

Oncological Outcome of Primary and Secondary Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-analysis

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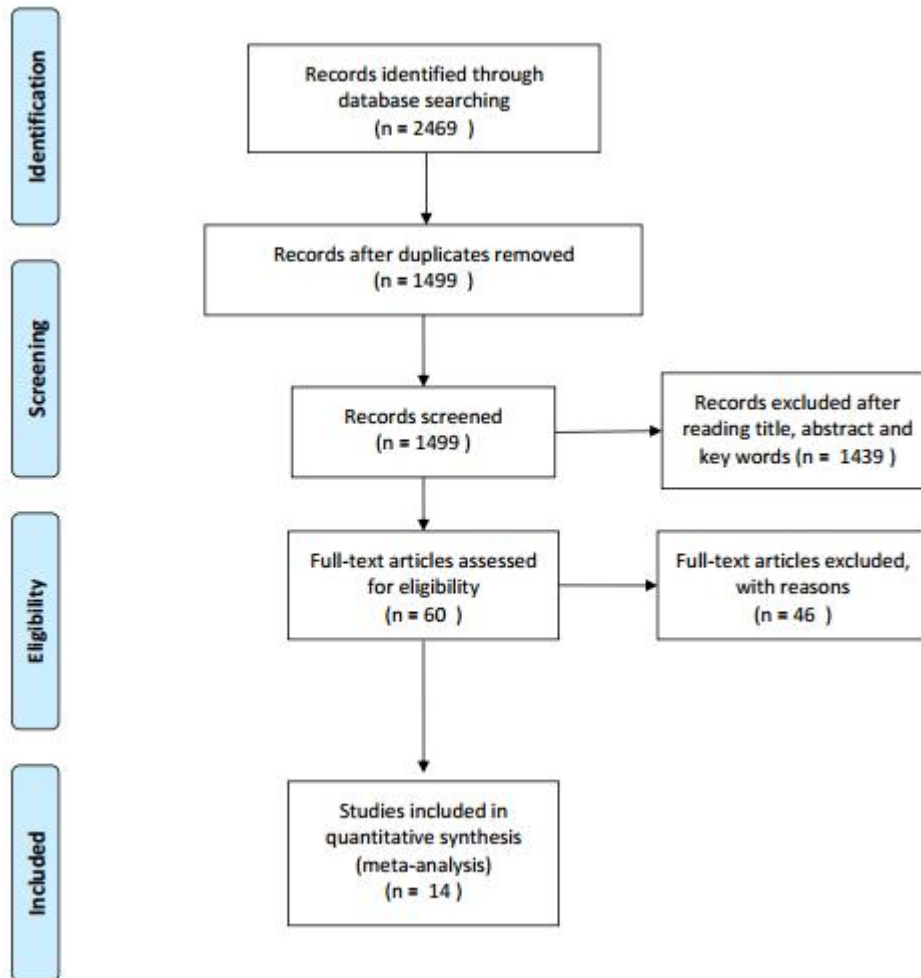


Figure S1 Flow chart of the literature search used in this meta-analysis. Of those studies, two studies (reference 6 and 15 in main text) were from a same medical center, in which data was not duplicate, and these studies were all include for pooled analysis

More information of full-text articles excluded

Abbreviation: MIBC, muscle-invasive bladder cancer; CSS, Cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

No.	Author	Year	Main results	Reason for not including in pooled analysis
1	Brant ¹	2017	Among non-neoadjuvant chemotherapy patients, secondary MIBC was significantly less prevalent in patients who achieved pathologic response compared with those who did not respond (3.6% vs. 25.2%, P<0.01).	Inadequate information. CSS was not available.
2	Zakaria ²	2016	Presumed secondary MIBC had a slightly better prognosis, regarding OS.	Histopathologic or staging clinical information was lacking and primary and secondary MIBC were indirectly presumed. CSS was not available.
3	Pietzak ³	2016	-	Abstract
4	Brant ⁴	2016	-	Abstract
5	Moschini ⁵	2016	-	Abstract
6	Mallen ⁶	2015	-	Inadequate information. CSS was not available.
7	Pietzak ⁷	2015	-	Abstract
8	Pietzak ⁸	2015	Secondary MIBC was associated with upstaging and had a worse OS.	Inadequate information. CSS was not available.
9	Parra-Lopez ⁹	2014	-	Abstract
10	Pellucchi ¹⁰	2014	-	Abstract
11	Alexandra ¹¹	2013	-	Abstract

