Radiotherapy and Oncology 141 (2019) 130–136

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Long-term survival and complications following bladder-preserving brachytherapy in patients with cT1-T2 bladder cancer

Charlotte S. Voskuilen [a,1], Judith Bosschieter [a,b,1], Erik van Werkhoven [c], Kees Hendricksen [a], André N. Vis [b], Thelma Witteveen [d], Bradley R. Pieters [e], Max Burger [f], Axel Bex [a,g], Henk G. van der Poel [a], Luc M. Moonen [d], Simon Horenblas [a], Jakko A. Nieuwenhuijzen [b], Bas W.G. van Rhijn [a,f,*]

[a] Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam; [b] Department of Urology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam; [c] Department of Biostatistics, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital; [d] Department of Radiation Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam; [e] Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, The Netherlands; [f] Department of Urology, Caritas St. Josef Medical Center, University of Regensburg, Regensburg, Germany; and [g] Department of Urology, Royal Free London NHS Foundation Trust, University College London, United Kingdom

ARTICLE INFO

Article history:
Received 9 May 2019
Received in revised form 25 September 2019
Accepted 26 September 2019
Available online 17 October 2019

Keywords:
Brachytherapy
Bladder-preserving therapy
Bladder cancer
Interstitial radiotherapy
Urinary bladder neoplasm

ABSTRACT

Background and purpose: Radical cystectomy (RC) is considered standard treatment for muscle-invasive bladder cancer (BC) and high-risk non-muscle invasive BC. In selected cases, bladder-sparing treatment using brachytherapy can be offered. We examined the outcome after brachytherapy in comparison to RC in terms of survival, complications and bladder preservation in patients with cT1G3-T2N0M0 BC.
Materials and methods: Between 1988 and 2016, 301 patients underwent brachytherapy in two centres. Overall survival (OS) and disease specific survival (DSS) after brachytherapy and RC were assessed using Kaplan-Meier curves. Cox proportional hazards modelling was used to determine variables associated with OS and DSS. Local recurrences, bladder preservation and salvage cystectomy (SC) after brachytherapy were reported. Complications after brachytherapy, RC and SC were compared using CTCAE criteria.
Results: Median follow-up was 9.6 years (95% confidence interval (CI): 8.8–10.4) after brachytherapy and 10.6 years (95% CI: 10.0–11.2) after RC. Five/10-year OS was 66%/49% after brachytherapy and 68%/53% after RC ($p = 0.4$). Five/10-year DSS was 73%/67% after brachytherapy and 75%/65% after RC ($p = 0.8$). Intravesical recurrence occurred in 58/259 brachytherapy patients after which salvage cystectomy was performed in 32 patients. In total, 84% of brachytherapy-treated patients preserved their bladder. The brachytherapy cohort experienced less high grade complications than the RC cohort ($p = 0.02$).
Conclusion: In selected patients with solitary, ≤5 cm cT1G3-T2N0M0 bladder tumours brachytherapy is a bladder-sparing therapy with good survival outcome and with a favourable complication rate compared to RC.

 Radiotherapy and Oncology 141 (2019) 130–136

Radical cystectomy (RC) is still considered standard of treatment for patients with non-metastatic muscle-invasive bladder cancer (MIBC) and high-risk non-muscle-invasive bladder cancer (NMIBC) refractory to intravesical therapy in most countries [1]. However, RC has significant morbidity and mortality [2].

In an effort to preserve the bladder, alternative treatment strategies have been developed. Trimodal therapy (TMT), comprising transurethral resection of the tumour (TURBT), followed by concurrent chemoradiation has been recognized as an alternative to RC for select patients in several international guidelines [1,3]. Another bladder preservation strategy includes a combination of TURBT, low-dose external beam radiation (EBRT) and brachytherapy. According to Dutch guidelines, this combination can be offered to patients with solitary cT1G3/T2G1-3, ≤5 cm, cN0M0 bladder cancer (BC) as a bladder-sparing alternative to RC [4–6]. However, despite promising results achieved with brachytherapy, its use remains controversial [7]. The main concern is long-term oncological safety and late toxicity.

Given the lack of prospective studies comparing brachytherapy to RC, we performed an observational study to examine outcome in terms of survival, complications and bladder preservation of brachytherapy for cT1G3-T2N0M0 BC. In addition, we compared survival and complications of patients treated with brachytherapy with a matched population of patients treated with RC for cT1G3-T2N0M0 BC.

* Corresponding author.
E-mail address: basvanrhijn@hotmail.com (B.W.G. van Rhijn).
[1] Authors contributed equally.

https://doi.org/10.1016/j.radonc.2019.09.026
0167-8140/

Materials and methods

We retrospectively analysed patients who underwent brachytherapy or RC for cT1G3-T2 BC between 1988 and 2016 in two hospitals in Amsterdam: the Netherlands Cancer Institute (NCI-AVL) and the Amsterdam UMC Vrije Universiteit Amsterdam (VUMC). In the NCI-AVL, patients were identified from a prospectively maintained institutional BC database. In the VUMC, patients treated with brachytherapy were retrospectively identified. Patients with non-urothelial histology were excluded from analysis. Previously, the outcomes of two smaller series with a shorter follow-up were described by Nieuwenhuijzen et al. ($n = 108$) [8] and Bosschieter et al. ($n = 26$) [9]. We now present the results of a larger cohort with a median follow-up of 10 years.

