

# Bladder preservation with brachytherapy compared to cystectomy for T1-T3 muscle-invasive bladder cancer: a systematic review

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## Abstract

**Purpose:** Radical cystectomy currently is the treatment of choice in muscle-invasive bladder cancer. However, cystectomy is associated with considerable morbidity. Bladder sparing treatment consists of transurethral resection of the tumor (with or without partial cystectomy), external beam radiotherapy, and brachytherapy. The purpose of this study is to compare bladder preservation with brachytherapy to cystectomy by a systematic review.

**Material and methods:** A systematic review was conducted using PubMed electronic database. Article selection was done independently by two authors. Data were extracted on cause-specific survival and overall survival at 2, 5, and 10 years. Comparison of the two treatment modalities was done by a Weibull survival analysis with metaregression analysis and estimation of Hazard Ratio's (HR's) with 95% confidence intervals (CI).

**Results:** Large differences in tumor staging and tumor grading were found between cystectomy and bladder sparing series. The adjusted HR's for cause-specific survival and overall survival were 1.27 (95% CI: 1.15-1.40) and 0.85 (95% CI: 0.84-0.87), respectively for bladder sparing relative to radical cystectomy.

**Conclusions:** Robustness of the analysis is hampered by the retrospective character of the study and differences in patient characteristics. For selected cases, bladder sparing by brachytherapy leads to at least similar overall survival compared to radical cystectomy for muscle invasive bladder cancer.

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**Key words:** bladder neoplasms, brachytherapy, cystectomy, meta-analysis, systematic review.

## Purpose

Urothelial carcinoma of the bladder, comprising 90% of all primary bladder tumors, is the fourth most prevalent type of cancer in men. The number of estimated new cases and estimated deaths for 2013 are 72,570 and 15,210, respectively [1]. Currently, the treatment of choice in muscle invasive bladder cancer (MIBC) is radical cystectomy with pelvic lymphadenectomy. Stein *et al.* reported a 5 and 10 year overall survival of 60% and 43%, respectively [2]. Comparable results were reported by Park *et al.* [3] and Ghoneim *et al.* [4]. Park *et al.* reported a 5 year survival of 61% [3]. Overall survival rates were stratified by lymph node negative and lymph node positive patients by Ghoneim *et al.*, who reported a five and ten year overall survival rate of 62%, 56%, 27%, and 23%, respectively [4]. Important prognostic factors for survival are extravesical tumor extension and lymph node status [2-4]. Radical cystectomy comes with considerable morbidity such as erectile dysfunction, urinary leakage, urinary tract infection, and most important of all lost of normal bladder function [5].

Bladder preserving therapy may then offer an alternative to radical cystectomy with a possible reduction of side effects. A treatment modality for organ preservation is partial cystectomy preferably preceded by cisplatin-based neoadjuvant chemotherapy [6]. Compared to radical cystectomy, partial cystectomy results in a comparable cause-specific survival in a highly selected group of patients. However, 38% of the patients treated with partial cystectomy experienced intravesical tumor recurrence [7]. In a review of the literature, Kuczyk *et al.* reported a local recurrence after partial cystectomy varying between 38% and 78% after partial cystectomy, based on available literature [8]. Herr *et al.* provided data on local recurrence for patients with muscle invasive bladder cancer treated with only transurethral resection. Bladder recurrence with muscle invasive tumors was 34% [9]. In a highly selected group of 13 patients, partial cystectomy after neoadjuvant chemotherapy resulted in 38% intravesical recurrences, of which 23% were invasive [10].

To increase local tumor control, some groups advocate combining organ-preserving surgery of the bladder

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with external beam radiotherapy and brachytherapy (EB-BRACH) [11]. This multi-modality approach can be considered in patients with a solitary, stage pT1-pT3,  $\leq 5$  cm bladder cancer [12]. Recent studies have shown that this multimodality strategy has good results in a selected group of patients [12-14]. An advantage of this conservative approach is the preservation of bladder function. Another conservative approach for muscle-invasive bladder cancer is chemoradiation. In a recent randomized study, fluorouracil-mitomycin C chemoradiation resulted in significantly better loco-regional disease-free and overall survival compared to radiotherapy alone [15]. In contrast to brachytherapy, also large T2-4 and multifocal tumors are candidate for chemoradiation. Compared to brachytherapy, external beam radiotherapy (EBRT) has the potential risk of increased toxicity, because of a larger radiation volume, to particularly the small bowel.

