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En-bloc resection versus conventional transurethral resection for patients with non-muscle-invasive bladder cancer (Protocol)

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[Intervention Protocol]

En-bloc resection versus conventional transurethral resection for patients with non-muscle-invasive bladder cancer

Kim van Putten[1], Robin WM Vernooij[2], Richard P Meijer[1], Xiaoye Zhu[3]

[1]Department of Oncological Urology, University Medical Center Utrecht, Utrecht, Netherlands. [2]Department of Nephrology and Hypertension and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands. [3]Department of Urology, Radboudumc, University Medical Center, Nijmegen, Netherlands

Contact address: Kim van Putten, Department of Oncological Urology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht, 3584 CX, Netherlands. k.vanputten-2@umcutrecht.nl, kimmetje_p@hotmail.com.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of en-bloc resection compared with conventional transurethral resection for the best approach of bladder cancer in patients with non-muscle-invasive bladder cancer.

BACKGROUND

Description of the condition

Urothelial bladder cancer causes significant morbidity and mortality (Burger 2013). Worldwide, bladder cancer in both sexes is the 11th most commonly diagnosed cancer (7th in men and 19th in women). The global age-standardized incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women. Bladder cancer is the 14th leading cause of cancer deaths worldwide. The age-standardized mortality rate (per 100,000 person/years) was 3.2 for men versus 0.9 for women in 2012 (Bray 2018).

Bladder cancer incidence and mortality rates vary worldwide, mainly due to differences in risk factors, detection, and diagnostic practices, and availability of treatments. However, these variations are partly caused by the different methodologies used in data collection (differences in coding and registration practices (Antoni 2017), and the subsequent quality of the data (Burger 2013). The decrease in incidence of and mortality due to bladder cancer seen in some, mostly low- or middle-income countries, possibly reflects the reduced impact of causative agents (Bosetti 2011; Chavan 2014; Jemal 2010). Overall an increase in incidence is seen, possibly due to an aging global population (Kramer 2014; Chavan 2014), and improved detection mechanisms and screening (Cumberbatch 2015). As the second most common urological tumour, bladder cancer represents a growing healthcare problem, accounting for a large part of total healthcare costs worldwide (Brausi 2002; Kramer 2015; Sievert 2009). Moreover, bladder cancer confers the largest financial burden per patient of all types of malignant tumours (Cooksley 2008).

The most important risk factor for bladder cancer, accounting for approximately 50% of cases, is tobacco smoking (Babjuk 2016; Cumberbatch 2016). Other well-established risk factors for bladder cancer include: 1) infection with *Schistosoma haematobium* (Burger 2013), specifically a chronic endemic cystitis based on recurrent infection with the parasitic trematode; and 2) occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons and chlorinated hydrocarbons, which are excreted renally (Chavan 2014; Colt 2014; Freedman 2011; van Osch 2016). The latter concerns mainly occupations in the industrial setting, which process paint, dye, metal, and petroleum products. Work-safety guidelines applied in industrial plants have reduced these occupational exposure risks, resulting in a similar incidence of bladder cancer compared with the general population (Babjuk 2016). Dietary patterns, environmental pollution, and genetic predisposition are other suggested and suspected risk factors for bladder cancer (Figueroa 2016; Steinmaus 2014; Vieira 2015). In most parts of the world outside of Africa, high tobacco consumption is the major cause of bladder cancer; while in most parts of Africa, infection with *S haematobium* is the predominant cause (Chavan 2014).

Bladder cancer can be differentiated between transitional cell carcinoma (90% of cases) and squamous cell carcinoma of the bladder (Witjes 2018). Tobacco smoking is associated with transitional cell carcinoma, while *S haematobium* infection causes mainly squamous cell carcinoma (Burger 2013).

Approximately three-quarters of newly diagnosed bladder cancers present with a non-muscle-invasive disease, being confined to the mucosa (stage Ta, carcinoma in situ) or submucosa (T1) (Babjuk 2016). This percentage shows a rise in a younger population of patients (< 40 years of age) (Compérat 2015). Compared to muscle invasive bladder cancer (T2-4), patients with non-muscle-invasive bladder cancer, being TaT1 or carcinoma in situ (CIS), are more prevalent due to the higher incidence and better outcome due to a lower cancer-specific mortality (Sylvester 2005; Witjes 2018).

The 2017 TNM classification is used for staging (Table 1). For grading, both 1973 and 2004 World Health Organization (WHO) grading classifications are used. Non-muscle-invasive bladder cancer is defined as confined to the mucosa (Babjuk 2016; Babjuk 2018a; Sobin 2009).