Brachytherapy

Selection criteria for brachytherapy are shown in Table 1. Diagnosis and staging consisted of TURBT and computed tomography (CT) of the chest/abdomen/pelvis. Tumour size was estimated at cystoscopy. All patients underwent EBRT (15–20 × 2 Gy) prior to brachytherapy catheter insertion to prevent tumour cell seeding [10]. The clinical target volume included only the bladder. Up to two weeks after EBRT, the flexible plastic tubes for afterloading interstitial radiation therapy were inserted. Either an open retropubic approach or a robot-assisted laparoscopic (RAL) approach was used as previously described [9]. In brief, 3 to 4 brachytherapy catheters were inserted through the bladder wall at the tumour area with a minimal bilateral 5 mm margin from the tumour/scar. Entry and exit sites into the bladder were marked with metal clips. In case of a RAL-approach, the tumour area was identified by simultaneous cystoscopy. In some cases, the insertion of brachytherapy catheters was combined with partial cystectomy (PC) of the tumour/scar. In the VUMC, a pelvic lymph node dissection (LND) was routinely performed. In the NCI-AVL, a limited LND was performed in case of suspicion of lymph node metastasis (LNM) during surgery. In case of proven LNM at pathology, adjuvant chemotherapy was considered. Afterloading therapy for VUMC patients consisted of pulsed-dose rate (PDR) brachytherapy in the Academic Medical Center (29 × 1.04 Gy, Paris-system dosimetry) [11]. In the NCI-AVL, patients were treated with 40 Gy low-dose rate brachytherapy until 2003. From 2003 onwards, either high-dose rate (10 × 2.5 Gy) or PDR (29 × 1.02 Gy) brachytherapy was used. These radiation schedules are considered radiobiologically equivalent.

Radical cystectomy

Diagnosis and staging before RC was similar to diagnosis and staging before brachytherapy. All RC patients underwent PLND. None of the patients were treated with neoadjuvant chemotherapy. Adjuvant chemotherapy was considered in case of pN+ disease. In order to create more comparable groups in terms of estimated risk of recurrence and survival, we excluded patients who underwent RC instead of brachytherapy for oncological reasons (i.e. multiple tumours, tumour size >5 cm or concomitant CIS). Patients who underwent RC instead of brachytherapy due to impaired bladder capacity, patient's preference or due to a tumour location unsuitable for brachytherapy (i.e. tumour located in the bladder neck or the prostatic urethra) were included in the RC cohort.

Follow-up and salvage treatment

Follow-up included a yearly CT-abdomen/pelvis and chest X-ray for both patient groups. Follow-up after brachytherapy also included cystoscopy with urine cytology at 3-monthly intervals for the first 2 years and 6-monthly intervals thereafter. Bladder function after brachytherapy was assessed by interviews. Transurethral resection was performed when in doubt of tumour recurrence. NMIBC recurrences were treated by TUR with or without additional intravesical chemo- or immunotherapy. MIBC recurrences were treated by salvage cystectomy (SC), provided that no systemic disease was found and general condition was sufficient. Whilst SC was not systematically offered to all patients with NMIBC recurrence, patients with a high-risk tumour or failed intravesical treatment were also considered for SC.

Complications

Acute (≤90 days) and late (>90 days) complications after brachytherapy, RC and SC were retrospectively assigned according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [12].

Statistical analysis

Median follow-up was calculated using the reverse Kaplan-Meier method. Bladder recurrence after brachytherapy was defined as a lesion in the bladder confirmed by histological evaluation. Pelvic LN recurrences and pelvic soft tissue recurrences after brachytherapy were separately reported. Local recurrence after RC was defined as recurrence in soft tissue in the true pelvis.

Kaplan-Meier curves for overall survival (OS), disease-specific survival (DSS) after brachytherapy and RC were constructed and compared using the log-rank test. Starting point for time-to-event analyses was the implantation date of brachytherapy catheters or date of RC. OS was defined as time-to-death (any cause). DSS was defined as time-to-death due to BC or treatment related death. A multivariable Cox proportional-hazard model was used to evaluate potential prognostic factors for OS and DSS. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (Armonk, NY, IBM Corp.). Tests were two-sided and the significance level was set at 0.05.

