Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: an optical coherence tomography study

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Aims
Restenosis of drug-eluting stents (DESs) might be different from that of bare metal stent restenosis in diverse ways including mechanisms and time course; however, these have not been fully examined. To gain insight into the mechanisms and time course of DES restenosis, we evaluated the characteristics of restenotic lesions of first generation DES using optical coherence tomography (OCT).

Methods and results
We compared the morphological characteristics of early in-stent restenosis (<1 year: E-ISR, n = 43), late ISR (1–3 years: L-ISR, n = 22), and very late ISR (>3 years: VL-ISR, n = 21). OCT qualitative restenotic tissue analysis included the assessment of tissue structure [homogeneous or four types of heterogeneous intima (thin-cap fibroatheroma (TCFA)-like, layered, patchy or speckled pattern)], the presence of the peri-strut low intensity area (PLIA), microvessels, disruption with cavity, and intraluminal material and was performed at every 1 mm slice of the entire stent length. In addition to a greater trend for heterogeneous intima at the later phase, TCFA-like pattern image, intra-intima microvessels were increased from the early to the very late phase. On the other hand, the speckled pattern image was decreased from the early to the very late phase.

Conclusion
The OCT morphological characteristics of DES restenotic tissue varied at different time-points. OCT images in early DES ISR might be associated with delayed arterial healing, and neoatherosclerosis might contribute to late catch-up phenomenon (L-ISR and VL-ISR) after DES implantation.

Keywords
Optical coherence tomography ● Drug-eluting stent ● Restenosis

Introduction
Although drug-eluting stents (DESs) have proved more effective in reducing restenosis than bare metal stents (BMSs),¹ DESs are not free of restenosis and are limited by stent thrombosis.² BMS restenosis usually occurs in the early phase (until 6 months) or, to a lesser extent, very late phase (beyond 4 years). Neointima after BMS implantation have been considered as stable. However, clinical and pathological studies demonstrated that atherosclerotic change can develop within the neointima of a BMS, leading to very late restenosis or late stent thrombosis of the BMS.³,⁴ Recently, Nakazawa et al.⁵ reported that this phenomenon
(neatherosclerosis) is a frequent finding in DESs and occurs earlier than in BMSs. Restenosis of a DES may show a different time course from that of a BMS and occasionally occurs >1 year after stent implantation (i.e. late catch-up phenomenon).5–7 In addition, previous optical coherence tomography (OCT) reports showed various OCT image patterns of DES restenotic tissue being different from early BMS restenotic tissue.6,7 According to these reports, the mechanism and time course of DES re-
etnosis might be different from that of BMS restenosis. To gain
insight into the mechanisms and time course of DES restenosis,
we evaluated the presence of numerous morphological character-
istics as visualized with OCT, and compared these images between
cases with early (<1 year), late (1–3 years), and very late (>3 years)
restenotic lesions of first generation DESs (Cypher, Cordis Corp., Miami Lakes, FL, USA and Taxus, Boston Scientific, Natick, MA, USA, respectively).

**Methods**

**Study design and population**

Patients with first in-stent restenosis (ISR) of first generation DESs were enrolled in this study. ISR was defined as >50% of diameter sten-
osis within the stent segment. ISR was classified into early ISR (E-ISR), late ISR (L-ISR) or very late ISR (VL-ISR) to evaluate the time course of 
DES restenosis, as previously reported for BMS restenosis. E-ISR was def-
ined as the first ISR observed within 1 year after stent implantation.3 Patients with ISR after 1 year were divided into two groups (L-ISR and
VL-ISR) using the median follow-up duration (3 years) in order to
divide patient numbers with the detected late catch-up phenomenon
equally. L-ISR was defined as the first ISR observed between 1 and
3 years after stent implantation, which was not detected at the first
short-term follow-up angiography (within 1 year after stent implant-
ation).7 VL-ISR was defined as the first ISR observed >3 years after
stent implantation and not detected at the previous follow-up an-
giography. Short-term follow-up angiography was performed due to: (i) the
scheduled follow-up of the implanted stent; or (ii) evidence of myocar-
dial ischaemia. Long-term follow-up angiography (>1 year) was per-
duced due to: (i) the scheduled follow-up of other treated
segment; or (ii) evidence of myocardial ischaemia. A prospective
protocol was approved by the institutional review board to perform
an OCT study in all patients with ISR on coronary angiography, pro-
voked patients met the eligibility criteria as well as had given written
informed consent.

