Overall survival, disease specific survival and local recurrence outcomes in patients with muscle invasive bladder cancer treated with external beam radiotherapy and brachytherapy: A systematic review

Registration: PROSPERO registration number is: CRD42019129349

Authors: Liam Mannion[1], Cecilia Bosco[1], Rajesh Nair[3], Vinod Mullassery[2], Deborah Enting[2], Emma-Louise Jones[2], Mieke Van Hemelrijck[1], Simon Hughes[2]

Authors' Affiliations:

1. Translational Oncology and Urology Research, King's College London, London, United Kingdom
2. Guy's Cancer, Guy's and St. Thomas' NHS Foundation Trust, London
3. Urology Dept., Guy's and St. Thomas' NHS Foundation trust. London

Corresponding author:

Liam Mannion
King's College London
Translational Oncology and Urology Research
3rd Floor Bermondsey Wing, Guy's Hospital
London
SE1 9RT
United Kingdom
Liam.Mannion@city.ac.uk

Key words: Muscle invasive bladder cancer, interstitial brachytherapy, radical cystectomy, external beam radiotherapy, organ preservation

Support

No financial conflicts of interest to disclose

ABSTRACT

Introduction: Neoadjuvant chemotherapy followed by radical cystectomy (RC) and pelvic lymph node dissection (PLND) is the standard radical management for muscle-invasive bladder cancer (MIBC). However, major pelvic surgery is not suitable for all patients and combined modality therapy (CMT) offers an alternative for patients who want to retain their bladder. Brachytherapy (BT) as part of CMT has been offered in selective cases of bladder cancer.

Objectives: To evaluate the clinical effectiveness of BT for solitary urinary bladder tumours in terms of survival, local recurrence, and adverse events.

Methods: A systematic review was conducted using defined search terms using online databases. Articles that discussed the use of BT as part of multi-modality treatments for MIBC were included.

Results: Searches returned 112 articles of which 20 were deemed suitable for analysis. 15 of the 20 articles reported overall survival (OS) at 5 years: 2747 patients were at risk and 1670 were alive after 5 years (60.7%): 7 studies reported OS at 10 years, with 817 patients at risk and 350 alive after 10 years (42.85%). Disease specific survival (DSS) at 5 years was reported in 4 studies: 371 patients were at risk and 279 alive (75.2%) at 5 years. Local recurrence was reported across all 20 studies with an average rate of 14.8% (0-32%).

Conclusion: There is low quality evidence to suggest that CMT with a BT boost is well tolerated and results in a DSS and OS at 5 years of around 75% and 60% respectively.

INTRODUCTION

Neoadjuvant chemotherapy followed by radical cystectomy (RC) and pelvic lymph node dissection (PLND) is the standard radical management for muscle invasive bladder cancer (MIBC) (1). Surgical techniques continue to advance, with robotic cystectomy (RARC) becoming increasingly popular. RARC results in less blood loss and a reduction in immediate post-surgical complications when compared to open retropubic surgery (2,3), however to date no longer term advantages have been demonstrated.

However, major pelvic surgery is not suitable or acceptable for all patients. Bladder preservation using combined modality therapy (CMT): maximal transurethral resection of the bladder tumour, chemotherapy and radiotherapy, is an alternative for selected patients, with comparable outcomes to RC when salvage cystectomy is offered for muscle-invasive recurrence (4). CMT usually incorporates external beam radiotherapy (EBRT) without a brachytherapy (BT) boost. BT is well established technique for the treatment of certain cancers (e.g. adenocarcinoma of the prostate, and squamous cell carcinoma of the cervix), however its use to treat bladder cancers is not common practice. Bladder BT involves the delivery of high dose localised radiation using sealed radioactive sources passed either directly into the tumour, or through flexible catheters placed through and in close proximity to the tumour. Robotic-assisted laparoscopic brachytherapy (RALB) is a further refinement allowing the placement of these catheters using a minimally invasive technique (5).

To date only one systematic review has attempted to compare the outcomes from RC and CMT with a brachytherapy boost (6). However, the authors concluded that due to the retrospective nature of the data analysed any differences in overall survival and cancer-specific survival were likely to reflect selection bias rather than a true treatment effect.

Other reviews have been conducted analysing RC versus CMT without the use of BT (7,8). In a 2015 review by Arcangeli et al. CMT was not associated with a statistically

significant survival advantage (5-year OS: 57% v 52% p = 0.4). Similarly, in a 2018 systematic review by Garcia-Perdomo et al. no difference in OS was found between CMT or RC (HR 1.06; 95%CI:0.85-1.31), however cancer-specific survival was better in the RC arm (HR:1.23 ;95%CI: 1.04-1.46) (7).

The purpose of this systematic review is to assess available evidence on survival, recurrence rates and toxicity for patients who receive CMT that includes BT (CMT-BT) for MIBC and includes studies described in previous reviews in addition to those published since 2014.

METHODS

Data sources

A systematic review was conducted using the *Preferred reporting items of systematic reviews and meta-analysis* (PRISMA) guidelines using predefined search terms (Figure 1) (9) for ~ 50 days throughout January and February 2019. The detailed protocol for this systematic review is also registered on PROSPERO (CRD42019129349). The following databases were searched by two independent investigators (LM and CB): PubMed, OVID (Medline + EMBASE), Google Scholar, and conference sites (British Uro-oncology Group/ESTRO). Hand searching and retrospective searching of relevant published literature was also undertaken.

Search strategy

The search terms were “brachytherapy OR interstitial radiotherapy AND urinary bladder cancer OR bladder tumour/cancer/neoplasm/muscle invasive bladder cancer AND survival*”. Abstracts and full manuscripts were individually read by two authors with any discordance mediated by a third member (MVH). Data on the treatment of MIBC with BT is primarily reported in retrospective studies. This is one of the justifications for conducting this review, as systematically reviewing these individual studies will provide missing information. A detailed description of the searches can be found in the supporting material.

Rationale for inclusion and exclusion criteria

Due to the relatively uncommon use of BT as a technique to treat MIBC, it was expected that many included studies would be retrospectives of small-medium cohort sizes, and to the best of our knowledge there has not been a randomised controlled trial looking at RC versus CMT (including BT). We included all studies that treated patients with tumours that had spread into the detrusor muscle and did not exclude the study if they also included patients with intermediate or high-grade non-muscle invasive bladder cancer (NMIBC). Publications were considered from anywhere in the world if the full text was available in English. To reduce bias, enhance credibility, and provide an accurate generalisation of the results, studies that followed up patients for at least 6 months were considered. No publication year limitation was set and all studies that met the inclusion criteria were considered.

Study selection and data extraction

Duplicates were removed and articles selected according to our inclusion criteria, irrelevant studies were removed based on title and abstract screening. After screening the titles and abstracts, full-text reports were assessed for eligibility. Any discrepancies were discussed with a third review author (MVH). The following data was extracted under the following headings: Authors and year of publication, type of study, country of origin, number of patients, BT technique + EQD2 (Gy), EBRT EQD2 (Gy), stage, reported outcomes, median follow up (FU) (months), 5y OS (%), 5y DSS (%), and local recurrence rate (%).

Risk of bias individual studies

The Joanna Briggs Checklist for Quasi experimental non-randomised studies was used to critically analyse the risk of bias in each individual study and determine the quality of the studies available (10) (table 3).

Sources of funding

No funding was declared for included studies except for the large multi-centre retrospective by Koning et al. (11) - they declared that their department received grants from Nucletron/Elekta for unrestricted research.

Data synthesis

The summary measures were based on the 5y OS rates, 5y DSS rate, and local recurrence (%) of MIBC treated with CMT that included BT.

Outcomes included in the study were:

- 5-year survival defined as patients surviving 5 years or more after CMT-BT
- DSS defined as % of people in the study who had not died from MIBC within a defined time period (2 or 5 years)
- Disease recurrence outcomes defined as local recurrence of disease within the bladder either superficial, infiltrating or both after CMT-BT followed up for at least 6 months

Analysis

Statistical data and error reporting within included studies was not sufficiently homogenous, therefore a systematic narrative synthesis was undertaken instead of a meta-analysis according to Cochrane's narrative synthesis guidelines (12).

Results

Identified studies and their characteristics

112 articles were identified through database searches, after duplicates were removed 81 articles remained. A further 54 articles were removed after the inclusion/exclusion criteria were applied, reasons for exclusion can be found in *figure 1*. Twenty-seven articles were deemed suitable for a full text read, with seven subsequently being excluded leaving 20 remaining articles for final analysis.

In all studies patients had transurethral resection of their bladder tumours (TURBT) carried out to confirm histology, staging (presence of muscle invasion), and in some cases debulking of the tumour before EBRT. The decision as to whether the patient was suitable for BT was a joint decision between the urologist and radiation oncologist based on a post-TURBT cystoscopy. Partial cystectomies were carried out for select

cases, specifically for patients that had diverticular tumours (13–15), distal ureteric tumours (14,16) , or thick (1cm+) residual tumours located at the bladder dome (14,17). In one study, nine patients had partial cystectomies, as it was deemed necessary for the correct insertion of the catheters (18). Detailed study descriptions and results are contained in *Table 1*.

