Physical and Histopathological Assessment of the Effects of Metallic Stents on Radiation Therapy

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Metallic stent/Dose perturbation/Bile duct/Microspace dosimetry/Thermoluminescent sheet.

To evaluate whether simultaneous metallic stent (MS) placement and radiotherapy are feasible, phantom and animal experiments were performed. The interface dose by external irradiation (EI) or intracavity irradiation (II) to 5 kinds of MS was measured using the charge-coupled device (CCD) camera with a thermoluminescent (TL) sheet, and backscatter and absorption were evaluated using composite method. Lineac 10 MV X-ray irradiated the MS in close contact with the TL sheet. II was performed using 192Ir, and the irradiation dose transmitted through the MS was measured using the TL sheet. The ratio of the CCD value of the MS wire region to that of the MS non-wire region was defined as the dose perturbation factor (DPF). Furthermore, the effects of a combination of 60Co gamma-ray EI and MS placement in the normal common bile duct were histopathologically evaluated in dogs. In the phantom experiments of EI, in backscatter by the MS, the DPF was 1.09 for CZ, and 1.03 for Pal, but no backscatter was detected in the remaining 3 MS. In absorption by the MS, the DPF was 0.92, 0.97, 0.97, and 0.98 for CZ, Wall, Pal, and Vel, respectively, but no absorption was detected in U. Flex. In those of II, the DPF of absorption was 0.91, 0.98, and 0.98 for CZ, U. Flex, and Wall, respectively, but no absorption was detected in Pal and Vel. The animal experiments showed infiltration of inflammatory cells and fibrosis in the case of both MS placement and EI. These changes were marked in EI treating after MS placement, but neither severe ulcer nor perforation was found. In conclusion, these results suggested that the effect of MS should be considered carefully when simultaneous MS placement and EI is performed clinically.

INTRODUCTION

When the digestive tract, bile duct, blood vessels, or tracheae are stenosed, a metal device, called a metallic stent (MS), is placement for dilatation of the constructed region. Dilatation is induced by several methods, such as MS elasticity and a balloon. MS with various shapes have been developed using various materials,1–4) and MS placement is widely performed as a useful method for the treatment of luminal stenosis caused by benign diseases or malignant tumors. In radiotherapy of malignant tumors after MS placement, secondary electron beams and scatter induced by the placed MS cause dose perturbation at the interface between the MS and surrounding tissues, suggesting the possibility of an over and under dose. Therefore, it will be essential to evaluate practical dose distribution if micro space dosimetry is available in vivo. In this study, we performed external beam irradiation and intracavity irradiation of 5 MS for tracheal, esophageal and vascular in phantom experiments, and measured dose perturbation, such as backscatter and absorption, at the interface between the MS and surrounding tissues using a thermoluminescent (TL) sheet. Furthermore, MS causing high backscatter was placed in the normal common bile duct of mongrel dogs, and the effects of the MS and external beam irradiation were pathologically examined.

doi:10.1269/jrr.07049
METHODS AND MATERIALS

Phantom experiments

(1) MS

The following 5 MS were used: tracheal MS (covered Z (CZ); stainless steel(SUS316L), 0.4 mm diameter), esophageal MS (Ultra Flex (U. Flex); Nitinol, 0.18 mm diameter), MS for arteries in the lower limb (Wall; cobalt alloy, 0.12 mm diameter) (Palmaz (Pal); stainless steel(SUS316L), 0.25 mm diameter), and MS for the coronary artery (Velocity (Vel); stainless steel(SUS316L), 0.15 mm diameter)\(^1\text{-}^4\) (Fig. 1).

(2) Irradiation methods

External beam irradiation: Irradiation was performed with linear accelerator (10 MV X-ray; source-MS distance 100 cm; field size at MS, 10 cm \(\times\) 10 cm; ML20M, Mitsubishi Electric Co., Tokyo, Japan) at 6 Gy to a 1–5 cm\(^2\) MS piece produced by cutting it, and a TL sheet (made of BaSO\(_4\):Eu doped) (Nemoto & Co., Tokyo, Japan) placed between 2 polymethyl methacrylate (PMMA) plates in a water phantom at a depth of 5 cm (Fig. 2).

Intracavity irradiation: The esophageal MS placed on 17...

