Original paper

Robot-assisted brachytherapy of the bladder with long distance support using video conferencing

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Abstract

Purpose: The frontline treatment for localized muscle-invasive bladder carcinoma (MIBC) is radical cystectomy. However, a significant percentage of this population is elderly with either severe co-morbidities or suboptimal general health, increasing the per- and post-operative risk when undergoing a radical cystectomy. Conservative treatment options have been implemented such as robot-assisted laparoscopic brachytherapy (RALB), a minimally invasive therapeutic approach ensuring excellent results in terms of local control, survival, and low morbidity. The treatment was supported successfully long distance using videoconferencing by an expert group from the Netherlands.

Material and methods: An 81-year-old man was treated with RALB. The patient was submitted to external beam radiotherapy (EBRT) in a total dose of 40 Gy in 20 fractions. A partial cystectomy followed by implantation of three catheters along the scar and brachytherapy was completed. A total dose of 25 Gy in 10 fractions was administered with dose points calculated at 5 mm from the catheters.

Results: Dose planning was characterized by an homogeneity index of 62.3% and overdose index of 19.7%. Other conformity indexes were analyzed. Patient was discharged at the fourth day after the procedure. The clinical response after 6 months was documented.

Conclusions: The previously reported good rates of tumor control and survival, and the excellent tolerance and low morbidity support RALB as a promising approach for selected groups of patients with localized MIBC. This case illustrates the ability to expand efficiently this technique, particularly among inexperienced medical teams.

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Key words: bladder cancer, robotic brachytherapy, video-conferencing.

Purpose

Bladder cancer is a common disease on the elderly with a peak incidence at 75 years [1]. The higher age and concomitant comorbidities are usually associated with the use of tobacco and constrains the treatment options in these patients. The standard treatment of localized muscle invasive bladder cancer (MIBC) is still considered to be a radical cystectomy with pelvic lymph node dissection. The combined modality therapy (CMT) for bladder preservation with neoadjuvant chemotherapy, transurethral resection of bladder tumor (TURBT), or partial cystectomy and external beam radiotherapy (EBRT), results in low rate of late relapses and similar survival outcomes in long-term survivors [2]. Another effective, safe, and less toxic treatment option in the context of bladder sparing, which has been a treatment option for several decades in selected patients, is the trimodality therapy (TMT) consisting of minimal surgery, including TURBT or partial cystectomy, EBRT and brachytherapy [3,4,5,6,7]. In 2009, bladder surgery has become advanced with the introduction of robot-assisted laparoscopic procedures combined with high-dose-rate brachytherapy [8,9].

The authors describe the first patient with MIBC being treated in Portugal with bladder-sparing treatment integrating robot-assisted laparoscopic brachytherapy (RALB) with the main aim to demonstrate the ability to efficiently expand this technique, notably among inexperienced medical teams, using videoconferencing support of an expert team at long distance.

Case report

Pre-operative evaluation

An 81-year-old male, with non-insulin dependent diabetes and hypertension, was admitted in another institution with symptoms, which had evolved over 4 months characterized by mild pelvic pain, frequency and nocturia at 2 to 3 hour intervals, urgency, dysuria, and moderate hematuria. Patient was assisted in other institution and had realized only an ultrasonography and a computed tomography (CT) scan, which confirmed a tumor with maximum 5 cm diameter located in the bladder dome with no presence of positive pelvic lymph nodes. A magnetic resonance imaging (MRI)

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or positron emission tomography/computed tomography (PET-CT) had not been requested. The patient underwent TURBT in February 2016, and the pathology proved a high grade invasive solitary urothelial carcinoma of the bladder with invasion of the muscular layer.

Chemotherapy followed by radical cystectomy was proposed, and after three cycles of carboplatin and gemcitabine, the therapy was discontinued due to severe toxicity consisting of peripheral neuropathy, anorexia, and marked weakness. The initially proposed radical cystectomy was refused by the patient.

The patient chose to have a second opinion about alternative treatment options and resorted to another center.Because of toxicity of the neoadjuvant chemotherapy experienced by the patient, he rejected a chemoradiation option. ^{18}F-FDG PET-CT scan confirmed a metabolically active solitary tumor located in the bladder dome without other regional or distant lesions. The post-chemotherapy coronal and axial T1- and T2-weighted MRI (3 Tesla) images, and T1 VIBE FS post-gadolinium sagittal images showed a remaining solid lesion of the bladder dome measuring 3.8 cm × 2.2 cm, with some alteration of the signal of the deep bladder wall, suggesting a T2bN0M0 bladder tumor (Figure 1).

