



Clinical

Intracoronary Brachytherapy for Restenosis: 20 Years of Follow-Up

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ABSTRACT

Background/purpose: Intracoronary brachytherapy (ICB) has mainly been used to treat in-stent restenosis following percutaneous coronary intervention and was virtually abandoned about 20 years ago. However, patients treated with this strategy are still alive and some teams continue to perform this therapy. We aimed to investigate the very long-term clinical outcome of patients treated with ICB.

Methods/materials: A total of 173 consecutive patients who had been treated with ICB at a large tertiary referral centre between 1998 and 2003 were included. The primary endpoint of the study was all-cause mortality. The secondary endpoints were as follows: occurrence of major adverse cardiac events (MACE, defined as all-cause death, non-fatal myocardial infarction, or target vessel revascularization), cardiac death, and presence of angina at the end of follow-up.

Results: Patients' mean age at the time of ICB was 64 ± 10 years and 77% were male. Restenosis (bare metal stent vs. balloon angioplasty) was the only indication for ICB. Unstable angina was present in 34% of the patients. Follow-up was available for 166 patients. After a mean follow-up of 20 ± 1.3 years, 66% of the patients had died (including 74 patients (67%) with cardiac death). Cumulative MACE rate at 20 years was 96%.

Conclusions: Very long-term follow-up of patients with in-stent restenosis treated with ICB confirmed a high all-cause mortality rate mainly due to cardiac causes and MACEs.

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1. Introduction

Intracoronary brachytherapy (ICB), using either beta or gamma radiation sources, was an effective and established treatment modality between 1996 and 2003 for the management of bare metal stent (BMS) in-stent restenosis (ISR) [1]. Intra-coronary radiation therapy can reduce neointimal proliferation by inhibiting smooth muscle cell replication [1]. ICB was shown to reduce major adverse cardiac events (MACE) after 5 years of follow-up [2]. However, over time, doubts have emerged about the durability of the anti-proliferative effect. In addition, concerns have arisen about adverse events, such as an increased risk of subacute and late thrombosis and cardiac death [3], which led to a shift away from ICB.

Since the advent of drug-eluting stents (DES) in 2002 and the subsequent decrease in restenosis, the use of ICB has dramatically decreased in clinical practice. By around 2005, ICB had become obsolete [4–6]. However, Negi et al. reported their experience with the use of ICB following recurrent DES-ISR, with good results after 3 years of follow-up [7]. Studies regarding the very-long term follow-up are scarce [8].

Abbreviations: ICB, intracoronary brachytherapy; ISR, in-stent restenosis; MACE, major adverse cardiac event; MI, myocardial infarction; TVR, target vessel revascularisation.

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2. Methods

2.1. Patient and data collection

This retrospective study was conducted at a University Hospital in the French part of Switzerland. At that time, our hospital was a large tertiary referral centre and was an expert centre in ICB, with patients referred from several other centres. The study was approved by the institutional ethics committee. All patients provided written informed consent for the use of their data before coronary angiography. A total of 215 consecutive patients who had been treated with ICB between 1998 and 2003 were considered for inclusion. During the preliminary analysis, 42 patients were excluded due to lack of follow-up, either because they were foreigners, because they had been referred from another hospital to be treated with ICB, or because their data were not available. Patient data were collected from a dedicated ICB database developed on site during the period when this treatment was available. The referring physician and/or cardiologist of each patient were contacted in order to obtain information about the occurrence of adverse events, treatments, and angina status.

The relevant municipal authorities of each patient's place of residence were contacted to find out the patients' current vital status before contacting their physicians. Due to the long follow-up duration, we

encountered difficulties in collecting all the patient information, which was particularly accounted for by the destruction of paper forms by the attending physicians if the patients had died >10 years ago, by the change of attending physician, and by the transition to computerised patient records. Survival follow-up was available for 166 patients (96 %) (Fig. 1). Patient follow-up data could be collected in full in 76 % of cases.

2.2. Clinical endpoints and definitions

2.2.1. The primary endpoint of the study was all-cause mortality

The secondary endpoints were occurrence of MACEs, cardiac death, and presence of angina at the end of follow-up. MACEs included all-cause death, first non-fatal myocardial infarction (MI), defined as a new Q-wave or twofold increase in cardiac enzymes, and target vessel revascularization (TVR), defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. Cardiac death was defined as a fatal MI or cardiac arrest not related to cancer or infection. Angina was graded using the Canadian Cardiovascular Society (CCS) classification.

2.3. Statistical analysis

Continuous variables are presented as mean \pm standard deviation. Categorical variables are presented as number and percent. Statistical analysis and figures were carried out using Prism 9 (GraphPad Software, La Jolla, California, USA).

