Clinical Device-Related Article
Ni-Cr-Co alloy ureteral stent: scanning electron microscopy and elemental analysis characterization after long-term indwelling

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Abstract: We report the first preliminary study on metal-alloy ureteral stent after long indwelling times. The aim is to analyze by physical–chemical characterization of the stent after use and to evaluate the material performance in this human *in vivo* case study. Six Resonance® metallic stents (Cook Ireland) were inserted in six patients for 6, 10, 11, 12, 24, and 36 months. The stents were then collected and studied by Field Emission Scanning Electron Microscopy (FESEM) and Energy Dispersive Spectroscopy (EDS), gaining information about the metal stent surface and the amount and nature of the formed encrustation. The stents were all draining adequately, despite the presence of the bacterial biofilm layer in all stents. This layer was more dense and compact as the indwelling time increased. Some slight precipitation of inorganic compounds, such as brushite and calcium oxalate was observed. No epithelial tissue in growth was recorded. These preliminary results with Resonance® metallic ureteral stents suggest the feasibility of a long-term approach in patients with chronic ureteral obstruction. The durability of the metal stent, the lack of epithelial tissue ingrowths and limited pain or discomfort to patients were proven over long time periods. The long-term use of these stents is therefore feasible, avoiding the continuous exchange of the stent, decreasing hospital costs and increasing the quality of life of patients affected by malignant pelvic tumors. © 2010 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 94B: 501–507, 2010.

Key Words: metallic stent, long-term urinary drainage, electron microscopy, energy dispersive spectroscopy, ureteral strictures

INTRODUCTION

Long-term urinary drainage for patients with malignancy or recurrent benign disease is distressing, both for patients and for surgeons. Percutaneous nephrostomy and polymeric double J-stent[1] placements are currently used in this setting. However, the success rate is often low and the need for frequent changes of stent significantly impairs the quality of life of the patients.

In light of this, a number of metallic stents, such as the Nitinol self-expandable stent, were introduced in clinical practice. These stents, however, are associated with a high rate of migration, stone encrustation, and obstruction because of urothelial ingrowths.[2,3] To prevent the hyperplastic reaction associated with this kind of stent, Dacron coated metallic stent were used with promising results[4] to further increase the effectiveness of double J stent. Despite the success of these covered metal stents, there are still a number of disadvantages associated with this technique. The most common problems are insufficient relief of the obstruction, immediate recurrence of the obstruction after stent removal and the need to replace the stents frequently.

To reduce the encrustation, tumor ingrowth and the need for frequent stent changing, a Nickel-Chromium-Cobalt-Molybdenum alloy double-pigtail ureteral stent (Resonance® stent, RS, Cook Ireland LTD)[5] was introduced as a drainage solution (for up to 12 months) with promising results both in malignant and benign recurrent disease.

The aim of this study is to evaluate the phenomenon of encrustation on RS with a morphological and elemental analysis by Scanning Electron Microscopy (SEM) and Energy Dispersive Spectroscopy (EDS) after long indwelling times. To our knowledge, no papers were published focusing specifically on electron microscopy and elemental analyses of RS.

PATIENTS AND METHODS

The present prospective study involved patients with ureteral obstruction because of malignancy or benign recurrent disease with the need for long-term (>6 months) ureteral stenting. Six patients matched these criteria; clinical data such as age, gender, and indication to stent positioning were recorded (see Table I). All subjects enrolled in this study gave their informed consent. The mean patient age was 60.8. The Resonance® stents (RS) were provided by Cook Ireland and the entire study was performed at S. Giovanni Battista Hospital, University of Turin, Turin, Italy. All patients were treated with RS (6 F, 26 cm). This stent

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TABLE I. Clinical Data of the Six Patients in This Study