Considering advanced age of the patient, co-morbidities, inherent life expectancy, refusal to undergo radical cystectomy, and the fact that the tumor fulfilled the selection criteria of the GEC-ESTRO recommendations [1,3] (Table 1), the option of a conservative treatment with minimal resection, EBRT, and brachytherapy as a boost in the context of bladder preservation was proposed. The patient and his relatives, very concerned about toxicity, were informed about this strategy including robotic surgery by a skilled team, as the most safe and accurate approach to increase the radiation dose to the residual tumor and the most conservative surgical procedure as an alternative to radical cystectomy. Informed consent was duly clarified and signed. In July 2016, the patient initially underwent complete transurethral resection of the residual bladder tumor. Pathology confirmed a persistent high-grade solitary tumor involving the muscle layer. Random biopsies showed no further disease in other bladder sites.

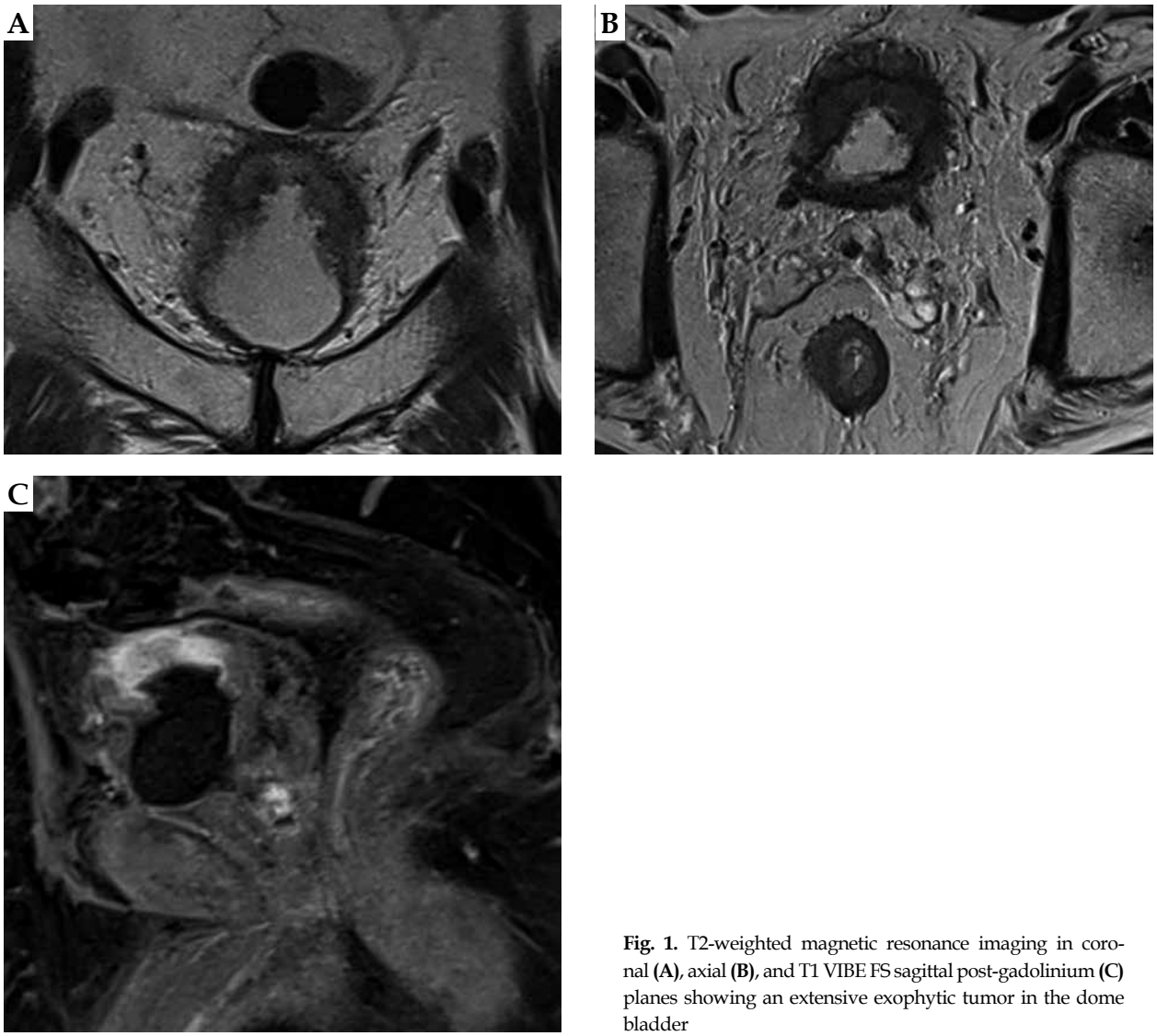

Fig. 1. T2-weighted magnetic resonance imaging in coronal **(A)**, axial **(B)**, and T1 VIBE FS sagittal post-gadolinium **(C)** planes showing an extensive exophytic tumor in the dome bladder

