Appendix

Table s1) Actual Search Strategies

OVID

Database(s): **Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily, EBM Reviews - Cochrane Central Register of Controlled Trials** January 2020**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to February 27, 2020**, Embase** 1974 to 2020 February 28
Search Strategy:

#	Searches
1	(muscle* adj1 invasive*).mp.
2	Neoplasm Invasiveness/ and Muscle Neoplasms/
3	Carcinoma, Transitional Cell/ and Muscle Neoplasms/
4	1 or 2 or 3
5	Urinary Bladder Neoplasms/
6	(bladder adj3 (cancer* or neoplasms*)).mp.
7	5 or 6
8	4 and 7
9	MIBC.mp.
10	"muscle invasive bladder cancer"/
11	8 or 9 or 10
12	(methotrexat* and vinblastin* and doxorubicin* and gemcitabin* and cisplat*).mp.
13	(GC or MVAC).mp.

14	Methotrexate/
15	Vinblastine/
16	Doxorubicin/
17	Cisplatin/
18	gemcitabine/
19	14 and 15 and 16 and 17 and 18
20	12 or 13 or 19
21	11 and 20
22	21 not ((exp animals/ or exp nonhuman/) not exp humans/)
23	limit 22 to english language [Limit not valid in CDSR; records were retained]
24	limit 22 to no language specified [Limit not valid in CDSR; records were retained]
25	23 or 24
26	remove duplicates from 25

SCOPUS

1	(muscle* w/1 invasive*)
2	(bladder w/3 (cancer* or neoplasms*))
3	1 and 2
4	MIBC
5	3 or 4
6	(methotrexat* and vinblastin* and doxorubicin* and gemcitabin* and cisplat*)
7	(GC or MVAC)
8	6 or 7
9	5 and 8
10	INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)

11	9 not 10
12	DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
13	11 not 12
14	LANGUAGE(english)
15	13 and 14

Table s2) Baseline characteristics of included studies

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
Conference abstracts					
Matulay, 2019 (USA)	Consecutive high-risk, clinically node negative muscle invasive bladder cancer patients who underwent radical cystectomy	NR	501	2005-2017	60
Wright, 2013 (USA)	Patients with T2-T4 urothelial carcinoma of the bladder who underwent radical cystectomy	NR	78	2003-2011	NR
Yokomizo, 2013 (Japan)	Patients diagnosed as muscle invasive bladder tumor, T2- T4aN0M0 and underwent neoadjuvant GC or MVAC	NR	101	2005-2012	NR

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
	chemotherapy followed by radical cystectomy				
Lee, 2019 (South Korea)	Patients with urothelial carcinoma (cT2-4aN0-1M0) who received neoadjuvant chemotherapy from January 2011 to December 2017 in Asan Medical Center	NR	277	2011-2017	NR
Miron, 2019 (USA)	patients with stage T2-4N0-1 muscle invasive bladder cancer treated with neoadjuvant chemotherapy with a plan for a curative cystectomy	NR	58	NR	56
Mitra, 2011 (USA)	Patients who received neoadjuvant chemotherapy with HD-MVAC or GC	NR	38	2008-2010	NR

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
	followed by radical cystectomy for at least T2 bladder cancer				
Culine, 2020 (France)	Pure or mixed urothelial bladder cancer with >T2N0M0	Neuroendocrine tumors	500	2013-2018	NR
Peer reviewed journal articles					
Fukui, 2016 (Japan)	Patients with muscle invasive bladder cancer treated with neoadjuvant chemotherapy followed by radical cystectomy.	Patients who did not undergo radical cystectomy due to metastatic progression during neoadjuvant chemotherapy or impaired performance status caused by severe infection and weight loss after neoadjuvant chemotherapy	59	2005-2014	126

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
Yeshchina, 2012 (USA)	Patients treated with platinum-based systemic chemo-therapy for clinical stage T2-T4aN0-N2M0 bladder cancer	Patients receiving induction or salvage systemic chemotherapy, patients receiving non-cisplatin (carboplatin)-based chemotherapy	114	1988-2010	28.4(33.9)
Van De Putte, 2015 (Netherlands)	Consecutive patients with cT3-4a and/or regional (N+) and/or paraaortal/paracaval node-positive (M+) urothelial carcinoma of the bladder	Patients with visceral metastases or lymph node metastases above the diaphragm or patients with ≤cT2 muscle invasive bladder cancer without lymphovascular invasion	166	1990-2001	NR
Alva, 2011 (USA)	Consecutive patients who underwent radical cystectomy for high-risk bladder cancer, who had muscle invasive bladder cancer or clinical evidence of extravesical	Patients who had pure nonurothelial histology, who had a history of upper urinary tract cancer, who withheld consent, or who were lost to follow up	152	1990-2007	43.2