Case no	Sex	Age (years)	Clinical Data and Stenting Indication	Stent Removal After
1	F	58	Advanced uterus carcinoma, with extrinsic compression of **right** ureter. A RS was placed and a neo-adjuvant chemotherapy was started. At the end of therapy patients underwent "exenteratio pelvis" at Gynecological Dept. Stent was removed during intervention. (**malignant ureteral obstruction**)	6 months
2	M	65	Locally advanced prostate cancer after external beam radiotherapy and hormonal therapy. (ie hormonal escape). RSs were placed **bilaterally**.[a] **(malignant ureteral obstruction)**	10 months
3	M	64	**Right** ureteral stenosis due to partial cistectomy for a large transitional cell carcinoma in bladder diverticulum. Patients refused reintervention and was treated with stent positioning **(benign ureteral obstruction)**	11 months
4	F	70	**Right** ureteral stenosis in patient with previous uterus cancer treated with surgery and external beam radiotherapy 10 years earlier. **(benign ureteral obstruction)**	12 months
5	F	49	Recurrence of uterus cancer with extrinsic compression of **left** ureter. Chemotherapy was started the day after the RS positioning **(malignant ureteral obstruction)**	24 months
6	M	59	Chronic **left** ureteral stenosis in patient "stone former" previously undergone multiple retrograde procedures (ureteroscopy) with solitary kidney. **(benign ureteral obstruction)**	36 months

[a] Only one stent was analyzed.
In three cases (50%) the ureteral obstruction was benign, whilst it was malignant in the other ones.

consisted of a tight spirally coiled metal wire forming a double pig-tail stent, without end or side holes and with an internal safety wire welded to both closed ends.

Previously, patients 2, 3, 6 had ureteral stenting with polyurethane double J and had experienced repeated stent obstruction and urinary tract infections. Patient 4 had previously undergone traditional stent substitution every 3–4 months. Since she required a longer period of indwelling, a RS was proposed. Patients 1 and 5 had no traditional stent before RS. The metallic stent placement was chosen after discussion of the therapeutic alternative solutions with each of the patients.

Double J RS was placed using a retrograde approach during cystoscopy as suggested by the stent producer. In each case a retrograde uretero-pylegraphy was performed at the start of the procedure in order to evaluate the excretory system. Ciprofloxacin (500 mg twice a day) was administered for prophylaxis for the first 4 days after the procedure. Any occurrence of technical problems and violations of aseptic conditions during the procedures were recorded. The antibiotic therapy administrations, other therapeutic interventions administered during the period of indwelling, the presence of fever, infections or urinary symptoms were also recorded.

After the procedure, the follow-up included urine analysis and culture on day 15 and every subsequent three months. In addition, a complete blood count, serum creatinine levels, and ultrasonography were performed on day 30, and every 3 months thereafter. All patients received instructions to present themselves at the institution in the event of experiencing side pain, fever, dysuria, hematuria, or vomiting.

The RS were removed after 6 (pt. 1), 10 (pt. 2), 11 (pt. 3), 12 (pt. 4), 24 (pt. 5) and 36 (pt. 6) months. For patient 1, the stent was removed by surgical intervention (radical hysterectomy). For patients 2–6 the stents were removed (or substituted) by cystoscopic procedure. Patients 5 and 6 refused the stent substitution after 12 months, thus the stents were substituted once the consent of patient was given. Patient 6 was unavailable for follow-up from month 15 to 35, hence no clinical data was available for this period. The follow up was repeated at month 35.

Characterization of RS after the indwelling period was carried out using morphological and compositional analysis and the results obtained were compared with a reference RS before use. The stents were randomly cut into different pieces and characterized by means of a Field Emission Scanning Electron Microscopy (Assing FESEM Supra 25, Göttingen, Germany) for the morphological characterization of the stent surface. They were also analyzed by Energy Dispersive Spectroscopy (EDS, Oxford Instrument INCA X-Sight, Oxford Instrument, Göttingen, Germany) at 10kV, to collect data about the chemical composition of the stent material and the deposited encrustations. Both analyses were performed on the coils at the external surface of the metal stent, on a cross section of a cut piece of the stent (thus analyzing a single coil), on the closed end of the pig-tail, and on the internal safety wire (Figure 1). The same measurements were also performed on a reference stent without indwelling to evaluate the metal surface modification.

All the data were analyzed with the PC application Statistica (Microsoft, Tusla, Okla) on a desktop computer.

RESULTS

Clinical data

No technical problems or violations of aseptic conditions during the endoscopic procedures were recorded. In all cases retrograde uretero-pylegraphy, performed at the start of the procedure, showed ureteral obstruction with various degrees of excretory system dilatation.