The median age of a patient was 64.8 years (58.3-73): 80.8% (n = 2243) were male and 19.2% (n = 532) female. All tumours were staged according to the *Union for international cancer control* cTNM method. The majority of tumours were within radical treatment intent range T1-T3, except for three studies which included patients with T4 tumours (11,16,19). These patients had previously received EBRT, which was unsuccessful, and were subsequently offered salvage BT for local control. All patients received EBRT before BT except for two studies. In one of these studies patients received BT as a monotherapy with or without adjuvant chemotherapy (20): and in the other, BT was delivered as a monotherapy, with EBRT or RC being offered if unsuccessful (21). BT was delivered via a range of techniques. Fifteen studies delivered BT to patients via low dose rate (LDR) or a combination of LDR and later pulsed dose rate (PDR) if the study included patients over many years (due to changes in technology). LDR brachytherapy (dose rate range 0.4-2Gy/h) was initially delivered using caesium-137 which was later replaced by iridium-192. PDR brachytherapy is radiobiologically comparable to LDR brachytherapy, however the treatment is delivered using a remote afterloading technique. The radiation is then delivered as short pulses over several hours. Two studies delivered pulsed high dose rate (10 x 2.5Gy – 3# per day on consecutive days) BT via catheters implanted by RALB (5,14).

Efficacy outcomes

15 out of the 20 studies included in this review report OS outcomes at 5 years. Furthermore, other outcomes including disease-free survival and disease-specific survival were also reported (Table 1). The median time to follow up was 40 months (range 12-196 months). Due to study heterogeneity 5-year OS ranges from 12-89% with a median of 60.7% of patients alive at 5 years (2747 patients in total and 1670 alive at 5 years, Figure 2). Seven studies reported OS at 10 years (range 25-67%), with

817 patients at risk at the start and 350 alive after 10 years (42.8%). DSS was reported in five studies (range 70-82.8%), one of which reported 87% of patients were symptom and disease-free at two years (14). Four studies reported that at five years a combined number of 371 patients were at risk and 279 alive (75.2%). Local recurrence (LR) was reported across all studies. The median LR rate was 14.8% (range 0-32%). Of note the study that reported a 0% LR rate was small (n = 16) and included only patients with recurrent tumours (20).

Adverse events

Acute and late adverse events (AE) were recorded across most studies except by Zhou et al. who reported no complications following brachytherapy. The most commonly used reporting system was the Radiation Therapy Oncology Group (RTOG), used by seven studies followed by the Common Terminology Criteria for Adverse Events (CTCAE), used for five (Table 4). AEs of any grade occurred in 491 (16.5%) patients with 8.9% (267/2974) being in the acute phase ($\leq$ 3 months) and 7.5% (224/2974) as late AEs. Acute side effects experienced by patients were largely confined to the bladder and included 36 patients (1.2%) with G3-4 urinary frequency and 10 (0.3%) with hydronephrosis. Significant late effects include bladder necrosis, reported in 164 (5.8%) patients. Other common adverse effects included wound healing issues, urinary frequency, haematuria, and bladder necrosis, a complete description can be found in Table 2.

Discussion

The main outcomes reported in studies investigating the efficacy of CMT-BT for MIBC were OS and DSS. When adjusted for stage, OS was consistent across the studies, however the studies that reported the highest OS (70-80%) included NMIBC in their results and had a small number of patients (18,22,23). The average DSS at 5 years was 75.2%. There is no randomised data comparing RC and CMT-BT. As only a select patient population is suitable for the latter, any comparison would be associated with an inherent selection bias. For example, DSS post RC has been reported to range from 52.3% to 58.9% (median follow-up ranging from 6.1-6.7 years), but these figures

reflect the inclusion of patients with tumours not amenable to CMT-BT (24). When adjusted for age, stage and grade, no statistically significant difference has been demonstrated for 5-year DSS between BT and RC (25). Bladder preservation with CMT alone is also an accepted management option for suitable patients, with overall survival and disease specific survival comparable to RC when salvage cystectomy is used for muscle invasive local recurrences (2). Based on this approach, bladder preservation with CMT-BT could also be considered with the option of a salvage cystectomy if required. The median LR rate across all of studies was 14.8%, some studies did report high local recurrences (> 30%) (21,26,27). In the study by Van der Steen-Banasik et al. (26) twenty-five local recurrences occurred within the bladder, thirteen of which had a salvage cystectomy. Two of the LR where non-infiltrating and were treated successfully with chemotherapy (Mitomycin C), and the other ten were inoperable due to metastasis. They also reported that nine (11.8%) were true implant recurrences where the BT boost was delivered. Similarly, in the Williams et al. (21) study eleven patients (7%) required a cystectomy due to local recurrences within the bladder. These higher percentages agree with studies that treated patients with CMT without brachytherapy. A retrospective study (n = 155) that included patients treated with CMT from 2006-2012 reported a LR rate of 32.9% and a distant recurrence rate of 21% (28). In our study differences were observed in the reported results across several clinical variables – as discussed below.

There was heterogeneity regarding eligibility criteria for CMT-BT within the cohort of studies analysed. However, for the majority the consensus was that the optimal patients had small (<5cm diameter), solitary, histologically proven transitional cell carcinoma with no evidence of concomitant carcinoma in situ. Tumour stage was an independent predictor for DSS in some studies. Van Onna et al. reported a hazard ratio 19.8 ($p = 0.01$) for T3 versus T1 tumours (18). Van der steen-Banasik et al. reported a 5y DDS of 80% for T1 and 60% for T2b (27). Nieuwenhuijzen et al. reported that tumour stage and age showed an association with OS, but not with DSS (29).

The majority of patients received a short course of EBRT before the BT boost, with the clinical target volume (CTV) being the whole bladder or the whole bladder + regional

lymph nodes. EBRT was deemed essential before the BT to lower the risk of graft metastases when surgically implanting the catheters, whilst also irradiating regional lymph nodes. Patients who did not have their nodes irradiated underwent dissection after EBRT. However, a study looking at bladder only versus whole pelvis chemoradiation reported no difference in 5y OS (52.9% vs 53% p = 0.8) or organ preservation (58.9% vs 57.1% p = 0.8) (29). In addition, the nodal doses delivered within the CMT-BT studies (20x2Gy/fraction and 3-4x3.5Gy/fraction) were lower than the standard doses used to treat microscopic nodal disease. In view of this the role of pelvic nodal irradiation is debatable.

Differences in techniques to deliver BT also had an impact in the studies' results. For instance, the study with the largest patient cohort, a multicentre retrospective (n = 1040), reported a 5y OS rate of 62%, with a LR rate of 13%. The BT technique utilised had an impact on the success of the treatment, with PDR being superior to LDR for local control upon multivariate analysis (p = 0.0034), HDR was excluded due to small patient numbers. However, BT technique was deemed non-significant on overall survival (p = 0.53) The increased clinical effectiveness of PDR compared to LDR-BT was thought to be due to advancements in 3D dose optimisation software and the efficacy of PDR (11). Furthermore, the study by Aluwini et al. (15) included patients who had been treated prior to 1992 with LDR, and subsequent patients treated with PDR. They reported a LR rate of 22.2% in the LDR group and 19.6% in the PDR group (no statistically significant difference). Two studies used RALB to place the catheters instead of open surgery (5,30). Patients had a shorter mean duration of hospital stay and quicker recovery times compared to open catheter insertion. In the Bosschieter et al. the average hospitalisation stay time for RALB was five days whereas as other studies estimate the average hospitalisation stay for open surgery as 16 days (31).

CMT-BT related adverse events were clinically acceptable. In the acute setting grade 3-4 urinary symptoms (frequency, reflux, leakage) were the most common symptoms, along with delayed wound healing. The incidence of the latter declined as BT techniques evolved, and was uncommon after 1983 (19,27,32). Other AEs directly related to the BT catheters were rare. However, in the study by Moonen et al. two

patients had their sigmoid colon perforated due to improper placement of the BT catheters, and death has also been reported due to surgical complications (2.2%)(16,21). In the studies with robust reporting of adverse events, the acute grade 5 complication rate was 0.2%. This is comparable to the 90 day mortality rate post RC, although the patient populations will differ (2). 7.5% of patients experienced a late AE post CMT-BT; with most reported complications being grade 3-4 (only 0.2% of formally documented late complications were Grade 1-2). The most commonly reported late grade 3-4 AEs related to bladder necrosis (5.2%), but were usually asymptomatic findings at follow-up cystoscopy. Of note, none of the studies in this review assessed Patient Reported Outcome Measures (PROMS) or objective measures of long-term bladder function (urodynamics).

None of the studies analysed in this review assessed patient quality of life (QOL) with validated tools. However, other studies have assessed QOL post-cystectomy and post bladder preservation with CMT alone. One study reported that potential changes in bowel habit and psycho-sexual health following RC were significant factors when deciding on treatment (33). Loss of sexual desire and orgasm disorders are frequently reported post cystectomy for women (34) whilst men may experience erectile dysfunction (35). In line with CMT alone, CMT-BT has the potential to offer selected patients with bladder cancer both curative treatment with a smaller detrimental long-term impact on their psychosexual wellbeing (35).

Conclusion

Brachytherapy as part of CMT for MIBC is not a standard technique. Most retrospective studies have been confined to highly-specialised centres, largely located in the Netherlands. There is no randomised data available comparing the efficacy of CMT-BT, CMT alone, and RC, and all retrospective series are prone to selection bias. Our systematic review demonstrates that CMT-BT confers a 5-year DSS of 75%, and a 5-year OS of 60%. It is an effective treatment in experienced centres for a selected patient population who wish to preserve their bladder. In such patients, CMT-BT is well tolerated with an acceptable safety-profile.