Two weeks post-TURB, EBRT of 40 Gy in 20 fractions started using image-guided volumetric modulated arc therapy, with the target volume defined by the whole bladder and regional iliac lymph nodes up to the aortic bifurcation. Ten days after EBRT, a new cystoscopy and MRI revealed 9 mm thick tumor and absence of other suspicious locoregional lesions or lymph nodes.

Brachytherapy treatment

The surgical procedure was carried out three weeks after EBRT by the patient's wishes and contrary to the followed therapeutic protocol comprising 10 to 15 days of interval between both therapies. All treatment phases including robotic surgery, catheter implantation, and planning dosimetry were long distance supported using videoconferencing by the expert medical team of Rijnstate Hospital in Arnhem, the Netherlands, consisting of a urologist, a radiation oncologist, and a physicist. This team was able to initially assess the entire clinical process with the consent of the patient and his family and participated in the therapeutic decision prior to treatment. They had access to EBRT planning and dosimetry, the response with endoscopic evaluation and MRI images, and especially to the entire surgical procedure in real time through three monitors in the operative theater, allowing the evaluation of laparoscopic images, cystoscopy and contacting whenever necessary urologists and radiation oncologists involved.

Table 1. Patient selection criteria according GEC-ESTRO recommendations [1,3]

1. Patients with operability criteria, tolerating a general anesthesia
2. Solitary tumor with a maximum diameter of 5 cm
3. No concurrent carcinoma in situ elsewhere in the bladder
4. A tumor classified cT2-T3 following the UICC TNM 7 ed. classification [10]
5. Tumor not located in the bladder neck and close to prostatic urethra in male patients
6. No distant metastases

GEC-ESTRO – Groupe Européen de Curiethérapie European Society for Radiotherapy and Oncology, UICC – Union for International Cancer Control

In the Trendelenburg position, the laparoscopic camera and three robotic trocars were inserted into the abdominal cavity and subsequently connected to the Da Vinci robot. The cystoscope was also inserted to define the tumor mapping and to monitor the resection of the tumor within the bladder. The mapping of the tumor area was ensured with the aid of the light of the cystoscope being visible in the abdominal cavity via laparoscopy. Initially, lymph node dissection was performed followed by partial cystectomy with resection of the residual tumor and margins, which was