12	Koga ¹²	2013	-	Irrelevant topic
13	Husillos-Alonso ¹³	2013	Secondary MIBC had a similar tumor progression rate compared to primary MIBC (24.1% v.s. 23.5%).	Inadequate information.
14	Ma ¹⁴	2013	MIBC with prior history of urothelial carcinoma was associated with both CSS (HR 3.235, CI 1.211-8.644, P=0.019) and RFS (HR 2.713, CI 1.231-5.978, P=0.013) and weakly associated with OS (P=0.064).	MIBC with prior history of urothelial carcinoma was not exactly equal to secondary MIBC. If this study was included in pooled analysis, the conclusion drawn in the study would be further confirmed.
15	Ciudin ¹⁵	2012	-	Abstract
16	Ciudin ¹⁶	2012	-	Abstract
17	Ciudin ¹⁷	2012	-	Abstract
18	Ciudin ¹⁸	2011	-	Abstract
19	Ploeg ¹⁹	2011	-	Inadequate information.
20	Villavicencio ²⁰	2010	-	Less than 10 patients in secondary MIBC group and/or primary MIBC.
21	Brookman-Amissah ²¹	2009	-	Abstract
22	Guzzo ²²	2009	-	Abstract
23	Huguet ²³	2008	-	Irrelevant topic

24	Ferreira ²⁴	2007	Secondary MIBC had similar prognosis compared to primary MIBC (5 years survival: 57.9% v.s. 52.2%).	Data is inconsistency. According to the study, patients between 1993 and 2005 were included and manuscript was accepted for publication on October 11, 2006. Theoretically, the maximum follow-up time should be less than 166 months. However, figure 1 suggests that the maximum follow-up time is more than 180 months. If this study was included in pooled analysis, no significant changes would be observed.
25	May ²⁵	2007	-	Duplicate publication
26	McLaughlin ²⁶	2007	-	Irrelevant topic
27	Louie-Johnsun ²⁷	2007	-	Irrelevant topic
28	Kassouf ²⁸	2006	-	Less than 10 patients in secondary MIBC group and/or primary MIBC.
29	Jeon ²⁹	2005	-	Less than 10 patients in secondary MIBC group and/or primary MIBC.
30	May ³⁰	2004	-	Duplicate publication
31	Hornak ³¹	2004	Secondary MIBC had worse prognosis compared to primary MIBC (3 years survival: 15.4% v.s. 23%).	Full article is not available. The study is in Slovak. We requested for full-text through ResearchGate, but no reply was received.
32	Knap ³²	2003	Patients with primary invasive in lamina propria (T1) progressing to MIBC and with primary non-invasive (Ta, CIS) progressing to MIBC had a significantly poorer outcome compared to primary MIBC.	Inadequate information. The prognosis of the overall secondary MIBC was not clear.