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 . Vol. 71, European Urology . AMSTERDAM : Elsevier B.V ; p. 462–75.
2. Bochner G; Sjoberg, D; Silberstein, J; Paz, G; Donat, S; Coleman, J; Mathew, S; Vickers, A; Schnorr, G BD. Comparing open radical cystectomy and robot-assisted laparoscopic radical cystectomy: a randomized clinical trial. Eur Urol. 2015;67(6):1042–50.
3. Kukreja JB, Shah JB. Advances in surgical management of muscle invasive bladder cancer. Indian J Urol IJU J Urol Soc India. 2017;33(2):106.
4. Scarpato KR, Morgans AK, Moses KA. Optimal management of muscle-invasive bladder cancer–a review. Res reports Urol. 2015;7:143.
5. 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. 2017 Jun 12;
6. Pieters B, Bos M, Ordonez-Marmolejo R, Rasch C. PO-1042: Comparison of cystectomy and organ preservative brachytherapy for bladder cancer in a systematic review. Radiother Oncol. 2014 Apr 2;111:S161–S161.
7. García-Perdomo HA, Montes-Cardona CE, Guacheta M, Castillo DF, Reis LO. Muscle-invasive bladder cancer organ-preserving therapy: systematic review and meta-analysis. World J Urol. 2018;36(12):1997–2008.
8. Arcangeli G, Arcangeli S, Strigari L. A systematic review and meta-analysis of clinical trials of bladder-sparing trimodality treatment for muscle-invasive bladder cancer (MIBC) . Vol. 94, Critical Reviews in Oncology and Hematology . NEW YORK : Elsevier Ireland Ltd ; p. 105–15.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.
10. Institute JB. Checklist for Quasi-Experimental Studies (non-randomized experimental studies).
11. Koning C. C. E., 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 Nov;23(11):2948–53.
12. Ryan R. Cochrane Consumers and Communication Review Group: data synthesis and analysis. Cochrane Consum Commun Rev Group, available http//cccrg cochrane org (accessed 10 June 2019)[Google Sch. 2013;
13. Bosschieter J, Vis AN, Van Der Poel HG, Moonen L, Horenblas S, Pieters BR, et al. VE10 - Robot assisted laparoscopic implantation of brachytherapy catheters. Eur Urol Suppl. 2016 Sep;15(7):313.
14. van der Steen-Banasik EM, Smits GAHJ, Oosterveld BJ, Janssen T, Visser AG. The Curie-Da Vinci Connection: 5-Years' Experience With Laparoscopic (Robot-Assisted) Implantation for High-Dose-Rate Brachytherapy of Solitary T2 Bladder Tumors. Int J Radiat Oncol Biol Phys. 2016 Aug;95(5):1439–42.

15. Aluwini S, van Rooij PHE, Kirkels WJ, Boormans JL, Kolkman-Deurloo I-KK, 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 Mar;88(3):611–7.
16. Rozan R, Albuisson E, Donnarieix D, Giraud B, Mazeron JJ, Gerard JP, et al. Interstitial iridium-192 for bladder cancer (a multicentric survey: 205 patients). Int J Radiat Oncol Biol Phys. 1992;24(3):469–77.
17. Aluwini S, Liem E, Boormans J, Antonisse I, Praag JO, Kirkels W, et al. Long-term Treatment Outcome of Local Recurrences After Bladder Preservation With Brachytherapy for Bladder Carcinoma. Int J Radiat Oncol Biol Phys. 2015 Nov 2;93(3):E216–7.
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 Jul;56(1):113–22.
19. 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(2):115–20.
20. Zhou Y-M, Feng X, Zhou B-C, Fan Y-F, Huang Y-L. Evaluation of therapeutic effects of 125I particles brachytherapy for recurrent bladder cancer. Oncol Lett. 2018 Mar 29;15(3):3453–7.
21. Williams GB, Trott PA, Bloom HJ. Carcinoma of the Bladder Treated by Interstitial Irradiation . Vol. 53, British journal of urology . England ; 1981. p. 221–4.
22. van der Werf-Messing BH, van Putten WL. Carcinoma of the urinary bladder category T2,3NxM0 treated by 40 gy external irradiation followed by cesium137 implant at reduced dose (50%) . Vol. 16, International journal of radiation oncology, biology, physics . United States ; 1989. p. 369–71.
23. Blank LECM, Koedooder K, van Os R, van de Kar M, van der Veen JH, Koning CCE. Results of Bladder-Conserving Treatment, Consisting of Brachytherapy Combined With Limited Surgery and External Beam Radiotherapy, for Patients With Solitary T1-T3 Bladder Tumors Less Than 5 cm in Diameter. Int J Radiat Oncol Biol Phys. 2007 Oct;69(2):454–8.
24. Gschwend JE, Dahm P, Fair WR. Disease Specific Survival as Endpoint of Outcome for Bladder Cancer Patients Following Radical Cystectomy . Vol. 41, European Urology . Switzerland : Elsevier B.V ; 2002. p. 440–8.
25. 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 Aug;48(2):239–45.
26. 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 Nov;93(2):352–7.
27. Van der Steen-Banasik EM, Visser AG, Reinders JG, Heijbroek RP, Idema JG, Janssen TG, et al. Saving bladders with brachytherapy: implantation

technique and results. Int J Radiat Oncol Biol Phys. 2002 Jul;53(3):622.
28. Anghel RM, Gales LN, Trifanescu OG. Outcome of urinary bladder cancer after combined therapies . Vol. 9, Journal of medicine and life . Romania : Carol Daila University Foundation ; 2016. p. 153–9.
29. Tunio M.B.B.S., F.C.P.S. MA, Hashmi M.B.B.S., M.S., M.C.P.S. A, Qayyum M.B.B.S., M.D., M.C.P.S. A, Mohsin M.S.B.S., F.C.P.S. R, Zaeem M.Sc A. Whole-Pelvis or Bladder-Only Chemoradiation for Lymph Node–Negative Invasive Bladder Cancer: Single-Institution Experience . Vol. 82, International Journal of Radiation Oncology, Biology, Physics . United States : Elsevier B.V ; 2012. p. e457–62.
30. van der Steen-Banasik E, Smits G, Oosterveld B, Janssen T, Haverkort MAD, Wijburg C, et al. 6 Years' Experience with HDR Brachytherapy in Bladder Implantations Performed Laparoscopically in Solitary Bladder Tumors. A Prospective Study. Brachytherapy. 2016 May 2;15:S58–S58.
31. Nap-van Klinken A, Bus SJEA, Janssen TG, Van Gellekom MPR, Smits G, Van der Steen-Banasik E. Interstitial brachytherapy for bladder cancer with the aid of laparoscopy. J Contemp Brachytherapy. 2014 Jul;6(3):313–7.
32. Moonen LM, Horenblas S, van der Voet JC, Nuyten MJ, Bartelink H. Bladder conservation in selected T1G3 and muscle-invasive T2-T3a bladder carcinoma using combination therapy of surgery and iridium-192 implantation . Vol. 74, British journal of urology . England ; 1994. p. 322.
33. Henningsohn L, Steven K, Kallestrup EB, Steineck G. Distressful symptoms and well-being after radical cystectomy and orthotopic bladder substitution compared with a matched control population . Vol. 21, Urologic Oncology: Seminars and Original Investigations . 2003. p. 166–7.
34. Zahran MH, Fahmy O, El-Hefnawy AS, Ali-El-Dein B. Female sexual dysfunction post radical cystectomy and urinary diversion . Vol. 19, Climacteric . ABINGDON : Taylor & Francis ; 2016. p. 546–50.
35. Murali-Krishnan S, Pang KH, Greco F, Fiori C, Catto JW, Vavassori VL, et al. Bladder-sparing treatment in MIBC: where do we stand? Minerva Urol Nefrol. 2019 Apr;71(2):101–12.
36. 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 Aug;72(2):147–57.
37. Wijnmaalen A, Helle PA, Koper PCM, Jansen PP, Hanssens PE, Boeken Kruger CGG, et al. Muscle invasive bladder cancer treated by transurethral resection, followed by external beam radiation and interstitial iridium-192 . Vol. 39, International Journal of Radiation Oncology, Biology, Physics . OXFORD : Elsevier Inc ; 1997. p. 1043–52.
38. Mazeron J-J, Crook J, Chopin D, Claude Abbou C, Le Bourgeois J-P, Auvert J, et al. Conservative treatment of bladder carcinoma by partial cystectomy and interstitial iridium 192 . Vol. 15, International Journal of Radiation Oncology, Biology, Physics . United States : Elsevier Inc ; 1988. p. 1323–30.
39. Straus KL, Littman P, Wein AJ, Whittington R, Tomaszewski JE. Treatment of bladder cancer with interstitial iridium-192 implantation and external beam irradiation . Vol. 14, International Journal of Radiation Oncology, Biology, Physics . United States : Elsevier Inc ; 1988. p. 265–71.

40. van der Werf-Messing B, Menon RS, Hop WCJ. Cancer of the urinary bladder category t2, t3, (N XM 0) treated by interstitial radium implant: Second report . Vol. 9, International Journal of Radiation Oncology, Biology, Physics . United States : Elsevier Inc ; 1983. p. 481–5.
41. 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 Off J Eur Soc Med Oncol. 2012;23(11):2948–53.

