Clinical Decision Making Tools for IVUS-Based Treatment Planning

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Abstract

Intracoronary radiation therapy reduces the restenosis rate after coronary angioplasty. In the trials so far, the prescription of radiation has been done in many different ways. Different radioactive beta and gamma sources and delivery systems (5 Fr catheter, sizable centering balloons) have been used. This results in a very wide range of doses delivered in the arterial wall.

In order to retrospectively estimate the dose delivered in a coronary segment on structures such as the lumen or the external elastic lamina, we have developed a PC-based 3-d treatment planning system for intravascular brachytherapy using IVUS pullbacks data (iPlan™). An anatomical segmentation tool is provided that also reads the outputs of commercially available IVUS analysis softwares. Dose-volume and surface histograms are calculated using the AAPM TG43 protocol formalism of sources used clinically. An application is illustrated with 27 patients treated by PTCA and β-brachytherapy.

1. Introduction

Intracoronary radiation therapy (ICRT) is a new therapeutic modality to prevent restenosis. Positive results observed in animal experiments have supported the blossoming of numerous clinical trials. The strong reduction of the restenosis rate for the treatment of in-stent restenosis using γ-radiation[1, 2] contrasts with more controversial data observed with the use of β-radiation as adjunctive therapy after percutaneous angioplasty (PTCA) of de novo lesions.[3, 4] The benefits are not observed for all the patients and the reported late lumen loss demonstrates large standard deviation. We hypothesized that this phenomenon may be related to the dose of radiation delivered to the coronary vessel wall. Teirstein, for example, has already reported that γ-therapy was only effective when the minimum dose to the furthest point of the adventitia was at least 8 Gy.[5]

Our aim was to develop a treatment planning system for ICRT based on the intravascular ultrasound (IVUS) assessment of the treated coronary segment. We wanted to demonstrate the relationship between angiographic or IVUS parameters changes and the actual dose deposited to different coronary structures such as the luminal surface or the external elastic lamina (eel). The dose was derived from dose-volume histograms (DVH) computed on the 3-d IVUS pullbacks using a method recently described.[6, 7]

2. Material and methods

Spatial dose evaluation methods consist of visualizing dose distributions from treatment delivery devices superimposed with patient anatomical data. In the field of radiation therapy, this type of display is often referred to as isodose lines. IVUS automated pullbacks give the anatomical map of the artery. Once the anatomical data are obtained, the isodoses can be calculated and mapped to the anatomy and displayed to the physician. Assuming that the catheter containing the radioactive source is lying in the same position as the IVUS catheter, it is possible to measure the distance from the source to any vascular structure and calculate the dose rate when the activity and physical characteristics of the source are known.[8] This is illustrated in figure 1.

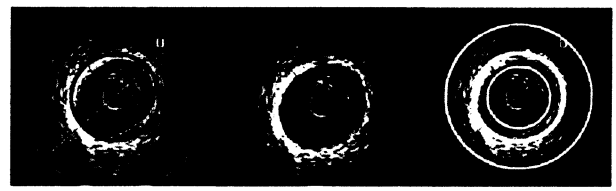

Figure 1. Isodoses of 32, 16 (bold) and 8 Gy superimposed on an IVUS cross-section for a γ-^{192}Ir (left) and a β-^{90}Y/Sr (right) sources positioned at the IVUS catheter location (16 Gy prescribed at 2 mm from the center of the delivery catheter).

This type of process may give the clinician an opportunity to retrospectively evaluate the influence of dose on the success or side effects of the treatment at a particular location. However, the evaluation of the overall dosimetry in the arterial wall from successive cross-sectional images is difficult. Dose-volume histograms (DVH) have been introduced in radiotherapy to condense

the large body of information of the complete 3-d dose distribution data into a plot summarizing graphically the radiation distribution throughout the target volume and the anatomical structures of interest.[9]

Quantitative dose evaluation methods such as dose volume histograms (DVH) and dose surface histograms (DSH) will provide a snapshot view of the dose-volume relationship for a particular treated segment. DVH have been proven to be a powerful dose evaluation tool for the physician. DVH summarize the dose distribution information for a region of interest and identify characteristics such as dose uniformity and hot or cold spots. To calculate a DVH, the dose distribution data must be available for the region of interest. The histogram is a plot of the accumulated volume of those elements receiving a dose in a specified dose interval versus a set of equal-spaced dose intervals. The cumulative DVH have been the most widely used in radiation therapy. The cumulative DVH are displayed with each bin representing the volume that receives a dose greater than or equal to an indicated dose level. The coronary segment corresponding to the IVUS pullback is subdivided into small voxels, in which the dose is computed.