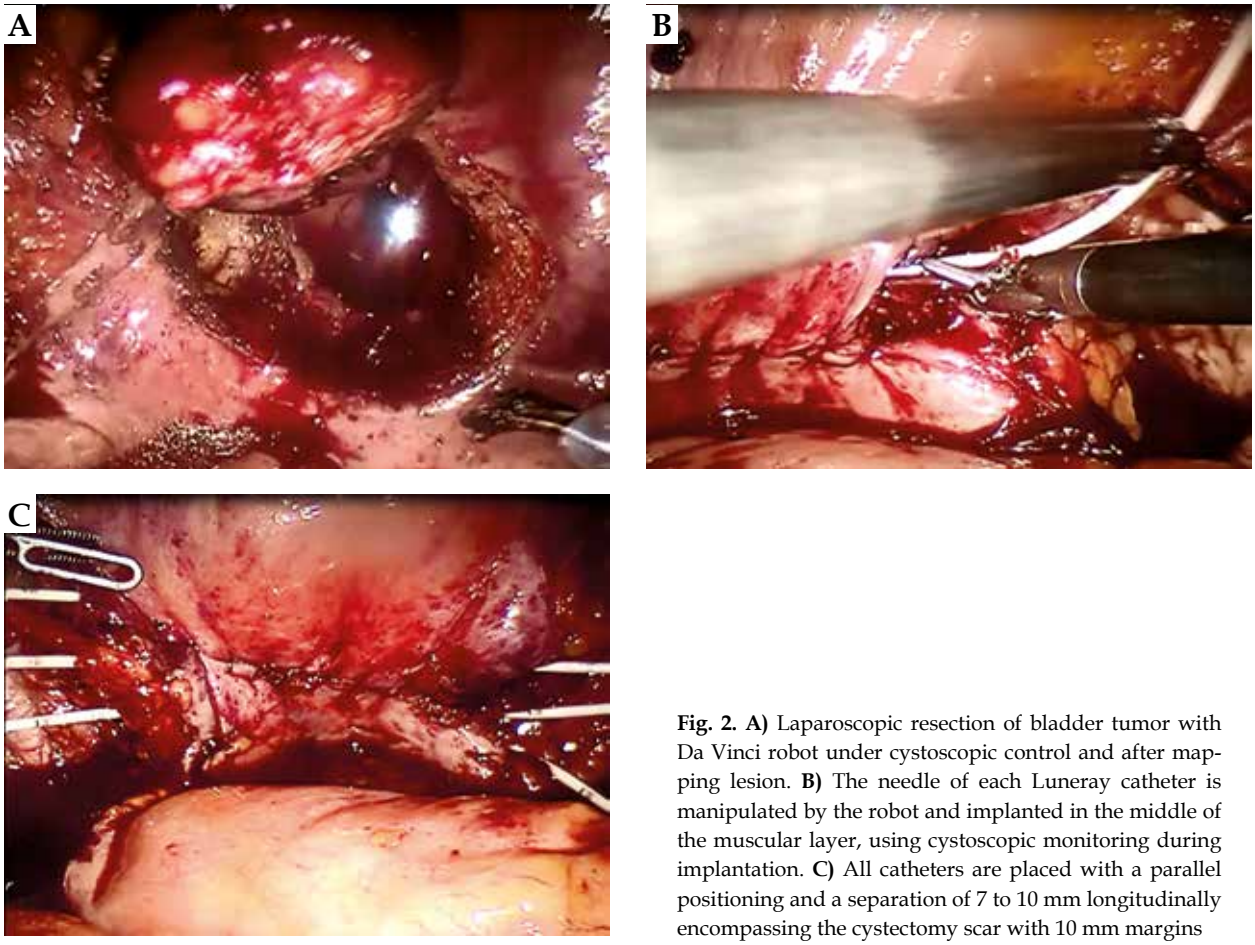

Fig. 2. A) Laparoscopic resection of bladder tumor with Da Vinci robot under cystoscopic control and after mapping lesion. **B)** The needle of each Luneray catheter is manipulated by the robot and implanted in the middle of the muscular layer, using cystoscopic monitoring during implantation. **C)** All catheters are placed with a parallel positioning and a separation of 7 to 10 mm longitudinally encompassing the cystectomy scar with 10 mm margins

hampered by the presence of a nearby bladder diverticulum (Figure 2A). After adequate suturing, three 50 cm Luneray catheters with needles of 67 mm in length and a radius of 75 mm required to involve whole length of the scar, specifically developed for this procedure (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) were implanted. The radiation oncologist inserted the needle of each catheter through the skin of the abdomen, in a precise location according to the orientation of the bladder implant given by the urologist. The urologist positioned the catheters within the bladder wall, using cystoscope monitoring during implantation, to ensure that they remain intramural and do not enter intravesically, and also to allow the endoscopic evaluation of the implant control with regard to the extent and location of the scar (Figures 2B and C).

Each needle was then pulled out through the skin at the other side of the abdomen, and then removed from the catheter. All three catheters were implanted this way, with a parallel positioning, separated by 7 to 10 mm, two of them placed parallel, at either side of the cystectomy scar with margins of about 5 mm. The third was placed in between the others to ensure that the prescription isodose could adequately cover all target because of a slight divergence of the lateral catheters due to the presence of the diverticulum. Two titanium clips were placed laparoscopically with the robotic trocars at both ends of the catheters in the external wall of the bladder, to define the clinical target volume (CTV), and facilitate the visualization of the tumor area to be treated on the CT images and in the dose planning system. On both sides of the abdomen, fixating buttons were attached to the catheters and then the patient was transferred to the recovery room.

