Ureteric response to abdominal radiotherapy and metallic double-pigtail ureteric stents: a pig model

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OBJECTIVE
To examine the safety and compatibility of full-length metal ureteric stents with abdominal radiotherapy.

MATERIALS AND METHODS
Four ureteric stents (Resonance™, Cook Urological, Ireland) (RS) and four RSs specially modified to contain thermocouples were placed unilaterally in eight pigs. The contralateral ureters of the same pigs served as their controls, and contained two polymeric ureteric catheters and two similar specially modified to contain thermocouples, while the remaining four control ureters remained intact. All pigs were exposed to abdominal radiotherapy. The dose rate was ≈5.3 Gy/min and a total radiation dose of 10 Gy was administered. Throughout the treatment the temperature was monitored by the RSs and catheters containing the thermocouples. The pigs were killed at 1 day (four), 7 days (two) and 15 days (two) after treatment, and all ureters examined histologically.

RESULTS
There was no statistically significant increase in RS and catheter temperature throughout the treatment in any of the treated pigs (P > 0.05). All histological lesions reported were due to radiation treatment. There were no differences in histology between the ureters containing RSs and controls.

CONCLUSION
RS usage is unrelated to any increase in stent temperature during abdominal radiotherapy and does not cause any further deterioration in the histology of the ipsilateral ureter, additional to that caused by the initial treatment.

KEYWORDS
abdominal radiotherapy, full metal, double-pigtail, stent

INTRODUCTION
The full metal double-pigtail ureteric Resonance™ stent (RS; Cook Urological, Limerick, Ireland) is an incompressible stent composed of nonmagnetic nickel–cobalt–chromium–molybdenum alloy. RS usage is indicated for the management of patients with malignant, extrinsic ureteric obstruction [1–3]. Studies have shown that it provides satisfactory drainage of the upper urinary tract, even in cases of extrinsic compression sufficient enough to occlude the standard polymeric stents [3]. However, there is limited clinical experience with this novel stent for its safety and compatibility, when it is combined with other anticancer treatments such as abdominal radiotherapy (RT). Considering that high-energy irradiation to metal structures in the body causes low-dose energy back-scatter and absorption, concerns have been raised that RT would result in increase in stent temperature to harmful levels for the ipsilateral ureter [4]. Moreover, the effect of the energy back-scatter on the histology of the stented ureters remains unknown. Thus, we designed an experimental study to assess whether RT was safe in ureters stented with the RS.

MATERIALS AND METHODS
Eight domestic pigs (20–25 kg) were used for the experiment; the protocol was approved by the Animal Care Committee of our institution. For this experiment four different kinds of ureteric catheters were used; five original RS and two double-pigtail polymeric ureteric (PU) catheters (C-Flex®, Cook Urological) were used as controls to examine the effect of abdominal RT on the histology of the ureter. Also, three RS and two PU catheters were modified to introduce thermocouples into the lumen, to monitor stent temperatures during the procedure. In all, 13 units of precision fine-wire thermocouples (Omega Engineering Inc., Stamford, USA) were placed inside all distal, middle and proximal portions of the modified RS, and in both the distal and proximal portions of the PU catheters (the small diameter of the PU catheter lumen did not allow a third thermocouple to be placed in the middle portion). The modified version of the RS lacked the pigtail design; this was deemed necessary because it was impossible to attach thermocouples to a ‘standard’ RS. The thermocouples inserted in the lumen of the modified RS had their distal ends exiting from the one side of the catheter. To create
the ‘thermocouple’ catheter two small holes were made on the proximal and distal portion of an original catheter, and 1 cm of the proximal end of each thermocouple exited the lumen through these holes (Fig. 1). The remaining segment of the thermocouple exited from the distal side of the catheter, after running inside the lumen. All thermocouples were connected to the appropriate data-logger (Yokogawa Europe, Amersfoort, the Netherlands) and data from temperature measurements of each thermocouple were stored separately.