In this study, a systematic review with meta-regression analysis is performed to investigate if conservative treatment with brachytherapy will result in similar survival outcome as radical cystectomy.

## Material and methods

A systematic review was conducted of the literature published on radical cystectomy and bladder brachytherapy for muscle invasive bladder cancer between January 1981 and December 2012 available in the PubMed database. Two different searches were done to identify articles on radical cystectomy and brachytherapy. Terms used for the search were *bladder neoplasms* in combination with *survival*, *survival analysis*, *treatment outcome*, *treatment efficacy*, and *treatment effectiveness*. These terms were combined with *cystectomy* or *brachytherapy*. Also synonyms of the terms were used (Table 1).

The search for articles on radical cystectomy identified 2325 articles. Articles were further selected by reading the title and abstract, after which 537 articles remained. We excluded reviews, case reports, articles with a population of 30 or less patients, median follow-up 24 months or less, node positive disease, other stages than T1-T3, uncommon histology (small cell carcinoma, rhabdomyosarcoma i.e.) and salvage cystectomy. Only articles written in English were included. Because brachytherapy studies did not use neoadjuvant chemotherapy, which is a known predictive factor for treatment outcome, we excluded studies with patients who received neoadjuvant chemotherapy. Data stratified by biological markers were not used. From different studies and based on the same patient cohort, the article with the largest cohort, most recent publication date or most thorough data analysis was included.

The search for articles on brachytherapy identified 57 articles, which were further selected by reading the title and abstract. Thirty-two articles remained. Two articles were excluded, because the patient population was  $\leq 30$ . Articles derived from patients who were included in the large multi-institutional series of Koning *et al.* [12] were excluded to avoid analysis of double data. In total, 7 studies were included.

Two authors independently did article selection and data extraction (MB and RO). The following data were extracted from the articles: year of publication, number of patients, type of study (randomized controlled trial, cohort and case-control), median follow-up time, mean or median age, total number of patients, number of patients in each tumor stage (T1-T3), differentiation grade, tumor size, multifocality (yes vs. no), adjuvant chemotherapy (yes vs. no), overall survival (OS) at 2, 5, and 10 years with standard errors and cause-specific survival (CSS) at 2, 5, and, 10 years with standard errors. Missing standard

**Table 1.** Keyword search terms

Search	Search Terms Cystectomy	Hits
1	Cystectomy [Mesh] OR Cystectomy [Tiab] OR Cystectomies [Tiab]	10631
2	Urinary Bladder Neoplasms"[Mesh] OR Bladder Neoplasm*[Tiab] OR Bladder Tumor*[Tiab] OR Bladder Cancer*[Tiab]	46397
3	Survival[Mesh] OR Survival[Tiab] OR Survival Analysis[Mesh] OR Treatment Outcome[Mesh] OR Treatment Outcome[Tiab] OR Treatment Efficacy[Tiab] OR Treatment Effectiveness[Tiab]	1110945
4	#1 AND #2 AND #3	2924
5	#3 Limits: 1981/01/01 to 2012/12/01 and studies published in English	2325
Search	Search Terms Brachytherapy	Hits
1	Brachytherapy [Mesh] OR Brachytherapy [Tiab]	17547
2	Urinary Bladder Neoplasms"[Mesh] OR Bladder Neoplasm*[Tiab] OR Bladder Tumor*[Tiab] OR Bladder Cancer*[Tiab]	46397
3	Survival[Mesh] OR Survival[Tiab] OR Survival Analysis[Mesh] OR Treatment Outcome[Mesh] OR Treatment Outcome[Tiab] OR Treatment Efficacy[Tiab] OR Treatment Effectiveness[Tiab]	1110945
4	#1 AND #2 AND #3	69
5	#3 Limits: 1981/01/01 to 2012/12/01 and studies published in English	57

errors for survival time were estimated using the number of patients at risk. The number of patients in each pathological tumor stage was used, if mentioned. When the pathological tumors stage was not mentioned, we used clinical tumor staging.

### Statistics

The two treatment modalities were compared using overall survival and cause-specific survival. The Weibull survival analysis was used to analyze survival differences between the two groups. Differences between the groups were expressed as hazard ratio's (HR) with 95% confidence interval (95% CI). For analysis a fixed-effect model was applied. Studies, which presented only data stratified by tumor stage, were imported as separated studies into the database. A stepwise multivariate regression analysis was performed on the  $\ln(-\ln(\text{probability of survival}))$  as the dependent variable.