The calculation of dose within a specified volume is a standard means employed in radiation oncology for planning teletherapy (external) or brachytherapy treatments. Dose calculation methods can be grouped into Monte Carlo methods and semi-empirical methods. Monte Carlo dose calculation methods use physical interaction principles to calculate the dose distribution of an irradiated medium. Even though Monte Carlo can be very accurate it is generally not used because the amount of time required to get an accurate answer is excessive. Instead, most dose calculation involves the use of tabulated data generated from dose measurements or Monte Carlo calculations to perform a very fast and generally accurate assessment of the dose distribution. To determine the dose rate at a specific point from a radioactive source, the physical location, activity of the source(s) and the 3-d coordinates of the specific point must be known. Calculation of the dose at distances of 5 mm or less from a radioactive source is difficult to model accurately. For vascular brachytherapy, the American Association of Physicists in Medicine (AAPM) Task Group No. 60 (TG-60) has presented a standardized method for calculating the sub-millimeter dose distribution around β- and γ-emitting catheter-based systems (seeds and wires)[10], which is a modification of the AAPM TG-43 protocol for calculating the dose distribution around interstitial sources. The TG-43 method uses tabulated dose distribution data, which is collected via dose measurements or Monte Carlo modeling techniques. These measurements are used to develop various tables based on the position and orientation of the source to the point of calculation.

IVUS imaging: In our patients treated with coronary brachytherapy, we have tried to systematically perform IVUS prior to the insertion of the radiation delivery catheter. Intracoronary nitrates were administered before the coronary segments were examined. The ClearView™ (CardioVascular Imaging System - CVIS, Sunnyvale, CA) was used with IVUS catheter incorporating a 30 MHz single-element rotating transducer in a 2.9 Fr. sheath (~1 mm). The ECG-gated image digitization system (EchoScan, TomTec, Munich, Germany) received the video signal input from the IVUS console, and the ECG signal from the patient. This system steered the ECG-gated stepping pullback device by steps of 0.2 mm. Images were acquired at end-diastole for heart cycles falling within a predetermined range (0.125 s) around the heart rate of the patient. Premature beats and RR-intervals outside this range were excluded and the IVUS catheter remained stationary. This system assures segment to segment independence by not imaging during the axial movement of the IVUS catheter which occurs during the cardiac cycle. We use a contour detection program developed in our laboratory[11] for the automated 3-d analysis of the IVUS images corresponding to the irradiated segment. The contours of the lumen-intima and the media-adventitia (external elastic lamina, eel) boundaries are identified on two longitudinal views using a minimum-cost based analysis algorithm. These contours are used to guide automated contour detection in every planar cross-sectional image.

Dose volume histograms methodology: Selection of the IVUS segment matching the irradiated site was based on anatomical landmarks such as side branches or bifurcations. An angiogram was performed after the placement of the delivery catheter to establish and document the relationship between the anatomical landmarks and the gold markers of the delivery catheter. The anatomical landmarks closest to either of the gold markers were used as reference points. This angiographic reference point was identified during a contrast injection with the IVUS imaging element at the same position as the gold marker. The image from the IVUS imaging element was recorded and the reference point identified. During the subsequent pullback, this reference point was recognized and used for selecting the area subject to the analysis. The contours of the EchoScan program were processed with a software written in MatLab (The MathWorks, Inc., Natick, MA) to compute the distances between the centre of the source and both the lumen-intima interface and the eel in 24 pie-slices (15°) in all cross-sections corresponding to the fully irradiated segment (25 mm), excluding the dose fall-off zone. Dose volume histograms were computed retrospectively using an intracoronary treatment planning system (iPlan™, Atlanta, GA, US Patent 6,083,167) developed in Emory University. This therapy planning system incorporates a dose calculation engine based on a AAPM TG-43 method