Inclusion criteria consisted of patients: (i) with first ISR after first
generation DES implantation on angiography; and (ii) amenable for
OCT study. Exclusion criteria were: (i) left main coronary artery
disease; (ii) totally occluded lesion; (iii) bifurcation stenting lesion;
(iv) bypass graft lesion; (v) multiple stenting lesion; (vi) cardiogenic
shock; (vii) left ventricular ejection fraction <30%; (viii) serum creatin-
ine >2 mg/dL and (ix) ST-elevation myocardial infarction. After diag-
nostic cardiac catheterization, patients who met the eligibility criteria
were invited to participate in this study.

**Quantitative coronary angiography**

Off-line quantitative coronary angiography (QCA) was conducted using the view that revealed the highest degree of stenosis. The sever-
ity of coronary stenosis was measured using the Cardiovascular Me-
asurement System (CMS-MEDIS Medical Imaging System, Leiden, The
Netherlands). For every patient, angiograms were analysed at the
time of OCT examination. Lesion length, reference diameter, 
minimal luminal diameter and percent diameter stenosis (%DS) were
calculated by a single operator who was blinded to clinical character-
istics. Analysis of angiographic frames was performed in the end-
diastolic stage. The angiographic restenotic lesion type was classified as:
focal restenosis : <10 mm in length (IA: articularation or gap, IB: 
margin, IC: focal body, ID: multifocal) or diffuse restenosis :
>10 mm in length (II: intra-stent, III: proliferative).8

**OCT imaging**

After completion of coronary angiography and before any intervention,
patients were evaluated with OCT. OCT imaging was performed using the
OCT imaging system (M2 OCT system, LightLab Imaging, West-
ford, MA, USA) using the occlusion balloon catheter (Helios, LightLab
Imaging, Westford, MA, USA) method. The detailed specifications and
the OCT procedure have been described elsewhere.9

**OCT quantitative and qualitative analysis**

OCT analysis was performed using the LightLab OCT imaging propri-
etary software (LightLab Imaging, Westford, MA, USA). Both qualitative
and quantitative analyses of OCT images were performed by
experienced analysts who were blinded to clinical and angiographic
lesion characteristics. The following analyses, including lumen and
stenor areas or morphological appearance, were performed at 1 mm
longitudinal steps throughout the pull-back from the distal stent
edge to the proximal stent edge. At every frame, the lumen and
stenor were manually traced, and the neointimal hyperplasia (NII)
area (stenor area – lumen area) was calculated. Percent NIH area
was also calculated as (NIH area/stenor area) × 100.

To evaluate the morphological appearance of the restenotic tissue,
the pattern of restenotic tissue structure in the cross-sectional images
at every 1 mm interval was categorized: (i) homogeneous intima: rest-
enotic tissue has uniform optical properties and does not show focal
variations in the backscattering pattern (Figure 1A)10, (ii) heteroge-
neous intima: homogeneous intima was further categorized into four
types: (i) type 1: thin-cap fibroatheroma (TCFA)-like pattern; presence of
an area with marked signal attenuation with a diffuse border; and
fibrous cap thickness at the thinnest part ≤65 μm and an angle of
lipidic tissue ≥180 (Figure 1B)11,12, (iii) type 2: layered pattern; resteno-
tic tissue consists of concentric layers with different optical properties
(thick high scattering layer and a low scattering layer with stent strut
(Figure 1C)13,14; (iii) type 3: patchy pattern; patchy and highly echolucent
regions throughout the layers (Figure 1D)14 or (iv) type 4: speckled
pattern; restenotic tissue consists of a heterogeneous speckled band
(Figure 1E).14 In addition, we also evaluated the perist- strut low intensity
area (PLIA), defined as a region around stent struts with homogeneous
lower intensity than the surrounding tissue on OCT images without
signal attenuation (Figure 1F)15,16 and neovascularization, which was
defined as small vesicular or tubular structures differentiated from
any side branches with a diameter <200 μm. Neovascularization was
classified into intra-intima (Figure 1G) or peri-stent (Figure 1H)
by the location of the microvessels.3 Moreover, peri-stent ulcer-like
appearance, defined as a hollow shape (>90°/frame) in the vessel
wall adjacent to the stent struts (Figure 1I)17 was also evaluated. The
proportions of cross sections (CSs) per stent with the above described
qualitative findings with respect to the total numbers of analysed CSs
were reported. We also evaluated the presence of (i) disrupted intima
(discontinuity of lumen border) with visible cavity (Figure 1J)3 and (ii)
intraluminal materials (protruding mass into the lumen and dimension
>250 μm). Intraluminal materials were categorized by the presence of
shadowing (Figure 1K and L).3 When the reading of the qualitative
analysis by two observers differed, a consensus was reached and used as the final decision.

