**Supplementary Methods:**

Information sources and search strategies: Searches were not restricted by language or study type but were restricted to human subjects. We searched the grey literature resources such as conferences, dissertations, reports, and other unpublished studies found in EMBASE. We performed forward and backward citation chaining and searched references of the included articles as well as later articles citing our included article.

Inclusion and exclusion criteria: We excluded studies that did not report response to therapy. Single patient case reports, animal studies, abstracts, review articles and non-English literature were not included in this analysis.  We identified and linked multiple reports of the same study and excluded them if duplicated or not relevant. We combined reports that described different findings from the same study and excluded papers that reported previously published results.

Data extracted for review: The variables extracted from each study were: study information and setting (country, design, sample size), patient demographics, pathologic/histologic features, type of intravesical therapy used, response to intravesical therapy.

**Supplementary Table 1:** Ovid MEDLINE and EMBASE search strategies

**Ovid Medline ALL (1946 to October 25, 2019)**

|  |
| --- |
| Administration, Intravesical/ |
| Conservative Treatment/ |
| (intravesical or intra-vesical).ti,ab,kw. |
| Conservative adj2 (management or therap\* or treatment\*).ti,ab,kw. |
| "bladder sparing".ti,ab,kw. |
| (BCG or (bacill\* ADJ calmette) or (calmette adj guerin) or epirubicin or thiotepa or "mitomycin C").ti,ab,kw. |
| OR/1-6 |
| Urethral Neoplasms/ |
| Urinary Bladder Neoplasms/ |
| Carcinoma, Transitional Cell / |
| OR/8-10 |
| Carcinoma in Situ/ |
| (urothelial or urethra\*).ti,ab,kw. |
| 12 and 13 |
| ((bladder or urothelial or transitional or urethra\*) ADJ3 (cancer\* or carcinoma\*)).ti,ab,kw. |
| OR/11,14,15 |
| (urothelium or (prostatic ADJ (urethra\* or duct\*))).ti,ab,kw. |
| And/7, 16, 17 |
| exp ANIMALS/ NOT HUMANS.sh. |
| (animal\* or canine or dog or dogs or murine or rabbit\* or rat or rats or mouse or mice or pig or pigs or primate or primates or veterinar\*).ti,ab,kf. |
| OR/19,20 |
| 18 not 21 |

**Ovid Embase (1947 to 2019 October 25)**

|  |
| --- |
| Conservative Treatment/ |
| Epirubicin/ |
| Intravesical drug administration/ |
| Mitomycin C/ |
| Mycobacterium bovis BCG/ |
| Thiotepa/ |
| (intravesical or intra-vesical).ti,ab,kw. |
| Conservative adj2 (management or therap\* or treatment\*).ti,ab,kw. |
| "bladder sparing".ti,ab,kw. |
| (BCG or (bacill\* ADJ calmette) or (calmette adj guerin) or epirubicin or thiotepa or "mitomycin C").ti,ab,kw. |
| OR/1-10 |
| Bladder Cancer/ |
| Bladder Carcinoma/ |
| Non Muscle Invasive Bladder Cancer/ |
| Urethra Cancer/ |
| Urethra Carcinoma/ |
| Urinary Tract Carcinoma/ |
| Transitional Cell Carcinoma/ |
| OR/12-18 |
| Carcinoma in Situ/ |
| (urothelial or urethra\*).ti,ab,kw. |
| 20 and 21 |
| ((bladder or urothelial or transitional or urethra\*) ADJ3 (cancer\* or carcinoma\*)).ti,ab,kw. |
| OR/ 19, 22, 23 |
| Prostate Urethra/ |
| (urothelium or (prostatic ADJ (urethra\* or duct\*))).ti,ab,kw. |
| OR/ 25,26 |
| And/11, 24, 27 |
| (exp ANIMAL/ or exp ANIMAL MODEL/ or exp ANIMAL EXPERIMENT/ or EXPERIMENTAL ANIMAL/ or NONHUMAN/) NOT exp HUMAN/ |
| (animal? or canine or dog or dogs or murine or rabbit\* or rat or rats or mouse or mice or pig or pigs or primate or primates or veterinar\*).ti,ab,kw. |
| OR/29,30 |
| 28 not 31 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 2:** Modified New-Castle Ottawa scale Tool for risk of bias assessment of case reports and case-series. | | | | | | | | | | | | |
| 1. Did the patient(s) represent the whole case(s) of the medical center? | | | | | | | | | | | | |
| 2. Was the diagnosis correctly made? | | | | | |  | |  | | | |  |
| 3. Were other important diagnosis excluded? | | | | | | | |  | | | |  |
| 4. Were all important data cited in the report? | | | | | | | |  | | | |  |
| 5. Was the outcome correctly ascertained? | | | | | | | |  | | | |  |
|  |  |  | |  | |  | |  | | | |  |
| **Supplementary Table 3:** Risk of bias assessment for individual studies | | | | | | | | |  |  |  | |
| Study | | | Question 1 | | Question 2 | | Question 3 | | Question 4 | Question 5 | Risk of bias | |
|  | | | Yes/No | | Yes/No | | Yes/No | | Yes/No | Yes/No |  | |
| Bretton, 1989 | | |  | |  | |  | |  |  |  | |
| Orihuela, 1989 | | |  | |  | |  | |  |  |  | |
| Solsona, 1991 | | |  | |  | |  | |  |  |  | |
| Ovesen, 1993 | | |  | |  | |  | |  |  |  | |
| Palou, 1996 | | |  | |  | |  | |  |  |  | |
| Canda, 2004 | | |  | |  | |  | |  |  |  | |
| Palou Redorta, 2006 | | |  | |  | |  | |  |  |  | |
| Taylor, 2007 | | |  | |  | |  | |  |  |  | |
| Gofrit, 2008 | | |  | |  | |  | |  |  |  | |
| Total: 9 studies | | |  | |  | |  | |  |  |  | |
|  | | | Low | |  | |  | |  |  |  | |
|  | | | Intermediate | | | |  | |  |  |  | |
|  | | | High | |  | |  | |  |  |  | |
|  | | |  | |  | |  | |  |  |  | |
|  | | | Yes | |  | |  | |  |  |  | |
|  | | | No | |  | |  | |  |  |  | |