3. Results

3.1. Patient characteristics

Overall, 173 patients were included. Their demographic characteristics are presented in Table 1. The mean age of the study population was 64 ± 10 years at the time of intervention, with 77 % of them being males. As expected, ISR was the only indication for ICB. Coronary risk factors were as follows: diabetes mellitus (33 % of patients), current smoking (14 %), past smoking (51 %), hyperlipidaemia (89 %), and hypertension (80 %). Regarding coronary status, 47 % of patients had single-vessel disease, 25 % two-vessel disease, and 27 % three-vessel disease. Prior MI and prior coronary artery bypass grafting (CABG) was found in 52 % and 23 % of patients, respectively.

Table 1
Baseline clinical characteristics.

Baseline clinical characteristics	
Number of patients	173
Complete follow-up regarding overall survival	166 (96 %)
Lost to follow-up	7 (4 %)
Age, years, mean \pm SD	64 ± 10
Follow-up duration, years, mean \pm SD	20 ± 1.3
Male gender	128/166 (77 %)
Risk factors	
Diabetes mellitus	51/161 (33 %)
Smoking	23/161 (10.7 %)
Hyperlipidaemia	144/161 (89 %)
Hypertension	129/161 (80 %)
Coronary status	
Single-vessel disease	78/165 (47 %)
Two-vessel disease	42/165 (25 %)
Three-vessel disease	45/165 (27 %)
Prior CABG	81/156 (52 %)
Prior myocardial infarction	37/159 (23 %)
Target vessel	
Left anterior descending artery	68/166 (40 %)
Left circumflex artery	40/166 (24 %)
Right coronary artery	56/166 (34 %)
Saphenous vein graft	7/166 (4 %)

CABG: coronary artery bypass grafting; SD: standard deviation.

3.2. Procedural characteristics and medications

The target vessel was the left anterior descending coronary artery in 40 % of patients, the left circumflex artery in 24 %, the right coronary artery in 34 %, and a saphenous vein graft in 4 %. Indication to proceed to coronary angiography was unstable angina in 34 % of cases. The mean radiation dose was 24 ± 10 Gy, with a mean dwell time of $4 \text{ min } 28 \text{ s} \pm 2 \text{ min } 18 \text{ s}$. The procedural success rate was 98.1 %. Inability to bring the radiation source into the vessel was the only procedural complication. Regarding treatments, 82 % of patients received dual antiplatelet therapy with aspirin and clopidogrel for a minimum of 6 months after ICB.

3.3. Outcomes

Survival follow-up was available for 166 patients (96 %). A total of 7 patients were lost to follow-up, either because the patient or their attending physician could not be located or because the attending physician refused to cooperate.

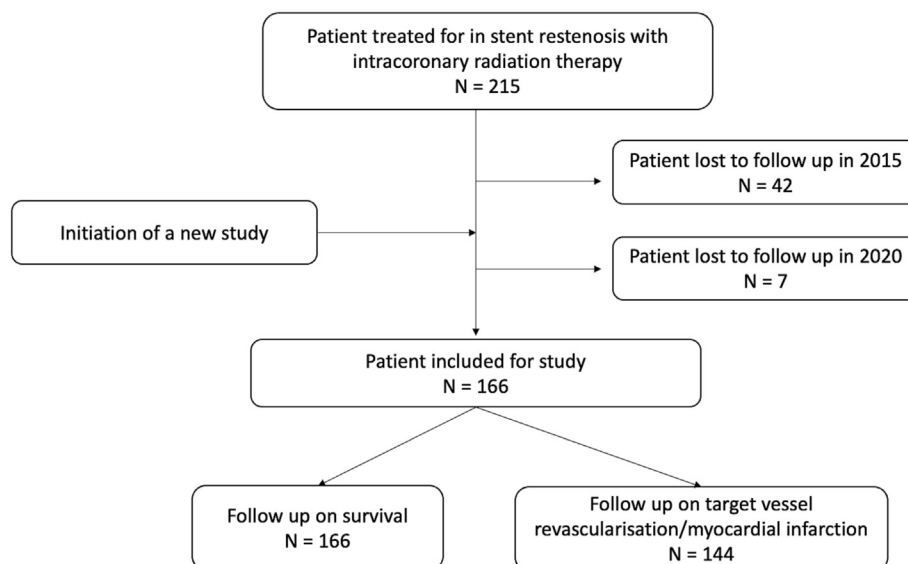


Fig. 1. Study flowchart.