using catheter-based delivery systems with the following radiation sources: $^{90}Sr/Y$, ^{32}P, ^{125}I, and ^{192}Ir. For this study, the dosimetry used in iPlan™ was based on the method discussed by Soares et al. for calibrating β-sources and includes anisotropy factors to account for the dose fall-off on the end of the seeds on the transverse axis.[12] iPlan™ has the following features: AAPM TG-43 dose engine, spatial dose evaluation, anatomical delineation, dose volume histograms, dose surface histograms, statistical reporting, documentation of plan, on a PC-based platform. For each patient, a spatial dose distribution, cumulative dose surface histograms for the luminal (DS_{LUM}) and eel (DS_{EEL}) contours and a cumulative dose volume histogram for the plaque + media (DV_{P+M}) of the irradiated segment were calculated for the $^{90}Sr/Y$ source train. The maximum voxel dose, minimum voxel dose, and average voxel dose were recorded as well as two dose volume measurements, D90 and D10. D90 is the dose received by at least 90% of the volume/surface of tissue. D10 is the dose received by at least 10% of the volume/surface of tissue (figure 2). Thus, the D90 and D10 doses represent a dose value based on a percentage of volume covered as opposed to the minimum and maximum doses which are the dose values given to a single voxel.

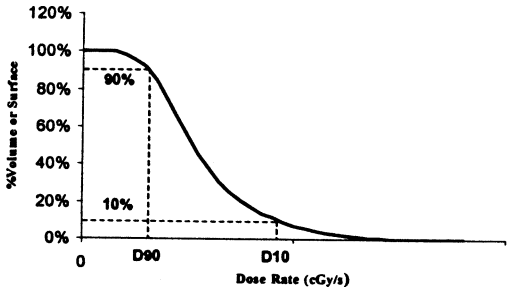

Figure 2. Dose volume histogram shows percentage of volume of vessel wall treated to a certain dose. D90 is the dose received by at least 90% of the volume/surface of tissue. D10 is the maximum dose received by at least 10% of the volume/surface of tissue.

Study population: 27 consecutive patients presenting with de novo coronary stenosis, successfully treated with balloon angioplasty followed by ICRT were analyzed. Patients receiving a stent were excluded from the analysis. Radiation was delivered within the framework of brachytherapy trials conducted in our institution that were approved by our Investigational Review Board. All patients gave written informed consent. The isotope used was the pure β-emitting $^{90}Sr/Y$. Patients were randomized to receive 12 to 18 Gray at 2 mm off source axis. ICRT was performed with the BetaCath System™ (Novoste Corp., Norcross, GA). The radiation source train consists of a series of twelve independent 2.5 mm-long cylindrical seeds that contain the $^{90}Sr/Y$ source.

Quantitative coronary angiography (QCA) was performed pre-, post-procedure and at 6-month follow-up in > 2 orthogonal matched projections with the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands) after intracoronary administration of nitrates. The following measurements were obtained: minimum lumen diameter (MLD), reference diameter, percent diameter stenosis (%DS). Acute gain was defined as MLD post-procedure minus MLD pre-intervention. Late lumen loss was defined as MLD post-procedure minus MLD at 6-month follow-up. The late loss index was computed as the ratio of the late loss over the acute gain. Relative gain and loss were computed respectively as the gain and the loss divided by the reference diameter. Restenosis at 6 months was defined as a %DS>50 %. The fully irradiated segment of the vessel was analyzed.