On the day of the surgery, a planning CT was made with 1 mm slice thickness. Fiducial markers were inserted inside the catheters enabling their reconstruction. A dose planning with source stop positions or dwell time active positions between the surgical clips were then generated using a brachytherapy treatment planning system (Oncentra Brachy, Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). Dose points at 5 mm from the catheters were used and dwell time optimization was performed. In order to reduce excessive high dose regions around the catheters the dwell times were manually improved. The dose distribution was evaluated and the best plan approved, with an homogeneity index (HI) of 62.3% and an overdose index (OI) of 19.7%, confirming the quality of the dose plan according the values followed by Arnhem's team (HI ≥ 50% and OI ≤ 28%) (Fig. 3) [8]. HI represents the size of the part of the target volume that receives 100% to 150% of the prescribed dose and is defined by $HI = (V_{100} - V_{150})/V_{100} \times 100\%$ [11, 12]. The OI represents the size of the part of the target volume that receives more than 200% of the prescribed dose and is defined by $OI = V_{200}/V_{100} \times 100\%$ [12]. The first fraction was performed with this dosimetric plan and evaluated by both physicists still in video conferencing. Subsequently, a new dosimetric study with manual optimization was done considering the CTV defined as the bladder scar after partial cystectomy between clips, with 5 mm of margins in all directions. The CTV was encompassed by the 100% reference isodose in the next nine fractions performed in the next three days. Also, the non-involved bladder outside the CTV and the organs at risk such as small bowel loops in the vicinity of the bladder, the sigmoid, and rectum were contoured. The registered dose-volume parameters and conformity indexes are presented in Table 2. An acceptable conformity index (CI) of 0.93 was found together with a healthy tissues conformity

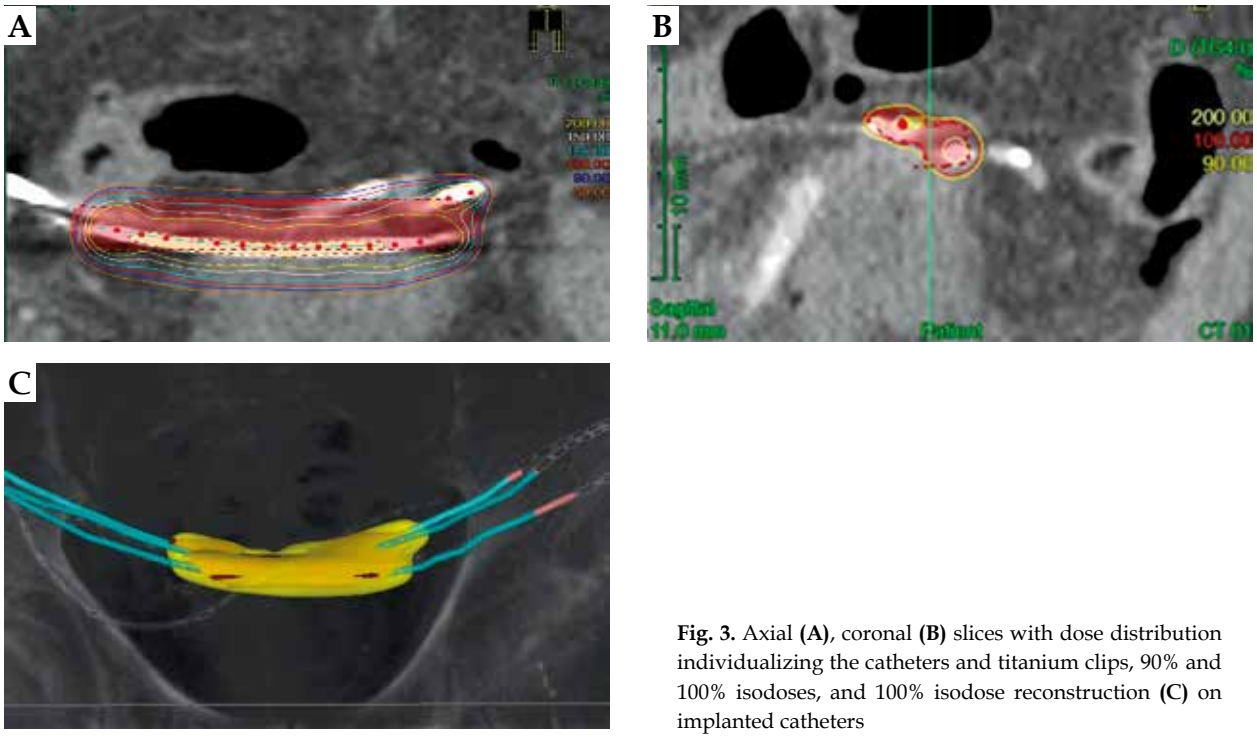

Fig. 3. Axial **(A)**, coronal **(B)** slices with dose distribution individualizing the catheters and titanium clips, 90% and 100% isodoses, and 100% isodose reconstruction **(C)** on implanted catheters

index (HTCI) of 0.57 [13]. This was considered a minor deviation caused by the bigger volume of the reference isodose than the target volume due the fact that the dose was prescribed to points at 5 mm from the source positions. The OARs received a dose far below the dose constraints.