Type of treatment (cystectomy vs. EB-BRACH), percentage of patients with tumor stage  $\geq Tis \leq T2$ , percentage of patients with grade 3, median age (if not available the mean age was used), and adjuvant chemotherapy

(yes vs. no) were the independent covariates entered into the model. Associations with a  $p$ -value  $\leq 0.05$  (two-sided) were considered as significant. The analysis was performed using IBM SPSS Statistics Version 19.0 (PASW 19.0, Chicago, IL, USA).

### Results

In total, 19 articles were used for this analysis; 7 articles on brachytherapy and 12 articles on radical cystectomy. All articles were retrospective cohort studies. The characteristics of the included articles are summarized in Table 2 and 3. Patient characteristics and 5 and 10-year survival rates are summarized in Table 4. Analysis was done on 2, 5, and 10 year overall and cause-specific survival.

#### Overall survival

A significant lower OS was found for cystectomy than for brachytherapy in both univariate- and multivariate analysis. The HR of overall survival was 0.79 (95% CI: 0.77-0.81) for brachytherapy relative to cystectomy in univariate analysis. This yields a 5 and 10 years survival of

**Table 2.** Summary of selected articles

First author	Year of publication	Number of patients	Median follow-up (months)	Adjuvant chemotherapy used?
Cystectomy				
Cheng L [16]	2000	148	60	Yes
Nieuwenhuijzen JA [17]	2005	77	30	No
Pagano F [40]	1991	64	41	No
Quek ML [41]	2003	86	NM	No
Madersbacher S [42]	2003	320	31	No
Jeon SH [43]	2005	41	77	No
Dhar NB [44]	2008	239	30	NM
Stein JP [45]	2009	41	NM	Yes
Shariat SF [46]	2009	398	57	No
May M [47]	2011	78	47	No
Hautmann RE [48]	2012	560	38	No
Neuzillet Y [49]	2012	75	58	Yes
Brachytherapy				
Koning CCE [12]	2012	1040	48	No
Rozan R [13]	1992	205	51	No
Pernot M [14]	1996	85	84	No
De Crevoisier R [19]	2004	58	52	No
Williams GB [50]	1981	89	NM	No
Mazon JJ [51]	1988	85	NM	No
Van der Werf-Messing BHP [52]	1989	90	NM	No

NM – Not mentioned

**Table 3.** Surgical and radiation characteristics for the selected brachytherapy articles

First author	Extent of resection at time of implantation	Target volume for EBRT	Dose	EBRT technique	Brachytherapy isotope and modality	Sequencing
Koning CCE [12]	No resection in 76% and PC in 24%	NM	EBRT: 10-55 Gy Brachytherapy: 25-60 Gy	NM	LDR, PDR, HDR	Brachytherapy after EBRT
Rozan R [13]	PC Homo- and bilateral LND	Bladder: 21.5% Pelvis: 78.5%	EBRT: mean 11 Gy Brachytherapy: 30-50 Gy	<sup>60</sup> Co or linear accelerator (5.5 MV-25MV)	<sup>192</sup> Ir LDR	Brachytherapy after EBRT
Pernot M [14]	No resection and PC No LND and homo- and bilateral LND	NM	EBRT: 3 x 3.5 Gy Brachytherapy: 30-50 Gy	APPA, 25 MV	<sup>192</sup> Ir LDR	Brachytherapy after EBRT Postoperative EBRT for thick tumors
De Crevoisier R [19]	PC Homo- and bilateral LND	Pelvis	EBRT: 5.5-17 Gy Brachytherapy: 50-70 Gy	APPA	<sup>192</sup> Ir LDR	Brachytherapy after EBRT
Williams GB [50]	No resection	No EBRT performed	NM	No EBRT performed	<sup>198</sup> Au and <sup>182</sup> Ta LDR	Only brachytherapy
Mazeron JJ [51]	PC Homo- and bilateral LND	Pelvis	EBRT: 1 x 8.5 Gy If N+: 30 Gy post brachytherapy Brachytherapy: 30-60 Gy	APPA, 25 MV	<sup>192</sup> Ir LDR	Brachytherapy after EBRT 30 Gy EBRT post brachytherapy if N+
Van der Werf-Messing BHP [52]	No resection	Pelvis	EBRT: 20 x 2 Gy Brachytherapy 25 Gy	APPA	<sup>137</sup> Cs LDR	Brachytherapy after EBRT