33	Hornak ³³	2003	-	Duplicate publication
34	Larsson ³⁴	2003	-	Inadequate information.
35	Yeo ³⁵	2002	Primary MIBC had higher tumor grade and lower five-year survival rate compared to secondary MIBC ($P < 0.05$).	Data is inconsistency. According to the patients&methods part, the follow-up time was ranging from 36 to 98 months. However, figure 1 suggests that the minimum follow-up is less than 24 months. If this study was included in pooled analysis, no significant changes would be observed.
36	Vaidya ³⁶	2001	-	Inadequate information.
37	Huguet-Perez ³⁷	2001	-	Less than 10 patients in secondary MIBC group and/or primary MIBC.
38	Bassi ³⁸	1999	-	Inadequate information.
39	Irani ³⁹	1997	-	Inadequate information.
40	Fossa ⁴⁰	1992	-	Inadequate information.
41	Stockle ⁴¹	1988	-	Inadequate information.
42	Malmstrom ⁴²	1987	-	Inadequate information.
43	Droller ⁴³	1983	-	Less than 10 patients in secondary MIBC group and/or primary MIBC.
44	Hopkins ⁴⁴	1983	-	Less than 10 patients in secondary MIBC group and/or primary MIBC.
45	Kaye ⁴⁵	1982	-	Inadequate information.
46	Boileau ⁴⁶	1980	-	Inadequate information.

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	No. of studies	Pooled HR (95% CI)	Chi ² (P value)	I ²
Total	13	1.29(1.07-1.56)	23.64(0.02)	49.2%
Publication year				
2002-2011	7	1.33(0.91-1.94)	15.41(0.02)	61.1%
2012-2016	6	1.26(1.03-1.53)	7.66(0.18)	34.7%
Region				
Europe	8	1.29(0.96-1.73)	15.91(0.03)	56.0%
Others	5	1.31(1.01-1.70)	7.55(0.11)	47.0%
No. of patients				
<200	8	1.34(0.99-1.81)	12.02(0.10)	41.8%
≥200	5	1.25(0.97-1.62)	11.24(0.02)	64.4%
Quality score				
<6	7	1.50(1.17-1.94)	10.52(0.10)	43.0%
≥6	5	1.05(0.82-1.34)	6.11(0.19)	34.5%
HR estimation				
Univariate	7	1.17(0.95-1.43)	7.93(0.24)	24.4%
Multivariate	6	1.47(1.07-2.03)	12.40(0.03)	59.7%

HR: hazard ratio, CI: confidence interval

Table S1 Subgroup analysis for cancer-specific survival in model I.

	No. of studies	Pooled HR (95% CI)	Chi ² (<i>P</i> value)	<i>I</i> ²
Total	13	1.19(0.90-1.56)	48.77(<0.001)	75.4%
Publication year				
2002-2011	7	1.33(0.91-1.94)	15.41(0.02)	61.1%
2012-2016	6	1.07(0.74-1.56)	26.87(<0.001)	81.4%
Region				
Europe	8	1.29(0.96-1.73)	15.91(0.03)	56.0%
Others	5	1.07(0.65-1.76)	27.04(<0.001)	85.2%
No. of patients				
<200	8	1.34(0.99-1.81)	12.02(0.10)	41.8%
≥200	5	1.05(0.68-1.61)	30.95(<0.001)	87.1%
Quality score				
<6	7	1.31(0.79-2.17)	39.87(<0.001)	85.0%
≥6	5	1.05(0.82-1.34)	6.11(0.19)	34.5%
HR estimation				
Univariate	6	1.11(0.85-1.44)	6.73(0.24)	25.7%
Multivariate	7	1.29(0.83-1.99)	42.03(<0.001)	85.7%

HR: hazard ratio, CI: confidence interval

Table S2 Subgroup analysis for cancer-specific survival in model II.