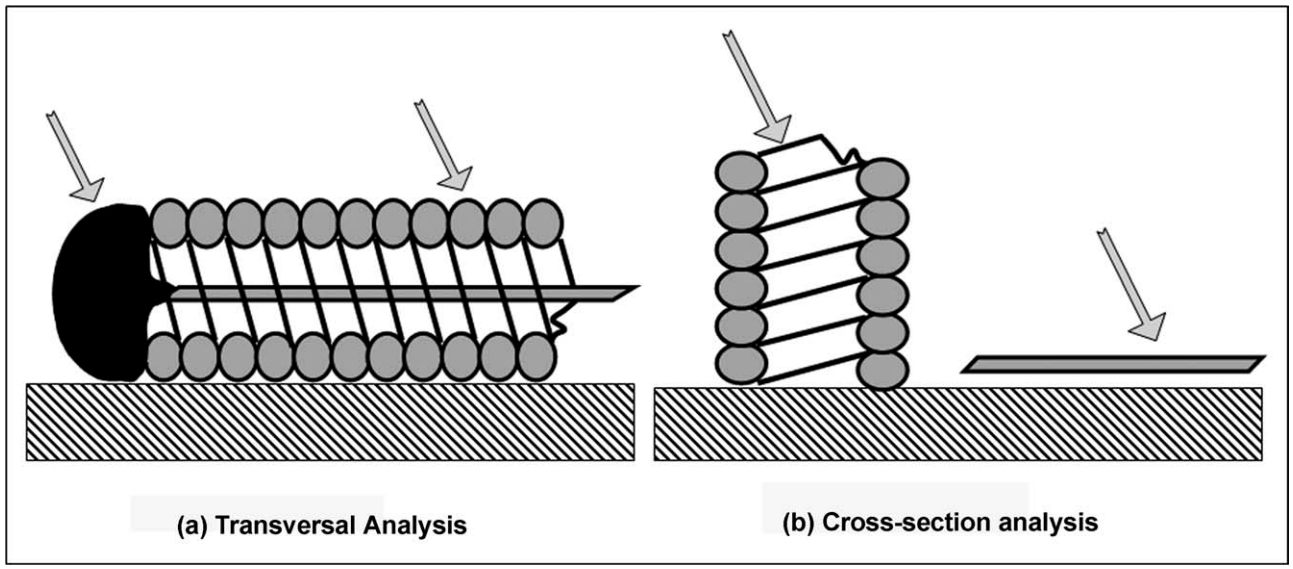


FIGURE 1. Scheme of the characterization modality of the Ni Cr Co alloy stent: (a) Transversal analysis of the external coils; (b) Analysis of the cross section of a cut piece and of the internal safety wire.

None of the patients reported fever, side pain or voiding symptoms during the period of study. Urine culture was negative in all cases. Follow-up examination revealed no differences in blood count, serum creatinine and ultrasonographic features of kidney and ureter with respect to the baseline values. For patient 6, follow-up analyses after 35 months revealed no increase in blood count serum creatinine with respect to baseline values. Surprisingly, RS did not show hydronephrosis of the left kidney.

Patients 5 and 6 reported macroscopic hematuria, which solved itself spontaneously. The same patients reported bladder discomfort at 24 and 35 months after the procedure. For this reason the patients gave their consent to stent replacement. Until stent substitution they were treated with antimuscarinics. Neither stent migration nor technical problems during stent removal were experienced.

Stent analysis

Stent before the Insertion. A reference stent without indwelling was morphologically and chemically analyzed. The spiral coils forming the ureteral stent [Figure 2(a)] and its closed end [Figure 2(b)] were polished and smooth. The higher magnification [Figure 2(c)] revealed some defects and micropores of about 1–10 μm on the metal alloy surface. Elemental analysis (EDS) showed the presence of nickel, chromium, and cobalt, and a low fraction of molybdenum. Figure 3 shows the relative ratio of the elements at the reference stent surface and their variability range. These values were used as references for the indwelled stents.

Stent after indwelling. An increase of the encrustation level with the indwelling time was observed. After 6 months of indwelling (pt. 1), the metal alloy stent showed some sporadic encrustation [Figure 4(a)]. After 10, 11, and 12 months of indwelling (respectively, patients 2, 3 and 4), the stents showed a higher degree of encrustations [Figures 4(b–d)] with respect to the previous RS of pt. 1. In particular the encrustation thickness was measured to be around 5–6 μm in the 11-months-stent [Figure 4(c)]. Encrustation was more compact and principally consisted of bacteria biofilm. Stents of pts. 5 and 6, after 24 and 36 months of indwelling were both visibly encrusted (Figure 5). The encrustation layer was compact and uniform and coated most of the external surface of the coils.