Results

In total, 301 patients underwent brachytherapy (NCI-AVL $n = 294$, VUMC $n = 7$) between 1988 and 2016 Patients with variant histology ($n = 9$) and patients with urachal adenocarcinoma ($n = 26$) and patients with cN+ ($n = 7$) were excluded, leaving a total of 259 evaluable brachytherapy patients. Baseline characteristics are shown in Table 2. An open and a robot-assisted laparoscopic approach was used in 91% (235/259) and 9.3% (24/259) of patients, respectively. PC was performed in 32/259 (12%) of patients. Reasons for PC were: tumour in a diverticulum ($n = 10$, 31%), tumour in the bladder dome ($n = 11$, 34%), residual macroscopic tumour after TURBT ($n = 6$, 19%) and concurrent ureteral reimplantation ($n = 2$, 6.2%). In three patients (9.4%), the reason for PC was not recorded. In total, 16/259 patients (6.2%) underwent ureteral reimplantation, because the tumor was close to the ureteral orifice and resection was performed. LND was performed in 32/259 (12%) brachytherapy patients. Seven patients underwent elective LND (VUMC) and 23 patients underwent LND due to suspicious LN during surgery. Additionally, one patient underwent LND as a staging procedure in the referring hospital and one patient insisted on undergoing LND. Six out of 32 (19%) patients had LNM proven at pathology. These patients all had suspicious LN during surgery. Two of these 6 patients with LNM received adjuvant chemotherapy.

Between 1988 and 2016 914 patients underwent RC for BC in the NCI-AVL, of whom 227 underwent RC for cT1G3-T2N0M0 BC.

Table 1
Selection criteria for brachytherapy.

Solitary tumour with a maximum diameter of 5 cm
Clinical stage T1-T2
No concomitant carcinoma in situ elsewhere in the bladder
Tumour not located in the bladder neck or the prostatic urethra in male patients
No distant metastasis (N0M0)

Table 2
Baseline patient and tumour characteristics.

		Brachytherapy		RC		*P*-value
Total number of patients		259		60		
Median age in years (IQR)		64 (55–72)		60 (54–67)		0.11
		n	%	*n*	%	
Sex	Male	199	76.8	42	70.0	0.32
	Female	60	23.2	18	30.0	
cT stage	cT1	26	10.0	6	10.0	1
	cT2	233	90.0	54	90.0	
Grade	G2	17	6.6	4	6.7	1
	G3	242	93.4	56	93.3	
Histology	Urothelial carcinoma	249	96.1	56	93.3	0.62
	+ squamous cell diff.	7	2.6	3	5.0	
	+ glandular diff.	3	1.1	1	1.7	
Tumour diameter	<3 cm	133	51.4	13	21.7	0.006*
	3–5 cm	97	37.5	26	43.3	
	Unknown	29	11.2	21	35.0	
Prior recurrence rate	Primary	232	89.6	44	73.3	0.002
	Recurrence	27	10.4	16	26.7	
pN stage	pN0	26	81.3	55	91.7	0.2**
	pN1-3	6	18.8	5	8.3	
	pNx	227		0		

Abbreviations: Diff.: differentiation, IQR: interquartile range, RC: radical cystectomy
* Excluding patients with unknown tumour size
** Excluding patients with pNx

These patients were no candidates for brachytherapy for the following reasons: multiple tumours ($n = 135$, 59%) tumour size >5 cm ($n = 16$, 7.0%), concomitant CIS ($n = 16$, 7.0%), tumour location unsuitable for brachytherapy ($n = 27$, 12%), impaired bladder capacity ($n = 6$, 2.6%) and patients' preference ($n = 5$, 2.2%). In 22 (9.7%) patients the reason for RC instead of brachytherapy was not recorded. Patients who underwent RC instead of brachytherapy for oncological reasons (multiplicity, tumour size >5 cm and/or CIS) were excluded ($n = 167$), leaving a total of 60 RC patients for comparison to the brachytherapy cohort. Baseline characteristics of RC patients are also shown in Table 2. Five out of 60 (8.3%) patients had LNM at pathology, of whom one received adjuvant chemotherapy. In the RC group, the majority of tumours (43%) were 3–5 cm, while in the brachytherapy group the majority of tumours (51%) were < 3 cm ($p = 0.006$). In the RC group, more patients had a history of NMIBC (27% vs 10% in the brachytherapy group, $p = 0.002$).

Median follow-up was 9.6 years (95% confidence interval (CI): 8.8–10.4) after brachytherapy and 10.6 years (95%CI: 10.0–11.2) after RC. A total of 129/259 and 27/60 patients died in the brachytherapy and RC group, respectively. Kaplan-Meier curves of OS and DSS are shown in Fig. 1. Five/10-year OS after brachytherapy was 66% (95%CI: 59–71) and 49% (95%CI: 43–57), 5/10-year OS after RC was 68% (95%CI: 61–73) and 53% (95%CI: 48–59; $p = 0.4$). Five/10-year DSS after brachytherapy was 73% (95%CI: 67–77) and 67% (95%CI: 60–73), 5/10-year DSS after RC was 75% (95%CI: 66–78) and 65% (95%CI: 58–72; $p = 0.8$). Uni- and multivariable analyses for OS and DSS are shown in Table 3. No prognostic factors for OS and DSS were found.