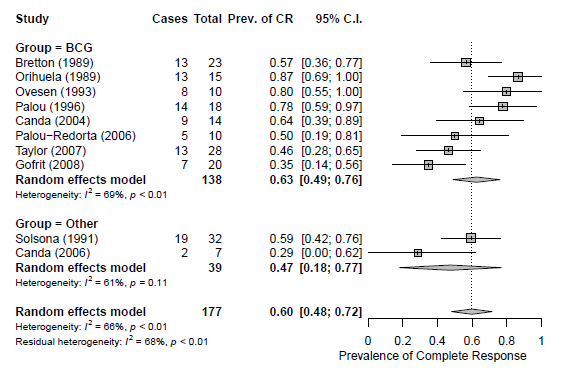
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| --- | --- | --- | --- |
| **Supplementary Table 4**: BCG strain and schedule | |  |  |
| **Study** | **BCG strain** | **Maintenance** | **No. induction courses used (6 wk)** |
| **Author, year** | **(Y=yes; N=no)** |
| Bretton, 1989 | Pasteur | N | 1 |
| Orihuela, 1989 | Pasteur | N | 1 |
| Ovesen, 1993 | Danish | N | 1 or 2a |
| Palou, 1996 | Connaught | Nb | 1 |
| Canda, 2004 | Connaught or Tice | N | 1 or 2c |
| Palou Redorta, 2006 | Connaught | N | 1 to 5d |
| Taylor, 2007 | Not specified | Y | 1 or 2e |
| Gofrit, 2008 | Connaught | Y | 1 or 2f |
|  |  |  |  |
| a Patients with persistent CIS in mucosal bladder or high grade cytology without disease progression received a second course of BCG using 6 instillations every second week | | | |
| b Unclear if patients in PUC group received maintenance | | |  |
| c 5 patients in CR group needed one course of BCG and 2 patients needed two courses of BCG. | | | |
| d One patient received 2 courses of induction BCG (CR in prostate but not in bladder); 1 patient received 2 courses of BCG for CR; 2 patients received 5 courses and 2 patients received 2 courses | | | |
| e Induction only x 6 weeks before 1995; maintenance was given 1995-1999; patients underwent a second course of BCG if they did not completely respond to initial treatment (did not specify how many needed a second course). | | | |
| f If there was disease persistence a second course of BCG was given. Starting March 1995 maintenance was also given (12 patients received maintenance) | | | |

|  |  |
| --- | --- |
| **Supplementary Table 5**: Response to therapy definitions | |
| **Study** | **Definition of response** |
| **Author, year** |
| Bretton, 1989 | Progression defined by development of muscle infiltration, metastases or occurrence of disease refractory to TUR and BCG that requires a change in therapy |
| Orihuela, 1989 | Progression was defined if change in therapy other than TUR was required, if cystectomy was required, if MIBC developed in bladder or prostate or if metastases occurred |
| Ovesen, 1993 | Patients with persistent CIS after second course of BCG were advised to undergo radical cystectomy (no response). Complete response was defined as normal selected site mucosal biopsies and normal urinary cytology. |
| Palou, 1996 | Did not specify |
| Canda, 2004 | Post treatment biopsies without evidence of tumor and a negative urine cytology. Treatment failure was considered need for change in therapy after initial course of treatment due to tumor persistence or recurrence. |
| Palou Redorta, 2006 | Response was considered complete when bladder biopsies and loop resection biopsies of the PU were normal, when cystoscopy was normal and cytology was negative. Tumor progression was defined as stromal infiltration or metastatic disease. |
| Taylor, 2007 | Complete response was defined as no histologic evidence of tumor recurrence and negative urine cytology |
| Gofrit, 2008 | Did not specify |