After primary assessment of bladder cancer, a transurethral resection is the gold standard strategy of choice. The goal of this procedure is complete removal of the tumour and adequate pathological classification with the lowest possible morbidity to the patient (Babjuk 2016; Babjuk 2018b).

Description of the intervention

Traditional transurethral resection is performed systematically in fractions (exophytic part of the tumour, the underlying bladder wall, and the edges of the resection area) using an electrical wire loop via a resectoscope (Babjuk 2016). In contrast, a basic principle of oncological surgery is to remove the entire lesion (Hurle 2016). En-bloc tumour resection, which is not a new concept, differs from traditional resection since the goal is not to fragment the tumour. It can be performed using different energy sources. The technique is performed using electrical (monopolar or bipolar), laser cautery (holmium/thulium), and more recently water-jet. Water-jet resection is a novel technique in transurethral resection, and uses a water-jet as a resection tool instead of a laser beam (Islas-García 2016; Kramer 2011; Migliari 2015; Zhang 2015). En-bloc resection is believed to be a safe, effective, feasible, and reliable technique. Some even believe it to be superior, or at least non-inferior, in accuracy compared to conventional transurethral resection (Hurle 2016; Kramer 2017; Migliari 2015). Nowadays both methods, en-bloc resection and conventional transurethral resection, are used with a worldwide variation based on surgeons' preference. The strategy of resection depends on size and location of the lesion. European guidelines recommend performing a resection en-bloc or in fractions, not specifying in what case to choose what strategy (Babjuk 2016). Although randomized trials have been undertaken for this comparison, high-quality systematic reviews including an assessment of the quality of the evidence (e.g. GRADE approach) are lacking. The results of a Cochrane Review might help to determine in which cases one or other technique is preferred.

Adverse effects of the intervention

Transurethral bladder tumour resection is one of the most commonly performed procedures by practicing urologists and residents of urology (Richards 2014). A possible major complication is bladder perforation, in some cases caused by an obturator nerve reflex. Other complications include bleeding, urinary tract infection, and urethral stricture (Collado 2000; Traxer 2004). Novel techniques are introduced frequently but should be studied, reviewed carefully, and only applied when added value is established. The downside of applying a novel technique is its learning curve (Richards 2014).

How the intervention might work

The rationale of preference of en-bloc resection over conventional resection is a reduction of tumour recurrence rate and progression rate because of better pathological classification (meaning inclusion of detrusor muscle in the specimen) and avoidance of seeding of microscopic floating tumour cells, which may occur during conventional resection (Kramer 2014).

Furthermore, by using the en-bloc technique, a more complete resection may be performed and thereby reduce the rate of re-resection (Mariappan 2010), usually required when sampling does not include muscularis propria. In line with this avoidance of seeding of microscopic floating tumour cells and inadequate sampling without musculus propria, we expect fewer complications because of just one single operation instead of multiple procedures and subsequently necessary anaesthetics, shorter operation time and hospitalization time, ultimately leading to lower general healthcare costs and higher quality of life (Richards 2014). Routinely guideline recommended re-resections for high-grade tumours.

Why it is important to do this review

En-bloc resection might offer better staging of bladder tumours and may result in less recurrence or progression, or both. Furthermore, en-bloc resection could result in fewer re-resections because of more a radical primary resection (Kramer 2017). The EAU Guideline has defined en-bloc resection as 'feasible' in selected tumours (Babjuk 2018a). Benefits in diagnostic accuracy, reduction of recurrences, decrease of complications, and, indirectly, reduction of healthcare costs associated with management of non-muscle-invasive bladder cancer may be elucidated with this review.

OBJECTIVES

To assess the effects of en-bloc resection compared with conventional transurethral resection for the best approach of bladder cancer in patients with non-muscle-invasive bladder cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We will include studies regardless of their publication status or language of publication. We will include randomized controlled trials (RCTs) or quasi-RCTs. Full reports and other types of reports, such as conference proceedings, are eligible for inclusion. We will exclude cross-over designs due to the nature of the intervention and control.

We will include studies that meet the inclusion criteria but do not report one or more of our primary or secondary outcomes.

Types of participants

We will include adults of both genders with suspected non-muscle-invasive bladder cancer. We will exclude patients with suspected T3/4, N+, or M+ disease (Table 1). We will contact study authors if we require further clarification to determine the health status of the included patients. Should we identify studies in which only a subset of participants are relevant to this review, we will include such studies if data are available separately for the relevant subset.