EBRT – external beam radiotherapy, APPA – anterior-posterior opposing portals, MV – megavolt, PC – partial cystectomy, LND – lymph node dissection, N+ – pathologic lymph nodes, LDR – low-dose rate, PDR – pulsed-dose rate, HDR – high-dose rate, NM – not mentioned

62% and 45% after brachytherapy, and 54% and 36% after cystectomy. In the multivariate analysis, the HR was 0.85 (95% CI: 0.84-0.87). This yields a 5 and 10 years survival of 62% and 45% after brachytherapy, and 57% and 40% after cystectomy. Covariates that remained in the multivariate analysis were type of treatment, percentage of patients with tumor stage  $\geq Tis \leq T2$ , median age and adjuvant chemotherapy. The estimated survival curves adjusted for confounders for OS are illustrated in Figure 1.

#### Cause-specific survival

No significant difference was found in CSS between brachytherapy and radical cystectomy with univariate analysis ( $p$ -value 0.713). With adjustment for confounders, a significant difference between both treatments was seen. The HR was 1.27 (95% CI: 1.15-1.40) for brachytherapy relative to radical cystectomy. This yields a 5 and 10 years survival of 71% and 57% after brachytherapy, and 76% and 64% after cystectomy. Covariates that remained in the multivariate analysis were type of treatment, percentage of patients with tumor stage  $\geq Tis \leq T2$  and median age. The estimated survival curves adjusted for confounders for cause-specific survival are illustrated in Figure 2.

#### Discussion

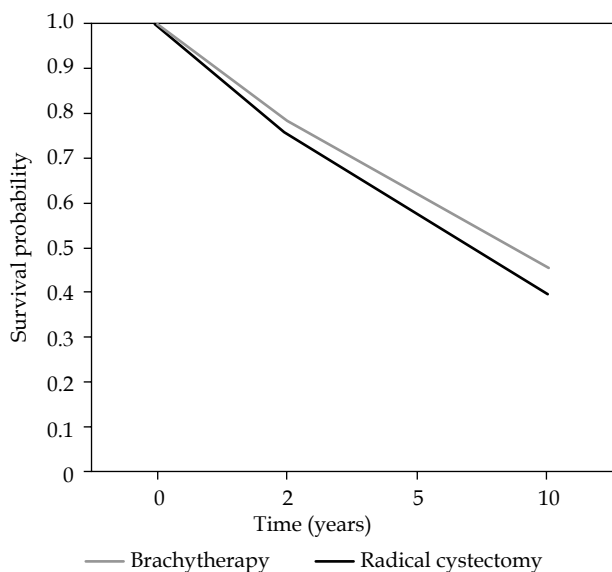
The purpose of this systematic review is to compare results of radical cystectomy with bladder preservation

by brachytherapy combined with EBRT and in most cases, partial cystectomy. This review has some limitations considering the non-randomized character of this analysis. Patient characteristics varied among both treatment groups. Comparison of brachytherapy series to cystectomy series can be hampered by differences in tumor staging. The cystectomy cohort consisted of a larger amount of patients with tumor stage T3. Furthermore, the brachytherapy group included only patients with tumors less than 5 cm. It is likely that patients in the cystectomy group had tumors with sizes exceeding 5 cm, but this remains unknown for most included studies since tumor size is not a criterion for cystectomy treatment and therefore often not reported. Tumor diameter and tumor stage were not significantly related to local control, as reported for both brachytherapy [12] and cystectomy [16]. However, Cheng *et al.* did find that tumor diameter and tumor stage are significantly associated with CSS with HRs of 1.2 (95% CI: 1.1-1.4), and 1.4 (95% CI: 1.1-1.9), respectively [16]. Furthermore, Nieuwenhuijzen *et al.* reported that tumor stage was significantly related to overall survival and disease-specific survival with HRs of 2.2 (95% CI: 1.0-4.7) and 2.4 (95% CI: 1.0-6.1) [17]. When bladder preservation is done, as it is the case for brachytherapy no pathological tumor staging information is obtained. The reported tumor staging is based on clinical ground after a cystoscopy, transurethral resection of tumor (TUR), bimanual palpation, and CT or MRI investigation. Clin-