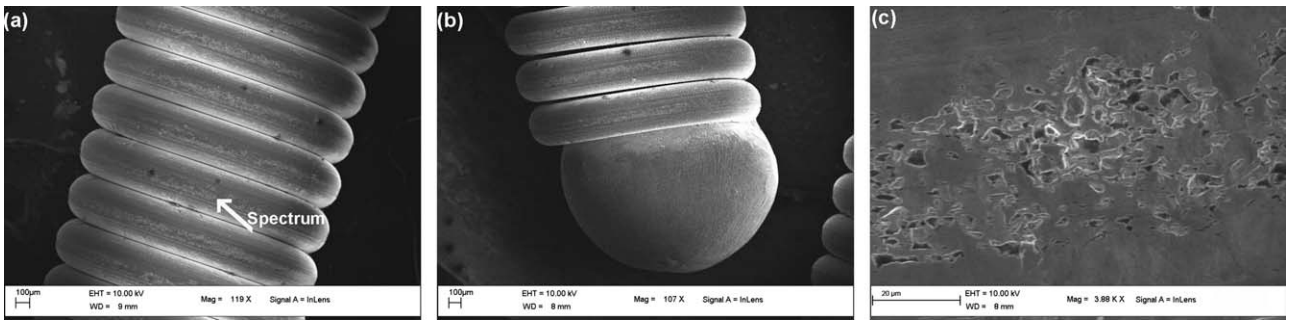
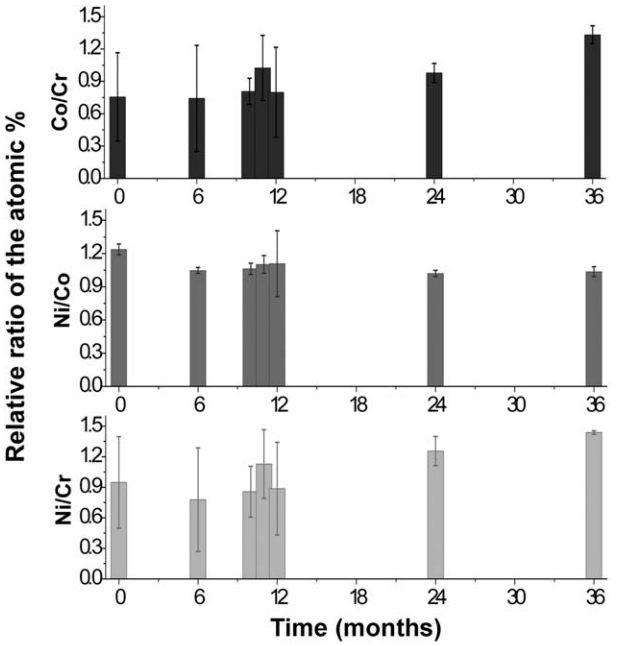


FIGURE 2. The Resonance® stent without indwelling as a reference for the indwelled samples: (a) Transversal section; (b) End of the pig-tail; (c) Magnification of the metal surface.



Relative ratio	Reference	6 months	10 months	11 months	12 months	24 months	36 months
Ni /Cr	0.95 ± 0.45	0.78 ± 0.51	0.86 ± 0.25	1.13 ± 0.34	0.89 ± 0.45	1.25 ± 0.14	1.44 ± 0.02
Ni/Co	1.24 ± 0.05	1.05 ± 0.03	1.06 ± 0.05	1.10 ± 0.08	1.11 ± 0.29	1.02 ± 0.03	1.04 ± 0.04
Co/Cr	0.76 ± 0.41	0.74 ± 0.49	0.81 ± 0.12	1.02 ±0.30	0.79 ± 0.42	0.98 ± 0.09	1.33 ± 0.08

FIGURE 3. Graphs (top) and table (bottom) of the relative ratio and variation range between the elements from metal stent surface, calculated from the EDS analyses: comparison between the stent after 6, 10, 11, 12, 24 and 36 months of indwelling and the reference stent.

Elemental analysis showed high levels of carbon and oxygen in all analyzed stents, indicating the presence of bacterial biofilm. The precipitation of sodium chloride (NaCl) and calcium oxalate (CaC_2O_4) was also assessed in all samples. In Figure 5(d) two arrows indicate the points of the EDS analysis on a coil of the 3-years-RS. Spectrum 1 (see Table II) showed a significant amount of oxygen, nitrogen, and carbon, indicating the presence of the bacteria biofilm. Potassium chloride (KCl) and brushite ($CaHPO_4 \cdot 2H_2O$) were also individuated from the relative ratio between the constituting elements (i.e., Ca and P are present in the same amount in the Spectrum 2 - see Table II, as in the chemical formula of the brushite).