To test for inter-observer variability of the qualitative OCT analysis, a total of 100 CSs within the restenotic lesions from 10 patients by each 10 CSs were selected and analysed independently by two observers not involved in the primary data analysis. One of the observers repeated the analysis 1 week later to assess the intra-observer variability.

Statistical analysis
Categorical variables are expressed as numbers (percentages). Continuous variables are expressed as mean ± standard deviation. Comparisons between groups were performed with a one-way ANOVA test for continuous variables and with the χ² test or Fisher’s exact test for categorical variables. When the one-way ANOVA was significant, differences between series of data were determined using Tukey’s test. The reproducibility of qualitative variables was assessed with a κ-test. A P-value of <0.05 was considered statistically significant. All statistical analysis was performed using SPSS software (SPSS, Inc., Chicago, IL, USA).

Results
Reproducibility of qualitative OCT analysis
Inter-intra-observer variability (kappa values) for the qualitative OCT assessment was as follows: 0.87/0.90 for restenotic tissue structure (homogeneous vs. heterogeneous intima); 0.82/0.85 for TCFA-like pattern image; 0.76/0.79 for layered pattern image; 0.84/0.82 for patchy pattern image; and 0.82/0.77 for speckled pattern.

Figure 1 Qualitative optical coherence tomography (OCT) analysis. (A) Homogeneous intima; restenotic tissue has uniform optical properties and does not show focal variations in the backscattering pattern. (B–E) Heterogeneous intima. (B) Thin-cap fibroatheroma (TCFA)-like pattern: signal poor area with diffuse lumen border. (C) Layered pattern: restenotic tissue consists of concentric layers with different optical properties (thick high scattering layer and a low scattering layer with stent strut). (D) Patchy pattern: patchy and highly echolucent regions throughout the layers. (E) Speckled pattern: restenotic tissue consists of a heterogeneous speckled band. (F) The peri-strut low intensity area (PLIA); defined as a region around stent struts with homogeneous lower intensity than the surrounding tissue on OCT images without signal attenuation. (G and H) Microvessels: differentiated from any side branches was defined (≤200 μm) and categorized as intra-intima (G) or peri-stent (H). (I) Peri-strut ulcer-like appearance: defined as a hollow shape (>90°/frame) in the vessel wall adjacent to the stent struts. (J) Disrupted intima with the visible cavity; irregular surface with visible cavity of the intima because of disruption. (K and L) Intraluminal materials with shadowing (K) or without shadowing (L) defined as the materials that protruded into the vessel lumen with dimension >250 μm (arrow).
Patient enrolment
Between July 2009 and June 2011, 2666 patients treated with implantation of a first generation DES underwent CAG. Of these patients, 159 patients (6.0%) had ISR and 91 patients who met the eligibility criteria for this study underwent OCT. However, five patients were excluded because of poor OCT images. Forty-three patients were detected with an ISR lesion within 1 year after stent implantation. On the other hand, 43 patients were detected with an ISR lesion beyond 1 year after stent implantation (late catch-up phenomenon). Then, we defined L-ISR as ISR detected 1–3 years after stent implantation and VL-ISR as over 3 years after stent implantation in order to divide patient numbers with detected late catch-up phenomenon into two groups equally. The final distribution of the study sample consisted of 43 stents in 43 patients with E-ISR, 22 stents in 22 patients with L-ISR, and 21 stents in 21 patients with VL-ISR enrolled.