In total, 105/259 patients had recurrent BC after brachytherapy vs 19/60 patients after RC (Supplementary Table 1). Median time to recurrence was 1.6 years (IQR 0.8–3.1, range 0.1–17.2 years) after brachytherapy and 1.1 years (IQR 0.5–2.9, range 0.2–5.2 years) after RC. Of the patients who developed a recurrence after brachytherapy, the recurrence site was soft tissue in the true pelvis in 2/105 (1.9%), pelvic LN in 4/105 (3.8%), distant in 41/105 (39%) and the bladder in 58/105 (55%) patients (Supplementary Table 1). All patients with pelvic LN recurrence ($n = 4$) underwent palliative chemotherapy and died due to metastatic disease after a median of 8 months (range 1.1–23 months). Treatment and outcome of bladder recurrence after brachytherapy are summarized in Fig. 2. Bladder recurrences ($n = 58$) occurred after a median follow-up of 1.9 years (IQR 0.22–3.7 years, range 0.22–17.1 years). Seventeen out of 58 (29%) bladder recurrences were true infield recurrences and 22/58 (38%) were located elsewhere in the bladder. In 19/58 (33%) patients, it was unknown whether the tumour was a true infield recurrence. In 25/58 (43%) patients the recurrence was NMIBC and in 33/58 (57%) MIBC. Thirty-two patients underwent SC (24 for MIBC and 8 for NMIBC). Five out of 32 patients underwent SC with palliative intent. In these cases secondary local control could not be achieved. Three more patients did not achieve secondary local control due to a recurrence in the surgical bed after SC. Four patients developed a local (i.e. soft tissue in the true pelvis) recurrence after RC and 15 patients developed distant metastasis (Supplementary Table 1). These patients were all treated with palliative intent.

The bladder was preserved in 217/259 (84%) of brachytherapy patients. Thirty-two patients underwent SC and 10 patients underwent cystectomy because of a small non-compliant bladder.

Complications are listed in Table 4. Early (≤90 days) complications occurred in 12% (32/259) of the brachytherapy patients, whereas after RC early complications occurred in 40% (24/60) of patients ($p < 0.001$). Late (>90 days) complication rates were similar after brachytherapy and RC (18% vs 17%, $p = 0.8$). After RC, all

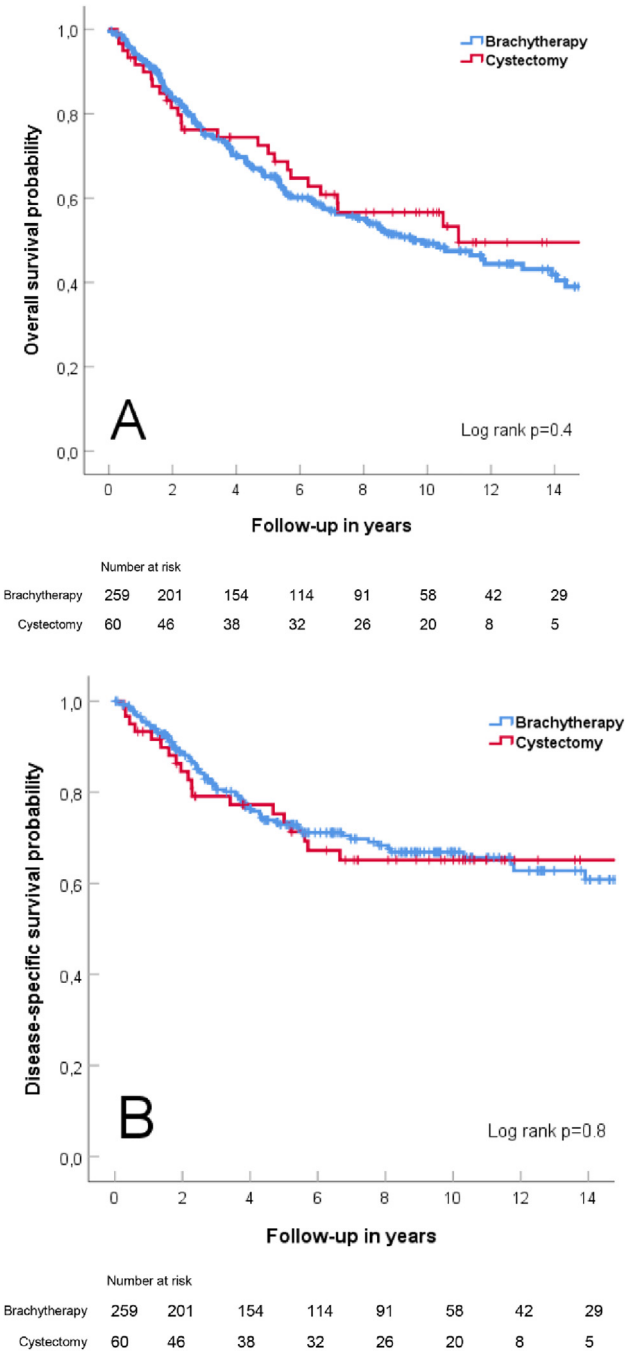

Fig. 1. Kaplan-Meier curves showing (A) overall survival and (B) disease-specific survival for patients treated with brachytherapy ($n = 259$) vs radical cystectomy ($n = 60$).

late complications were grade 3–4 (10/10, 100%); whilst after brachytherapy, 63% (29/46) of late complications were grade 3–4 ($p = 0.02$). Mortality ≤90 days was 1.7% after RC ($n = 1$, sepsis) and 0.4% ($n = 1$, myocardial infarction) after brachytherapy. After SC, early and late complications occurred in 31% (10/32) and 22% (7/32) of patients, respectively. One patient died within 90 days after SC due to kidney insufficiency.