To assess the eventual changes in the metal alloy composition over time, the atomic percentages of the metal elements were collected by EDS analyses. The relative ratios of nickel, chromium and cobalt and their variation range are reported in Figure 3 as an average of the statistical measurements. These values show a slight difference from the reference values. In particular, the 2- and 3-years-RS show a slight decrease in the chromium content from the reference value.

Statistical analyses

The mean percentage of the metal stent surface covered by the encrustation, as evaluated by FESEM analyses for each cutting surface, was significantly lower for patient 1 than for the other patients ($p < 0.05$). However, significantly higher percentage values were found for patient 4 ($p < 0.05$) with respect to the other patients. A spearman correlation test did not find correlations between the number of months and the mean percentage of encrustation extension ($p > 0.05$).

DISCUSSION

The application of expandable metallic stents is of great clinical importance in the treatment of vascular[6] and biliary stenosis.[7,8] It has been used for benign prostatic hyperplasia[9] and urethral strictures[10] with poor results. The use of such stents in the treatment of malignant and recurrent benign ureteral obstruction has been limited to experimental studies. This has been largely due to a restricted number of patients[2] or further complications because of internal hyperplasia.[11] An 11-year-study was recently published on the follow-up of 55 patients, where the obstruction was caused by malignancy or recurrent benign disease. Although the thermo-expandable stent showed improved drainage, secondary diseases were found due to migration, encrustation, and fungal infection.[12]

Metal stent complications mainly arise because of ureteral obstruction by tissue ingrowths.[13,14] In light of this, several authors have investigated the use of coated metal stents designed to prevent tissue ingrowths.[3] Despite the reduced urothelial ingrowths with the Dacron coated stents, a pronounced inflammatory reaction or tissue necrosis surrounding the stents was reported. This led to ureteral obstruction and hydronephrosis necessitating changing of the stent.[3]

A newly developed Resonance® stent (RS) has been recently proposed. This stent consists of a double J catheter made by an alloy composed of cobalt, chromium, and nickel. It has a unique design, as it has no end holes and the urine drainage instead takes place through a tight spiral coil, which also provides high stent flexibility. RS shows high compressive and radial strength, and is able to withstand up to 25 times more extrinsic compression than plastic stents. A study in pig models, which simulated extrinsic ureteral obstruction because of malignant disease sufficient to occlude a standard stent, showed that the RS could maintain effective and continuous urine drainage.[15] Nagele et al.[16] managed 14 patients with both benign and malignant diseases for a mean 8.6 months. The presence of encrustation was reported on two stents and seven of them were removed due to persistent hematuria, severe dysuria, pain and insufficient drainage.[16] Wah, Irving and Cartledge[5] reported an initial study on the Resonance® metallic ureteral stent. Positioning the stents via an antegrade approach was performed in 15 patients having malignant ureteral obstruction. Although the average indwelling time was only 6 months, with a maximum indwelling time of 1 year, this study indicated the possibility of providing adequate long-term urinary drainage in patients with malignant ureteral obstruction, but without significant pelvic disease.