Types of interventions

We plan to investigate the following comparisons of experimental intervention versus comparator intervention. We will investigate the difference between bipolar and monopolar resection if necessary.

Experimental interventions

- En-bloc resection (including electrical, laser (holmium/thulium) and water-jet hybrid knife resection).

Comparator interventions

- Conventional transurethral resection (electrical resection).

Comparisons

- En-bloc resection versus conventional transurethral resection.

Types of outcome measures

Primary outcomes

- Tumor recurrence (dichotomous outcome).
- Serious adverse events (Clavien grade 4-5) (dichotomous outcome).

Secondary outcomes

- Progression rate (dichotomous outcome).
- Presence of detrusor muscle in histopathological sample (dichotomous outcome).
- Re-resection (dichotomous outcome).
- Adverse events (Clavien grade 1-3) (dichotomous outcome).

Method and timing of outcome measurement

The main time point of interest is 'end of trial' defined as the point of time with the longest follow-up duration from time of randomization. We will also extract and present the outcome data reported at other time points after randomization, if applicable.

- Tumor recurrence: defined as the proportion of patients with tumour recurrence that is identified with visual or pathological confirmation by three years after the procedure.
- Progression rate: defined as the proportion of patients that are identified as having progression of their tumour (upstaging) (defined as progression in T-stadium according to 2009 TNM (Tumor-Node-Metastasis) classification of urinary bladder cancer (Sobin 2009)) or upgrading (defined as progression in WHO grading of 1973 (Mostofi 1973) and 2004 (Eble JN) by three years after the procedure). Any form of progression, non-muscle-invasive to muscle invasive, but also CIS [carcinoma in situ] and low to high-grade progression will be considered as progression.
- Adverse events: defined as the number of patients that experience adverse events, including excessive bleeding, bladder perforation, need for transfusion, re-operation, re-admission, longer duration of indwelling catheter, urinary tract infection, and urethral stricture at the end of the trial. The adverse events are scored in grade 4 to 5 or grade 1 to 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute 2017).
- Presence of detrusor muscle in histopathological sample: defined as the proportion of patients identified as having detrusor muscle in their histopathological sample at the end of the trial.

- Re-resection: defined as the proportion of patients that require a re-resection within three months of TURBT [transurethral resection bladder tumor] (due to concerns about incomplete resection).

To assess the certainty of the evidence for imprecision in our 'Summary of findings' tables (Johnston 2013), we will try to find any published information about a clinically important difference for the dichotomous outcomes (tumour recurrence, progression rate, presence of detrusor muscle in histopathological sample, re-resection, and adverse events). However, if this is not available, we will use a relative risk reduction (RRR) or a risk ratio (RR) of at least 25%, based on guidance in Guyatt 2011b.

Search methods for identification of studies

We will perform a comprehensive search with no restriction on the language of publication or publication status. We plan to rerun searches within three months prior to anticipated publication of the review.

Electronic searches

We will search the following sources from inception of each database (Appendix 1).

- CENTRAL.
- MEDLINE (via PubMed/Ovid).
- Embase (via Ovid).
- Scopus.
- Google Scholar.
- Web of Science.

We will also search the following.

- ClinicalTrials.gov (www.clinicaltrials.gov/).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/).

If we detect additional relevant keywords during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms and will document the changes.

Searching other resources

We will try to identify other potentially-eligible trials or additional publications by searching the reference lists of retrieved included trials, reviews, meta-analyses, and clinical guidelines. We will also contact study authors of included trials to identify any further studies that we may have missed. We will search abstract proceedings of relevant meetings, including European Association of Urology (EAU), American Urological Association (AUA), and ASCO-GU of the preceding three years for unpublished studies.

Data collection and analysis

Selection of studies

We will use reference management software to identify and remove potential duplicate records (EndNote 2016). Two review authors (KvP, XZ) will independently assess the titles, abstracts, or both, of records identified in the search against the predefined inclusion criteria to determine which studies we should assess further. Two review authors (KvP, XZ) will investigate all potentially-relevant records as full-text, will map records to studies, and will classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a; Higgins 2017). We resolve any discrepancies through discussion or arbitration by a third review author (RM). If resolution of a disagreement is not possible, we will designate the study as 'awaiting classification' and we will contact study authors for clarification. We will document reasons for exclusion of studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. We will present an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

We will develop a dedicated data abstraction form that we will pilot test ahead of time based on the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). For studies that fulfil the inclusion criteria, two review authors (KvP, XZ) will independently abstract the following information, which we will record in the 'Characteristics of included studies' table.