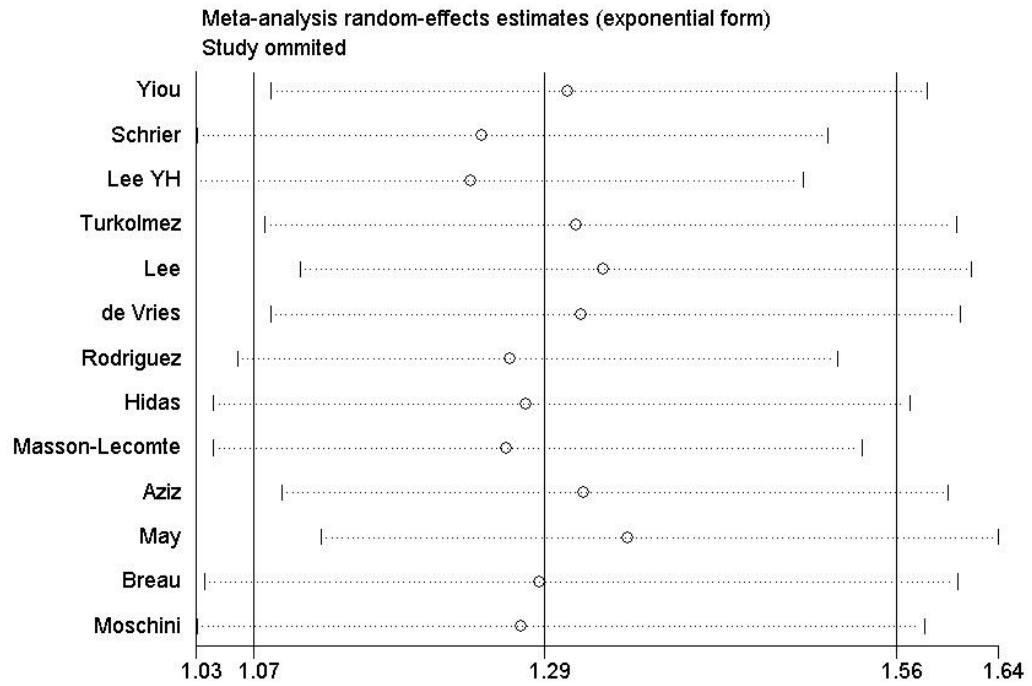


Figure S2 Sensitivity Analyses by omitting a single study each time in model I.

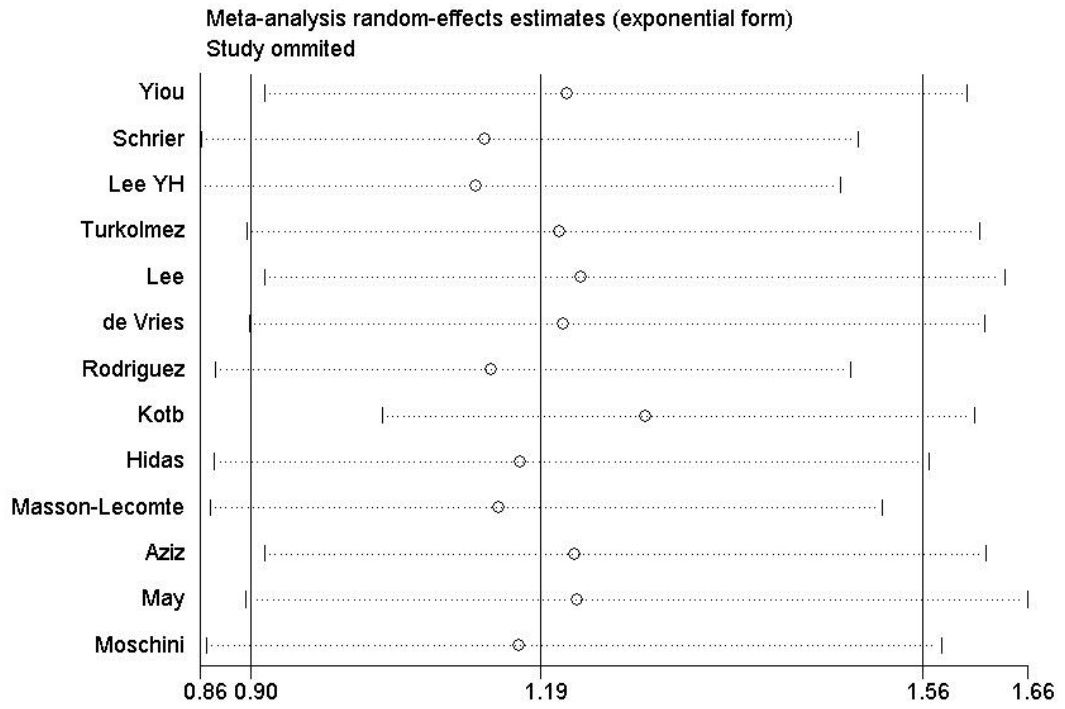


Figure S3 Sensitivity Analyses by omitting a single study each time in model II.