Clinical characteristics
Clinical characteristics of the study population are listed in Table 1. There were no significant differences between the groups except for the kind of stents implanted. About 90% of patients in VL-ISR were treated with the Cypher stent.

QCA analysis
QCA findings of the restenotic lesion, shown in Table 2, revealed that there were no significant differences in any parameters and the restenotic pattern between the three groups. In addition, no patient presented with angiographic evidence of thrombus.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
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<td><strong>Demographics</strong></td>
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<td>Age, year</td>
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<td>Male gender (%)</td>
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<td>Hypertensiona (%)</td>
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<td>Hyperlipidaemab (%)</td>
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<td>Previous MI (%)</td>
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<td>CABG (%)</td>
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<tr>
<td><strong>Reason for stenting (%)</strong></td>
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<tr>
<td>Stable angina</td>
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<td>Unstable angina</td>
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<td>STEMI</td>
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<td><strong>Clinical presentation at OCT (%)</strong></td>
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<tr>
<td>Asymptomatic</td>
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<tr>
<td>Stable angina</td>
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<tr>
<td>Unstable angina</td>
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<td><strong>Reason for follow-up CAG (%)</strong></td>
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<td>Scheduled</td>
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<td>Evidence of ischaemia</td>
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<td><strong>Vessel (%)</strong></td>
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<td>LAD</td>
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<td>LCX</td>
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<td>RCA</td>
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<td><strong>Stent (%)</strong></td>
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<td>Cypher</td>
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<td>TAXUS</td>
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<td><strong>Target lesion revascularization</strong></td>
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<td>Follow-up period, years</td>
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<td>Median (quartile), years</td>
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Data are presented as mean ± SD, or the number of patients/arteries (percentage).
E-ISR, early in-stent restenosis; L-ISR, late in-stent restenosis; VL-ISR, very late in-stent restenosis; MI, myocardial infarction; CABG, coronary artery bypass surgery; STEMI, ST-elevation myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.
aHypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of an antihypertensive drug.
bHyperlipidaemia was defined as total cholesterol level ≥ 240 mg/dl, or medication use.
cDiabetes was defined as diet controlled and oral agent treated or insulin treated.
OCT analysis
The results of OCT quantitative and qualitative analyses of the entire stent are shown in Table 3 and Figure 2. Per lesion/stent, the proportions of CSs with the qualitative findings with respect to the total number of analysed CSs were reported.

In the quantitative analysis of the entire stent, there were no significant differences in any parameter. In addition to a greater trend

Table 2  Quantitative coronary angiography analysis

<table>
<thead>
<tr>
<th></th>
<th>E-ISR, n = 43</th>
<th>L-ISR, n = 22</th>
<th>VL-ISR, n = 21</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Length (mm)</td>
<td>11.2 ± 6.4</td>
<td>11.9 ± 7.0</td>
<td>10.5 ± 4.8</td>
<td>0.25</td>
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<tr>
<td>Reference diameter (mm)</td>
<td>2.6 ± 0.4</td>
<td>2.4 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>0.36</td>
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<tr>
<td>Minimal lumen diameter (mm)</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>1.0 ± 0.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>58.3 ± 8.9</td>
<td>59.1 ± 9.4</td>
<td>64.8 ± 10.3</td>
<td>0.77</td>
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</tbody>
</table>

Restenotic pattern (%)
- Focal: 21 (48.8), 9 (40.9), 9 (42.9) 0.85
- Articulation or gap (IA): 3 (7.0), 0 (0), 0 (0) 0.41
- Margin (IB): 11 (25.6), 5 (22.7), 3 (14.3)
- Focal body (IC): 6 (14.0), 3 (22.7), 3 (14.3)
- Multifocal (ID): 1 (2.3), 1 (4.5), 3 (14.3)

Diffuse: 22 (51.2), 13 (59.1), 12 (57.1) 0.85
- Intra-stent (II): 15 (34.9), 8 (36.4), 7 (14.3) 0.80
- Proliferative (III): 7 (16.2), 5 (22.7), 5 (23.8)

Data are presented as mean ± SD, or the number of lesions (percentage). E-ISR, early in-stent restenosis; L-ISR, late in-stent restenosis; VL-ISR, very late in-stent restenosis.