Table 1: Included studies details and results

STUDY DETAILS											RESULTS		
Author	**Year of pub.**	**Type of study**	**Country**	**Median age**	**Male/female patients**	**Selection criteria**	**Brachytherapy dose EQD2 (Gy)**	**EBRT dose EQD2 (Gy)**	**Reported outcomes**	**Median follow up (months)**	**OS 5y %**	**DSS%**	**Local recurrence**
Bosschieter et al. (5)	2017	Retrospective (multi-centre)	Netherlands	73 (61–77)	15/8	Solitary T1G3 or T2G1–3 UC of 5 cm or cN0M0 UraC	RAL implantation PDB: 34.38	40	DFS, LRFS, CFS at 1 + 2y	12	n/a	n/a	3 (11%)
Zhou et al. (20)	2017	Retrospective analysis	China	58.3 (43-65)	13/3	The average size tumour treated was 9.3cm (3.5-21.2cm). All tumours were recurrences.	Interstitial: LDR (only half-life given)	n/a	OS, PFS at 5y	12	12	n/a	0
Van der Steen-Banasik et al. (14)	2016	Retrospective	Netherlands	70	57 (both)	T2 solitary bladder tumour diameter 5 cm without carcinoma in situ (CIS)	RAL implantation (HDR): 25.56	40	OS, DFS, DSS, LC at 2y	24	n/a	87 (2y)	3 (7%)
Aluwini et al. (15)	2014	Retrospective	Netherlands	67.9 (36-88)	133/49	Solitary, histologically proven MIBC (urothelial carcinoma) without clinical evidence of nodal or distant metastases. Exclusion criteria were CIS, tumour at the bladder neck or trigone, diameter of the (tumour) area to be treated >5 cm, and multifocal tumours.	Interstitial (LDR or PDR): 26.25	40	LRFS, SCFS, OS, CFS, DMFS 5, 10y	105.5	65	n/a	40 (21%)
Koning et al. (11)	2011	Multi-centre retrospective study	Netherlands	66 (28–92)	811/229	Stage pT1–T3, cN0 or pN0, cM0, unifocal carcinoma and size ≤5 cm diameter.	Interstitial (LDR, HDR or PDR): 64.12	32.5	LRFS, MFS, DFS, OS 1,3, 5y	65	62	n/a	136 (13%)
Van der Steen-Banasik et al. (26)	2009	Prospective registration study	Netherlands	68.3 (8.9)	67/9	Solitary T1, Grade 3 or T2 tumours < 5 cm in patients fit for surgery and with sufficient bladder function	Interstitial (LDR): 35.34	59.06	DSS, OS, CFS 5, 10y	68.4	57	71 (5y)	25 (33%)
Van onna et al. (18)	2008	Retrospective analysis	Netherlands	64	92/19	Patients with a solitary T1G3–T2Gall, tumour ≤5 cm without CIS or metastases, who were fit for surgery.	Interstitial (LDR or PDR): 52.5	63	OS, DSS, DFS 5, 10, 15y	74.4	70	82 (5y)	30 (27%)

Blank et al. (23)	2007	Retrospective analysis	Netherlands	65 (40-84)	94/28	Stage pT1 (n = 30), pT2 (n =81) , and pT3 (n = 11) pN0 (n=24) pNx (n= 98). Transitional cell carcinoma n= 111 patients, adenocarcinoma (n = 6), other (n= 5). The tumour grade was Grade 1-2 (n= 16) , Grade 3 (n=103), Grade 4 (n= 3). instillation n=12.	Interstitial (LDR or PDR): 60.51	34.58	LC, DRFS, RFS, OS 5, 10y	60	73	n/a	25 (20%)
Nieuwenhuijzen et al. (25)	2005	Retrospective analysis	Netherlands	63 (31-88)	89/19	Solitary lesion with a diameter of ≤5 cm; clinical T1G3 and T2 stages; fit for surgery; and adequate bladder capacity (estimated subjectively by patient-interviews).	Interstitial (LDR): 44.74	30	DSS, OS, 5 10y	68	65	75 (5y)	23 (21%)
De Crevoisier et al. (36)	2004	Retrospective analysis	France	62 (37-79)	54/4	Superficial and infiltrating intravesical unifocal TCC less than 5 cm in size, without iliac node involvement on intraoperative frozen section. A few patients with T3, node negative tumours who refused radical surgery were accepted for the protocol.	Interstitial (LDR): 122.55	10.37	LC, OS 5y	76	pT1 (89) pT2 (60) pT3 (38)	n/a	13(22%)
Van der steen-banasik et al. (27)	2002	Retrospective analysis	Netherlands	68 (46-88)	58/5	T2 tumours with poor degree of differentiation, vascular invasion, pathologic findings on intravenous pyelography, more than 1 transurethral resection, and T3 tumours (n = 8) T2G3 (n = 37), and T3a (n = 4).	Interstitial (LDR and PDR): 46.33	28.57	LC, DSS 5y	58.8	n/a	70 (5y)	20 (32%)
Wijnmaalen et al. (37)	1997	Retrospective analysis	Netherlands	67 (36-82)	50/16	Solid tumour surface diameter of less than 5 cm	Interstitial (LDR): 74.63	25.85	DFRS, OS 5y	26	48	n/a	7 (11%)
Pernot et al. (19)	1996	Retrospective analysis	France	62 (34-84)	76/9	Unifocal tumours less than 5 cm and not infiltrating deep muscle	Interstitial (LDR): 112.8	12.47	LC, CSS, OS 5y	84	69	n/a	3 (3%)

Moonen et al. (32)	1994	Retrospective analysis	Netherlands	63 (32-79)	34/6	(i) Solitary lesions with a diameter< 5 cm: (ii) high-grade T, stages and T2 T3 stages (muscle invasion but with no extension through the bladder wall): (iii) no history of cancer elsewhere in the bladder: (iv) fit for surgery: (v) adequate bladder capacity as estimated subjectively by the patients themselves.	74	30	LC, OS 5y	40	86	n/a	2 (16%)
Rozan et al. (16)	1992	Retrospective analysis	France	62 (35-85)	177/28	Mean tumour size was 2.9 cm; pathological stages: pTis (n = 1); pT1, (n = 98), pT2 (n = 66), pT3a (n = 26); pT3b (n = 9), pT4 (n = 1); unknown (n = 4)	Interstitial (LDR): 99.68	15.68	OS 5y	51	62.3	n/a	35 (17%)
Van der werf-messing et al. (22)	1989	Retrospective analysis	Netherlands	65 (37-78)	79/19	T2 or T3 growth with a diameter up to 5 cm	Interstitial (LDR): 124.15	40	OS 5y	At least 60	80	n/a	6 (12.5%)
Mazeron et al. (38)	1988	Retrospective analysis	France	61 (34-78)	75/10	Superficial and infiltrating unifocal bladder tumors ≤5 cm in diameter and technically amenable to partial cystectomy. All grades and histologies were accepted, but not those tumors with macroscopic extravesical extension.	Interstitial (LDR): 86.25	15.41	DFS 5y	60	n/a	n/a	13 (15%)
Straus et al. (39)	1988	Retrospective analysis	USA	64 (37-78)	8/6	(a) single lesions less than or equal to 5 cm; (b) no evidence or CIS on random bladder biopsies; (c) absence of grossly positive pelvic lymph nodes at the time of limited pelvic lymph node dissection; (d) absence of tumor invasion of structures other than prostate; (e) medical operability: (f) no previous pelvic irradiation, and (g) adequate bladder capacity.	Interstitial (LDR): 69.94	36.42	LC, OS 2y	22	n/a	n/a	1 (7%)
Van der werf-messing et al. (40)	1983	Retrospective analysis	Netherlands	65 (range not given)	333/61	Patients with a growth category T2, or T3, with a diameter not exceeding 5 cm	Missing data	11.81	OS, 5, 10y	114	47.5	n/a	25 (6%)
Williams et al. (21)	1981	Retrospective analysis	UK	Missing data	147 (both)	Patients with stage T1-T3. T1 (n = 47); T2 (n = 76); T3 (n =24)	Missing data	Missing data	OS 5, 10y	Missing data	46	n/a	46 (31%)

*Table 2: Reported acute and late adverse events related to combined modality therapy for bladder cancer**

Adverse events (N = 2974)				
	Patients n (%)			**Patients n (%)**
Acute any grade	**267 (8.9)**		**Late any grade**	**224 (7.5)**
Grade 1-2	**43 (1.4)**		**Grade 1-2**	**6 (0.2)**
Delay in wound healing	27 (0.9)		Fistula	5 (0.1)
Early complications non-specific	6 (0.2)		Urethral pain requiring catheterisation	1 (0.03)
Wound infection	4 (0.1)		**Grade 3-4**	**218 (7.3)**
Transient radiation cystitis	3 (0.1)		Necrosis without complaints (bladder)	156 (5.2)
Urine retention	2 (0.06)		Necrosis with complaints (bladder)	18 (0.6)
Moderate scrotal and penile oedema	1 (0.03)		Telangiectasia	15 (0.5)
Grade 3-4	**216 (7.2)**		Urinary frequency	10 (0.3)
Urinary frequency	40 (1.3)		Recurrent cystitis	5 (0.1)
Ureteric reflux	36 (1.2)		Urethra stricture requiring surgery	2 (0.06)
Urinary leakage	27 (0.9)		Hydronephrosis that required nephrectomy	2 (0.06)
Fistula	26 (0.8)		Infection due to bladder necrosis after TURB	1 (0.03)
Wound healing problems	19 (0.6)		Bladder necrosis that required partial cystectomy	1 (0.03)
Psychological problems	13 (0.4)		Persisting vesicocutaneous fistula	1 (0.03)
Hydronephrosis	10 (0.3)		Bladder calcification	1 (0.03)
Gastrointestinal complications involving the ileum	8 (0.2)		Small bowel necrosis	1 (0.03)
Necrosis (bladder)	7 (0.2)		Radiation cystitis requiring cystectomy	1 (0.03)
Bladder bleeding/haematuria	6 (0.2)		Small capacity bladder requiring palliative ileal conduit	1 (0.03)
Bowel complications	5 (0.1)		Enterovesical fistula requiring urinary diversion and temporary ileostomy	1 (0.03)
Radiation cystitis	4 (0.1)		Pyelonephritis requiring ureteric implantation	1 (0.03)
Scar implant	3 (0.1)		Urine leakage requiring catheter	1 (0.03)
Sigmoid perforation	3 (0.1)		**Grade 5**	**0 (0)**
Infection of the urinary tract	2 (0.06)			