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**Fig. 1.** Five metallic stents (MS) used in this experiment. Abbreviation: CZ = Covered Z stent, U.Flex = Ultra Flex stent, Wall = Wall stent, Pal = Palmaz stent, Vel = Velocity stent.

**Fig. 2.** Scheme of phantom experiments. Irradiation was performed with 10 MV X-ray at 6 Gy to MS and a TL sheet fixed between two 1-cm PMMA plates in a water phantom at a depth of 5 cm. Each MS placed on cylindrical plastic were tightly rolled with a TL sheet, and irradiation was performed at a dose of 6 Gy on the MS surface in a water phantom using an iridium source (dose rate, 3–6 Gy/min) at the intracavity center.

J. Radiat. Res., Vol. 48, No. 6 (2007); http://jrr.jstage.jst.go.jp
mm diameter cylindrical plastic or the vascular MS placed on 10 mm diameter cylindrical plastic and coronary artery MS placed on 3 mm diameter cylindrical plastic were tightly rolled with a TL sheet, and irradiation was performed at a dose of 6 Gy on the MS surface in a water phantom using an iridium source (dose rate, 3–6 Gy/min) (microSelectron-HDR 192Ir, remote afterloading system, Nucletron, Veenendaal, The Netherlands) at the intracavity center (Fig. 2).

(3) Measurement methods
To measure backscatter, a TL sheet was placed in front of the MS, i.e., on the side of the radiation source, whereas, to measure absorption, it was placed behind the MS, i.e., on the opposite side to the radiation source. The TL sheet was measuring 10 mm × 10 mm × 0.2 mm, and the particle size was 0.03 mm diameter. The irradiated TL sheet was processed using a cooled CCD two-dimensional readout system (CC2RS). The CC2RS consisted of the heating system, by which irradiated TL sheets were heated, and the cooled CCD camera (ST9XE, SBIG, Santa Barbara, CA, USA), by which images were collected (Fig. 3). The camera was a UV model (CCD type of accumulating photon charge; number of pixels, 512 × 512; pixel size, 0.02 mm × 0.02 mm; gradient, 16 bit; cooling system, dual Peltier element). The CCD values of the MS wire and non-wire regions were measured, and backscatter and absorption were evaluated. Since the CCD value is proportional to the irradiation dose, the ratio of the CCD value of the MS wire region to that of the MS non-wire region was defined as the dose perturbation factor (DPF). Perturbation value (PV) was defined as formula:

PV = DPF - 1

To measure the scatter of lower levels, measurement was performed 5–7 times, and composite photographs were produced using several images. The covered stent was used in the experiment after removal of its cover.

Animal experiments
In 4 adult mongrel dogs (about 15 kg) under anesthesia by intravenous injection of 50 mg pentobarbital, the duodenum was incised after laparotomy, and a MS was placement in the common bile duct using a 5.5 Fr sheath inserted from the Vater papilla as the introducer under fluoroscopy. The MS used was made of stainless steel with a wire diameter of 0.26 mm, it had 6 bends, a length of 10 mm, and a stent diameter of 8 mm (original Gianturco type).5) External beam irradiation alone (experiment 1), MS placement alone (experiment 2), MS placement after external beam irradiation (experiment 3), and external beam irradiation after MS placement (experiment 4) were performed. External beam irradiation was performed in the anterior-posterior parallel-opposed beams field at a total dose of 30 Gy/3 fractions/3 weeks using 60Co gamma-ray (Thoratron 60, AECL, Mississauga, Canada). In experiment 3, MS placement was performed 1 week after the completion of external beam irradiation, and in experiment 4, external beam irradiation was started 2 weeks after MS placement. The dogs were sacrificed 4 weeks after the completion of treatment, and cholangiography was performed using 50 % meglumine sodium amidotrizoate. The common bile duct was excised, fixed with 10 % formalin, and embedded in paraffin. Sections were produced, and histologically examined after hematoxylin-eosin or Masson trichrome staining. Morphologically, the mucosa, muscle layer of the mucosa, submucosal issues, external tunica, and the presence or absence and degree of inflammatory cells or parenchymal fibrosis were examined. The study was conducted according to the Guidelines for Animal Welfare and Experimentation.
RESULTS

Phantom experiments

External beam irradiation

In backscatter by the MS, the DPF was 1.09 for CZ, and 1.03 for Pal, but no backscatter was detected in the remaining 3 MS (Fig. 4). In absorption by the MS, the DPF was 0.92, 0.97, 0.97, and 0.98 for CZ, Wall, Pal, and Vel, respectively, but no absorption was detected in U. Flex (Fig. 4). The PV of the maximum backscatter was 0.088 for CZ, that maximum of absorption was –0.081 (Fig. 5).