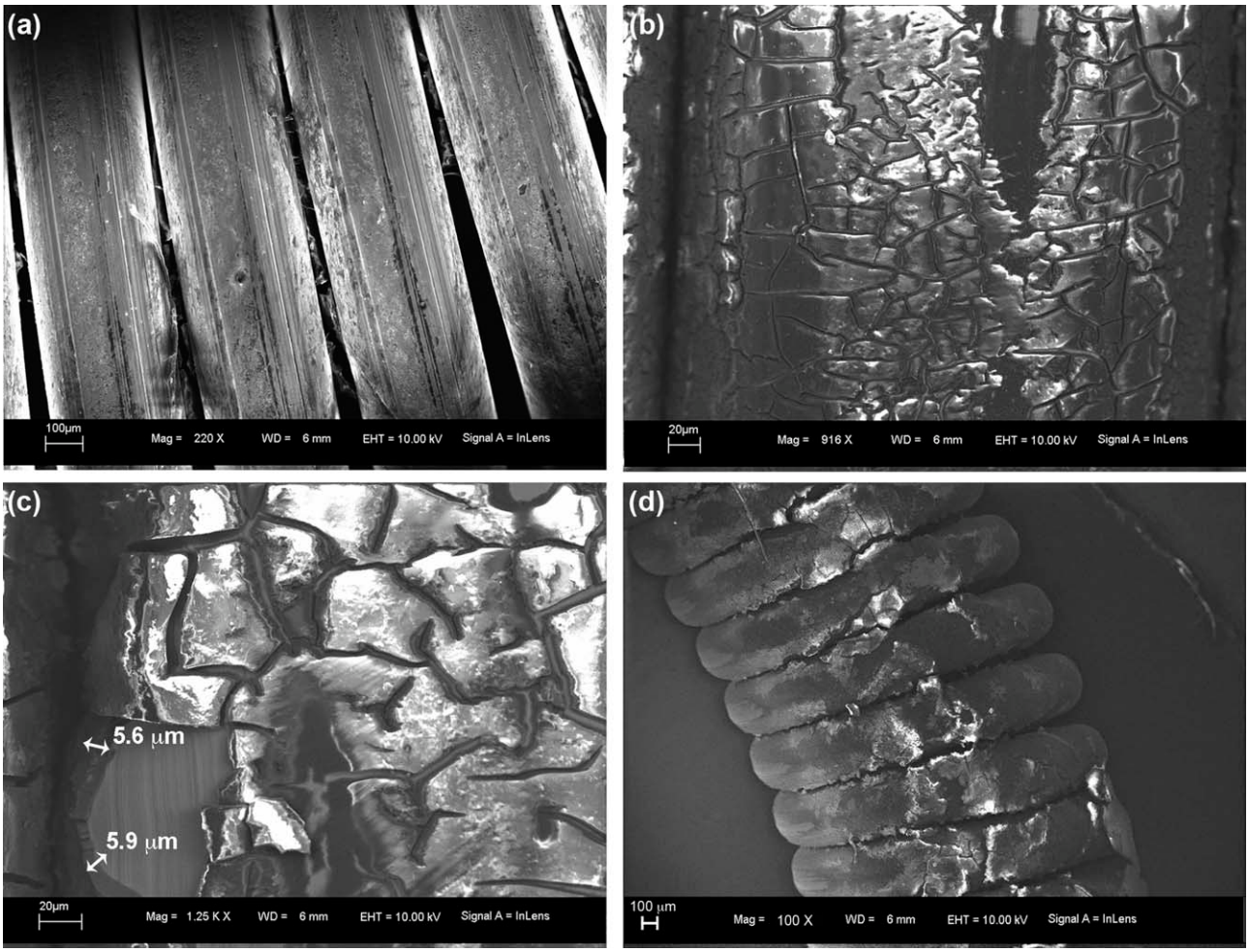


FIGURE 4. Micrographs of the indwelled stents after (a) 6 months, transversal view; (b) 10-months, magnification of the transversal view; (c) 11-months, magnification of the encrustation and its thickness in the transversal view; (d) 12-months, transversal view.

To date, no paper has focused specifically on the electron microscopy and elemental analysis of RS, especially after prolonged indwelling time. This article seeks to address this by reporting the results of a planned study involving the use of RS in six patients for the treatment of malignant or benign recurrent ureteral strictures over long time periods.

As far as the patient selection is concerned, patients were chosen requiring long time ureteral stenting. In some cases, the patients had experienced previous plastic stent obstruction with the need for frequent stent changing. Patients with both malignant and benign disease were included in the study, in light of the encouraging literature data.[17]

The manufacturer-recommended indwelling time for the RS is 12 months. Although this recommendation was typically followed, one patient (pt. 5) refused the stent changing due to personal reasons. Since symptoms or hydronephrosis were absent, the observation was prolonged to 24 months. In another case (pt. 6), the patient not only refused the stent changing but was also unavailable for follow-up for 35 months after the indwelling procedure. After these periods, both patients experienced urinary symptoms and gave their consent for stent substitution. Since this provided a unique possibility to study RS stent after a prolonged indwelling time, it was decided not to exclude the patients from the study.

There were no technical problems during the stent positioning. The RS were placed in a retrograde manner as suggested by the manufacturer. Preliminary ureter dilatation was not necessary for any of the patient. This was probably due to the fact that the patients already had ureteral stents.