Table 3  Optical coherence tomography analysis of entire stent

<table>
<thead>
<tr>
<th>Analysis of entire stent</th>
<th>E-ISR, n = 43</th>
<th>L-ISR, n = 22</th>
<th>VL-ISR, n = 21</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of observed cross sections</td>
<td>22.7 ± 8.3</td>
<td>20.6 ± 6.3</td>
<td>21.6 ± 6.2</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Quantitative analysis
- Mean lumen area, mm²: 4.0 ± 1.6, 3.7 ± 1.0, 4.5 ± 1.4 0.1
- Mean stent area, mm²: 7.2 ± 2.2, 6.9 ± 1.5, 8.2 ± 1.8 0.08
- Mean neointimal hyperplasia area, mm²: 3.2 ± 1.5, 3.2 ± 1.3, 3.6 ± 1.5 0.49
- Mean % neointimal hyperplasia area, %: 42.4 ± 15.7, 44.8 ± 14.2, 41.2 ± 14.9 0.71

Qualitative analysis
- Homogeneous intima*, %: 72.8 ± 23.6, 68.1 ± 24.0, 58.2 ± 22.8 0.07
- Heterogeneous intima*, %: 27.1 ± 23.6, 31.5 ± 24.1, 41.8 ± 22.5 0.07
- TCFA-like pattern, %: 2.2 ± 7.9, 14.3 ± 19.1, 34.6 ± 25.7 <0.001
- Layered pattern, %: 6.7 ± 10.1, 11.6 ± 9.4, 6.3 ± 5.5 0.09
- Patchy pattern, %: 2.8 ± 7.7, 2.7 ± 8.2, 0.2 ± 0.8 0.33
- Speckled pattern, %: 15.4 ± 22.3, 3.0 ± 8.0, 0.7 ± 3.4 <0.001

Microvessels*
- Peri-stent, %: 5.0 ± 6.7, 3.9 ± 5.7, 5.7 ± 7.2 0.65
- Intra-intima, %: 0.3 ± 1.5, 3.9 ± 8.7, 5.5 ± 8.6 0.01
- Peri-strut low intensity area, %: 14.4 ± 14.2, 9.6 ± 11.9, 1.9 ± 5.3 0.001
- Peri-stent ulcer-like appearance, %: 1.2 ± 4.4, 2.7 ± 7.8, 6.9 ± 10.7 0.08

Disrupted intima with visible cavity 0 (0%), 3 (13.6%), 6 (28.6%) 0.002
- Intraluminal material: 4 (9.3%), 4 (18.2%), 6 (33.3%) 0.06
- With shadowing: 1 (2.3%), 1 (4.5%), 5 (23.8%) 0.01
- Without shadowing: 4 (9.3%), 4 (18.2%), 5 (23.8%) 0.28

Data are presented as mean ± SD, or number of lesions (percentage). E-ISR, early in-stent restenosis; L-ISR, late in-stent restenosis; VL-ISR, very late in-stent restenosis.

*Qualitative analysis in entire stent including restenotic tissue structure (homogeneous or heterogeneous), microvessels, peri-strut low intensity area, and peri-stent ulcer-like appearance were calculated as (numbers of cross-sections with the findings/numbers of analysed cross-sections) × 100.
for heterogeneous intima at the later phase, the TCFA-like pattern and intra-intima microvessels were more frequently observed in the VL-ISR group, whereas the speckled pattern image and PLIA were more frequently detected in the E-ISR group. TCFA-like pattern image and intra-intima microvessels were significantly increased from the early to the very late phase, whereas the speckled pattern image was significantly decreased from the early to the very late phase. Disrupted intima with cavity, intraluminal materials with shadowing were more frequently detected in the VL-ISR group.

Analysis at the minimum lumen area (MLA) site is shown in Table 4 and Figure 3. Similar to the entire stent analysis, the TCFA-like image was more frequently observed in the VL-ISR group and the speckled pattern image was more frequently observed in the E-ISR group.

In addition, we compared the incidence of disrupted intima with cavity, intraluminal material, microvessels, and PLIA between each type of OCT images (homogeneous and classified four heterogeneous patterns) (Table 5). The incidence of disrupted intima with visible cavity, intraluminal materials (with/without shadowing),
and intraluminal microvessels was significantly higher in TCFA-like OCT images.