Intracavity irradiation

The DPF of absorption was 0.91, 0.98, and 0.98 for CZ, U. Flex, and Wall, respectively, but no absorption was detected in Pal and Vel. Backscatter measurement was not performed (Fig. 4). The PV of maximum absorption was –0.087 for CZ (Fig. 5).

Animal experiments

Intracavity:

In experiments 1–4, obstruction of the bile duct was not observed. The inner diameter of the bile duct was 3 mm in experiment 1. In experiments 2–4, local dilatation of the bile duct was observed in the MS placed region. The inner diameter of the bile duct was 7 mm, and the MS diameter was 8 mm in experiment 2. In experiment 3, the inner diameter of the bile duct was 5 mm, and the MS diameter was 7 mm. In experiment 4, the inner diameter of the bile duct was 4 mm, and the MS diameter was 7 mm. The inner diameter of the bile duct was 3 mm in the region without MS placement.

Mucosa, submucosal tissues, and external tunic:

Experiment 1: The mucosa of the common bile duct was in a relatively good condition, and neither erosion nor ulcer was observed. In the proper mucosal lamina to external tunic region, a very small number of lymphocytes were observed, but neither inflammation nor fibrosis was detected. The blood vessels were well maintained (Fig. 6a).

Experiment 2: Most part of the MS was buried in the proper mucosal region, but some part of the MS was exposed to the lumen, and the mucosa was partially erosive. Infiltration of a large number of lymphocytes and plasma cells and a small number of neutrophils was observed in some regions of the proper mucosal lamina, submucosal layer, and external tunic. There was mild parenchymal fibrosis (Fig. 6b).

Experiment 3: The MS was buried in the proper mucosal lamina to submucosal layer region. The mucosa partially showed erosion, but it was relatively well maintained. In the submucosal layer, infiltration of a relatively small number of lymphocytes and plasma cells was observed. Fibrosis was observed, but the degree was between those in experiments 2 and 4 (Fig. 6c).

Experiment 4: As in experiment 3, the MS was buried in the proper mucosal lamina to submucosal layer region. The mucosa was partially erosive, and infiltration of a relatively large number of lymphocytes, plasma cells, and neutrophils was observed, but neither severe ulcer nor perforation was found. Marked fibrosis was observed in the submucosal layer to external tunic region, but no abnormalities were detected in the vascular wall (Fig. 6d).

|        | CZ  | U.Flex | Wall | Pal | Vel |
|--------|-----|--------|------|-----|-----|
| 10MX Back scatter | ND | ND    | ND   | ND  | ND  |
| 10MX Absorption    | ND  | ND    | ND   | ND  | ND  |
| 192Ir Intra cavity Absorption | ND | ND    | ND   | ND  | ND  |

Fig. 4. Composite operating image after read-out of various stents using CC2RS. Abbreviation: ND = not detected.
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DISCUSSION

Generally, high-energy X-ray irradiation to metals in the body causes low-energy back scatter and absorption, and the amount of backscatter or absorption is considered to depend on the photon energy, incidence angle, irradiation field, atomic number of metals, thickness, and surface area. It has been reported that backscatter of high-energy X-ray irradiation by dental metals and internal immobilization metals used for orthopedic treatment measured in phantoms was increased by 14–70%. In these studies, measurement was performed using a phantom and an ionization chamber or a thermoluminescence dosimeter (TLD). These methods have associated problems, such as involving complicated preparation of experimental materials, aeration, and inaccuracy of measurement of the interface between the metal and tissues. Since backscatter by thin metal MS is very limited in a small region, measurement of backscatter using an ionization chamber without a spatial resolution function and TLD is impossible. Li, et al. performed irradiation of a steel ring stent model (wire with a 1 mm diameter, 0.5 and 2.0 mm space) using 6, 10 MV X-ray, and reported that dose perturbation at the interface between the stent and surroundings was 14–21% by Monte Carlo simulation. This dose perturbation was higher than that of our study, probably because thick wire (1 mm) and narrow spaces were used in their study.