The continuous monitoring of the whole procedure by the expert team provided the intervening team an extreme confidence, allowing a profitable discussion from the decision of partial cystectomy, the resection of larger lymph nodes and the catheters implantation. Both teams also participated actively in the brachytherapy planimetry such as dose coverage, dose homogeneity, reduction of high dose volumes and dose minimization in OAR.

Postoperative course

Brachytherapy was delivered to a total dose of 25 Gy in 10 fractions with an Iridium-192 (^{192}Ir) source using an HDR afterloader (micro-SelectronHDR, Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). The first fraction was given on the day of surgery and the remaining 9 fractions on the following three days, 3 per day with a minimum interval of 4 hours. After the treatment, the catheters were removed and the patient was discharged. No intra-operative or post-operative complications were recorded, and blood loss was less than 50 cm^3. Two weeks after surgery, the Foley catheter was removed. Pathology confirmed an invasive urothelial carcinoma, sized 27 × 16 mm^2, with invasion of the muscular layer and without lymphovascular or perineural invasion. The surgical margins were free above 0.8 mm and seven resected bilateral iliac lymph nodes were negative. The disease was staged as T2aN0R0. At three and six months follow-up, the patient has significantly improved in terms of urgency and frequency, which now occurred at 5 to 6 hour intervals. The cystoscopy revealed no evidence of other suspicious lesions and a normal mucosal surface of the remaining bladder (Figures 4A and B). T2-weighted MRI showed a mild bladder wall thickening, a post-surgical lymphocele and absence of suspicious lymph nodes (Figures 4C and D). Further follow-up will be performed quarterly with cystoscopy, and alternating CT and MRI imaging.

Discussion

Radical cystectomy of localized MIBC recognize an overall survival at 5 and 10 years of 60% and 45%, respectively [14]. Perioperative mortality is reported in the range of 1.2% to 3.2% at 30 days, and 2.3% to 8.0% at 90 days. Numerous long-term side effects are not negligible, such as urinary dysfunction, urinary incontinence, urinary infections, and especially the loss of normal bladder function, often poorly tolerated by these patients [15,16,17,18,19].

Quality of life is compromised, often significantly, even with the most modern techniques of radical cystectomy, urinary diversion, and orthotopic neo-bladder construction [20,21]. The CMT comprising chemoradiotherapy gives similar outcomes as RC, but avoiding associated morbidity and mortality, and thereby improving the patients' quality of life [2,21,22,23].

Table 2. Brachytherapy dose-volume parameters, quality, and conformity indexes [11]

Dose parameters	Values
V_{100}	8.62 cm^3
V_{150}	4.44 cm^3
V_{200}	2.32 cm^3
V_{100} non-involved bladder (outside of CTV)	0.01 cm^3
D_{2cc} non-involved bladder (outside of CTV)	142.18 cGy
$D_{0.1cc}$ non-involved bladder (outside of CTV)	222.51 cGy
Rectum D_{2cm^3}	13.77 cGy
Rectum $D_{0.1cm^3}$	24.35 cGy
Sigmoid D_{2cm^3}	98.86 cGy
Sigmoid $D_{0.1cm^3}$	136.21 cGy
Small bowell D_{2cm^3}	105.09 cGy
Small bowell $D_{0.1cm^3}$	147.77 cGy
Homogeneity Index (HI) (≥ 50%)	62.3%
Overdose Index (OI) (≤ 28%)	19.7%
Conformity Index (CI)	0.92
Healthy Tissues Conformity Index (HTCI)	0.57
Conformation Number (CN)	0.52
Conformal Index (COIN)	0.52

V_{100}, V_{150}, V_{200} – volume of the anatomic volume receiving 100%, 150%, 200% of the prescribed dose, $D_{0.1cm^3}$, D_{2cm^3} – minimum dose to the most exposed 0.1 cm^3, 2 cm^3

Bladder cancer is more prevalent in the elderly population with severe medical comorbidities and impaired renal or hepatic function. Most of these patients are in poor general condition to undergo radical cystectomy or even to tolerate concurrent chemoradiotherapy. Chemoradiotherapy, usually including cisplatin or carboplatin concurrent with high dose EBRT, even with modern techniques such as IMRT, is less frequently but still associated with considerable risk of treatment-related toxicity and worsening of overall quality of life, particularly in patients with age-related declines in performance status and medical comorbidities who are less likely to complete CMT [24,25].