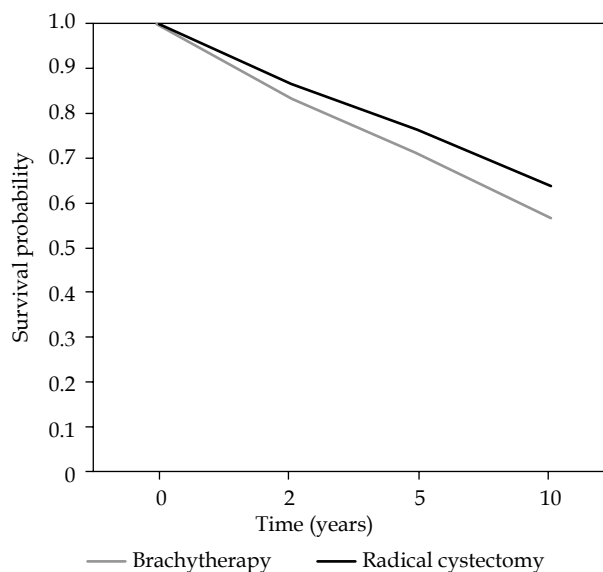
**Table 4.** Patients' characteristics and survival rates

First author	Median/ Mean age	Percentage Tis-T2	Percentage ≥ T3	Percentage Grade 1-2	Percentage Grade 3	Adjuvant chemotherapy used?	Overall survival rates		Cause-specific survival rates	
							5-year	10-year	5-year	10-year
<b>Cystectomy</b>										
Cheng L [16]	65	70	30	UK	UK	Yes			T1: 0.80 T2: 0.88 T3: 0.60	T1: 0.73 T2: 0.88 T3: 0.58
Nieuwenhuijzen JA [17]	63	100	0	20.8 <sup>1</sup>	75.3 <sup>1</sup>	No	0.67	0.58	0.72	0.72
Pagano F [40]	60	100	0	50.5	49.5	No	T1: 0.76 T2: 0.68			
Quek ML [41]	68	0	100	UK	UK	No	0.47	0.31		
Madersbacher S [42]	66	63	37	4.7	95.3	No	T1: 0.65 T2: 0.65 T3: 0.40	T1: 0.37 T2: 0.45 T3: 0.30		
Jeon SH [43]	63	59	41	88	22	No	T2: 0.75 T3: 0.47			
Dhar NB [44]	67	53	47	UK	UK	UK	T2: 0.66 T3: 0.46			
Stein JP [45]	66	56	44	UK	UK	Yes	T2: 0.85 T3: 0.56	T2: 0.75 T3: 0.37		
Shariat SF [46]	69	63	37	UK	UK	No			0.80	0.70
May M [47]	67	100	0	UK	UK	No	0.62	0.50	0.78	0.72
Hautmann RE [48]	6	72	28	UK	UK	No	T2: 0.55 T3: 0.45	T2: 0.44 T3: 0.30		
Neuzillet Y [49]	65	100	0	UK	UK	Yes	0.70	0.58		
<b>Brachytherapy</b>										
Koning CCE [12]	66	90	10	UK	UK	No	0.62	0.44		
Rozan R [13]	62	82	18	35.6 <sup>4</sup>	45.9 <sup>4</sup>	No	0.67		0.83	
Pernot M [14]	62	71	29	UK	UK	No	0.71	0.45	0.77	0.58
De Crevoisier R [19]	62	88	12	UK	UK	No	T1: 0.69 T2: 0.60 T3: 0.38	T1: 1.00 T2: 0.70 T3: 0.38	T1: 1.00 T2: 0.56 T3: 0.38	
Williams GB [50]	NM	100	0	61.8	38.2	No	T1: 0.57 T2: 0.33	T1: 0.29 T2: 0.15		
Mazoner JJ [51]	61	94	6	47.6 <sup>3</sup>	45.6 <sup>3</sup>	No			0.77	
Van der Werf-Messing BHP [52]	65	53	47	17.8	82.2	No	T2: 0.71 T3: 0.57			