Discussion

RC with urinary diversion is considered standard treatment for MIBC and NMIBC refractory to intravesical therapies. In an effort to preserve the bladder, several alternative treatment modalities have emerged. In order to be considered as a true alternative to RC, bladder-sparing treatments should preserve sufficient bladder function without jeopardizing oncological outcome. In this study, we showed that highly selected bladder cancer patients who were treated with the combination of TURBT, pre-operative limited EBRT and brachytherapy had similar long-term survival to selected patients who underwent RC. Furthermore, the bladder was preserved in the vast majority of brachytherapy patients. In addition, comparison to RC showed that brachytherapy was associated with fewer complications.

Although brachytherapy for BC is being used since 1980, it is not universally recognized as a therapeutic option for selected BC as, for example, is the case in localized prostate cancer. The main reason could be concern regarding oncological outcome. Several observational studies on survival after brachytherapy are available. In a multicentre cohort comprising 1040 brachytherapy patients, 5 and 10-year OS was 62% and 44% respectively [7]. Some smaller single centre studies reported 5-year OS rates between 63% and 67% after brachytherapy [13–15]. These findings are in line with our results (5 and 10-year OS after brachytherapy of 66% and 49%, respectively).

Unfortunately, prospective studies comparing outcomes after brachytherapy and RC are lacking. Besides our previous reported results in a smaller cohort [8], there is one other group that has evaluated the outcome after RC and brachytherapy retrospectively. Van der Steen-Banasik et al. compared outcome of 76 brachytherapy patients to 65 matched RC patients with solitary tumours ≤5 cm [16]. They found 5/10-year OS rates of 57%/33% in the brachytherapy group vs 52%/42% in the RC group ($p = 0.7$). In our study, OS and DSS after brachytherapy were also similar to OS and DSS after RC. However, these results should be interpreted with caution because of the limitations of a retrospective study design. This resulted in several differences between RC and brachytherapy groups. The RC group included more patients with a history of NMIBC, who are known to have a worse prognosis as compared to patients with primary MIBC [17]. Additionally, tumours were larger in the RC group (43% 3–5 cm in the RC group vs 38% in the brachytherapy group). Finally, a selection bias could not be avoided. Therefore, our analysis does not demonstrate a comparison of two totally equal patient groups but rather shows the results of two treatment strategies in a selective subgroup of bladder cancer patients. The results demonstrate that outcomes of brachytherapy are promising in terms of tumour control and OS. Furthermore, with this strategy, the bladder can be preserved in a selected group of patients. Moreover, brachytherapy resulted in less early complications as compared to RC (12% vs 40%, $p < 0.001$). Although late complication rates did not differ between the two groups (18% vs 17%), the late complications were of a higher grade in the RC group (10/10, 100% after RC and 29/46, 63% after brachytherapy, $p = 0.02$). However, due to the retrospective character of our study low grade late complications are likely to be underscored in our cohort. This also explains the relatively high percentage of high grade complications as compared to low grade complications in both groups.

An important concern regarding brachytherapy is that it represents incomplete cancer surgery with the potential inability to salvage patients who recur. In our study, 58 patients developed a bladder recurrence after brachytherapy of whom 32 underwent SC. Our SC rate (32/259, 12%) is comparable to those of other brachytherapy series [16,18]. Importantly, secondary local control could be achieved in the majority of patients. Studies have shown that primary tumour stage at time of SC drives outcomes and that there is no difference in survival compared to stage-matched patients undergoing primary RC [19]. This underlines the importance of timely diagnosis in case of recurrence. Therefore, close

Table 3
Cox proportional hazard analysis for overall survival and disease-specific survival.

Overall survival		Univariable			Multivariable		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (continuous)		1.03	1.02–1.05	<0.001	1.03	1.02–1.05	<0.001
Sex	Male	1			1		
	Female	0.90	0.61–1.31	0.6	1.05	0.71–1.56	0.8
cT stage	T1	1			1		
	T2	1.24	0.74–2.08	0.4	1.26	0.75–2.14	0.4
Grade	G2	1			1		
	G3	1.29	0.71–2.34	0.4	1.35	0.73–2.47	0.3
Tumour diameter	<3cm	1			1		
	3–5 cm	1.38	0.98–1.93	0.07	1.39	0.98–1.97	0.06
	Unknown	1.01	0.61–1.65	0.7	1.07	0.63–1.83	0.6
Prior recurrence rate	Primary	1			1		
	Recurrence	1.03	0.66–1.61	0.9	1.07	0.63–1.74	0.7
Treatment	RC	1			1		
	Brachytherapy	1.17	0.77–1.77	0.5	1.17	0.75–1.81	0.5
Disease-specific survival		Univariable			Multivariable		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (continuous)		1.01	0.99–1.02	0.6	1.01	0.99–1.03	0.5
Sex	Male	1			1		
	Female	1.17	0.75–1.84	0.5	1.20	0.75–1.92	0.4
cT stage	T1	1			1		
	T2	1.49	0.72–3.07	0.3	1.47	0.70–3.08	0.3
Grade	G2	1			1		
	G3	2.20	0.80–6.00	0.12	2.23	0.81–6.14	0.12
Tumour diameter	<3cm	1					
	3–5 cm	1.37	0.88–2.11	0.15	1.35	0.87–2.11	0.2
	Unknown	1.13	0.65–1.74	0.7	1.20	0.63–2.30	0.6
Prior recurrence rate	Primary	1			1		
	Recurrence	0.96	0.54–1.74	0.9	1.08	0.59–1.99	0.8
Treatment	RC	1			1		
	Brachytherapy	0.92	0.56–1.50	0.7	0.98	0.58–1.67	0.9