|  |  |  |
| --- | --- | --- |
| **Suppl. Table 6**: Survival outcomes | | |
| **Study** | **Follow-up** | **DFS** | **PFS** | **RFS** | **DSS** | **OS** |
| **Author, year** | **(Months)** | **(months)** | **(Months)** |  |  |  |
| Bretton, 1989 | 51.6 | NR | 56 | NR | NR | Median OS not reached at follow-up of 105 mos |
| Canda, 2004 | 63 | 40 (BCG); 26 (epirubicin) | 59 (BCG); 62 (epirubicin) | NR | NR | 69 mos (BCG); 56 mos (epirubicin) |
| Taylor, 2007 | 90 | NR | NR | 5-year: 90%; 10-year: 66% | 89% at 90 mo. follow-up | 5-year: 74%; 10 year: 45% |
| Gofrit, 2008 | 52.5 | NR | NR | 5-year : 30% (bladder+prostate); 90% (prostate) | NR | NR |
| \*NR not reported | | | | | | |

|  |  |  |  |
| --- | --- | --- | --- |
| **Suppl. Table 7**: Outcomes of treatment failures across studies | | | |
| Study | Therapy | No. patients | No. requiring cystectomy (%) | No. developing metastatic disease (%) | Other |
| Bretton, 1989 | BCG | 23 | 7 (30) | 1 (4) | 1 partial cystectomy; 1 definitive dose EBRT |
| Orihuela, 1989 | BCG | 15 | 1 (7) | 0 | 1 recurrence in PU treated with TURP |
| Ovesen, 1993 | BCG | 10 | NR | NR | 1 recurrence of CIS in prostatic urethra; 1 invasive urethral tumor |
| Palou, 1996 | BCG | 18 | 3 (17) | 0 | 1 palliative TUR for PU progression |
| Palou Redorta, 2006 | BCG | 10 | 2 (20) | 1 (10) | 1 persistent TaG1 bladder tumor treated with TURBT; 1 progression to T1 treated with TURBT |
| Taylor, 2007 | BCG | 28 | 8 (29) | 0 | 2 inoperable; 1 died with disease from other causes; 1 recurred in upper tract treated with endoscopy; 1 recurred in upper tract and was treated with NU |
| Gofrit, 2008 | BCG | 20 | 5 (25) | NR | 1 MIBC treated with chemo/RT; 6 dead – 3 from upper tract UC, 2 from BC and 1 from unrelated cause. Did not describe treatment of 7 patients that recurred with NMIBC |
| Canda, 2004 | BCG | 14 | 2 (14) | 4 (29) | - |
| Solsona, 1991 | MMC/AMC | 32 | 8 (25) | 2 (6) | 1 radical RT; 2 inoperable due to comorbidity treated with palliative chemotherapy |
| Canda, 2006 | Epirubicin | 7 | 0 | 1 (14) | 2 patients were re-treated with BCG for NMIBC and had CR; two patients developed NMIBC and were treated with TUR of tumor for CR |

**Supplementary Figure 1**: Global complete response of patients treated with BCG vs other intravesical therapy



|  |  |
| --- | --- |
| **Supplementary Table 8**: Prostate and bladder tumor histology | |
| **Study** | **Bladder Tumor Histology** | **Prostate Tumor Histology** |
| **Author, year** |
| Bretton, 1989 | CIS alone n=16; CIS+Ta n=5; T1+CIS n=2 | CIS |
| Orihuela, 1989 | Papillary (not specified) n=3; CIS only n=3; CIS + papillary n=9 | Papillary not specified n=5; CIS n=10 |
| Solsona, 1991 | Ta n=7; T1G2 n=26; T1G3 n=3; 21 had concomitant CIS | CIS n=10; papillary n=22 |
| Ovesen, 1993 | All CIS | CIS |
| Palou, 1996 | T1G3 n=12; TaG2 n=3; CIS n=3 | CIS |
| Canda, 2004 | BCG group (n=12): T1 n=6; T1+CIS n=1; TaG1 n=1; TaG3 n=1; TaG2 n=3. Epirubicin group (n=7): T1 n=4; TaG2 n=2; TaG1 n=1 | BCG group (n=12): CIS n=2; TaG1 n=2; TaG2 n=3; T1G2 n=1; T1G3 n=2; T1G3+CIS n=2. Epirubicin group (n=7): TaG1 n=4; T1G2 n=2; T1G3 n=1 |
| Palou Redorta, 2006 | CIS n=2; T(any)G2+CIS n=1; TaG3 n=1; T1G3+CIS n=3; T1G1 n=1; T1G3 n=2; unknown n=1 | CIS |
| Taylor, 2007 | Not reported | Did not specify |
| Gofrit, 2008 | Ta n=12, T1 n=8; 14 of these had CIS (not specified); all patients with prostatic CIS also had CIS bladder; 95% of tumors were G2-3; 5% were G1 | CIS n=12; papillary (grade 2 n=6; grade 1 n=1; grade 3 n=1) |

**Supplementary Figure 2:** Global complete response stratified by papillary vs CIS tumors

