Intra-arterial Brachytherapy for Prevention and Managing Restenosis after Percutaneous Transluminal Angioplasty (PTA)

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Description

Intravascular brachytherapy in conjunction with percutaneous transluminal angioplasty (PTA) has been investigated primarily in the coronary arteries but also in the femoropopliteal system. In the coronary arteries, 2 clinical applications of intravascular brachytherapy have been investigated:

1. As a technique to reduce the risk of de novo restenosis after intracoronary stent placement (i.e., in-stent restenosis)

The risk of restenosis in patients who undergo percutaneous transluminal coronary angioplasty (PTCA) for coronary artery disease is estimated at 30%–50%, based on angiographic studies. Placement of stents as an adjunct to PTCA is one strategy to reduce restenosis; it is estimated that approximately 75% of PTCAs performed in the United States includes stent placement. However, even with stent placement, the restenosis rate (i.e., in-stent restenosis) is estimated at 20%. Intracoronary radiation has been investigated both as an alternative to stent placement to reduce the risk of restenosis and as a technique to reduce the risk of in-stent restenosis. This application of intracoronary brachytherapy is an off-label indication.

2. As a treatment of restenosis at the site of a prior intracoronary stent
As noted here, there is about a 20% risk of in-stent restenosis. Management of in-stent restenosis is notoriously ineffective, with recurrence rates of 30%–70%. Management has included PTCA alone, restenting, laser angioplasty, and rotational atherectomy. These therapies, however, are often ineffective, requiring medical management or surgical revascularization. Intracoronary brachytherapy is an alternative to these therapies for the management of in-stent restenosis.

Intravascular brachytherapy has also been investigated as an adjunct to percutaneous transluminal angioplasty of the femoropopliteal systems, as a technique to reduce the risk of a de novo restenosis, either in native or grafted vessels, both with or without stent placement. The greatest amount of clinical experience with intravascular brachytherapy is in the coronary artery system. However there are a number of important differences that preclude extrapolation of results from the coronary to the peripheral arterial system. There is greater anatomic variability in peripheral arteries than coronary arteries in factors such as length, diameter, thickness, curvature, and orientation. The larger size of peripheral arteries necessitates treatment with a high-energy gamma radiation source rather than the beta radiation, which is more commonly used for the coronary arteries. High-energy radiation sources cannot be administered in most catheterization laboratories or radiology suites, necessitating treatment in the radiation oncology department. This makes the logistics of treatment of the peripheral arteries more complex compared to the coronary arteries. The use of adjunctive agents, such as stenting and antiplatelet drugs, while extremely common in the coronary arteries, is not as well established for peripheral angioplasty. Stenting has not been definitively shown to be superior to angioplasty alone, although it is used by many experts for certain types of lesions such as longer segments of the iliac artery or ostial lesions of the aortic branch vessels.

The U.S. Food and Drug Administration (FDA) has approved devices intended for use in intracoronary brachytherapy, the Beta-Cath system (Novoste Corp), which delivers beta radiation, and the CheckMate system (Cordis), which delivers gamma radiation. In 2001, a second beta radiation device, the Galileo Intravascular Radiotherapy System (Guidant), was approved. Both of the beta devices have similar labeling approved by the FDA that limits the approved use of the devices to delivery radiation to “the site of successful percutaneous coronary intervention” for the treatment of in-stent restenosis in native coronary arteries with discrete lesions. The wording of the gamma device’s approval is slightly different, saying it is “for use in the treatment of native coronary arteries with in-stent restenosis following percutaneous revascularization using current interventional techniques.” There are currently no brachytherapy devices approved specifically for use in the peripheral arterial system. As of May 2007, the CheckMate and Galileo systems and devices for intravascular brachytherapy are no longer available, having been discontinued by their respective manufacturers. The Beta-Cath system is now manufactured and distributed by Best Vascular Inc.
Intravascular coronary brachytherapy using gamma or beta-emitting radiation may be considered **medically necessary** to treat restenosis of a previously-placed bare-metal stent in a native coronary artery.

Intravascular coronary brachytherapy using gamma or beta-emitting radiation is considered **investigational** to treat or prevent restenosis of drug-eluting stents.

Intravascular coronary brachytherapy using gamma radiation only may be considered **medically necessary** to treat in-stent restenosis of a non-native coronary artery (i.e., saphenous vein graft).

Intravascular coronary brachytherapy to reduce the risk of de novo restenosis, in conjunction with PTA with or without stent placement, is considered **investigational**.