Decreased bladder capacity of 150cc	1 (0.03)			
Recurrent bladder calculi requiring cystectomy	1 (0.03)			
Pyelonephritis secondary to ureteral stenosis	1 (0.03)			
Stone formation	1 (0.03)			
Osteomyelitis	1 (0.03)			
Life-threatening pulmonary embolism	1 (0.03)			
Pneumonia	1 (0.03)			
Grade 5	**8 (0.2)**			
Death due to surgical complications	4 (0.1)			
Operative death	2 (0.06)			
Cardiac arrest	1 (0.03)			
Myocardial infarction	1 (0.03)			

**Studies 5, 11, 14-16, 18-23, 25-27, 32, 36-40*

Table 3: JBL appraisal checklist for included studies

Study	1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	2. Were the participants included in any comparisons similar?	3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	4. Was there a control group?	5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	7. Were the outcomes of participants included in any comparisons measured in the same way?	8. Were outcomes measured in a reliable way?	9. Was appropriate statistical analysis used?		Comment
Bosschieter, 2017	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Yes	Include	DFS, LRFS, CFS reported using KP method
Zhou, 2017	Yes	Yes	Yes	Yes	Yes	Yes	n/a	Yes	Unclear	Include	OS and PFS measured P values
Mascarenhas, 2017	Yes	n/a	n/a	n/a	Yes	Yes	No	Unclear	Unclear	Exclude	Single case study, no endpoints measured
van der Steen-Banasik, 2	Yes	n/a	n/a	n/a	Yes	Yes	No	Yes	Unclear	Include	LC, OS, DFS,DSS reported
Aluwini, 2014	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	OS, LRFS, CFS, SCFS, DMFS
Koning, 2011	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Yes	Include	OS, DFS, LRFS, DMFS
van der Steen-Banasik, 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include	OS, DSS, CFS
van Onna, 2008	Yes	No	n/a	n/a	Yes	Yes	n/a	Yes	Yes	Include	OS, DFS, DSS
Blank, 2007	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Yes	Include	LC, OS, DFS, LRFS,
Nieuwenhuijzen, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include	OS, DSS
De Crevoisier, 2004	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Yes	Include	LC, DSS
Soete, 1997	Yes	n/a	n/a	n/a	Yes	No	n/a	Unclear	No	Exclude	No endpoints measured
van der Steen-Banasik, 2	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	LC
Wijnmaalen, 1997	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	OS, DFS,
Pernot, 1996	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	LC, OS
Moonen, 1994	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	LC, OS
Rozan, 1992	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	OS
van der Werf-Messing, 1989	Yes	n/a	n/a	n/a	Yes	Unclear	n/a	Yes	Unclear	Include	OS
Mazeron, 1988	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	DFS
Straus, 1988	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	LC, OS
van der Werf-Messing, 1983	Yes	n/a	n/a	n/a	Yes	Yes	n/a	Yes	Unclear	Include	OS
Williams, 1981	Yes	n/a	n/a	n/a	n/a	Unclear	n/a	Yes	Unclear	Include	OS

Table 4: Further detail on adverse events

Study ID	Total number of patients	Cases n (%)	Adverse effects system	Acute < 3 months	Late > 3 months
Bosschieter et al. (5)	**23**	**7 (30.4)**	Clavien-Dindo	Non-specific grade 1 (4) Accidentally removed BTC necessitating RAL repositioning (1) Drainage of an infected lymphocele (1)	Hydronephrosis developed (1)
Zhou et al. (20)	**16**	**0 (0.0)**			
Van der Steen-Banasik et al. (14)	**57**	**4 (7)**	Common Toxicity Criteria for Adverse Events	Life-threatening pulmonary embolism (1) Myocardial infarction (1)	Infection due to bladder necrosis after TURB (1) Recurrent cystitis requiring hospitalization (1)
Aluwini et al. (15)	**182**	**22 (12)**	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system	Wound healing (10)	Necrosis with complaints (12)
Koning et al. (41)	**1040**	**168 (16)**	Multiple		Necrosis (144) Fistula (24)
Van der Steen-Banasik et al. (26)	**76**	**21 (27.6)**	Common Toxicity Criteria for Adverse Events	Wound infections (6) Temporary psychotic (2) Urinary leakage (2) Ileus (1) Pneumonia (1) Cardiac failure (1)	Urine leakage (3) Fistula (5)
Van Onna et al. (18)	**111**	**28 (25.2)**	Common Toxicity Criteria for Adverse Events	Urgency (17) Hydronephrosis (7) Postoperative ileus (4)	
Blank et al. (23)	**122**	**5 (4)**	Common Toxicity Criteria for Adverse Events	Gastrointestinal compilations (2)	Reduced bladder capacity (3)
Nieuwenhuijzen et al. (25)	**108**	**2 (1.8)**	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system		Persisting vesicocutaneous fistula (1) Stricture of the urethra and ureters (1)
De Crevoisier et al. (36)	**58**	**33 (56.8)**	Common Toxicity Criteria for Adverse Events	Urinary frequency (16) Macroscopic haematuria (2) Infection of the proximal urinary tract (2)	Urinary frequency (10) Bladder calcification (1 patient) Ureteral stenosis requiring double-J stent (1) Small bowel necrosis (1)
Van der steen-banasik et al. (27)	**63**	**10 (15.8)**	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system	Wound infection (4) Urine retention (2) Temporary psychotic (2) Bladder bleeding requiring relaparotomy (1) Postoperative paralytic ileus (1)	

Wijnmaalen et al. (37)	**66**	**43 (65.1)**	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system	Frequency in urination (9) Mental distress (6) Vesicocutaneous fistula (2)	Telangiectasia (15) Necrosis without complaints (9) Necrosis with complaints (2)
Pernot et al. (19)	**85**	**32 (37.6)**	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system	Delay in wound healing (27)	Severe radiation cystitis (3) Hydronephrosis that required nephrectomy (2)
Moonen et al. (32)	**40**	**14 (35)**	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system	Wound infections (3) Urinary leakage (3) Psychological problems (3) Sigmoid perforation (1) Osteomyelitis (1) Haematoma (1) Accidental perforation of the sigmoid colon due to improper placement of catheters (2)	
Rozan et al. (16)	**205**	**13 (6.3)**	Not stated	Urinary leak (5) Death due to surgical complications (3)	Stenosis requiring surgery (1) Necrosis required partial cystectomy (1) Urinary diversion and temporary ileostomy for an entero-vesical fistula (1) Chronic cystitis and haematuria (1) Ureteral implantation due to pyelonephritis (1)
Van der werf-messing et al. (22)	**98**	**9 (9.1)**	Not stated	Non-specific complications (4) Necrosis without complaints (2) Death due to surgical complication (1) Stone formation (1) Bowel complications (1)	
Mazeron et al. (38)	**85**	**7 (8.2)**	Not stated	Urinary leakage (5)	Chronic cystitis (1) Pyelonephritis secondary to ureteral stenosis (1)
Straus et al. (39)	**14**	**6 (42.8)**	Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system	Transient radiation cystitis (3) Decreased bladder capacity of 150cc (1) Recurrent bladder calculi requiring cystectomy (1) Moderate scrotal and penile oedema (1)	
Van der werf-messing et al. (40)	**394**	**114 (28.9)**	Not stated	Necrosis without symptoms (62) Stone formation (29)	Necrosis with symptoms (4) Bladder cystitis (1)
Williams et al. (21)	**147**	**53 (36)**	Not stated	Ureteric reflux (36) Suprapubic urinary leak (12) Scar implant (3) Operative death (2)	

Figure 1: Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram of included studies on the treatment of MIBC with brachytherapy