**Discussion**

The main findings of this study are as follows: (i) the qualitative OCT findings of DES restenosis tissue were significantly different between early, late, and very late restenosis phases; (ii) TCFA-like pattern image and intra-intima microvessels were increased from the early to the very late phase; and (iii) the speckled pattern image was decreased from the early to the very late phase.

**OCT images in DES-ISR**

Heterogeneous OCT images in DES-ISR lesions showed differential patterns similar to a previous report and were categorized into four types. TCFA-like pattern image, which was also frequently observed in BMS VL-ISR (beyond 4 years after stent implantation) lesions as we have previously reported, is similar to the morphology seen with typical de novo atherosclerosis lesions. In this current study, some findings (presumably related to atherosclerosis) including intra-intima microvessels (closely associated with plaque progression and plaque haemorrhage), intraluminal materials with shadowing (suggested a red thrombus, whereas that without shadowing suggested a white thrombus), and disrupted intima with cavity [similar to an atherosclerotic plaque rupture in acute coronary syndrome (ACS) patients] were more frequently detected in the VL-ISR group. Those findings were most frequently observed with the TCFA-like pattern image in this study (Figures 2 and 3). Further, TCFA-like pattern image was significantly increased from the early to the very late phase, which had already been observed ~1 year after DES implantation (Figure 2). Assuming a correspondence between previously validated OCT characteristics of atherosclerotic plaques, our data suggest that the TCFA-like pattern image relate to neo-atherosclerosis in the DES and is associated with the mechanism of DES restenosis.

**Previous pathological study**

In their pathology study from autopsy cases, Nakazawa et al. have reported that neo-atherosclerosis was significantly more frequently observed in DES lesions (31%) than BMS lesions (16%; P < 0.001), and the median stent duration with neo-atherosclerosis was shorter in DES than BMS (DESs: 420 days; BMS: 2160 days, P < 0.001). Their histological results of neointima might support our hypothesis of neo-atherosclerosis in DESs.
Comparisons with previous studies

Using OCT, Kang et al.\textsuperscript{20} also reported neo-atherosclerosis of neointima in DES failure, especially late after implantation. With regard to the results, there is a difference (incidence of the TCFA-like image) between our and their data as follows: they showed that \(\approx 70\%\) of patients with late ISR (20 months after DES implantation) revealed the TCFA-like image, yet our data showed TCFA-like image in \(\approx 50\%\) of patients in the VL-ISR group and in \(\approx 30\%\) of the L-ISR group at the MLA site. Potential explanations include differences in the population characteristics between the two studies. Although ACS was dominant in their study (30 with stable and 20 with unstable angina), the majority of our study consisted of stable patients. Although ACS was dominant in their study (30 with stable and 20 with unstable angina), the majority of our study consisted of stable patients.

A Speckled pattern image was frequently observed in the early phase of atherosclerotic progression and lesion appearance. This result of PLIA might support our hypothesis that speckled pattern images were caused by delayed arterial healing of the DES.

Limitations

OCT has intrinsic limitations in the qualitative analysis of restenotic tissue. Inter-/intra-observer variability was generally good; however, the differentiation of the layered or speckled pattern image was difficult in some cases. In such cases, a consensus was reached and used as the final decision. In addition, there were few data about the correlation of OCT images of DES restenotic tissue and histological findings.\textsuperscript{14} Therefore, OCT findings of intimal tissue should be interpreted with caution.\textsuperscript{22} Secondly, there was a significant difference of the stent type between groups. Only two patients with ISR of the TAXUS stent were enrolled in the VL-ISR group. The Cypher stent was approved 8 years ago (August 2004), whereas the TAXUS stent was only 5 years ago (March 2007) in Japan. This difference of approval time may contribute to the difference of patient numbers, especially in the VL-ISR group. In addition, the present study focused on the first generation DESs, although second generation DESs are commonly used in current practice. Further studies are needed to examine whether this study finding is applicable to other DESs, especially second generation DESs.

Conclusion

The OCT morphological characteristics of DES restenotic tissue were different over a prespecified time course. OCT images in
DES E-ISR might be associated with delayed arterial healing, and neoatherosclerosis might contribute to the DES late catch-up phenomenon including L-ISR and VL-ISR.

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**References**