UK – Unknown



**Fig. 1.** Overall survival curves for brachytherapy and cystectomy, adjusted for confounders



**Fig. 2.** Cause-specific survival curves for brachytherapy and cystectomy, adjusted for confounders

ical staging often results in a different stage compared to pathological staging after a cystectomy. In about one third of the cases, clinical understaging is found for patients that have undergone cystectomy [18]. Only in the study of de Crevoisier *et al.* an attempt is done to correlate clinical with pathological staging [19]. They could do that, because all their patients received a partial cystectomy. The only discrepancy they saw was an upstaging for 3 clinical T2 cases to pathological T3. Considering the short period preoperative external beam dose (1-2 fractions) that was given, radiation downstaging was not expected. In our study cystectomy series are usually based on pathological staging and radiotherapy series on clinical staging. A discrepancy between clinical staging for brachytherapy and pathological staging for cystectomy is therefore plausible. This is a favorable bias for the cystectomy cohort, since clinical staging is more likely to understage the extent of the tumor [20]. Better survival outcome can be expected for the cystectomy cohort solely based on tumor stage selection bias.

Randomized data for comparison of these treatment modalities are lacking. Therefore, this study was necessarily limited to retrospective data. Local recurrence and disease-free survival had no endpoints in this analysis, because these data were unfortunately missing in most studies. Therefore, we had to exclude studies that only reported on local recurrence or disease-free survival. Another limitation of this systematic review is the exclusion of studies in which neoadjuvant chemotherapy was given. Neoadjuvant chemotherapy was exclusively given in cystectomy series and not in the brachytherapy series. From randomized studies and a systematic review, a 5-8% improvement in overall survival can be expected with the addition of neoadjuvant cisplatin-containing chemotherapy [21-24]. To have a fair comparison between cystectomy and brachytherapy groups, cystectomy studies with neoadjuvant chemotherapy were excluded from this systematic review. However, given the advantage of

neoadjuvant chemotherapy on overall survival, it should always be considered and discussed with patients.

This review shows no significant difference in CSS in the univariate comparison between brachytherapy and cystectomy. After adjustment for possible confounders, the hazard ratio was 1.27 for brachytherapy relative to radical cystectomy. However, due to the retrospective character of this review, it cannot be excluded that one or several biases have influenced the result of the analysis as discussed previously. Therefore, the evidence for a difference in CSS between brachytherapy and cystectomy is not robust. In addition, the analysis on CSS miss data of the largest brachytherapy cohort of Koning *et al.* [12], which means that this analysis is based on a smaller brachytherapy treatment group than the analysis for OS. Analysis of OS results in better outcomes for the brachytherapy group compared to radical cystectomy. This suggests that patients in the cystectomy group might be more likely to die from other causes than from recurrent cancer compared to the brachytherapy group, and therefore it may appear that OS is better in the brachytherapy group. However, this is not very likely considering the fact that important data for brachytherapy are missing in the analysis of CSS. Moreover, grading was not included in the statistical models, because this information was often not reported in the studies. For the studies that have reported on grade, it seems that in the cystectomy series more patients had high-grade tumors than in brachytherapy series. On the other hand, the significance of grade is questionable for T2 and higher stage tumors [25,26]. From this systematic review, we cannot assume that one treatment modality is superior to the other. Notwithstanding, these limitations and this review indicates that the management of selected cases of muscle invasive bladder cancer with brachytherapy as bladder sparing treatment modalities does not negatively affect survival. One recent brachytherapy article that was published after this systematic review is of Aluwini *et al.* This cohort was not

included in the Dutch cohort study of Koning *et al.* In the Aluwini study 192 patients with T2-T3b muscle-invasive bladder cancer and a median follow-up of 105.5 months are described. All patients underwent bladder conservative treatment with brachytherapy. The 5 and 10 year overall survival rates were 65% and 46%, whereas the cancer-specific survival at 5 and 10 years was 75% and 67% [27]. These figures are in accordance to the figures of the included articles of this systematic review and would not alter the results.

The outcomes of this review are consistent with other studies, although data remain limited. Literature describes two studies that compared brachytherapy with radical cystectomy in a single institution experience [17,28]. Nieuwenhuijzen *et al.* did not find a significant survival benefit from brachytherapy, but they emphasized the functional benefits of bladder preservation therapy. Of all patients with long-term survival, 90% preserved their own bladder [17]. Van der Steen-Banasik *et al.* compared 76 patients with cT1-cT2 bladder cancer treated with brachytherapy to 65 patients with cT2 bladder cancer, who would be eligible for treatment with brachytherapy, but treated with radical cystectomy. They found no difference in five and ten years disease-free survival. They concluded that for patients with solitary T1G3 or T2 bladder tumors less than 5 cm, bladder conservative treatment with EB-BRACH is a good alternative to radical cystectomy [28].