Abbreviations: CI: Confidence interval, HR: Hazard ratio, RC: radical cystectomy.

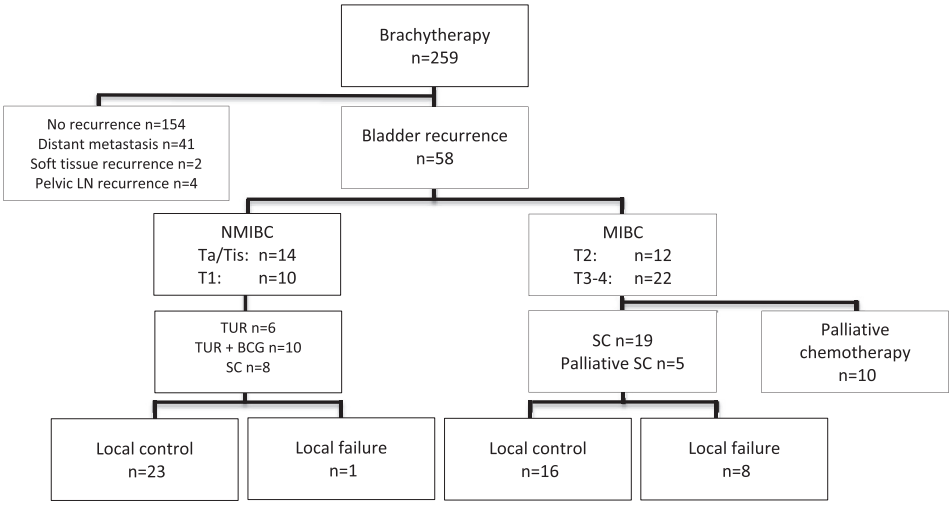

Fig. 2. Bladder recurrence and local control after salvage treatment in brachytherapy patients. Abbreviations: BCG: Bacillus Calmette-Guérin, MIBC: Muscle-invasive bladder cancer, NMIBC: Non-muscle-invasive bladder cancer, TUR: transurethral resection.

follow-up as outlined in the Material and Methods section is recommended after bladder-preserving treatment.

The value of a LND has not been established in bladder-sparing treatment modalities. In our study LND was not routinely performed in the majority of brachytherapy patients, whereas pelvic LND is a pivotal step in RC. The benefit of LND in brachytherapy patients is thought to be limited, since the selection criteria for brachytherapy include favourable prognostics (maximal cT2, solitary tumour and <5 cm). Pelvic LNM are less common in these patients. In our study, six patients had LNM at pathology. All these patients underwent LND due to clinically suspicious LN during surgery. On the other hand, four patients without suspicious LN during surgery developed a recurrence in the pelvic LN. In theory, patients who were not treated with LND could have been denied the option of adjuvant chemotherapy in case of LNM. Determining the value of a LND in brachytherapy patients would require a very large study. Until then, partly based on the described results here, we continue to perform LND in case of suspicious nodes. Similarly, the value of neoadjuvant chemotherapy in the context of TMT remains unclear. While neoadjuvant chemotherapy has a proven

Table 4
Complications after brachytherapy, radical cystectomy and salvage cystectomy determined according to the Common Terminology Criteria for Adverse Events (CTCAE).