The correct function of the thermocouples was evaluated before, during and after ESWL. Room temperature was indicated by correctly working thermocouples before and after use, while any damaged thermocouple gave uncertain values of 0–2500 °C during the treatment session. Before anaesthesia all pigs were allowed at least 72 h beforehand to recover from the stress of transportation. Food was withheld for 12 h before anaesthesia. A combination of ketamine, xylazine and atropine sulphate was administered to induce anaesthesia. All pigs were intubated and ventilated. Propofol 5% i.v. was used to maintain anaesthesia for the duration of the procedure. Postoperative analgesia, when indicated, was by i.m. morphine sulphate. Prophylactic, peri- and postoperative antibiotics were given to all the pigs.

To insert the catheters, each pig was placed supine and a 0.9 mm hydrophilic guidewire was placed bilaterally in each ureter via cystoscopy. A 5 F PU catheter (two) or a 5 F PU catheter specially modified to contain thermocouples (two) was introduced under fluoroscopic guidance in the right ureter of four pigs and positioned in the renal pelvis. The right ureter remained intact and served as a control in the remaining four pigs. After catheter placement, the guidewire was removed from the right ureter. A 5 F/9 F catheter/sheath was placed over the guidewire in the left ureter and introduced in the renal pelvis under fluoroscopic control. The 5 F catheter and the guidewire were removed leaving the 9 F sheath at place. A 6 F RS was inserted in the renal pelvis through the 10 F introducer sheath and then the sheath was removed, allowing the distal coil of the stent to form in the bladder. Three of these RS were specially modified to contain thermocouples. The arrangement of catheters and stents placed in each pig are listed in Table 1. All endoscopic interventions were performed in a standard operating room equipped with C-arm fluoroscope.

For the RT protocol and technique, the upper, lower and lateral limits of the irradiation field were demarcated on an X-ray simulator and included both ureters. All pigs were prepared to receive RT with anterior-posterior fields using a 6-MV linear accelerator. Treatment planning was based on CT series and appropriately individualized, aiming for a uniform dose distribution within the target volume (ureter) (Fig. 2). The fields were marked on the bare skin of the pigs using specially prepared ink. To maintain their position during RT the pigs were anaesthetized and placed in a custom-made immobilization system. The focus-to-skin distance was 100 cm, and the dose rate was ≈5.3 Gy/min. Planning and dosimetric calculations were carried out using the accelerator’s treatment planning system. To assure that the radiation would induce ureteric damage, a total dose of 10 Gy in one fraction was administered. The biologically effective dose of 10 Gy for developing late complications (ureteric stenosis) is 30 Gy (α/β ratio 5 Gy) [5].

During treatment the temperature was measured every 2 s; the data from each thermocouple were saved on a six-channel data logger, with each thermocouple connected to one of the channels. On the first day after the procedure all four pigs with
temperatures do not differ significantly ($P > 0.05$).

In general, the histological features in the resected ureters included epithelial denudation (detachment), acute and chronic inflammation, glandular metaplasia and regenerative changes. Epithelial denudation (detachment) represents mild epithelial damage due to catheter introduction and removal. It was present in ureters containing RS and modified RS resected at 0 and 7 days. There was no epithelial denudation at 15 days in all resected ureters. Regenerative changes, which are an indication of healing, appeared in most of ureters resected at 7 and 15 days. Acute (polymorphonuclear) and mild (+1) chronic (lymphohytic) inflammation of the epithelium was present in all resected ureters. Finally, granular metaplasia was present in almost half of the resected ureters on all samples of ureter resection (0, 7 and 15 days). Despite the differences in histology in ureters resected from pigs killed on different days, the histological features were similar in both the left and right (control) ureter of each pig (Fig. 4).

DISCUSSION

Metallic stents have been extensively used for managing malignant ureteric obstruction, uretero-ileal anastomotic strictures, PUJ obstruction and kidney transplantation [6–14]. Nevertheless, the application of these stents in the ureter has been associated with several complications, with the more prominent being urothelial hyperplasia through the stent struts, stent migration and encrustation [14–17]. The most recent development of metallic stents is the drug-eluting stent, which has been proposed for managing urothelial hyperplasia [17].