Radical cystectomy comes with good survival, but also with significant morbidity [29-31]. In selected cases, it is suggested that patients with muscle-invasive bladder cancer can be treated by partial cystectomy avoiding the morbidity of radical surgery [6,32]. Dalbagni *et al.* showed that 25% of patients with muscle invasive bladder cancer on transurethral resection had superficial disease or no tumor on the final pathological specimen, which favours a conservative treatment [33]. They also stated that it is important to distinguish between organ confined and non-organ confined diseases, since this is an important prognostic factor on survival. Bladder sparing treatment is most beneficial in organ confined T2 tumors, where it counterbalances the negative consequences following radical cystectomy [19]. It can be argued if the patients treated by partial cystectomy in the brachytherapy series did need radiation treatment at all. No definitive answer can be given, because of lack of randomized studies on this matter. Knoedler *et al.* found no difference in distant recurrence-free and cause-specific survival between radical and partial cystectomy in a matched controlled study [7]. However, reanalysis of their partial cystectomy data compared to the brachytherapy series of Koning *et al.* suggest an increased risk for local recurrence, which might be explained by avoidance of radiotherapy [38]. Brachytherapy can thus be complementary to surgical TUR or partial cystectomy by treating microscopical disease and improving intravesical tumor control.

In the study of Blank *et al.*, 8 out of 122 patients treated by brachytherapy, developed a muscle invasive tumor [39]. Of these eight patients, 3 patients (2.5%) were treated with salvage cystectomy, and in two patients no

further treatment was given because of prostate involvement. This indicates that the vast majority of the patients maintained their own bladder. Aluwini *et al.* reported a 10 year cystectomy-free survival of 85%, in which not only cystectomy for local recurrence or severe toxicity was considered as loss of bladder function, but also persisting grade  $\geq 3$  bladder toxicity [27]. Unfortunately, none of the brachytherapy articles from our systematic review report on bladder function. In the Blank *et al.* study late toxicity was low, with 5% of the patients having an impaired urinary function. In the majority of patients, bladder capacity (89%) and miction frequency (85%) improved or remained unchanged. The studies of Blank and Aluwini highlight the importance of bladder sparing techniques, and show that for selected group of patients bladder conservation for muscle-invasive bladder cancer is possible. The importance lies in the fact that patients preserve their bladder function with a normal to near-normal urinary function.

Common late effect is the development of ulceration at the implantation site. This late effect occurs in about 10% of the patients at 6 months post therapy, usually asymptomatic and self-limiting [12,14]. It is important to recognize this late effect and avoiding unnecessary biopsies. Fistula formation is very rare in 2-5% of cases [12,13].

Other bladder sparing treatment modalities that include radiation therapy, consist of chemoradiation with external beam radiotherapy (without brachytherapy) [15]. Patients with tumor stage T2-T4a are included for this treatment, but – as for brachytherapy – patients with T2 tumors represent the largest group. However, patient characteristics for this treatment group are less favourable than for brachytherapy. Five and ten year overall survival rates are 52% and 35%, respectively [40]. Piet *et al.* reported three year local control, and overall survival rates of 56% and 36%, respectively for T2-T4 bladder tumors treated with external beam radiotherapy, with the majority of patients in stage T2 [37]. These results are comparable to bladder conservation treatment with brachytherapy. By brachytherapy, however, the negative effects and complications of cisplatin-based chemotherapy, such as ototoxicity and renal function impairment can be avoided [38] and, more importantly, a high dose of external beam radiotherapy to the intestine can be prevented. Chahal *et al.* reported a gastrointestinal complication rate of 6.6%. Moreover, 2.3% of all patients needed surgical treatment for bowel strictures following radical radiotherapy [39].

## Conclusions

This systematic review with meta-regression analysis shows better results after brachytherapy than after cystectomy in terms of OS, but not in CSS for patients with muscle-invasive bladder cancer. The discrepancy can be explained by the differences in tumor stage and other non-identified confounders. However, it can be concluded that brachytherapy for selected cases yields at least a similar survival as radical cystectomy for muscle-invasive bladder cancer.

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## Disclosure

Authors report no conflict of interest.

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