Brachytherapy centers in the Netherlands advocate for TMT, integrating a moderate dose of pelvic EBRT with a brachytherapy boost using a minimally invasive procedure in the context of organ preserving treatment for selected MIBC patients. They have demonstrated a local control and survival similar to CMT with approximately 90% of the patients cured and retaining an effectively functioning bladder [6,8,9,23,26,27,28,29]. Thus, the preservation of a functioning bladder remains one of the most important advantages for selected patients of all age groups.

A total dose of 40 Gy in 20 fractions of EBRT is historically administered in the Netherlands, a country with

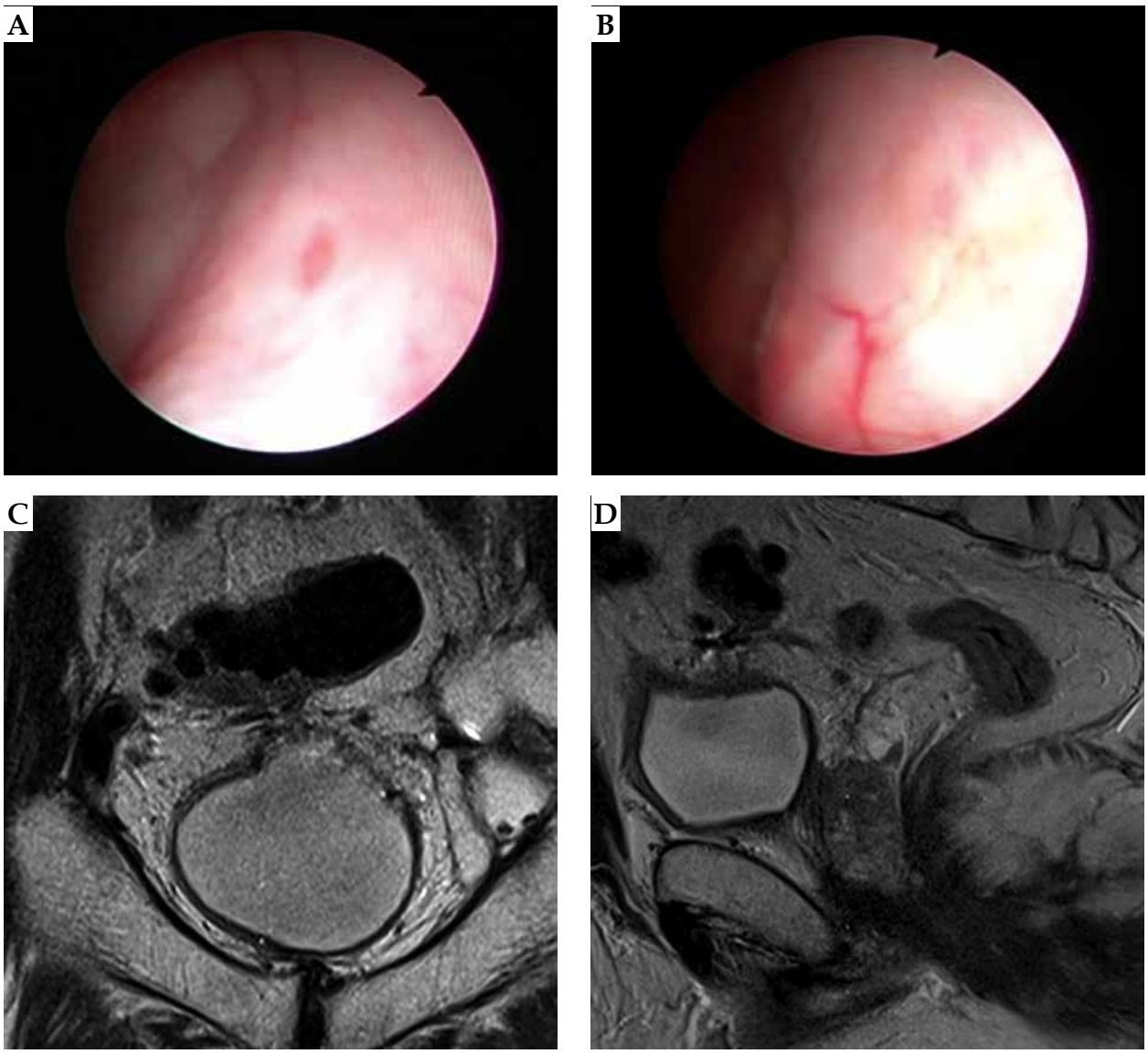

Fig. 4. Cystoscopy 6 months after treatment, showing unsuspected scar of the bed tumor and normal mucosa surface of remaining bladder **(A, B)**. T2 weighted MRI in coronal **(C)** and sagital **(D)** planes evidencing a mild dome bladder wall thickness and a post-dissection lymphocele

a long tradition of radiation treatment for bladder cancer being considered sufficient to sterilize involved pelvic lymph nodes [30,31].