The follow-up data obtained was encouraging for all of the patients. In particular, no fever, side pain or hydronephrosis were not recorded showing that the RS allowed adequate urine drainage. Two patients (33%) reported macroscopic hematuria, which solved itself spontaneously by increasing the fluid oral intake and without the need for invasive maneuvers. At the end of the follow-up period, patients 5 and 6 reported bladder discomfort (frequency/urgency symptoms). These conditions were improved by antimuscarinic administration, and eliminated with the stent substitution. It is well established that haematuria and urinary symptoms are common in patients with ureteral stents, and are not specifically related to RS.

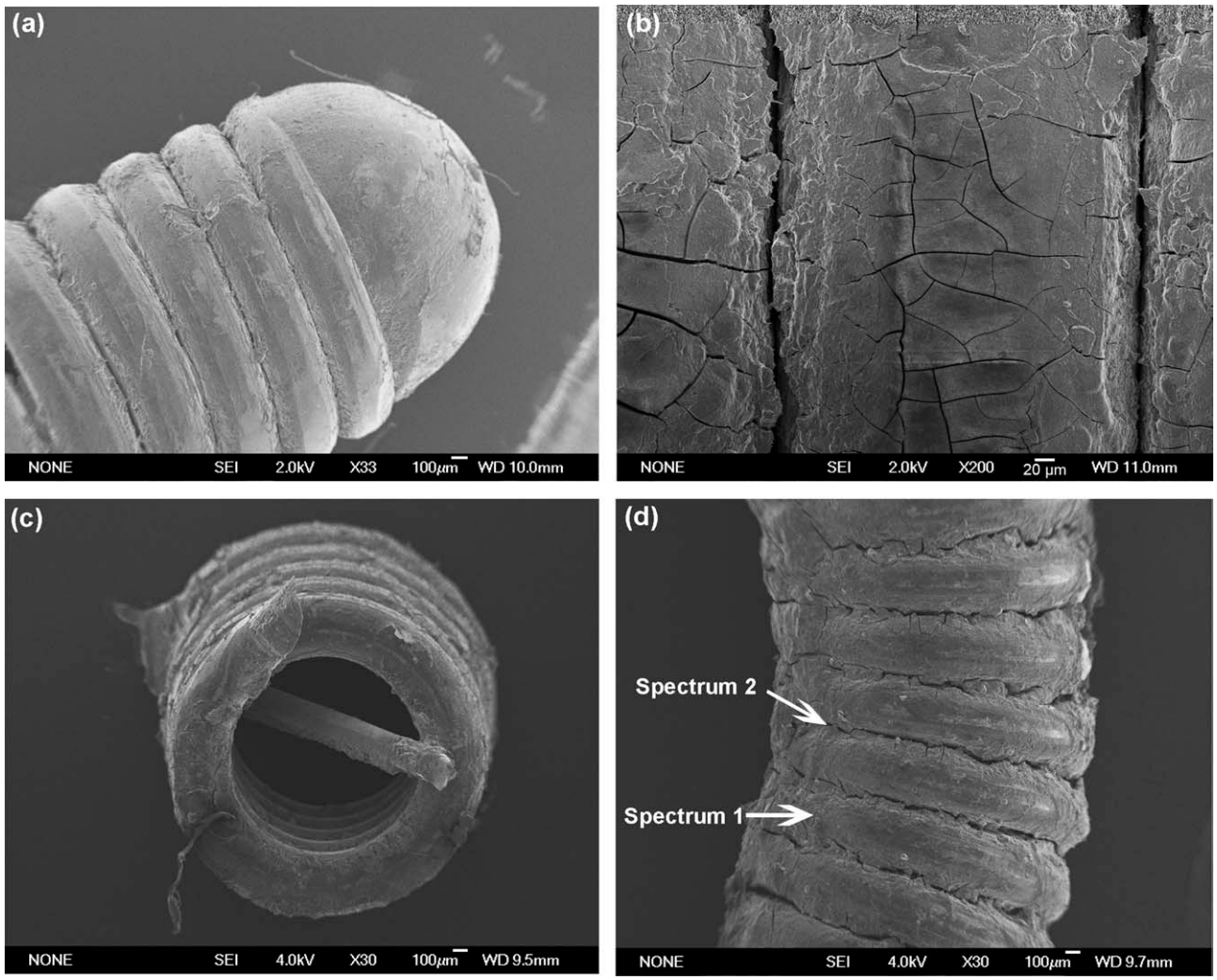


FIGURE 5. 24-months-stent: (a) Transversal view; (b) Magnification of the encrusted coils; 36-months-stent: (c) Cross section with the internal safety wire; (d) Transversal view of the pig-tail, where two EDS analyses were carried out (see Table II).