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
	tumor without metastatic disease, and received neoadjuvant chemotherapy without subsequent adjuvant chemotherapy				
Zargar, 2015 (International)	Patients who had resectable muscle-invasive bladder cancer (cT2–4aN0M0) and received at least three cycles of neoadjuvant chemotherapy prior to radical cystectomy	Patients with all other variant histology (other than pure Urothelial carcinoma or mixed histology with squamous and/or glandular differentiation) and cT4b disease	935	2000-2013	11(17.8)
Zargar, 2018 (International)	Patients with urothelial cancer cT3-4aN0M0 who received neoadjuvant chemotherapy and underwent cystectomy	NR	319	2000-2013	GC: 14.4 (6-34.8) dd-MVAC: 21.6 (6-49.2)

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
Nguyen, 2018 (France)	Patients who had indication of radical cystectomy (cT2-4aNxM0 or high risk T1) and received at least two cycles of neoadjuvant chemotherapy followed by radical cystectomy	Patients with any other histological type than pure urothelial carcinoma or mixed histology with squamous and/or glandular differentiation	40	2011-2015	21.5 Median
Okabe, 2018 (Hapan)	Muscle invasive bladder cancer patients who received neoadjuvant chemotherapy -GC therapy followed by radical cystectomy	Patients with node positive disease and distant metastases	132	2009-2015	NR
Fairey, 2013 (USA)	Patients with clinical stage T2-T4N0M0 urothelial cancer of the bladder treated with GC or M-VAC neoadjuvant chemotherapy	Patients who did not receive neoadjuvant chemotherapy, received non-GC or non-M-VAC neoadjuvant chemotherapy, had	116	1985-2011	96

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
		variant histology (non-urothelial) bladder cancer, or had clinical stage			
Kaneko, 2011 (Japan)	Patients who received a GC regimen as neoadjuvant chemotherapy for muscle-invasive bladder cancer who were diagnosed by transurethral resection of a bladder tumor	NR	22	2007-2011	NR
Lee, 2013 (USA)	Patients who had clinical organ confined T2-T4N0 urothelial bladder cancer and were treated with neoadjuvant chemotherapy	Patients with micropapillary or small cell/neuroendocrine tumors or undergoing salvage cystectomy following chemotherapy and radiation	87	2003-NR	NR

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
Pal, 2012 (USA)	Patients with muscle invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy	NR	61	1995-2010	28.7 (median)
Dash, 2008 (USA)	Patients with muscle invasive bladder cancer who received neoadjuvant chemotherapy with either MVAC or GC before undergoing radical cystectomy	Patients with clinical indication of metastatic disease, e.g., any adenopathy >2cm on pretreatment imaging, or patients who had non-transitional cell carcinoma	96	2000-2006	GC: 24 median MVAC: 48.1 median
Galsky, 2015 (International)	Patients with a diagnosis of cT2 through cT4aN0M0 urothelial cancer of the bladder	Patients who had not received any neoadjuvant chemotherapy or patients who had received treatment with regimens other than GC or MVAC	212	2005-2012	duration of follow-up was not unified not consistent across centers

Author last name, year (country)	Inclusion criteria	Exclusion criteria	Total No. of patients	Study period	Longest follow up (months)
Weight, 2009 (USA)	Consecutive patients with localized urothelial carcinoma of the bladder who underwent radical cystectomy	Patients who underwent a laparoscopic radical cystectomy, had non-muscle-invasive bladder cancer, underwent salvage radical cystectomy after chemoradiation, or participated in a phase 2 neoadjuvant protocol	117	2006-2007	NR
Kawamura, 2013 (Japan)	Patients who received neoadjuvant MVAC or GC and radical cystectomy for the management of muscle-invasive clinical stage T2-T4, N and, M0 bladder cancer	NR	58	NR	35.76(83.16)
Shindo, 2012 (Japan)	Patients who received MVAC or GC as presurgical or neoadjuvant chemotherapy followed by radical surgery	NR	27	2007-2011	NR

Table s3) Risk of bias assessment

Author last name, year (country)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Other (funding, conflict of interest)
Randomized controlled trial						
Culine, 2020 (France)	**Some concerns**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Author last name, year (country)	**Selection**		**Comparability**		**Outcome**	
Observational cohort studies						
Alva, 2011 (USA)	Low risk		Low risk		Some concerns	
Dash, 2008 (USA)	Low risk		Low risk		Some concerns	
Fairey, 2013 (USA)	Low risk		High risk		Some concerns	

Author last name, year (country)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Other (funding, conflict of interest)
Randomized controlled trial						
Culine, 2020 (France)	**Some concerns**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Author last name, year (country)	**Selection**		**Comparability**		**Outcome**	
Observational cohort studies						
Fukui, 2016 (Japan)	Low risk		Low risk		High risk	
Galsky, 2015 (International)	Low risk		Low risk		High risk	
Kaneko, 2011 (Japan)	Low risk		Some concerns		High risk	