Usually if EBRT is directed to the bladder and pelvic lymph nodes, a dissection is not performed but controversy about treatment approach to pelvic lymph nodes remains [32]. In this case, there was not a significant tumor response to the EBRT and the larger pelvic lymph nodes were removed considering the potential risk of occult pelvic lymph node involvement across all clinical stages. A more accurate pre-chemotherapy staging could have allowed a more informed decision and avoided the resection of these lymph nodes.

In addition, the poor tumor response and a thick residual tumor revealed in MRI after EBRT led to the decision of partial cystectomy instead of TURB according the GEC-ESTRO recommendations [1,3].

Aluwini *et al.* reported long-term results of a bladder preservation strategy for MIBC using limited surgery, EBRT, and interstitial brachytherapy in 192 patients [7]. The local recurrence free survival rate was 80% and 73%, and salvage cystectomy-free survival at 5 and 10 years was 93% and 85%. Radiation Therapy Oncology Group grade ≥ 3 late bladder and rectum toxicity were recorded in 11 patients (5.7%) and 2 patients (1%), respectively. Koning *et al.* published the largest cohort of 1,040 patients on brachytherapy for bladder cancer with local recurrence-free probability, metastasis-free probability, disease-free probability, and overall survival of 75%, 74%, 61%, and 63%, respectively [27]. Van der Steen-Banasik *et al.* performed RALB with Luneray catheters in 57 patients with MIBC, 17 also underwent partial cystectomy [9]. With an average follow-up of 2 years (range, 0.5-5.8 years), 4 patients developed bladder recurrence within the irradi-

ated volume (7%) and 6 elsewhere in the bladder (10.5%). The cumulative incidence competitive risk disease free survival (DFS), disease specific survival (DSS), and local control (CI) (95% confidence interval) at 2 years were respectively 71%, 87%, and 82%, and the overall survival was 59%.

The advantages of using a brachytherapy boost over EBRT alone are the accurate delivery of radiation at the precise site with a steep dose gradient and lower toxicity due to maximal sparing of the neighboring normal organs such as the small bowel, sigmoid, rectum, uterus, vagina, femoral heads, bone marrow of the pelvis, and neural structures of the sacrum, but also the remaining normal bladder tissue. For the implementation of RALB, the introduction of dedicated, highly maneuverable catheters with great flexibility and resistance to torsion was essential. These were specifically developed by the radiation oncology and urology team from Radiotherapiegroep and Rijnstate Hospital in Arnhem, the Netherlands, in collaboration with Nucletron, now part of Elekta (LunerayTM, Elekta AB, Stockholm, Sweden), pioneering the final design in early 2014 [33]. The laparoscopic and robot-assisted brachytherapy is an emerging technique with limited experience, but with potential advantages such as minimal blood loss, reduction of hospitalization time, and the preservation of the normal bladder function, as occurred with the patient described.

The clinical team previously received appropriate training in Arnhem, and subsequently implemented the first RALB treatment with their long distance support using video conferencing. The Hospital da Luz is a paperless medical center and a model medical education at distance, implementing several clinical programs, robotic surgery technical courses, and every two years an international cancer congress with the most modern therapeutic modalities, presented in real time using video conferencing for the whole World. This model helped to receive the skills of the most experienced Dutch team and allowed the efficient implementation of this therapy for the first time in our country.

Conclusions

The presented case demonstrates the feasibility to implement robotic-assisted brachytherapy of the bladder with long distance support using video conferencing and the ability to expand this technique efficiently, particularly among inexperienced clinical teams. The authors emphasize the importance of audiovisual telementoring considering that it may play a fundamental role in future training concepts and improved impact on medical education. RALB combined with minimally invasive surgery is an attractive bladder-sparing treatment for selected patients with MIBC with fast recovery, shortening of the hospitalization, and low morbidity. The recognized similar outcomes in terms of local control and survival support this modality as a good alternative to radical cystectomy in selected population. A superior long-term quality of life in these patients is expected, but an evidence must be prospectively validated.

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Disclosure

Authors report no conflict of interest.

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