	Brachytherapy $n = 259$		RC $n = 60$		SC $n = 32$	
	n	%	*n*	%	*n*	%
Complication rate ≤90 days	32	12	24	40	10	31
Complication rate >90 days	46	18	10	17	7	22
Grade 1–2 complications ≤90 days						
Ileus	1	0.4	4	6.7	–	–
Urinary tract infection	3	1.2	1	1.7	1	3.1
Wound infection	2	0.7	–	–	–	–
Abdominal abscess	2	0.7	–	–	–	–
Pneumonia	–	–	1	1.7	–	–
Bladder spasms	1	0.4	–	–	–	–
Delirium	1	0.4	–	–	–	–
Hematuria	1	0.4	–	–	–	–
Grade 3–4 complications ≤90 days						
Fascial dehiscence	–	–	4	6.7	1	3.1
Ureteric anastomotic leak	1	0.4	3	5.0	1	3.1
Infected lymphocele	3	1.2	1	1.7	–	–
Dislocated brachytherapy catheter	3	1.2	–		–	–
Hematuria	2		1	1.7	–	–
Hydronephrosis	1		1	1.7	–	–
Urinary tract infection	2	0.8	1	1.7	2	6.3
Wound infection	2	0.8	–		–	–
Infected urinoma	2	0.8	–	–	–	–
Sepsis	2	0.8	–	–	2	6.3
Pneumonia	–	–	2	3.3	–	–
Ileus	–	–	1	1.7	–	–
Intestinal anastomotic leak	–	–	2	3.3	1	3.1
Vesico-cutaneous fistula	1	0.4	–	–	–	–
Dislocated abdominal drain	1	0.4	–	–	–	–
Dehydration	–	–	1	1.7	–	–
Arterial thrombosis	–	–	–	–	1	3.1
Grade 5 complications ≤90 days						
Myocardial infarction	1	0.4				
Sepsis			1	1.7		
Grade 1–2 complications >90 days						
LUTS without hematuria	7	2.7	–		–	–
Hematuria	5	1.9	–		–	–
LUTS with hematuria	2	0.8	–		–	–
Urethral stenosis	1	0.4	–		–	–
Bladder perforation	1	0.4	–		–	–
Urinary tract infection	1	0.4	–		–	–
Grade 3–4 complications >90 days						
Ureteral stenosis	8	3.1	3	5.0	3	9.3
Contracted bladder	10	3.9	–	–	–	–
Stone formation radiation ulcer	5	1.7	–	–	–	–
Urethral stenosis	3	1.2	–	–	–	–
Vesico-vaginal/vesico-enteral fistula	2	0.8	1	1.7	2	6.3
Incisional/parastomal herniation	1	0.4	2	3.3	1	3.1
Urostomy stenosis	–	–	2	3.3	1	3.1
Intestinal obstruction	–	–	1	1.7	–	–
Sepsis	–	–	1	1.7	–	–

Abbreviations: LUTS: Lower urinary tract symptoms, RC: radical cystectomy, SC: salvage cystectomy.

OS benefit in MIBC patients treated with RC [20], studies have failed to demonstrate improvements in either OS or DSS after TMT [21,22]. Moreover, the survival benefit of neoadjuvant chemotherapy seems especially evident in patients with cT3-4a BC [23]. Since brachytherapy is offered to patients with maximal cT2 BC, we believe the benefit of neoadjuvant chemotherapy in this group will be limited.

Besides brachytherapy, other bladder-sparing treatments are emerging. The most-studied modality is TMT. A systematic review showed comparable survival outcomes after TMT and RC [22]. Comparison of bladder-sparing modalities is challenging because of varying selection criteria. For example, TMT is offered to patients with tumour stage cT2-T4, which makes it a possible treatment for a broader range of patients. A possible benefit of brachytherapy is that radio-sensitizing chemotherapy is not necessary because there is no expected benefit additional to the radio-biologically high-dose radiation to the tumour area in solitary cT1-T2 tumours. Consequently, possible side-effects of chemotherapy may be avoided. Furthermore, since EBRT prior to brachytherapy is low dose the risk of bowel toxicity may be lower than in EBRT as part of TMT.

Notwithstanding the aforementioned limitations, we believe our study is of merit since it represents the largest study on brachytherapy to date. Moreover, our median follow-up of 10 years is, to the best of our knowledge, the longest described for patients undergoing brachytherapy. Foremost, our study demonstrated that adequate patient selection is key in minimizing treatment aggressiveness and possible complications without negatively affecting oncological outcome.

In conclusion, bladder-preserving therapy with brachytherapy may be considered a reasonable treatment option in highly selected patients with a solitary bladder tumour ≤5 cm staged cT1G3/cT2N0M0. We reported a 10-year DSS of 67% after brachytherapy with bladder preservation in 84% of patients. Compared to RC, we found fewer high grade complications in the brachytherapy cohort. Strict patient selection is critical and patients should be counseled that long-term bladder monitoring is essential since the bladder remains a potential source of recurrence.

Source of funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.09.026.

References

[1] Alfred Witjes J, Lebret T, Compérat EM, Cowan NC, De Santis M, Bruins HM, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol 2017;71:462–75. https://doi.org/10.1016/j.eururo.2016.06.020.

[2] Winters BR, Wright JL, Holt SK, Dash A, Gore JL, Schade GR. Health related quality of life following radical cystectomy: comparative analysis from the medicare health outcomes survey. J Urol 2018;199:669–75. https://doi.org/10.1016/j.juro.2017.08.111.

[3] National Comprehensive Cancer Network. NCCN Guidelines – Bladder Cancer (Version 1.2019) 2019. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed August 2, 2019).

[4] Nederlandse Vereniging voor Urologie. Richtlijnmodule Brachytherapie bij de behandeling van patiënten met een spierinvasief blaascarcinoom; 2016.

[5] Dutch guideline Bladder Carcinoma, version 1.0. 2009. https://www.oncoline.nl/bladdercarcinoma.

[6] Pieters BR, van der Steen-Banasik E, Smits GA, De Brabandere M, Bossi A, Van Limbergen E. GEC-ESTRO/ACROP recommendations for performing bladder-sparing treatment with brachytherapy for muscle-invasive bladder carcinoma. Radiother Oncol 2016;122:340–6. https://doi.org/10.1016/j.radonc.2016.12.022.