- Study design.
- Study dates (if dates are not available the this was reported as such).
- Study settings and country.
- Participant inclusion and exclusion criteria.
- Participant details, baseline demographics.
- The number of participants by study and by study arm.
- Details of relevant experimental and comparator interventions such as dose, route, frequency, and duration.
- Definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups.
- Study funding sources.
- Declarations of interest by primary investigators.

We will extract outcomes data relevant to this Cochrane Review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we will attempt to obtain numbers of events and totals for population of a 2 x 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we will attempt to obtain means and standard deviations or data necessary to calculate this information.

We will resolve any disagreements by discussion, or, if required, by consulting a third review author (RV).

We will provide information, including trial identifier, about potentially relevant ongoing studies in the 'Characteristics of ongoing studies' table.

We will attempt to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximize yield of information by mapping all publications to unique studies and collating all available data. We will use the most complete dataset aggregat-

ed across all known publications. In case of doubt, we will give priority to the publication that reports the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (KvP, XZ) will independently assess the risk of bias of each included study. We will resolve disagreements by consensus or by consulting a third review author (RV).

We will assess risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2017; Higgins 2011b). We will assess the following domains:

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

We will judge risk of bias domains as 'low risk', 'high risk', or 'unclear risk' and will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b; Higgins 2017). We will present a 'Risk of bias' summary figure to illustrate these findings.

For selection bias (random sequence generation and allocation concealment) and reporting bias (selective reporting), we will evaluate the risks of bias at a trial level.

For performance bias (blinding of participants and personnel), we will evaluate the risk of bias separately for each outcome, and will group outcomes according to whether measured when reporting our findings in the 'Risk of bias' tables.

We also will assess attrition bias (incomplete outcome data) on an outcome-specific basis, and group outcomes with like judgements when reporting our findings in the 'Risk of bias' tables.

We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.

We define the following endpoints as subjective outcomes:

- Tumour recurrence.
- Serious adverse events (grade 4-5).
- Progression rate.
- Presence of detrusor muscle in histopathological sample.
- Re-resection.
- Adverse events (grade 1-3).

Measures of treatment effect

If we identify at least two included trials that provide data on a given outcome, we will express dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes measured using the same scale, we will use mean difference (MD) values with 95% CIs. In the case of continuous outcomes measuring the same concept but using different measurement scales, we will express the data as standardized mean differences with 95% CIs.

Unit of analysis issues

The unit of analysis will be the individual participant. If we identify trials with more than two intervention groups for inclusion, we will handle these in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c; Higgins 2017).

Dealing with missing data

We will contact the study authors to obtain missing data, if possible, and will perform intention-to-treat (ITT) analyses if data are available; otherwise we will perform available case analyses. We will investigate attrition rates, e.g. drop-outs, losses to follow-up, and withdrawals, and will critically appraise issues of missing data. We do not plan to impute missing data.

Assessment of heterogeneity

In the event of excessive heterogeneity unexplained by subgroup analyses, we will not report outcome results as the pooled effect estimate in a meta-analysis but will provide a narrative description of the results of each study.

We will assess heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); we will interpret the I^2 statistic as follows (Covidence; Deeks 2011):

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

If we identify heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting. If we include 10 studies or more investigating a particular outcome, we will use funnel plots to assess small study effects.

Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We therefore will interpret results with caution (Sterne 2011).

Data synthesis

We will perform all data synthesis using Review Manager 5 (Review Manager 2014). Unless there is sufficient evidence for homogeneous effects across studies, we will summarize data using a random-effects model. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the statistical guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017; Review Manager 2014). For dichotomous outcomes, we will use the Mantel-Haenszel method; for continuous outcomes, we will use the inverse variance method.

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics might introduce clinical heterogeneity, and plan to perform subgroup analyses with investigation of interactions:

- Based on different techniques of en-bloc resection (electrical versus laser versus water-jet hybrid knife). We will perform the subgroup analyses limited to the primary outcomes.

We will use the test for subgroup differences in Review Manager 5 to compare subgroup analyses if there is a sufficient number of included studies (Hozo 2005; Review Manager 2014).

Sensitivity analysis

We plan to perform sensitivity analyses in order to explore the influence of the following factors (when applicable) on effect sizes:

- Restricting the analysis by taking into account risk of bias, by excluding studies at 'high risk' or 'unclear risk'.