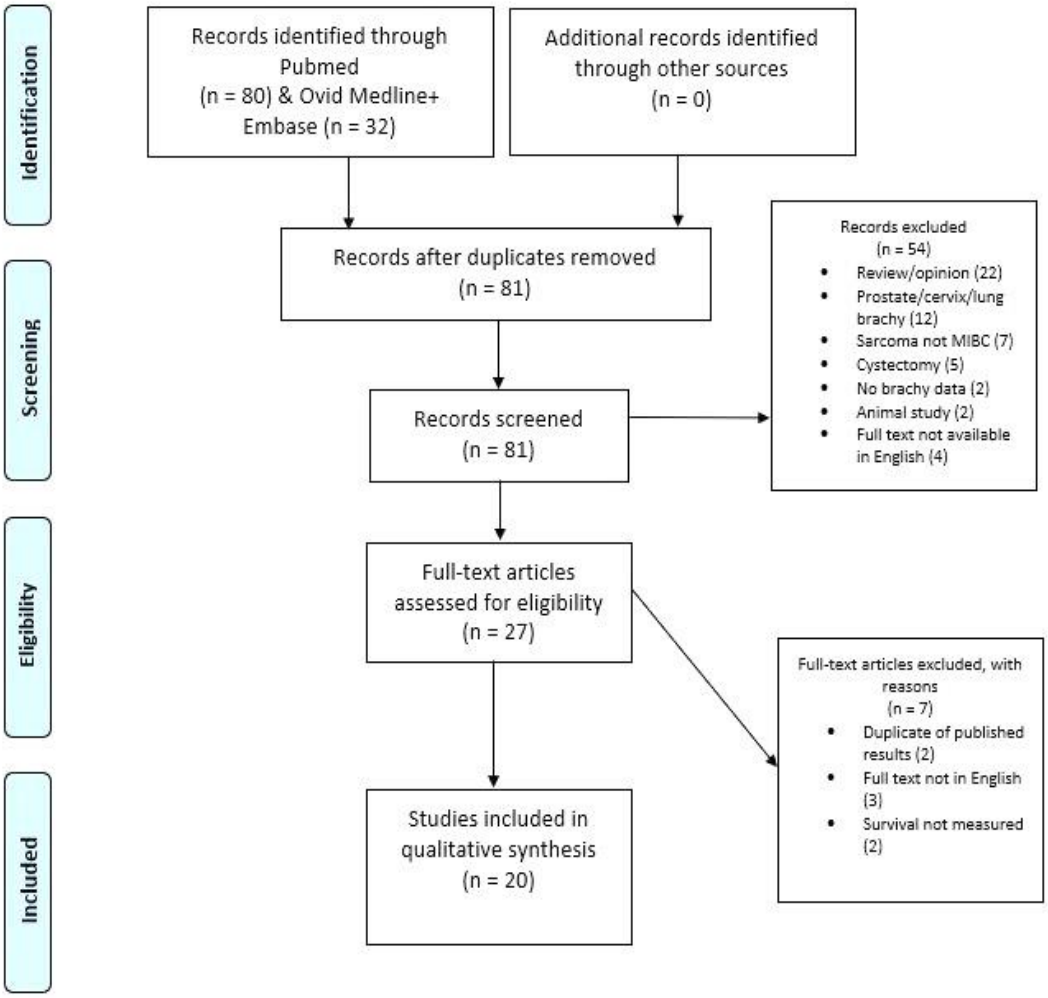
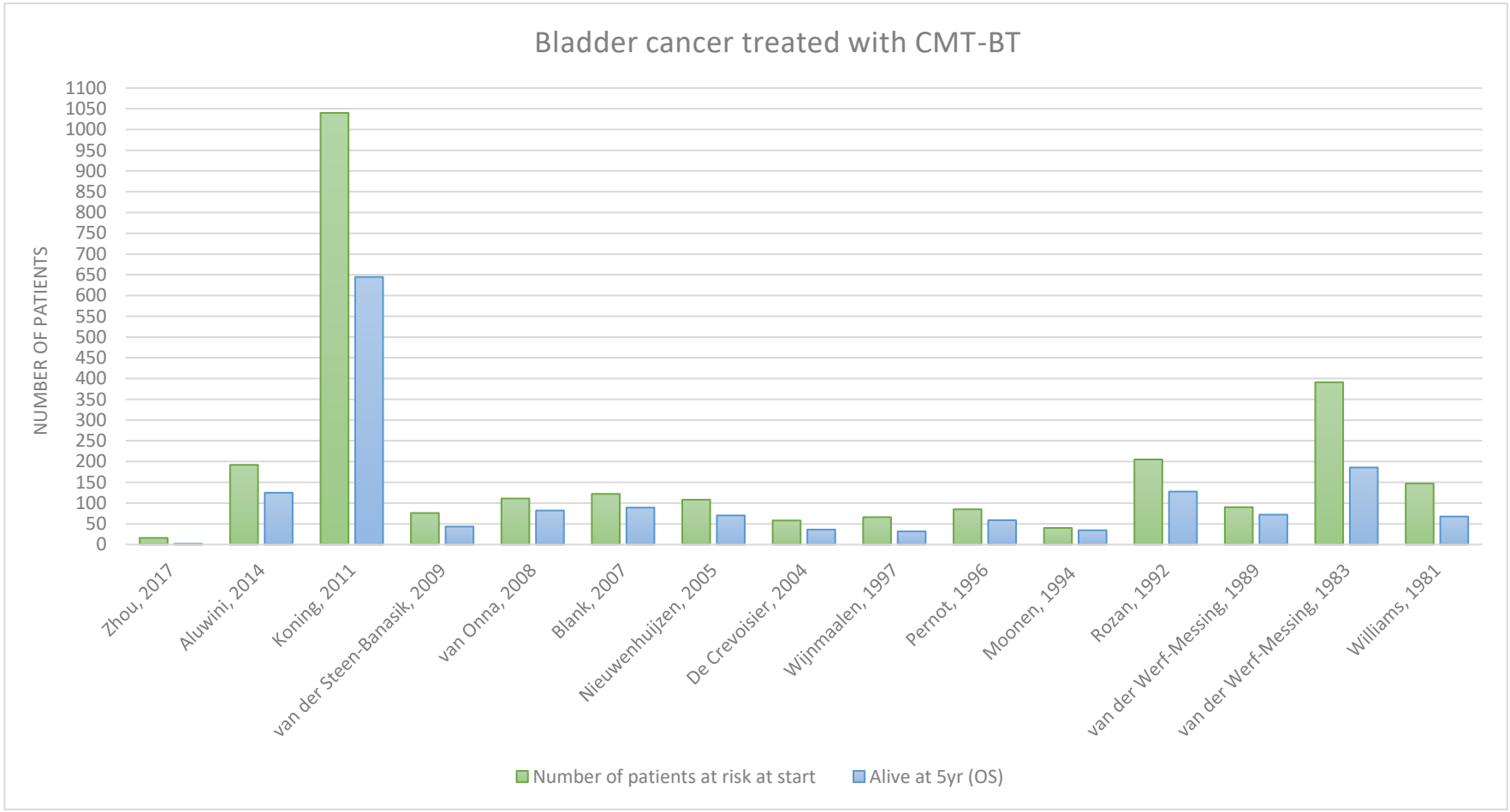


Figure 1: 5-year survival of patients treated with combined-modality therapy (including brachytherapy) 1981-2017



Supporting material

Please find detailed information as to how we carried out our searching and sifting process.

Search	Search terms	Hits
1	brachytherapy[MeSH Terms]) OR brachytherapy[Title/Abstract]) OR interstitial radiotherapy[Title/Abstract]	23317
2	urinary bladder neoplasms[MeSH Terms]) OR bladder tumour[Title/Abstract]) OR bladder cancer[Title/Abstract]) OR urinary bladder neoplasm[Title/Abstract]) OR muscle invasive bladder cancer[Title/Abstract]	58616
3	survival[MeSH Terms]) OR survival[Title/Abstract]) OR treatment outcome[MeSH Terms]) OR treatment outcome[Title/Abstract]) OR treatment result[Title/Abstract]	1628693
4 (builder search of pervious searches)	1 AND 2 AND 3	80

Figure 1: PubMed search details

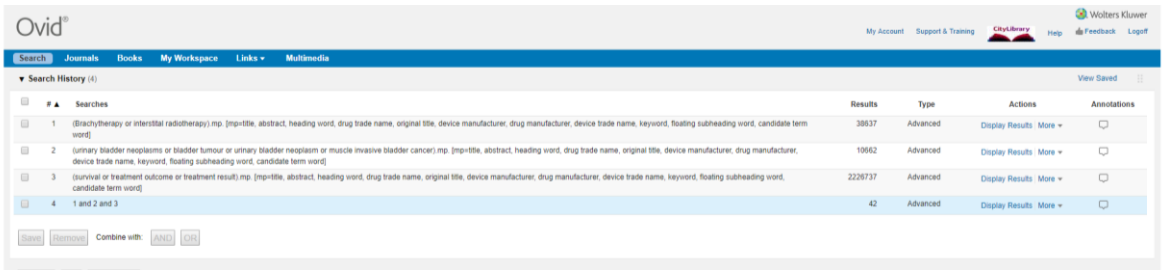


Figure 2: Ovid search details

- AMED (Allied and Complementary Medicine) 1985 to May 2019*
- CityLibrary Journals@Ovid
- EBM Reviews - ACP Journal Club 1991 to April 2019
- EBM Reviews - Cochrane Central Register of Controlled Trials March 2019
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 24, 2019
- EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012
- EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016
- EBM Reviews - Cochrane Clinical Answers April 2019
- EBM Reviews - Health Technology Assessment 4th Quarter 2016
- EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016
- Embase 1974 to 2019 Week 17
- Global Health 1973 to 2019 Week 16
- HMIC Health Management Information Consortium 1979 to January 2019
- Journals from Ovid
- Maternity & Infant Care Database (MIDIRS) 1971 to March 2019

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to April 30, 2019
- Social Policy and Practice 201904
- Ovid Nursing Database 1946 to April Week 3 2019

*Included databases in the OVID search

List of excluded studies

1: Saltzman AF, Cost NG. Current Treatment of Pediatric Bladder and Prostate Rhabdomyosarcoma. Curr Urol Rep. 2018 Feb 22;19(1):11. doi: 10.1007/s11934-018-0761-8. Review. PubMed PMID: 29468476. SARCOMA

2: Mascarenhas F, Maes K, Marques F, Formoso R, Antunes T. Robot-assisted brachytherapy of the bladder with long distance support using video conferencing. J Contemp Brachytherapy. 2017 Aug;9(4):375-382. doi: 10.5114/jcb.2017.69548. Epub 2017 Aug 30. PubMed PMID: 28951758; PubMed Central PMCID: PMC5611459. SURVIVAL NOT MEASURED

3: Cosset JM, Belin L, Wakil G, Flam T, Thiounn N, Pierrat N, Pontvert D, Savignoni A, Chauveinc L. Second malignancies after permanent implant prostate cancer brachytherapy: A single-institution study of 675 patients treated between 1999 and 2003. Cancer Radiother. 2017 May;21(3):210-215. doi: 10.1016/j.canrad.2017.02.003. Epub 2017 May 9. PubMed PMID: 28499661.PROSTATE