[7] Koning CCE, Blank LECM, Koedooder C, van Os RM, van de kar M, Jansen E, et al. Brachytherapy after external beam radiotherapy and limited surgery preserves bladders for patients with solitary pT1-pT3 bladder tumors. Ann Oncol 2012;23:2948–53. https://doi.org/10.1093/annonc/mds126.

[8] Nieuwenhuijzen JA, Pos F, Moonen LMF, Hart AAM, Horenblas S. Survival after bladder-preservation with brachytherapy versus radical cystectomy; a single institution experience. Eur Urol 2005;48:239–45. https://doi.org/10.1016/j.eururo.2005.03.022.

[9] Bosschieter J, Vis AN, van der Poel HG, Moonen LM, Horenblas S, van Rhijn BWG, et al. Robot-assisted laparoscopic implantation of brachytherapy catheters in bladder cancer. Eur Urol 2018;74:369–75. https://doi.org/10.1016/j.eururo.2017.05.054.

[10] van der Werf-Messing B. Carcinoma of the bladder treated by suprapubic radium implants – the value of additional external irradiation. Eur J Cancer 1969;5:277–85.

[11] Pierquin B, Dutreix A, Paine C, Chassagne D, Marinello G, Ash D. The Paris system in interstitial radiation therapy. Acta Radiol Oncol Radiat Phys Biol 1978;17:33–48.

[12] National Cancer Institute (NCI)/National Institute of Health (NIH). Common Terminology Criteria for Adverse Events v.5.0 (CTCAE). 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf.

[13] Pernot M, Hubert J, Guillemin F, Six A, Hoffstetter S, Peiffert D, et al. Combined surgery and brachytherapy in the treatment of some cancers of the bladder (partial cystectomy and interstitial iridium-192). Radiother Oncol 1996;38:115–20. https://doi.org/10.1016/0167-8140(96)82354-1.

[14] de Crevoisier R, Ammor A, Court B, Wibault P, Chirat E, Fizazi K, et al. Bladder-conserving surgery and interstitial brachytherapy for lymph node negative transitional cell carcinoma of the urinary bladder: results of a 28-year single institution experience. Radiother Oncol 2004;72:147–57. https://doi.org/10.1016/J.RADONC.2004.06.002.

[15] Aluwini S, Van Rooij PHE, Kirkels WJ, Boormans JL, Kolkman-Deurloo IKK, Wijnmaalen A. Bladder function preservation with brachytherapy, external beam radiation therapy, and limited surger in bladder cancer patients: long-term results. Int J Radiat Oncol Biol Phys 2014;88:611–7. https://doi.org/10.1016/j.ijrobp.2013.11.227.

[16] van der Steen-Banasik E, Ploeg M, Witjes JA, van Rey FS, Idema JG, Heijbroek RP, et al. Brachytherapy versus cystectomy in solitary bladder cancer: a case control, multicentre, East-Netherlands study. Radiother Oncol 2009;93:352–7. https://doi.org/10.1016/j.radonc.2009.04.020.

[17] Schrier BP, Hollander MP, Van Rhijn BWG, Kiemeney LALM, Witjes JA. Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. Eur Urol 2004;45:292–6. https://doi.org/10.1016/j.eururo.2003.10.006.

[18] van Onna IEW, Oddens JR, Kok ET, van Moorselaar RJA, Bosch JLHR, Battermann JJ. External beam radiation therapy followed by interstitial radiotherapy with iridium-192 for solitary bladder tumours: results of 111 treated patients. Eur Urol 2009;56:113–22. https://doi.org/10.1016/j.eururo.2008.07.043.

[19] Bruins HM, Wopat R, Mitra AP, Cai J, Miranda G, Skinner EC, et al. Long-term outcomes of salvage radical cystectomy for recurrent urothelial carcinoma of the bladder following partial cystectomy. BJU Int 2013;111:37–42. https://doi.org/10.1111/j.1464-410X.2012.11438.x.

[20] Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer —. NEJM 2003:859–66.

[21] Giacalone NJ, Shipley WU, Clayman RH, Niemierko A, Drumm M, Heney NM, et al. Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: an updated analysis of the Massachusetts general hospital experience. Eur Urol 2017;71:952–60. https://doi.org/10.1016/j.eururo.2016.12.020.

[22] Fahmy O, Khairul-Asri MG, Schubert T, Renninger M, Malek R, Kübler H, et al. A systematic review and meta-analysis on the oncological long-term outcomes after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer. Urol Oncol Semin Orig Investig 2018;36:43–53. https://doi.org/10.1016/j.urolonc.2017.10.002.

[23] Hermans TJN, Voskuilen CS, Deelen M, Mertens LS, Horenblas S, Meijer RP, et al. Superior efficacy of neoadjuvant chemotherapy and radical cystectomy in cT3-4aN0M0 compared to cT2N0M0 bladder cancer. Int J Cancer 2019;144:1453–9. https://doi.org/10.1002/ijc.31833.