The all-metal (nonmagnetic nickel-cobalt-chromium-molybdenum alloy) double-pigtail RS was introduced recently [1]. The stent is formed by a tight spiral coiled metal wire. The design of the stent prevents the protrusion of the hyperplastic urothelium or tumour ingrowth through the stent coil. Its metal alloy is considered to be resistant to encrustation. Current clinical and experimental data on RSs are limited. The first report of the successful use of this type of stent was published by Borin et al. [1]; the RS was used for relieving intractable ureteric obstruction due to retroperitoneal fibrosis secondary to breast cancer. Clinical data reported by Wah et al. [2], in 15 patients with malignant ureteric obstruction managed by inserting an RS, showed that adequate long-term urinary drainage of malignant ureteric obstruction without concomitant bulky pelvic disease was achievable with the use of the RS. In addition, Nagele et al. [3] inserted 18 RSs in the collecting systems of 14 patients with either benign or malignant disease. The mean follow-up was 8.6 months; encrustation was obvious on two stents. Persistent haematuria, severe dysuria, pain and insufficient drainage forced the investigators to remove seven stents. Also, it was found that patient comfort was associated with the selection of an appropriate length of stent.

Blascko et al. [18] compared the RS with standard ureteric stents in terms of urinary flow in an experimental study. Despite the RS providing less overall flow than the standard stent, extrinsic compression sufficient to occlude the standard stent did not affect the RS, which provided satisfactory drainage. Considering these data and especially the promising results of the use of RSs in patients with malignant disease, the question of the compatibility of the stent with therapies commonly used in these patients has been raised. Various investigators studied the effects of high-energy ionizing radiation on metallic stents and the surrounding tissues. In general, medical conditions such as malignant
biliary obstruction and oesophageal cancer are commonly treated by stenting, while concurrent external RT has been reported to improve the outcome [19–21]. Consequently, RT to anatomical sites containing these stents is not contraindicated. Tsuji et al. [4], in a well-designed study, examined the effect of external RT on five different kinds of metallic stents. RT was shown to be safe for the tissue containing the stent, although they reported that disturbance in the absorption of energy by the surrounding tissues is most likely to occur. The latter phenomenon was attributed to back-scatter energy and dose perturbation; the latter was reported to be <5% in most of the stents. Nevertheless, other investigators reported much higher perturbation rates of 14–21% [22]. Considering these results, we advocate that low-energy back-scatter and dose perturbation is expected to be higher in the RS, due to its atomic weight, metal thickness and solid metal construction. However, the present study was designed to investigate mainly the safety of RT in ureters containing RSs. Thus, the effectiveness of RT was not fully evaluated, and as a result, further investigation in the field is necessary.

To our knowledge, this is the first in vivo study to assess the temperature of metallic stents during RT. Radiation energy is not usually converted to heat during irradiation; e.g. the amount of energy that is absorbed during whole-body irradiation and converted to heat represents a temperature rise of 0.002 °C [23]. Moreover, thermal injury to the surrounding tissues of metal structures, such as metal stents, metallic dental or an internal immobilization prosthesis used in orthopaedics during RT, has never been reported. Our experimental work confirmed the above data, as RT did not increase significantly the temperature of the RS. Nevertheless, the most important evidence for the safety of the combination of RS with abdominal RT is the reported histological result. Despite all ureters examined during the 2 weeks after treatment showing severe histological lesions, there were no differences between control ureters and those containing PU stents or RS. This led us to attribute the observed histological deterioration to RT rather than RS usage. Consequently, RT of the RS appears to be safe for the ipsilateral ureter.

No significant temperature increase was detected within the stent during irradiation of ureters containing the RS. Moreover, there was no difference in the pathology of both RS-carrying and control ureters. In conclusion, the results of the present experimental study do not contraindicate the use of RS concomitantly with external RT. Nevertheless, further clinical studies are required to confirm the safety and compatibility of abdominal RT and RS usage.

CONFLICT OF INTEREST

None declared.

REFERENCES

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**Abbreviations:** RS, Resonance™ stent; RT, radiotherapy; PU, polymeric ureteric.