The TL sheet used in our study was produced by mixing BaSO₄ into teflon. The TL sheet was found to have very wide dynamic range of linear response. Our other experiment suggested that the TL sheet has a good energy response for evaluating back scatter energy level (unpublished data). The TL sheet is flexible and has high spatial resolution. The spatial resolution of the TL sheet is 0.062 mm corresponding to 8.1 line pairs/mm. Since both materials are water-insoluble, the sheet can be used in water by close contact with MS. Measurement of the irradiation dose in a very small region at the interface between the metal and surroundings is possible due to good resolution. By using this system, micro space dosimetry is available in a room without shading, and even in water. Furthermore, since two-dimensional images can be produced by detecting thermoluminescence, this system is useful for super selective measurement of the irradiation dose in regions around the radiation source, in which the irradiation dose is rapidly changed, and in a very small MS region. In our study, measurement was accurate due to low-noise images obtained by the reader using a cooled CCD camera and image-processing software, and its good operability, compared to that by the conventional image intensifier type reader used in our previous studies.

The wire diameter used in the present study was thickest at 0.4 mm diameter for CZ, and second thickest at 0.25 mm diameter for Pal, both of which were very thin. However, backscatter was detected in these MS, and the DPF was 1.09 for CZ and 1.03 for Pal. In the remaining thinner MS, no backscatter was detected, suggesting that the amount of scatter was smaller with thinner MS.

The DPF of absorption by the MS was 0.92 for CZ with the thickest wire, 0.97 for Pal with the second thickest wire, and 0.97 for Wall with the thinnest wire. In the remaining 2 MS, no absorption was detected, and no correlation was observed between absorption and wire diameter. This may be partially caused by the differences in wire composition and technical problems in the measurement using composite photographs. The increase in the backscatter dose around the MS was 9% by external beam irradiation from 1 port after CZ placement, and this increase cannot be clinically neglected. However, increases in the backscatter dose by external beam irradiation from 2 parallel-opposed ports may be lower. Among the 5 kinds of MS used in this study, the increases in backscatter dose by 4 MS (excluding CZ which showed 9% backscatter increase) were at maximum less than 5%, suggesting that the radiotherapeutic problem is not always serious as far as we examined. The maximal absorption was 9%, suggesting the necessity of paying attention to absorption.

In the animal experiments, to evaluate the damage to normal mucosal tissues, irradiation at the total dose of 30 Gy/3 fractions/3 weeks was performed. Carrasco et al. examined the tissue reaction in the bile duct of animals caused by MS placement, and reported that partial detachment and mucosal hyperplasia, and chronic inflammation and fibrosis of the submucosal layer were observed, and the degree was in proportion to the MS placement period. In the present study, mucosal hyperplasia was not detected, but chronic inflammation and fibrosis of the submucosal layer were observed. The degree of fibrosis was slightly increased by the combination of MS placement and external beam irradiation, and...
the degree of fibrosis was highest by external beam irradiation after MS placement. This may be not only due to differences in the MS placement period (4 weeks in the animal treated by MS placement after external beam irradiation, 8 weeks in the animal treated by external beam irradiation after MS placement), but also due to the increase in the absorption dose of scatter around the MS. The increase might be suggested to be more than 9% according to the phantom experiment, though it is impossible to evaluate the practical dose in vivo exactly. However, necrosis of the biliary wall was not observed, and most parts of the mucosa and blood vessels were maintained, suggesting that external beam irradiation did not cause severe damage to the bile duct.

**CONCLUSIONS**

In this study, dose perturbation at the interface between MS and the surrounding tissues was measured using a TL sheet, and the relative dose was evaluated by digital imaging. Dose perturbation by MS, except for CZ stent, was less than 5%, and no severe damage was caused by a combination of MS placement and external irradiation. Therefore, these results suggested that the effect of MS should be considered carefully when simultaneous MS placement and EI is performed clinically.

**ACKNOWLEDGEMENTS**

We would like to thank Dr. Yoshiko Yoshimura and Dr. Shohji Sakaguchi for metallic stent preparation. This investigation was supported in part by Grant-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan.

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Received on April 27, 2007
Revision received on July 5, 2007
Accepted on July 24, 2007
J-STAGE Advance Publication Date: September 29, 2007

J. Radiat. Res., Vol. 48, No. 6 (2007); http://jrr.jstage.jst.go.jp