some spiral designs even permit continuous flow during the period of irradiation.

**Table II.** Dose distribution for <sup>192</sup>Ir.

Depth (mm)	Dose (cGray)
3	1200
4	877
6	551
8	396
10	303

### Beta versus gamma radiation

Radioactivity is the process in which atomic nuclei spontaneously change their configuration and energy content. This event normally brings a change in the basic

element itself that is known as radioactive disintegration. This process is associated with emission of particulate or electromagnetic radiation. The particulate radiation is either  $\gamma$  emission or  $\beta$  emission.  $\beta$  particles are lightweight  $\beta$  particles and possess positive or negative charge. They can only travel through tissue over a limited distance. Gamma emission takes the form of electromagnetic radiation. The electromagnetic  $\gamma$  rays arise in the atomic nuclei and may have a very complicated spectrum consisting of many energy values.

In the cases of catheter-based endovascular brachytherapy both  $\beta$  and  $\gamma$  sources are being used (Table I).  $\beta$  radiation is related to lower penetration properties and more heterogeneous distribution of radiation in comparison to  $\gamma$  radiation. There is an ongoing discussion about the ideal isotope for endovascular brachytherapy. Radiation protection issues and the possibility to use a  $\beta$  isotope in a regular angiosuite make this isotope an attractive choice. In coronary arteries the efficacy of  $\beta$  radiation is proven although dose-finding studies are still ongoing.

Unlike in the coronary circulation most of the peripheral vessels treated are greater than 3 mm in diameter; in fact many are 7 to 10 mm in diameter. It is therefore necessary to use a  $\gamma$  radiation source because it would be difficult to irradiate the subintimal tissue with a  $\beta$  source centered in a large vessel. The main reason for this is the less rapid fall-off dose of the  $\gamma$  with the distance from the source.<sup>16</sup> The dose distribution for  $^{192}\text{Ir}$  is shown in Table II. The risk to the nearby nerves can be considered minimal.<sup>17</sup>

Although it would be possible to bring a high dose rate afterloader in the OR or angiosuite, room modifications necessary to meet radiation safety requirements make this impractical. Therefore treatment delivered by  $\beta$  radiation should take place in the radiation oncology department.

### **Clinical trials**

After the experimental and animal brachytherapy studies, many investigators were encouraged to initiate clinical studies in humans. Although Liermann and Schopohl were the first to perform such a study, using radiation in the peripheral vascular system, most of the development in this field and, therefore most of the research, derived from studies in coronary arteries. Following numerous studies that examined feasibility and the short-term safety, several large randomised trials generated the evidence of effectiveness in reduction of intimal hyperplasia. Initially in the cardiac setting, later in the peripheral vascular field.

#### *Coronary arteries*

Both  $\beta$  and  $\gamma$  emitters were used in the clinical trials for intracoronary brachytherapy. Although  $^{192}\text{Ir}$  is the only  $\gamma$  emitter in use, a large variety of  $\beta$  were tested, such as  $^{32}\text{P}$ ,  $^{90}\text{Y}$ ,  $^{90}\text{Sr}/^{90}\text{Y}$ ,  $^{188}\text{Re}$  and  $^{188}\text{W}$ . Radiation doses ranging from 8 to 30 gray were used, as well as a variety of delivery systems. The clinical studies using  $\beta$  emitters were initially carried



out to prevent in-stent restenosis. Later trials were designed to study the effectiveness in preventing restenosis in *de novo* lesions. The search for the ideal isotope and/or the most favorable has been ongoing. Based on the result of three randomised clinical trials using  $\gamma$  radiation, the investigators of these studies considered this therapy standard therapy for patients presenting with in-stent restenosis in the coronary arteries.<sup>18-20</sup> The most important randomised clinical trials using either  $\beta$  or  $\gamma$  emitters are summarized in Table III. At the time there were no randomised studies on radioactive stents.

**Table III.** Randomised clinical trials using catheter-based intracoronary brachytherapy for native coronary and in-stent restenosis.