Search strategy

Database: Embase <1974 to 2017 January 03>(on OVID)

- 1.exp bladder tumor/ (74306)
2. (bladder\$ adj3 (cancer\$ or carcinoma\$ or neoplas\$ or tumor\$r\$)).mp. (81689)
3. exp transitional cell carcinoma/ (22286)
4. (tcc or transitional cell).mp. (28444)
5. or/1-4 (93989)
- 6.((progress\$ or secondary or primar\$ or initia\$ or previous or prior) adj3 (muscle adj3 invas\$)).ti,ab,ot. (747)
7. ((progress\$ or secondary or primar\$ or initia\$ or previous or prior) adj3 (invas\$ adj3 (cancer\$ or carcinoma\$ or neoplas\$ or tumor\$r\$ or malignan\$ or disease\$ or muscle))).ti,ab,ot. (7778)
8. ((progress\$ or secondary or primar\$ or initia\$) adj3 (MIBC or MIT)).ti,ab,ot. (1012)
9. (muscle adj3 invas\$ adj6 (progress\$ or secondary or primar\$ or initia\$ or previous or prior)).ti,ab,ot. (1122)
10. (invas\$ adj3 (cancer\$ or carcinoma\$ or neoplas\$ or tumor\$r\$ or malignan\$ or disease\$ or muscle) adj6 (progress\$ or secondary or primar\$ or initia\$ or previous or prior)).ti,ab,ot. (11405)
11. ((MIBC or MIT) adj6 (progress\$ or secondary or primar\$ or initia\$)).ti,ab,ot. (1479)
12. secondary muscle-invasive bladder cancer.ti,ab,ot. (6)
13. primary muscle-invasive bladder cancer.ti,ab,ot. (6)
14. or/6-13 (13827)
15. exp cystectomy/ (22339)
16. (rc or cystectom\$).mp. (47546)
17. or/15-16 (47546)
18. cancer prognosis/ (66439)
19. exp Survival/ (933156)
20. Treatment Outcome/ (744598)
21. (surival\$ or prognos\$ or outcome\$).ti,ab. (2253231)
22. (os or dfs or css or dss).ti,ab. (129744)
23. or/18-22 (3252047)
24. 5 and 14 and 17 and 23 (522)

Database: MEDLINE(on OVID)

- 1.exp urinary bladder neoplasms/
- 2.((bladder\$ or urotheli\$) adj3 (cancer\$ or carcinoma\$ or neoplas\$ or tumor\$r\$ or malignan\$)).mp.
- 3.exp carcinoma, transitional cell/
- 4.bladder neoplasms/
- 5.(tcc or transitional cell).mp.
- 6.or/1-5

- 7.((progress\$ or secondary or primar\$ or initia\$ or previous or prior) adj3 (muscle adj3 invas\$)).ti,ab,ot
- 8.((progress\$ or secondary or primar\$ or initia\$ or previous or prior) adj3 (invas\$ adj3 (cancer\$ or carcinoma\$ or neoplas\$ or tumo?r\$ or malignan\$ or disease\$ or muscle))).ti,ab,ot
- 9.((progress\$ or secondary or primar\$ or initia\$) adj3 (MIBC or MIT)).ti,ab,ot
- 10.((muscle adj3 invas\$) adj6 (progress\$ or secondary or primar\$ or initia\$ or previous or prior)).ti,ab,ot
- 11.((invas\$ adj3 (cancer\$ or carcinoma\$ or neoplas\$ or tumo?r\$ or malignan\$ or disease\$ or muscle)) adj6 (progress\$ or secondary or primar\$ or initia\$ or previous or prior)).ti,ab,ot
- 12.((MIBC or MIT) adj6 (progress\$ or secondary or primar\$ or initia\$)).ti,ab,ot
- 13.(secondary muscle-invasive bladder cancer).ti,ab,ot
- 14.(primary muscle-invasive bladder cancer).ti,ab,ot
- 15.or/7-14
- 16.exp cystectomy/
- 17.(rc or cystectom\$).mp.
- 18.or/16-17
- 19.exp prognosis
- 20.exp Survival Analysis
- 21.Disease-Free Survival/
- 22.Survival Rate/
- 23.Treatment Outcome/
- 24.(surival\$ or prognos\$ or outcome\$).ti,ab.
- 25.(os or dfs or css or dss).ti,ab.
- 26.or/19-25
- 27.6 and 15 and 18 and 26