3. Results

QCA results are summarized in table. Patients were comparable to a Benestent-like population with unremarkable risks factors and non-complex lesions. Angiographic acute gain and late loss were comparable to similar PTCA patients in historic trials. The mean IVUS lumen diameter, derived from the lumen volume divided by the 25 mm of the pullback length, was 3.3 mm and the mean vessel diameter was 4.6 mm.

	preangioplasty	postirradiation	6-month follow up
Reference vessel diameter (mm)	2.96±0.54	2.96±0.61	2.78±0.55
Minimal lumen diameter (mm)	0.92±0.39	1.98±0.42	1.71±0.62
Diameter stenosis (%)	69±11	32±9	39±18
Acute gain (mm)		1.06±0.42	
Late luminal loss (mm)			0.27±0.58
Loss index (%)			26±60
Binary restenosis			7 (26 %)

Dosimetry

On average, $DS90_{EEL}$ was 5.1 Gy and $DV90_{P+M}$ was 7.0 Gy, for an average dose of 14.1 Gy prescribed 2 mm off source axis. Seven patients had a DS > 50% at follow-up within the fully irradiated segment. The sensitivity and specificity curves to predict a DS>50% at 6-month for $DS90_{EEL}$ crossed at 4.5 Gy. Sensitivity and specificity were then 0.58. No significant threshold could be found for $DS90_{LUM}$ and $DS50_{LUM}$. The Beta-Cath™ source has been recently recalibrated by the NIST and the doses prescribed to our patients were actually 15% higher than believed (e.g, a dose of 16.1 Gy has actually been given to the patients randomized to 14 Gy). The threshold of 4.5 Gy that we have derived for $DS90_{EEL}$ corresponds to an actual dose of 5.2 Gy.

A significantly lower loss (-0.01±0.39 vs. 0.47±0.62 mm, p=0.03), relative loss (-0.007±0.158 vs 0.15±0.21 mm, p=0.04) and loss index (-0.4±58 vs 44±56 %, p=0.06) were found in the 11 patients with a $DS90_{EEL}$ >

5.2 Gy. Similar results were found for the patients with a $DV90_{P+M}$ > 7.1 Gy. There was no difference in the clinical characteristics of the patients with a $DS90_{EEL}$ < or > than 5.2 Gy. The vessels with a $DS90_{EEL}$ > 5.2 Gy were smaller, had less plaque accumulation, but similar gain (1.15±0.38 vs. 0.93±0.46 mm, p=ns) and relative gain (0.36±0.10 vs. 0.35±0.15 mm, p=ns). None of the observed differences in the angiographic and IVUS parameters could predict a lower restenosis rate, loss and loss index at 6 month. Among the 11 patients with a $DS90_{EEL}$ > 5.2 Gy, the binary restenosis rate was 18% (2/11) compared to 31 % (5/16) when the dose delivered on 90 % of the eel was < 5.2 Gy. This difference did not reach statistical significance.

4. Discussion and conclusion

The threshold of 5.2 Gy for DS90eel that we find is in agreement with a previous IVUS analysis in which we have analysed 2-mm sub-segments of coronary arteries treated with brachytherapy. We could demonstrate that there was an increase of the luminal volume, related to an increase of the vessel volume larger than the plaque growth, when the $DS90_{EEL}$ was greater or equal to 6 Gy.[13] Several brachytherapy trials have demonstrated that in a majority of patients the luminal diameter at the site of the treated lesion may increase during the follow-up.[4] This phenomenon is induced by the positive remodeling of the vessel wall as demonstrated by IVUS.

The coordinate of the center of the IVUS catheter was used as a reference, and was considered at the same location as the center of the radiation train. This assumption is probably violated when looking at the differences in size of the IVUS and delivery catheters (2.9 vs. 5 F). However, the source does not occupy the center of the delivery catheter, and correction for this physical variability is difficult.

In conclusion, the body of additional information available from IVUS and derived dosimetry parameters like DVH improve our understanding of the mechanisms of action of ICRT and should be helpful for the comparison of trials based on different dosimetry strategies. Our ultimate goal will be to enable the clinician to make rapid, pre-treatment evaluation of the optimal radiation dose delivered to the patient based on figures of merit reflecting e.g. coverage, homogeneity, toxicity derived from the 3-d IVUS plan.

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