Mean follow-up duration was 20 ± 1.3 years. A total of 110 patients (66 %) died during follow-up, with death considered to be of cardiac origin in 74 (67 %). Fig. 2 shows the MACE subgroups. Cumulative survival at 1, 5, 10, 15, and 20 years was 90 %, 78 %, 59 %, 43 %, and 34 %, respectively. Cumulative MACE-free rate at 1, 5, 10, 15, and 20 years was 77 %, 54 %, 29 %, 14 %, and 4 %, respectively. TVR mainly consisted in percutaneous revascularization (75 %) and CABG (25 %).

At the end of the follow-up, angina symptoms were present in 24 % of patients, with the CCS angina grades being distributed as follows: Grade I (45 %), Grade II (37 %), and Grade III (18 %). Detailed patient follow-up outcomes are presented in Table 2.

4. Discussion

To our knowledge, this is the only study to have evaluated the outcome of patients who underwent ICB for ISR with a mean follow-up of 20 years and it confirmed the trend of high mortality of 66 %.

ICB was an established treatment option for patients presenting with BMS restenosis by the end of the 1990's and the beginning of the new millennium. ICB has gradually been superseded by the increasingly widespread DESs and was finally abandoned by around 2005.

There is little literature on follow-up beyond 15 years. Up to 5 years of follow-up, ICB has been associated with increased MACE rates between 5 months and 2 years after the procedure [9]. The most common event was found to be TVR [9,10]. This was further confirmed by studies such as the Washington Radiation for In-Stent Restenosis (WRIST) trial [11], the Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) trial [12], and the Gamma I trial [13]. Seabra Gomes et al. demonstrated a cumulative 10-year MACE-free rate of 42 % and a mortality of 25 % [14].

Radhoe et al. showed comparable clinical outcomes at 17 years of follow-up, with no survival difference and no MACE excess in the long term [8]. They observed a more pronounced increase in the MACE rate in the first 2 years, which was not maintained afterwards.

Table 2
Patient follow-up outcomes.

Patient follow-up outcomes	
Death from any cause	110/166 (66 %)
Non-cardiac death	34 (31 %)
Cardiovascular-related death	76 (69 %)
Angina class (end of follow-up)	
No angina	34/45 (76 %)
CCS 1	5 (45 %)
CCS 2	4 (36 %)
CCS 3	2 (18 %)
CCS 4	0 (0 %)
Cumulative TVR at 20 years	71/144 (49 %)
PCI/stent	53 (75 %)
CABG	18 (25 %)
Cumulative first non-fatal MI at 20 years	53/144 (37 %)

CABG: coronary artery bypass grafting; CCS: Canadian Cardiovascular Society; MI: myocardial infarction; PCI: percutaneous coronary intervention; TVR: target vessel revascularisation.

Our study confirmed a substantial progressive decline in adverse clinical events and mortality over time, with a cumulative 20-year MACE rate amounting to 96 %. At 2 years of follow-up, the percentage of first non-fatal MI and first TVR is in line with Radhoe et al. study. However, at 17 years, we observed a worse MACE-free rate and a cumulative survival rate of 11.4 % and 34 %, respectively. This could be explained by more comorbidities, more advanced coronary artery disease, and a higher age at the time of the intervention. Our study confirmed high mortality and MACE rates, but did not allow us to conclude whether this increased trend is specific to the ICB population in the absence of a control group. However, Fig. 2 shows approximately the same trend as shown in the previous study.

Follow-up studies for ISR showed a 5-year survival rate of 93–95 % in the absence of follow-up beyond 5 years [15,16]. This is significantly higher than the results obtained in our study.