Database: SCOPUS

((TITLE-ABS-KEY(bladder W/3 tumo?r*) OR TITLE-ABS-KEY(bladder* W/3 cancer*) OR TITLE-ABS-KEY(bladder* W/3 carcinoma*) OR TITLE-ABS-KEY(bladder* W/3 neoplasm*)) OR (TITLE-ABS-KEY(urothelial* W/3 tumo?r*) OR TITLE-ABS-KEY(urothelial* W/3 cancer*) OR TITLE-ABS-KEY(urothelial* W/3 carcinoma*) OR TITLE-ABS-KEY(urothelial* W/3 neoplasm*))) AND (TITLE-ABS-KEY(progres* W/4 invas*) OR TITLE-ABS-KEY(secondary W/4 invas*) OR TITLE-ABS-KEY(previous W/4 invas*) OR TITLE-ABS-KEY(prior W/4 invas*) OR TITLE-ABS-KEY(primary W/4 invas*) OR TITLE-ABS-KEY(initia* W/4 invas*) OR TITLE-ABS-KEY(progres* W/4 muscle) OR TITLE-ABS-KEY(secondary W/4 muscle) OR TITLE-ABS-KEY(previous W/4 muscle) OR TITLE-ABS-KEY(prior W/4 muscle) OR TITLE-ABS-KEY(primary W/4 muscle) OR TITLE-ABS-KEY(initia* W/4 muscle) OR TITLE-ABS-KEY(progres* W/4 MIBC) OR TITLE-ABS-KEY(secondary W/4 MIBC) OR TITLE-ABS-KEY(previous W/4 MIBC) OR TITLE-ABS-KEY(prior W/4 MIBC) OR TITLE-ABS-KEY(primary W/4 MIBC) OR TITLE-ABS-KEY(initia* W/4 MIBC) OR TITLE-ABS-KEY(progres* W/4 MIT) OR TITLE-ABS-KEY(secondary W/4 MIT) OR TITLE-ABS-KEY(previous W/4 MIT) OR TITLE-ABS-KEY(prior W/4 MIT) OR TITLE-ABS-KEY(primary W/4 MIT) OR TITLE-ABS-KEY(initia* W/4 MIT)) AND

(TITLE-ABS-KEY(cystectomy) OR TITLE-ABS-KEY(RC))

Database: Cochrane Library

Cochrane Library

1. MeSH descriptor Urinary Bladder Neoplasms explode all trees
2. (bladder* NEAR/3 (cancer* or carcinoma* or neoplas* or tumo?r*)):ti,ab,kw
3. MeSH descriptor Carcinoma, Transitional Cell explode all trees
4. (tcc or transitional cell):ti,ab,kw
5. #1 OR #2 OR #3 OR #4
6. (progress* or secondary or previous or prior):ti,ab,kw
7. (primar* or initia*):ti,ab,kw
8. (muscle NEAR/4 invas*):ti,ab,kw
9. (invas* NEAR/4 (disease* or transitional cell or muscle or tumo?r*)):ti,ab,kw
10. #8 OR #9
11. #6 AND #7 AND #10
12. (cystectomy or rc):ti,ab,kw
13. MeSH descriptor Cystectomy explode all trees
14. #12 OR #13
15. #5 AND #11 AND #14