4: Chargari C, Haie-Meder C, Guérin F, Minard-Colin V, de Lambert G, Mazeron R, Escande A, Marsolat F, Dumas I, Deutsch E, Valteau-Couanet D, Audry G, Oberlin O, Martelli H. Brachytherapy Combined With Surgery for Conservative Treatment of Children With Bladder Neck and/or Prostate Rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2017 Jun 1;98(2):352-359. doi: 10.1016/j.ijrobp.2017.02.026. Epub 2017 Feb 21. PubMed PMID: 28463154. SARCOMA

5: Fietkau R. [When is a nonsurgical approach possible for metastatic primary tumors and lymph node metastases of the urinary bladder and prostate?]. Urologe A. 2017 May;56(5):570-578. doi: 10.1007/s00120-017-0379-3. Review. German. PubMed PMID: 28424830. PROSTATE

6: Haidl F, Pfister D, Semrau R, Heidenreich A. [Second neoplasms after percutaneous radiotherapy]. Urologe A. 2017 Mar;56(3):342-350. doi: 10.1007/s00120-016-0277-0. Review. German. PubMed PMID: 27844130. REVIEW

7: Seitz G, Fuchs J, Sparber-Sauer M, Leuschner I, Godzinski J, Klingebiel T, Schuck A, Martus P, Dantonello TM, Koscielniak E. Improvements in the Treatment of Patients Suffering from Bladder-Prostate Rhabdomyosarcoma: A Report from the CWS-2002P Trial. Ann Surg Oncol. 2016 Nov;23(12):4067-4072. Epub 2016 Jul 7. PubMed PMID: 27387676. SARCOMA

8: Martelli H, Borrego P, Guérin F, Boubnova J, Minard-Colin V, Dumas I, Chargari C, Haie-Meder C. Quality of life and functional outcome of male patients with bladder-prostate rhabdomyosarcoma treated with conservative surgery and brachytherapy during childhood. Brachytherapy. 2016 May-Jun;15(3):306-311. doi:

10.1016/j.brachy.2016.01.001. Epub 2016 Feb 16. PubMed PMID: 26895712. SARCOMA
9: Luchey AM, Lin HY, Yue B, Agarwal G, Gilbert SM, Lockhart J, Poch MA, Pow-Sang JM, Spiess PE, Sexton WJ. Implications of Definitive Prostate Cancer Therapy on Soft Tissue Margins and Survival in Patients Undergoing Radical Cystectomy for Bladder Urothelial Cancer. J Urol. 2015 Nov;194(5):1220-5. doi: PROSTATE 10.1016/j.juro.2015.05.091. Epub 2015 Jun 6. PubMed PMID: 26055823.
10: Bos MK, Marmolejo RO, Rasch CR, Pieters BR. Bladder preservation with brachytherapy compared to cystectomy for T1-T3 muscle-invasive bladder cancer: a systematic review. J Contemp Brachytherapy. 2014 Jun;6(2):191-9. doi: 10.5114/jcb.2014.43777. Epub 2014 Jun 28. Review. PubMed PMID: 25097561; PubMed
Central PMCID: PMC4105649. REVIEW
11: Goossens-Laan CA, Leliveld AM, Verhoeven RH, Kil PJ, de Bock GH, Hulshof MC, de Jong IJ, Coebergh JW. Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer. Int J Cancer. 2014 Aug 15;135(4):905-12. doi: 10.1002/ijc.28716. Epub 2014 Jan 25. PubMed PMID: 24420527. NO BRACHY
12: Haie-Meder C, Mazeron R, Martelli H, Oberlin O. [Brachytherapy role in pediatric rhabdomyosarcomas]. Cancer Radiother. 2013 Apr;17(2):155-8. doi: 10.1016/j.canrad.2012.12.011. Epub 2013 Feb 8. Review. French. PubMed PMID: 23683937. SARCOMA
13: Hulshof MC, Pieters BR, Koning CC. [Bladder-conserving treatment for bladder cancer: potential of and developments in radiotherapy]. Ned Tijdschr Geneeskd. 2013;157(19):A5556. Review. Dutch. PubMed PMID: 23657098. REVIEW
14: Goossens-Laan CA, Visser O, Hulshof MC, Wouters MW, Bosch JL, Coebergh JW, Kil PJ. Survival after treatment for carcinoma invading bladder muscle: a Dutch population-based study on the impact of hospital volume. BJU Int. 2012 Jul;110(2):226-32. doi: 10.1111/j.1464-410X.2011.10694.x. Epub 2011 Nov 1. PubMed
PMID: 22044615. NO BRACHY
15: Heinzelmann F, Thorwarth D, Lamprecht U, Kaulich TW, Fuchs J, Seitz G, Ebinger M, Handgretinger R, Bamberg M, Weinmann M. Comparison of different adjuvant radiotherapy approaches in childhood bladder/prostate rhabdomyosarcoma
treated with conservative surgery. Strahlenther Onkol. 2011 Nov;187(11):715-21. doi: 10.1007/s00066-011-2261-3. Epub 2011 Oct 29. PubMed PMID: 22037652. SARCOMA
16: Das D, Chaudhuri S, Deb AR, Aich RK, Gangopadhyay S, Ray A. Treatment of cervical carcinoma with high-dose rate intracavitary brachytherapy: two years follow-up study. Asian Pac J Cancer Prev. 2011;12(3):807-10. PubMed PMID: 21627388. CERVIX
17: Pouessel D, Thariat J, Lagrange JL, Mottet N, Culine S. [Perioperative strategies in patients with muscle invasive bladder cancer]. Bull Cancer. 2010;97 Suppl Cancer de la vessie:5-9. doi: 10.1684/bdc.2010.1096. French. PubMed PMID: 20534384. FULL TEXT NOT IN ENGLISH
18: Jayram G, Katz MH, Steinberg GD. Radical cystectomy in patients previously

treated for localized prostate cancer. Urology. 2010 Dec;76(6):1430-3. doi: 10.1016/j.urology.2010.01.048. Epub 2010 Apr 8. PubMed PMID: 20381130. PROSTATE

19: Yee DS, Shariat SF, Lowrance WT, Sterbis JR, Vora KC, Bochner BH, Donat SM, Herr HW, Dalbagni G, Sandhu JS. Impact of previous radiotherapy for prostate cancer on clinical outcomes of patients with bladder cancer. J Urol. 2010 May;183(5):1751-6. doi: 10.1016/j.juro.2010.01.014. Epub 2010 Mar 17. PubMed PMID: 20299035; PubMed Central PMCID: PMC4295901. PROSTATE

20: Bevers RF, Battermann JJ, Gietema JA, Hulsbergen-Van de Kaa CA, de Reijke TM, Feller N, Witjes JA; De Nederlandse Vereniging voor Urologie; Vereniging van Integrale Kankercentra (VIKC). [Guideline on urothelial carcinoma of the bladder]. Ned Tijdschr Geneeskd. 2009;153:A956. Dutch. PubMed PMID: 20051162 OPINION.

21: Brown AP, Neeley ES, Werner T, Soisson AP, Burt RW, Gaffney DK. A population-based study of subsequent primary malignancies after endometrial cancer: genetic, environmental, and treatment-related associations. Int J Radiat Oncol Biol Phys. 2010 Sep 1;78(1):127-35. doi: 10.1016/j.ijrobp.2009.07.1692. Epub 2009 Nov 10. PubMed PMID: 19910129. CERVIX/GYNAE

22: Sandhu A, Mundt AJ. Radiation therapy for urologic malignancies in the elderly. Urol Oncol. 2009 Nov-Dec;27(6):643-52. doi: 10.1016/j.urolonc.2009.07.019. PubMed PMID: 19879475. OPINION

23: Lee DJ, Rothberg MB, McKiernan JM, Benson MC, Badani KK. Robot-assisted radical cystoprostatectomy in complex surgical patients: single institution report. Can J Urol. 2009 Jun;16(3):4664-9. PubMed PMID: 19497175. NO BRACHY

24: Thariat J, Caullery M, Ginot A, Hannoun-Lévi JM, Barrière J, Buthaud X, Marcié S, Bondiau PY, Housset M, Lagrange JL, Amiel J, Gérard JP. [State of the art and advances in radiotherapy for bladder cancer]. Prog Urol. 2009 Feb;19(2):85-93. doi: 10.1016/j.purol.2008.11.002. Epub 2008 Dec 16. French. PubMed PMID: 19168010. REVIEW

25: Martelli H, Haie-Meder C, Branchereau S, Franchi-Abella S, Ghigna MR, Dumas I, Bouvet N, Oberlin O. Conservative surgery plus brachytherapy treatment for boys with prostate and/or bladder neck rhabdomyosarcoma: a single team experience. J Pediatr Surg. 2009 Jan;44(1):190-6. doi: SARCOMA/PROSTATE 10.1016/j.jpedsurg.2008.10.040. PubMed PMID: 19159742.