Study	No.	ISR lesion	Source	Dose (Gy)	Follow-up (mth)	Restenosis (%)		P-value
						EBT	Placebo	
Teirstein <sup>18,21</sup> (97/00)	55	ISR	<sup>192</sup> Ir	26	36	33	64	<0.05
Waksman <sup>19</sup> (2000)	130	ISR	<sup>192</sup> Ir	15	6	19	58	0.001
Raizner <sup>20</sup> (2000)	105	N	<sup>32</sup> P	16,20,24	6	8	39	0.01
Leon <sup>22</sup> (2001)	252	ISR	<sup>192</sup> Ir	30	9	22	51	0.01
Popma <sup>23</sup> (2001)	476	ISR	<sup>90</sup> SR/Y	18 or 23	8	27	45	0.002
Waksman <sup>24</sup> (2002)	332	ISR	<sup>32</sup> P	20	9	26	52	0.0001

N= de novo; ISR= in-stent restenosis; EBT= endovascular brachytherapy

### Peripheral arteries

In the peripheral vasculature only  $\gamma$  radiation by a <sup>192</sup>Ir radiation source is feasible. Some randomised controlled studies showed very significant results in the superficial femoral artery after 6-12 months follow-up.

All randomised clinical trials using  $\gamma$  emitters in the peripheral arteries are summarized in Table IV.

**Table IV.** Randomised clinical trials using irradiation therapy after PTA in the femoropopliteal artery.

Study	No.	lesion	Source	Dose (Gy)	Follow-up (mth)	Restenosis (%)		P-value
						Radiation	Placebo	
Minar <sup>25</sup> (2000)	113	N/R	<sup>192</sup> Ir	12	6	28	54	<0.05
Zehnder <sup>26</sup> (2003)	100	R	<sup>192</sup> Ir	12	12	23	42	0.03
Pokrajac <sup>27</sup> (2005)	134	N/R	<sup>192</sup> Ir	18	12	42	67	<0.05
Tongeren <sup>28</sup> (2005)	60	N	<sup>192</sup> Ir	14	12	35	44	0.51
Wolfram <sup>29</sup> (2005)	88	N+S	<sup>192</sup> Ir	14	12	33	35	0.89
Diehm <sup>30</sup> (2005)	83	N/R	<sup>192</sup> Ir	14	36	36	53	0.16
Wolfram <sup>31</sup> (2006)	102	N/R	<sup>192</sup> Ir	12	60	73	73	0.99
Fritz <sup>32</sup> (2004)	95	N/R	EBI	21	12	46	33	0.29
Zabakis <sup>33</sup> (2005)	60	N+S	EBI	24	12	47	80	0.02
Therasse <sup>34</sup> (2005)	99	N	EBI	7,10,14*	12	65,48,25*	50	<0.001*
Zampakis <sup>35</sup> (2007)	60	N+S	EBI	24	36	55	71	0.04

N=de novo; R=recurrent; S=stent \*only significant after 14 gy

## Conclusions

With vascular brachytherapy an exciting era was entered for the interventionist in the battle against restenosis. Many questions were still to be answered, but the short term results were more than promising. At the time, many cardiology centers embraced this new technique as a standard, adjunctive treatment for some of their interventions and initiated a close co-operation with the radiotherapists. Peripheral vascular brachytherapy, and therefore using  $\gamma$  radiation, made this technique more cumbersome. Especially for these cases requirements and health care milieu regulations were very demanding.