Intravascular brachytherapy of the femoropopliteal system is considered **investigational**.

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**Policy Guidelines**

CPT coding for services associated with intracoronary brachytherapy may include a medical physicist, radiation therapist, and cardiologist. The following CPT codes may be used to describe the professional services associated with intracoronary brachytherapy:

**Radiation Therapy**

Medical physicist:

77370: Special medical radiation physics consultation

Radiation therapist

The planning and delivery of intracoronary brachytherapy requires multiple steps that are coded for individually by the radiation therapist. The modifier –26 indicates the professional component. The following CPT codes may be used.

99251-99255: Initial inpatient consultation for a new or established patient

Regarding these codes, it should be noted that in a survey of radiation therapists participating in intracoronary brachytherapy, 75% reported that they did not see the patient prior to the procedure. If so, these CPT codes would be inappropriate. (Radiology 2000; 217:723-28)

77263: Therapeutic radiology treatment planning; complex
77290: Therapeutic radiology simulation-aided field setting; complex
Simulation is generated from contrast-enhanced angiographic images
77336: Continuing medical physics consultation
Some claims programs will reject the above code when reported on the same day as 77370 (see above).
77300: Basic radiation dosimetry calculation
77327: Brachytherapy isodose calculation; intermediate
77431: Radiation therapy management with complete course of therapy consisting of 1 or 2 fractions only
77782, 77783, 77784: Remote afterloading high-intensity brachytherapy
The specific CPT code used will depend on the device. The CPT codes reflect the number of radiation sources in the device.
77470: Special treatment procedure
This CPT code is used when additional physician effort and work are required in cases of special procedures.
77331: Special dosimetry

Cardiologist
At the present time, no specific CPT code describes the cardiologist’s role in performing intravascular brachytherapy. One of the following CPT codes may be used:
93799: Unlisted cardiovascular service or procedure
36247: Selective catheter placement, arterial system; initial third order
36248: Selective catheter placement, arterial system; additional second order, third order and beyond
The above CPT codes represent possible coding options for the intravascular brachytherapy portion of the overall procedure, which typically includes PTCA with or without stent placement. Therefore, the following CPT codes describing PTCA may be used in conjunction with the above CPT codes.
92980: Transcatheter placement of an intracoronary stent(s); single vessel
92981: As above, with each additional vessel
92982: Percutaneous transluminal coronary balloon angioplasty, single vessel
92984: As above, with each additional vessel
92995: Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty, single vessel

92996: As above, with each additional vessel.

Rationale

This policy regarding intravascular coronary radiation therapy is based on a 2000 TEC Assessment (1) that offered the following observations and conclusions:

- There are 4 well-designed randomized clinical trials evaluating the effectiveness of brachytherapy for the management of in-stent restenosis in native coronary vessels. The outcomes of these trials indicate that patients with in-stent restenosis treated with brachytherapy do better than patients treated with PTCA alone or with PTCA and stenting. Angiographic data at 6 to 9 months show significant reduction in the restenosis rate in brachytherapy patients. More importantly, patients receiving brachytherapy have statistically significant reduction in target lesion revascularization rates.

- There are no randomized controlled trials supporting the use of intracoronary brachytherapy for the prevention of restenosis.

The policy regarding intravascular femoropopliteal radiation therapy is based on a 2002 TEC Assessment (2) that offered the following observations and conclusions:

- The scientific evidence consisted of 2 randomized trials comparing PTA plus brachytherapy with angioplasty alone. (3-5) Both trials had limitations that precluded conclusions on whether brachytherapy is efficacious for the population under consideration. The Vienna-2 trial was unblinded and had no placebo control. It also enrolled heterogeneous subgroups of patients. The second trial was single blinded with a sham brachytherapy placebo control. However, this trial only reported on 22 patients and used an unusual outcome measure as primary outcome.

- The TEC Assessment concluded that the evidence was insufficient to permit scientific conclusions regarding the brachytherapy as an adjunct to peripheral artery angioplasty.

Waksman and colleagues reported on the results of a trial that randomized 120 patients with in-stent restenosis in saphenous vein grafts to receive standard angioplasty and stenting or standard treatment plus intravascular gamma irradiation. (6) At 6 months, the restenosis rate was lower in those receiving intracoronary irradiation. As noted here, the FDA labeling for intracoronary brachytherapy is limited to its use as a treatment of in-stent restenosis, and its use for primary prevention of in-stent restenosis remains investigational. Serruys and colleagues reported on the results of a randomized trial of intracoronary brachytherapy as primary prevention in 112 patients. (7) The authors reported that the clinical outcomes of the irradiated group were inferior to those of the non-irradiated control group.