'Summary of findings' table

Main outcomes for 'Summary of findings' table

We will present a 'Summary of findings' table and will report the following outcomes, which are listed according to priority.

- Tumour recurrence.
- Serious adverse events (grade 4-5).
- Progression rate.
- Presence of detrusor muscle in histopathological sample.
- Re-resection.
- Adverse events (grade 1-3).

We will assess and present the quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and also to external validity (such as directness of results) (Guyatt 2008). For each comparison, two review authors (KvP, XZ) will independently assess the quality of evidence for each outcome as either 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT software (GRADEpro GDT). We will resolve any discrepancies by consensus, or, if necessary, a third review author (RV) will arbitrate. For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which will provide key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011a; Schünemann 2011). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table.

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None

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ADDITIONAL TABLES

Table 1. 2017 TNM (Tumor-Node-Metastasis) classification

T - Primary tumour	N - Regional lymph nodes	M - Distant metastasis
TX Primary tumour cannot be assessed	Nx Regional lymph nodes cannot be assessed	M0 No distant metastasis
T0 No evidence of primary tumour	N0 No regional lymph node metastasis	M1a Non-regional lymph nodes
Ta Non-invasive papillary carcinoma	N1 Metastasis in a single lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	M1b Other distant metastases
Tis Carcinoma in situ: "flat tumour"	N2 Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
T1 Tumour invades subepithelial connective tissue	N3 Metastasis in common iliac lymph node(s)	
T2 Tumour invades muscle		
T2a Tumour invades superficial muscle (inner half)		
T2b Tumour invades deep muscle (outer half)		
T3 Tumour invades perivesical tissue		
T3a Microscopically		
T3b Macroscopially (extravesical mass)		
T4 Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall		
T4a Tumour invades prostate stroma, seminal vesicles, uterus or vagina		
T4b Tumour invades pelvic wall or abdominal wall		

2016 TNM classification approved by the Union International Contre le Cancer (UICC) (Brierley 2017)

APPENDICES

Appendix 1. Draft search strategy

If we detect additional relevant keywords during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms and will document the changes.

CENTRAL

1. bladder cancer

2. bladder neoplasms

3. bladder tumor

4. bladder tumour

5. #1 or #2 or #3 or #4

6. en-bloc

7. en bloc

8. #6 or #7

5. #5 and #8

MEDLINE (via PubMed/OVID)

bladder cancer AND en-bloc

1. bladder cancer

2. bladder neoplasms

3. bladder tumor

4. bladder tumour

5. 1 or 2 or 3 or 4

6. en-bloc

7. en bloc

8. 6 or 7

9. (randomised controlled trial.pt. or controlled clinical trial.pt.or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals.sh not (humans.sh and animals.sh))

10. 5 and 8 and 9

Embase (via OVID)

bladder cancer AND en-bloc

1. bladder cancer

2. bladder neoplasms

3. bladder tumor

4. bladder tumour

5. or /1-4

6. en-bloc

7. en bloc

8. or/6-7

9. ((RANDOMIZED-CONTROLLED-TRIAL/ or RANDOMIZATION/ or CONTROLLEDSTUDY/ or MULTICENTER-STUDY/ or PHASE-3-CLINICAL-TRIAL/ or PHASE-4- CLINICAL-TRIAL/ or DOUBLE-BLIND-PROCEDURE/ or SINGLE-BLIND-PROCEDURE/) or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).ti,ab) not (animals.sh not (humans.sh and animals.sh))

10. 5 and 8 and 9

Scopus

bladder cancer or bladder neoplasms or bladder tumor or bladder tumour AND en-bloc or en bloc

Google Scholar

bladder cancer or bladder neoplasms or bladder tumor or bladder tumour AND en-bloc or en bloc

Web of Science

TOPIC: bladder cancer AND *TOPIC:* en-bloc

ClinicalTrials.gov

bladder cancer or bladder neoplasms or bladder tumor or bladder tumour AND en-bloc or en bloc

World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal

bladder cancer or bladder neoplasms or bladder tumor or bladder tumour AND en-bloc or en bloc

CONTRIBUTIONS OF AUTHORS

Kim van Putten (KvP): wrote the protocol.

Xiaoye Zhu (XZ): wrote the protocol.

Robin WM Vernooij (RV): wrote the protocol.

Richard P Meijer (RM): wrote the protocol.

All review authors read and approved the final protocol version.

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KvP has no known conflicts of interest.

XZ has no known conflicts of interest.

RV has no known conflicts of interest.

RM has no known conflicts of interest.

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