## References

- Mintz GS, Popma JJ, Pichard AD. Mechanisms of later arterial response to transcatheter therapy: a serial quantitative angiographic and intravascular ultrasound study. *Circulation* 1994; 90:124
- Post MJ, Borst C, Kuntz RE. The relative importance of arterial remodeling compared with intimal hyperplasia in lumen renarrowing after balloon angioplasty. A study in the normal rabbit and the hypercholesterolemic Yucatan micropig. *Circulation* 1994;89:2816-2821.
- van Lankeren W, Gussenhoven EJ, Honkoop J, Stijnen T, van Overhagen H, Wittens CH, Kranendonk SE, van Sambeek MR, van der Lugt A. Plaque area increase and vascular remodeling contribute to lumen area change after percutaneous transluminal angioplasty of the femoropopliteal artery: an intravascular ultrasound study. *J Vasc Surg* 1999;29:430-441.
- Enhamre A, Hammar H. Treatment of keloids with excision and postoperative X-ray irradiation. *Dermatologica* 1983;167:90-93.
- Bahrassa F, Datta R. Postoperative beta radiation treatment of pterygium. *Int J Radiat Oncol Biol Phys* 1983;9:679-684.
- Liermann D, Böttcher HD, Kollath J, Schopohl B, Strassmann G, Strecker EP, Breddin KH. Prophylactic endovascular radiotherapy to prevent intimal hyperplasia after stent implantation in femoropopliteal arteries. *Cardiovasc Intervent Radiol* 1994;17:12-16.
- Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J. Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model. *J Am Coll Cardiol* 1994;23:1491-1498.
- Waksman R, Robinson KA, Crocker IR, Gravanis MB, Cipolla GD, King SB 3rd. Endovascular low-dose irradiation inhibits neointima formation after coronary artery balloon injury in swine. A possible role for radiation therapy in restenosis prevention. *Circulation* 1995;91:1533-1539.
- Mazur W, Ali MN, Khan MM, Dabaghi SF, DeFelice CA, Paradis P Jr, Butler EB, Wright AE, Fajardo LF, French BA, Raizner AE. High dose rate intracoronary radiation for inhibition of neointimal formation in the stented and balloon-injured porcine models of restenosis: angiographic, morphometric, and histopathologic analyses. *Int J Radiat Oncol Biol Phys* 1996;36:777-788.
- Hall EJ, Miller RC, Brenner DJ. The basic radiology of intravascular irradiation. In: Waksman R, editor. *Vascular brachytherapy*. Armonk, NY: FuturaPublishing Co 1999:63-72.
- Mitchell JB. Radiation biology concepts for the use of radiation to prevent restenosis. In: Waksman R, editor. *Vascular brachytherapy*. Armonk, NY: FuturaPublishing Co 1999:83-102.
- Terasima T, Tolmach LJ. Changes in x-ray sensitivity of HeLa cells during the division cycle. *Nature* 1961;190:1210-1211.
- Hall EJ, Brenner DJ. The dose-rate effect revisited: radiobiological considerations of importance in radiotherapy. *Int J Radiat Oncol Biol Phys* 1991;21:1403-14.
- Parikh S, Nori D, Rogers D, Charytan C, Osian A, Al-Saloum M, Cavallo G. External beam radiation therapy to prevent postangioplasty dialysis access restenosis: a feasibility study. *Cardiovasc Radiat Med* 1999;1:36-41.
- Henschke UK, Hilaris BS, Mahan GD. Remote afterloading with intracavitary applicators. *Radiology* 1964;83:344-345.
- Liermann D, Bauernsachs R, Schopohl B, Böttcher HD. Intravascular irradiation therapy. In: Waksman R, editor. *Vascular brachytherapy*. Armonk, NY: FuturaPublishing Co 1999:395-405.
- LeCouteur RA, Gillette EL, Powers BE, Child G, McChesney SL, Ingram JT. Peripheral neuropathies following experimental intraoperative radiation therapy (IORT). *Int J Radiat Oncol Biol Phys* 1989;17:583-590.
- Teirstein PS, Massullo V, Jani S, Popma JJ, Mintz GS, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Morris NB, Leon MB, Tripuraneni P. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *New Engl J Med* 1997;336:1697-1703.
- Waksman R, White RL, Chan RC, Bass BG, Geirlach L, Mintz GS, Satler LF, Mehran R, Serruys PW, Lansky AJ, Fitzgerald P, Bhargava B, Kent KM, Pichard AD, Leon MB. Intracoronary gamma radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis (WRIST). *Circulation* 2000;101:2165-2171.
- Raizner AE, Oesterle SN, Waksman R, Serruys PW, Colombo A, Lim YL, Yeung AC, van der Giessen WJ, Vandertie L, Chiu JK, White LR, Fitzgerald PJ, Kaluza GL, Ali NM. Inhibition of restenosis with beta-emitting radiotherapy: report of the proliferation reduction with vascular energy trial (PREVENT). *Circulation* 2000;102:951-958.
- Teirstein PS, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Sirkin K, Cloutier DA, Leon MB, Tripuraneni P. Three year clinical and angiographic follow-up after intracoronary radiation:

- results of a randomized clinical trial. *Circulation* 2000;101:360–365.
22. Leon MB, Teirstein PS, Moses JW, Tripuraneni P, Lansky AJ, Jani S, Wong SC, Fish D, Ellis S, Holmes DR, Kerieakes D, Kuntz RE. Localized intracoronary gamma radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001;344:250–256.
  23. Popma JJ, Suntharalingam M, Lansky AJ, Heuser RR, Speiser B, Teirstein PS, Massullo V, Bass T, Henderson R, Silber S, von Rottkay P, Bonan R, Ho KK, Osattin A, Kuntz RE; Stents And Radiation Therapy (START) Investigators. Randomized trial of 90Sr/90Y beta-radiation versus placebo control for treatment of in-stent restenosis. *Circulation* 2002;106:1090–1096.
  24. Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L. Use of localized intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomized controlled trial. *Lancet* 2002;359:551–557.
  25. Minar E, Pokrajac B, Maca T, Ahmadi R, Fellner C, Mittlböck M, Seitz W, Wolfram R, Pötter R. Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty. *Circulation* 2000; 102:2694–2699.
  26. Zehnder T, von Briel C, Baumgartner I, Triller J, Greiner R, Mahler F, Do DD. Endovascular brachytherapy after percutaneous transluminal angioplasty of recurrent femoropopliteal obstructions. *J Endovasc Ther* 2003;10:304–311.
  27. Pokrajac B, Pötter R, Wolfram RM, Budinsky AC, Kirisits C, Lileg B, Mendel H, Sabeti S, Schmid R, Minar E. Endovascular brachytherapy prevents restenosis after femoropopliteal angioplasty: results of the Vienna-3 randomised multicenter study. *Radiother Oncol* 2005;74:3–9.
  28. Van Tongeren RB, van Sambeek MR, van Overhagen H, Coen VL, Schmitz PI, Gescher FM, Wittens CH, Vernhout RM, van Urk H, Levendag PC, Bruijninx CM. Endovascular brachytherapy for the prevention of restenosis after femoropopliteal angioplasty. Results of the VARA Trial. *J Cardiovasc Surg* 2005;46:437–443.
  29. Wolfram RM, Budinsky AC, Pokrajac B, Pötter R, Minar E. Vascular brachytherapy with 192Ir after femoropopliteal stent implantation in high-risk patients: twelve-month follow-up results from the Vienna-5 trial. *Radiology* 2005;236:343–351.
  30. Diehm N, Silvestro A, Do DD, Greiner R, Triller J, Mahler F, Baumgartner I. Endovascular brachytherapy after femoropopliteal balloon angioplasty fails to show robust clinical benefit over time. *J Endovasc Ther* 2005;12:723–730.
  31. Wolfram RM, Budinsky AC, Pokrajac B, Potter R, Minar E. Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty: five-year follow-up—prospective randomized study. *Radiology* 2006;240:878–884.
  32. Fritz P, Stein U, Hasslacher C, Zierhut D, Wannenmacher M, Pritsch M. External beam radiotherapy fails to prevent restenosis after iliac or femoropopliteal percutaneous transluminal angioplasty: results of a prospective randomized double-blind study. *Int J Radiat Oncol Biol Phys* 2004;59:815–821.
  33. Zabakis P, Kardamakis DM, Siablis D, Kalogeropoulou C, Karnabatidis D, Malatara G, et al. External beam radiation therapy reduces the rate of re-stenosis in patients treated with femoral stenting: results of a randomised study. *Radiother Oncol* 2005;74:11–16.
  34. Therasse E, Donath D, Lespérance J, Tardif JC, Guertin MC, Oliva VL, Soulez G. External beam radiation to prevent restenosis after superficial femoral artery balloon angioplasty. *Circulation* 2005;111:3310–3315.
  35. Zampakis P, Karnabatidis D, Kalogeropoulou C, Kardamakis DM, Katsanos K, Skouras T. External beam irradiation and restenosis following femoral stenting: long-term results of a prospective randomized study. *Cardiovasc Intervent Radiol* 2007;30:362–369