Studies are emerging that focus on the long-term outcomes of intracoronary brachytherapy. Of particular concern is the incidence of late stent restenosis. While conventional treatment of in-
stent restenosis is associated with early thrombosis, late stent restenosis is uncommon. Grise and colleagues reported a 5-year follow-up of 55 patients enrolled in a clinical trial of gamma irradiation as a treatment of in-stent restenosis. (8) Target lesion revascularization was required in 23.1% of the treatment group compared to 48.3% in the control group. There were 2 late revascularizations between 3 and 5 years in the treatment group, compared to none in the control group. Long-term anticoagulation therapy has been proposed as a strategy to reduce the incidence of late thrombosis. Meerkir and colleagues focused on the 2-year follow-up of 30 patients treated with intracoronary beta irradiation. (9) Late failures occurred in 7 of the 30 patients. Studies have also been reported on intracoronary beta irradiation with a novel liquid rhenium-188-filled balloon catheter with favorable outcomes. (10-14)

Comment

With the success of rapidly evolving drug-eluting stents, trials comparing brachytherapy to drug-eluting stents are needed to determine the appropriate role of brachytherapy in the treatment and prevention of restenosis. For example, Pohl and colleagues compared outcomes of 28 patients treated with intracoronary brachytherapy for in-stent restenosis with 28 patients treated with the implantation of a sirolimus-eluting stent for in-stent restenosis during 2 time-frames. (15) The authors found a lower incidence of recurrence of in-stent restenosis in patients treated with sirolimus-eluting stents. In addition, treatment with sirolimus-eluting stent implantation appeared to be safe and had a lower rate of late luminal loss than treatment with brachytherapy. The use of complex intravascular brachytherapy has been decreasing with the use of drug-eluting stents, and its future role in the treatment of in-stent restenosis is uncertain.

Regarding femoropopliteal irradiation as an adjunct to peripheral angioplasty and stenting, data continue to be inconclusive. Bonvini and colleagues reported on interim results of an ongoing randomized trial, focusing on thrombotic occlusion in those randomized to receive intravascular gamma irradiation. (16) Late occlusion was reported in 27% of those in the irradiated group compared to none in the control group. In the Vienna-3 trial, Pokrajac and colleagues reported restenosis rates to be significantly lower at 12-month follow-up in 134 patients randomized after femoropopliteal angioplasty to brachytherapy (41.7%) versus sham irradiation (67.1%). (17) However, the authors acknowledged some study limitations (small study size, high drop-out rate and angiographic follow-up in only 81% of patients). The Vienna-5 trial randomized 88 patients to PTA and femoropopliteal stent implantation with either gamma brachytherapy or sham irradiation and found no difference in recurrence rates at the 6- and 12-month follow-up between the 2 groups (33% with brachytherapy vs. 35% without at 6 months; and 59% with brachytherapy vs. 43% without at 12 months). (18)

2007 Update

Treating restenosis of bare-metal stents in native coronary arteries: A recent meta-analysis (19) pooled data from 11 separate randomized controlled trials (RCTs) comparing vascular brachytherapy versus PTA, with or without stent placement. In 7 of these trials, all patients were treated for in-stent restenosis, while 4 trials enrolled mixed populations (i.e., some primary lesions). In the 7 trials on pure in-stent restenosis, vascular brachytherapy significantly reduced the rate of major adverse cardiovascular events (MACE; RR=0.58; 95% CI: 0.50-0.67; p less than 0.001), restenosis (RR= 0.55; 95% CI: 0.48-0.64; p less than 0.001), and late lumen loss (standard mean difference= -0.69; 95% CI: -0.92, -0.46; p less than 0.001) at intermediate time points (defined as 6-24 months). Only 5 trials reported long-term outcomes (more than 3 years),
of which, only 3 studied pure in-stent restenosis. MACE was the only long-term outcome significantly reduced by vascular brachytherapy.