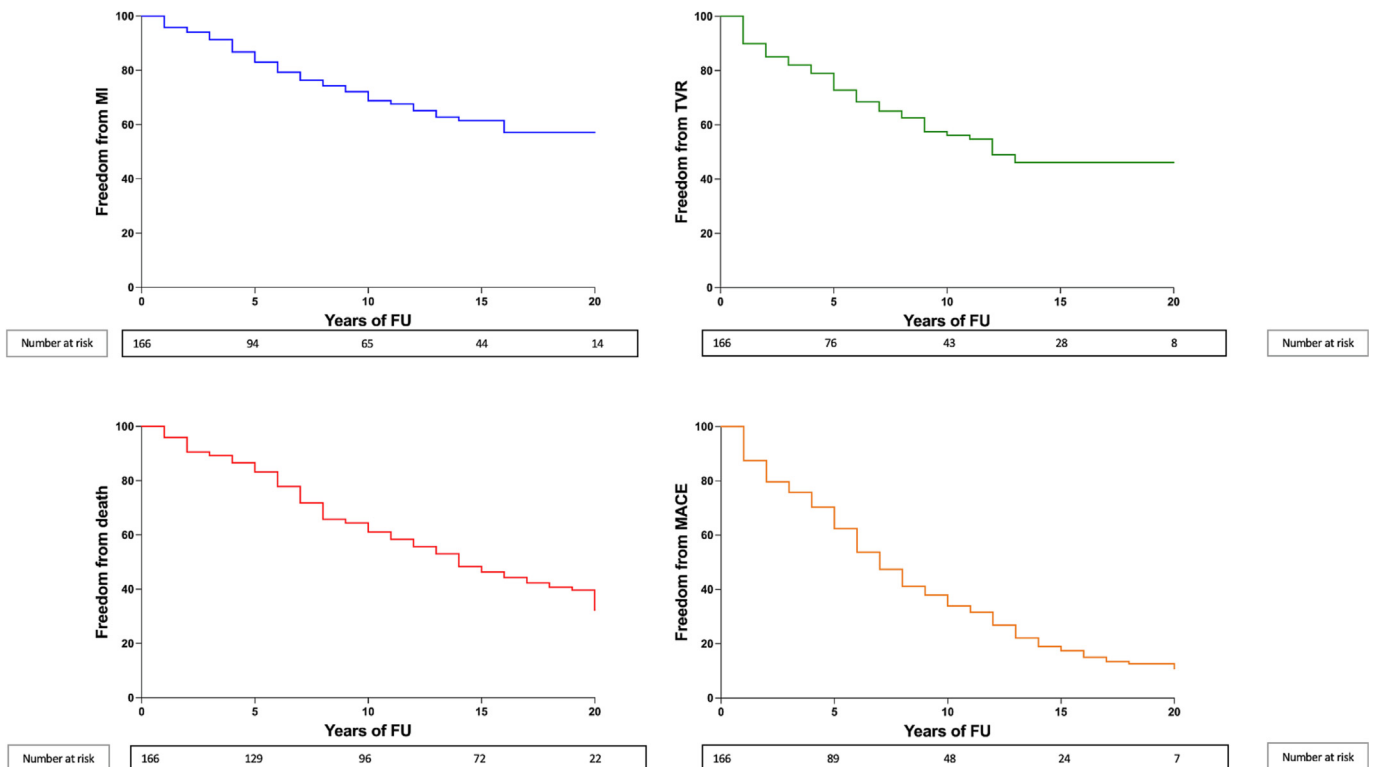


Fig. 2. Intracoronary beta radiotherapy (IRBT) follow up by subgroups. MACE: major adverse cardiac events, MI: myocardial infarction, TVR: target vessel revascularisation.

Overall, the follow-up studies after PCI showed a 10-year survival rate ranging from 70 to 80 % vs. 60 % in our study [17–23], which is mainly accounted for by the higher proportion of patients with advanced coronary artery disease in our population.

However, we can consider that most of the first events occurred early in the follow-up of ICB patients. Moreover, only the first cardiovascular event (MI or TVR) was taken into account in our study, and not the total number of events.

Despite these results, our study has many limitations, which should be kept in mind when interpreting the data. First, this was a retrospective single-centre study with no matched control group to compare our results with. Second, due to the very long-term follow-up and the fact that some patients came from other countries, several patients got lost to follow-up. We recognize that our study comprised at times incomplete data that, although being in agreement with those of the literature, may lead to biases in this regard, with the risk of over- or under-evaluation of the results. However, this study may have a persistent clinical impact, as patients who have undergone ICB need close clinical follow-up. In fact ICB has seen a resurgence in the United States and has been adopted by approximately 30 to 40 medical centers for the treatment of DES-ISR. Consequently, close attention should be paid to the progress of these patients.

5. Conclusions

In conclusion, our very long-term follow-up after ICB demonstrated high mortality and morbidity, thus warranting regular and stringent clinical follow-up in patients who have undergone this treatment 20 years ago or more.

CRedit authorship contribution statement

Adil Salihu and Eric Eeckhout designed the research study. Adil Salihu performed the research. Stephane Fournier provided help and advice on methodology and statistics. Adil Salihu and Stephane Fournier analyzed the data. Adil Salihu and Eric Eeckhout wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Study registration

Swiss Ethics: Study 2020-01280.

Impact on daily practice

Although intracoronary brachytherapy for managing in-stent restenosis was virtually abandoned about 20 years ago, some patients treated with this strategy are still alive. As illustrated in our 20-year follow-up, this population displays high morbidity and mortality, thus warranting regular and stringent clinical follow-up.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors report no conflict of interest in relation to this manuscript.

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