Surprisingly, RS of patient 6 provided an adequate urinary drainage and no hydroneprosis or increase of serum creatinine were recorded after 35 months.

The removal of the stents was performed without problems in all patients, regardless of the indwelling time.

After insertion, the metal stents were analyzed by Field Emission Scanning Electron Microscopy (FESEM) and Energy Dispersive Spectroscopy (EDS) to collect information about the metal stent surface and the amount and nature of the formed encrustation. The high number of analysis performed for each stent using these two techniques has the potential to reduce the quantification errors on the formed encrustation.

The formation of bacterial biofilm was found to grow more compact and dense as the indwelling time increased. After 6 months of indwelling the stent was poorly encrusted, whereas, after 2 and 3 years of treatment, the coils of the stents were completely covered by bacterial biofilm. Despite the increase of bacterial biofilm with indwelling time, epithelial tissue ingrowth and problems with stent removal were not observed in any of the patients. It seems clear that the bacterial biofilm did not cause pain or problems during the indwelling time and removal procedure.

TABLE II. Elemental Analysis of the 36-months-Stent, Carried Out on the Encrustation of the Coils [see Figure 5(d)]

Spectrum 1		Spectrum 2	
Element	Atom (%)	Element	Atom (%)
C	65.36	C	62.25
N	9.56	N	17.79
O	7.91	O	14.93
Na	0.26	Cl	0.59
Ni	5.94	K	0.46
Co	5.73	Na	0.23
Cr	4.13	P	0.27
Mo	1.11	Ca	0.25
		Cr	0.51
		Co	0.82
		Ni	0.79
		Mo	1.12

The precipitation of inorganic compounds, such as calcium oxalate, brushite, sodium and potassium chloride was sporadically detected in all the analyzed samples. However, it could not be excluded that these compounds are deposited on the surface of the metal alloy. Despite the high number of performed elemental analysis, it was not always possible to calculate the presence of these compounds from the obtained atomic percentages.

The alloy composition of the stent showed high variation levels (Figure 3), as given by the statistical measurements carried out on the stent surface. It should be noted that the percentages of the metal elements were collected under a biofilm layer, thus the analysis conditions differ from those of the reference stent. A clear trend for the alteration or degradation of the metal alloy surface with time could not be established, due largely to the small number of patients available for study. However, a slightly lower content of chromium was found in both stents after 2 and 3 years of indwelling whereas the levels of nickel and cobalt were in line with those of the reference stent. The ionization of metal implants in living tissue has been a very well known topic since 1960.[18] Chromium is related to carcinogenicity, mutagenicity, and hypersensitivity.[19,20] In the literature an *in vitro* test with CoCrMo and TiAl wear particles showed no toxic or mutagenic effect.[21] In a 10-year follow-up study of metal-on-metal total hip replacement,[22] the authors showed no increase in cancer incidence, nor detected an increased rate of renal failure. At present there are no reports on the effect of metal ion release from ureteral stents. Considering our clinical and physical-chemical results and those reported in the literature, we assume that the measured values of elements at the stent surface are clinically insignificant. However, further investigations on the stents after indwelling and on tissue levels of chromium in patients for longer time periods, that is, 3 years, should be carried out.

Although the initial costs of the metallic stent is higher then the plastic ones, RS is a useful and valid alternative for patients requiring long-term urinary drainage with malignant or benign recurrent disease. Although a detailed cost analysis was beyond the scope of this article, we can affirm that RS has reduced the need for stent changes, hospital admissions and the costs associated with this procedure. For the patients included in this study, RS proved an effective solution for long-term urinary drainage, even if their number is not statistically indicative.

CONCLUSIONS

Whilst acknowledging the limitations of this study because of the small population size, our results demonstrate that for the patients involved in this study, RS provides a safe and effective solution for malignant and benign recurrent ureteral obstruction. Electron microscopy and elemental analysis show that Ni-Cr-Co alloy is not largely altered or degraded by the urine and is not affected by epithelial ingrowths. Our preliminary data support the hypothesis that RS is a valid tool for long-term urinary drainage.

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