Three RCTs have directly compared vascular brachytherapy versus drug-eluting stents (DES) as treatments for in-stent restenosis. (20-22) Two of these were large, multicenter trials that randomized nearly 400 patients each. (20, 21), while the third was a single-center trial that closed early (n=37) because the vascular brachytherapy devices were no longer available. (22) In each of the 2 completed trials, DES significantly decreased the rate of target lesion revascularization and angiographic restenosis at 6–9 months by about half, when compared with vascular brachytherapy. However, longer-term follow-up data were not reported. Editorials published at the same time as these reports cited the marked decline in use of bare-metal stents for primary percutaneous interventions. (23, 24) The editorialists also had reservations about generalizing results from RCTs of vascular brachytherapy for restenosis in bare-metal stents to draw conclusions about effectiveness of vascular brachytherapy to treat restenosis in DES.

**Treating restenosis in drug-eluting stents**: Two clinical series reported on use of vascular brachytherapy to treat restenosis in a DES. One series (n=61) compared outcomes with a prior consecutive series (n=50) treated with repeat DES. (25) At 8 months after treatment, rates of target lesion and target vessel revascularization were similar in the 2 series, although the MACE rate was smaller in the vascular brachytherapy group than in the repeat DES group (9.8% vs. 2.4%; p=0.044). The second series only included 5 patients, all with recurrent stenosis after sequential treatment with sirolimus- and paclitaxel-eluting stents. (26) Further study is needed to determine if vascular brachytherapy is useful to treat restenosis in DES.

**In-stent restenosis in SVGs**: The 2007 literature search did not identify any new studies that might alter the recommendation of this policy that vascular brachytherapy may be considered medically necessary to treat in-stent restenosis of SVGs.

**Preventing restenosis after primary PTCA with or without stent placement**: Five studies reported on use of vascular brachytherapy to prevent restenosis after primary percutaneous interventions, including 3 with long-term (3.8 to 5 years) follow-up (27-29) and two with intermediate-term (9-16 months) follow-up. (30, 31) The studies with long-term follow-up reported that early benefit from vascular brachytherapy was not sustained because of delayed and progressive restenosis and thrombotic complications. In 1 of the studies, the delayed restenosis and thrombosis occurred despite the use of combined antiplatelet therapy. (29)

**Treating or preventing restenosis after angioplasty in femoropopliteal arteries**: Two studies reported long-term follow-up after endovascular brachytherapy to prevent restenosis in femoropopliteal arteries treated with balloon angioplasty. (32, 33) Both reported that brachytherapy delayed restenosis when measured after short-term follow-up, but these benefits were not sustained, and the rates of restenosis were similar in treated and control groups with longer follow-up.

**2008 Update**

The policy was updated with a MEDLINE search for the period May 2007 to June 2008. No studies were identified that would change the policy statement. For the treatment of bare metal stent restenosis, the previous update states that long-term follow-up comparing drug eluting stents to vascular brachytherapy is needed, given that the available studies were limited to 9 months of follow-up. Three studies were identified that address this issue; 2 randomized
controlled trials reporting 1-year (n=129) and 2-year (n=396) clinical outcomes and a retrospective cohort study with 3-year (n=360) outcomes. Most failure was symptom related in these studies as protocol angiography was limited to the initial 6- or 9-month follow-up. Park reported 1-year MACE (major adverse cardiovascular events) rates of 7.7 vs. 18.8% (p=0.07) in a study of 129 patients from Asia in the drug eluting stent (sirolimus) and vascular brachytherapy groups respectively. (34) This was driven primarily by statistically improved target lesion revascularization rates of 4.6% vs. 18.8% (p=0.01). Ellis et al reported 2-year target lesion revascularization rates of 10.1% and 21.6% (p=0.03, n=396) in the drug eluting stent (pacltaxel) and brachytherapy groups respectively. (35) However, there were no significant differences between the 2 groups with regard to death, myocardial infarction, or target vessel thrombosis at 24 months. A 5-year follow-up for this study is planned. Lastly, 3-year MACE-free survival was 92.5% in the drug eluting stent (sirolimus) treated cohort and 82.4% (p=0.03) in the brachytherapy cohort in a retrospective registry review of 360 patients from Asia reported by Lee. (36) These medium-term results are important; however, more information is needed regarding the long-term safety and efficacy of drug eluting stents. No studies were identified for other indications (drug eluting stent restenosis, saphenous vein graft stenosis, preventing stenosis in primary PTCA, or preventing restenosis in femoropopliteal arteries). Thus, no change to the vascular brachytherapy policy statements is warranted at this time.

References:

1. 2000 TEC Assessment; Tab 19.
2. 2002 TEC Assessment. Tab 22:


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