26: Da Pozzo L. Editorial comment on: External beam radiation therapy followed by interstitial radiotherapy with iridium-192 for solitary bladder tumours: results of 111 treated patients. Eur Urol. 2009 Jul;56(1):122. doi: 10.1016/j.eururo.2008.07.045. Epub 2008 Aug 21. PubMed PMID: 18722047. COMMENT

27: Herr HW. Editorial comment on: External beam radiation therapy followed by interstitial radiotherapy with iridium-192 for solitary bladder tumours: results of 111 treated patients. Eur Urol. 2009 Jul;56(1):121. doi: 10.1016/j.eururo.2008.07.044. Epub 2008 Aug 21. PubMed PMID: 18722045. OPINION/DUPLICATE

28: Pansadoro V, Emiliozzi P. Bladder-sparing therapy for muscle-infiltrating bladder cancer. Nat Clin Pract Urol. 2008 Jul;5(7):368-75. doi: 10.1038/ncpuro1145. Epub 2008 Jun 17. Review. PubMed PMID: 18560383. REVIEW

29: Kaouk JH, Hafron J, Goel R, Haber GP, Jones JS. Robotic salvage retropubic prostatectomy after radiation/brachytherapy: initial results. BJU Int. 2008 Jul;102(1):93-6. doi: 10.1111/j.1464-410X.2008.07570.x. Epub 2008 Apr 11. PubMed PMID: 18410443. PROSTATE
30: Kerst JM, Pos FJ, Visser O, Horenblas S. [New developments in the treatment of muscle-invasive bladder cancer]. Ned Tijdschr Geneeskd. 2008 Jan 26;152(4):187-92. Review. Dutch. PubMed PMID: 18320942. REVIEW
31: Jordana F, Lagrange JL, Gérard JP, Amiel J. [Role of the combination of external radiotherapy--partial cystectomy--interstitial brachytherapy in pT1 G3, pT2 and pT3 bladder tumors]. Ann Urol (Paris). 2005 Nov;39 Suppl 5:S104-12. Review. French. PubMed PMID: 16425727. REVIEW
32: Pos F, Horenblas S, Dom P, Moonen L, Bartelink H. Organ preservation in invasive bladder cancer: brachytherapy, an alternative to cystectomy and combined modality treatment? Int J Radiat Oncol Biol Phys. 2005 Mar 1;61(3):678-86. PubMed PMID: 15708245. REVIEW
33: Pos F, Moonen L. Brachytherapy in the treatment of invasive bladder cancer. Semin Radiat Oncol. 2005 Jan;15(1):49-54. Review. PubMed PMID: 15662607. REVIEW
34: Viegas CM, Araujo CM, Dantas MA, Froimtchuk M, Oliveira JA, Marchiori E, Souhami L. Concurrent chemotherapy and hypofractionated twice-daily radiotherapy in cervical cancer patients with stage IIIB disease and bilateral parametrial involvement: a phase I-II study. Int J Radiat Oncol Biol Phys. 2004 Nov 15;60(4):1154-9. PubMed PMID: 15519787. CERVIX
35: Nieuwenhuijzen JA, Horenblas S, Meinhardt W, van Tinteren H, Moonen LM. Salvage cystectomy after failure of interstitial radiotherapy and external beam radiotherapy for bladder cancer. BJU Int. 2004 Oct;94(6):793-7. PubMed PMID: 15476510. NO BRACHY
36: Greven K, Winter K, Underhill K, Fontenesci J, Cooper J, Burke T; Radiation Therapy Oncology Group. Preliminary analysis of RTOG 9708: Adjuvant postoperative radiotherapy combined with cisplatin/paclitaxel chemotherapy after surgery for patients with high-risk endometrial cancer. Int J Radiat Oncol Biol Phys. 2004 May 1;59(1):168-73. PubMed PMID: 15093913. CERVIX
37: Widmark A, Flodgren P, Damber JE, Hellsten S, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in urinary bladder cancer. Acta Oncol. 2003;42(5-6):567-81. Review. PubMed PMID: 14596515. REVIEW
38: Dunst J, Rödel C, Diestelhorst A, Heynemann H, Schrott KM, Sauer R. Radiochemotherapy for T1G3 bladder cancer. Front Radiat Ther Oncol. 2002;36:151-8. Review. PubMed PMID: 11842745. REVIEW
39: Pedraza V, Cueto J, Castillo I, Gonzalo C, Romero MJ, Zuluaga A. [Critical vision in the treatment of invasive vesical cancer with ionizing radiation]. Arch Esp Urol. 1999 Jul-Aug;52(6):662-74. Review. Spanish. PubMed PMID: 10484850. REVIEW
40: González González D, Haitze van der Veen J, Ypma AF, Blank LE, Hoestra CJ, Veen RE. [Brachytherapy for urinary bladder cancer]. Arch Esp Urol. 1999 Jul-Aug;52(6):655-61. Review. Spanish. PubMed PMID: 10484849. REVIEW
41: Movsas B, Chapman JD, Horwitz EM, Pinover WH, Greenberg RE, Hanlon AL, Iyer R, Hanks GE. Hypoxic regions exist in human prostate carcinoma. Urology. 1999

Jan;53(1):11-8. PubMed PMID: 9886581. PROSTATE
42: Hoffstetter S, Hubert J, Guillemin F, Peiffert D, Marchal C, Luporsi E, Pernot M. [Interstitial brachytherapy in infiltrating cancer of the bladder. The Nancy experience]. Cancer Radiother. 1998 Apr;2 Suppl 1:54s-61s. French. PubMed PMID: 9749080. FULL TEXT NOT IN ENGLISH
43: Zietman AL, Shipley WU, Heney NM, Althausen AF. The case for radiotherapy with or without chemotherapy in high-risk superficial and muscle-invading bladder cancer. Semin Urol Oncol. 1997 Aug;15(3):161-8. Review. PubMed PMID: 9394911. REVIEW
44: Vogt HG, Martin T, Kolotas C, Schneider L, Strassmann G, Zamboglou N. Simultaneous paclitaxel and radiotherapy: initial clinical experience in lung cancer and other malignancies. Semin Oncol. 1997 Aug;24(4 Suppl 12):S12-101-S12-105. Review. PubMed PMID: 9331131. LUNG
45: Durdux C, Housset M. [Radiotherapy and chemotherapy in infiltrating bladder tumors]. Rev Prat. 1997 Feb 15;47(4):392-5. Review. French. PubMed PMID: 9114525. REVIEW
46: Colvett KT, Althausen AF, Bassil B, Heney NM, McGovern FV, Young HH 2nd, Kaufman DS, Zietman AL, Shipley WU. Opportunities with combined modality therapy
for selective organ preservation in muscle-invasive bladder cancer. J Surg Oncol. 1996 Nov;63(3):201-8. Review. PubMed PMID: 8944067. REVIEW
47: Lybeert ML, Ribot JG, de Neve W, Goor C, Crommelin MA. Carcinoma of the urinary bladder: long-term results of interstitial radiotherapy. Bull Cancer Radiother. 1994;81(1):33-40. PubMed PMID: 7893521.
48: Skladowski K, McMillan TJ, Peacock J, Titley J, Steel GG. Cell-cycle progression during continuous low dose rate irradiation of a human bladder carcinoma cell line. Radiother Oncol. 1993 Sep;28(3):219-27. PubMed PMID: 8255999.NO BRACHY
49: De Neve W, Lybeert ML, Goor C, Crommelin MA, Ribot JG. T1 and T2 carcinoma of
the urinary bladder: long term results with external, preoperative, or interstitial radiotherapy. Int J Radiat Oncol Biol Phys. 1992;23(2):299-304. PubMed PMID: 1587750. FULL TEXT NOT AVAIABLE
50: Porter AT. The role of radiotherapy in the treatment of muscle invasive bladder cancer. Prog Clin Biol Res. 1990;353:23-34. Review. PubMed PMID: 2217424. REVIEW
51: Cox JD, Guse C, Asbell S, Rubin P, Sause WT. Tolerance of pelvic normal tissues to hyperfractionated radiation therapy: results of Protocol 83-08 of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 1988 Dec;15(6):1331-6. PubMed PMID: 3058657. NO BRACHY
52: Yeoh EK, Spittle MF. The treatment of carcinoma of the cervix and poor-risk endometrial carcinoma using the Cathetron at the Middlesex Hospital: experience since 1979. Clin Radiol. 1986 Mar;37(2):165-8. PubMed PMID: 3698502. CERVIX
53: Battermann JJ, Tierie AH. Results of implantation for T1 and T2 bladder tumours. Radiother Oncol. 1986 Feb;5(2):85-90. PubMed PMID: 3085168.
54: Shipley WU, Rose MA. Bladder cancer. The selection of patients for treatment by full-dose irradiation. Cancer. 1985 May 1;55(9 Suppl):2278-84. PubMed PMID:

3919933. OPINION
55: Gérard JP, De Laroche G, Ardiet JM, Romestaing P, Auque JR. [Iridium curietherapy in conservative treatment of infiltrating cancer of the bladder]. J Urol (Paris). 1985;91(3):139-44. French. PubMed PMID: 4045208. FULL TEXT NOT IN ENGLISH
56: Nag S, Blatnik A, Soloway M. Enhancement of high intensity Iodine-125 brachytherapy by cis-platinum in a murine bladder tumor model. J Urol. 1984 Jun;131(6):1225-8. PubMed PMID: 6539386. ANIMAL
57: van der Werf-Messing B, Menon RS, Hop WC. Carcinoma of the urinary bladder category T3NxMo treated by the combination of radium implant and external irradiation: second report. Int J Radiat Oncol Biol Phys. 1983 Feb;9(2):177-80. PubMed PMID: 6833019. DUPLICATE
58: Wijnmaalen A, Boeken Kruger CC. Organ preservation by external beam and afterloading interstitial radiation in patients with muscle infiltrating bladder cancer. Semin Urol Oncol. 2000 Nov;18(4):308-12. Review. PubMed PMID: 11101095. REVIEW
59: Moonen LM, Horenblas S, Pos F, Schaefer BS, Meinhardt W, Bartelink H. [Good results of bladder-preserving treatment in poorly differentiated and invasive bladder carcinoma using interstitial Iridium-192 radiotherapy]. Ned Tijdschr Geneeskd. 1996 Jul 6;140(27):1406-10. Dutch. PubMed PMID: 8766684.
60: van der Werf-Messing B, Menon RS, Hop WC. Cancer of the urinary bladder category T2, T3, (NxMo) treated by interstitial radium implant: second report. Int J Radiat Oncol Biol Phys. 1983 Apr;9(4):481-5. PubMed PMID: 6853251. DUPLICATE