Author last name, year (country)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Other (funding, conflict of interest)
Randomized controlled trial						
Culine, 2020 (France)	**Some concerns**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Author last name, year (country)	**Selection**		**Comparability**		**Outcome**	
Observational cohort studies						
Kawamura, 2013 (Japan)	Low risk		Low risk		Some concerns	
Lee, 2013 (USA)	Low risk		Some concerns		Some concerns	
Nguyen, 2018 (France)	Low risk		Low risk		Some concerns	

Author last name, year (country)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Other (funding, conflict of interest)
Randomized controlled trial						
Culine, 2020 (France)	**Some concerns**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**

Author last name, year (country)	Selection	Comparability	Outcome
Observational cohort studies			
Okabe, 2018 (Hapan)	Low risk	Low risk	High risk
Pal, 2012 (USA)	Low risk	Low risk	High risk
Shindo, 2012 (Japan)	Low risk	Low risk	Some concerns

Author last name, year (country)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Other (funding, conflict of interest)
Randomized controlled trial						
Culine, 2020 (France)	**Some concerns**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Author last name, year (country)	**Selection**		**Comparability**		**Outcome**	
Observational cohort studies						
Van De Putte, 2015 (Netherlands)	Low risk		High risk		Some concerns	
Weight, 2009 (USA)	Low risk		High risk		Some concerns	
Yeshchina, 2012 (USA)	Low risk		Low risk		Some concerns	

Author last name, year (country)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Other (funding, conflict of interest)
Randomized controlled trial						
Culine, 2020 (France)	**Some concerns**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Author last name, year (country)	**Selection**		**Comparability**		**Outcome**	
Observational cohort studies						
Zargar, 2015 (International)	Low risk		Low risk		Some concerns	
Zargar, 2018 (International)	Low risk		Low risk		Low risk	

Table s4) Summery of Findings Table: GC vs MVAC for MIBC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: 1 years)												
3 [1,2,3]	observational studies	serious [a,b]	not serious	not serious	very serious [c,d]	none	31/140 (22.1%)	39/154 (25.3%)	**OR 0.84** (0.43 to 1.67)	**32 fewer per 1,000** (from 126 fewer to 108 more)	⨁◯◯◯ VERY LOW	
All-cause mortality (follow up: 2 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
3 [1,2,3]	observational studies	serious [a,b]	not serious	not serious	very serious [c,d]	none	51/140 (36.4%)	62/154 (40.3%)	**OR 0.8** (0.5 to 1.3)	**52 fewer per 1,000** (from 151 fewer to 64 more)	⨁◯◯◯ VERY LOW	

All-cause mortality (follow up: longest)

6 [1,2,3,4,5,6]	observational studies	not serious	serious [e]	not serious	serious [d]	none	128/320 (40.0%)	128/276 (46.4%)	**OR 0.68** (0.35 to 1.32)	**93 fewer per 1,000** (from 231 fewer to 69 more)	⨁◯◯◯ VERY LOW	

Overall survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
5 [2,6,7,8,9]	observational studies	serious [a,b]	not serious	not serious	serious [d]	none	-/700	-/321	**HR 0.97** (0.43 to 2.19)	**-- per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	

Recurrence (follow up: 1 years)

3 [2,3,10]	observational studies	very serious [a,b]	not serious	not serious	very serious [c,d]	none	34/158 (21.5%)	37/186 (19.9%)	**OR 1.13** (0.62 to 2.03)	**20 more per 1,000** (from 66 fewer to 136 more)	⨁◯◯◯ VERY LOW	

Recurrence (follow up: 2 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
3 [2,3,10]	observational studies	very serious [a,b]	not serious	not serious	very serious [c,d]	none	45/158 (28.5%)	57/186 (30.6%)	**OR 0.92** (0.57 to 1.46)	**17 fewer per 1,000** (from 105 fewer to 86 more)	⨁◯◯◯ VERY LOW	

Recurrence (follow up: longest)

3 [2,3,10]	observational studies	serious [a]	serious [e]	not serious	very serious [c,d]	none	45/158 (28.5%)	63/186 (33.9%)	**OR 0.75** (0.32 to 1.74)	**61 fewer per 1,000** (from 198 fewer to 133 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
Downstaging												
13 [1,2,3,5,7,8,9,10,11,12,13,14,15]	observational studies	very serious [a,b]	not serious	not serious	serious [d]	none	425/988 (43.0%)	259/650 (39.8%)	**OR 1.24** (0.90 to 1.71)	**53 more per 1,000** (from 25 fewer to 133 more)	⨁◯◯◯ VERY LOW	
pCR												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
15 [1,2,3,4,5,7,8,10,11,12,13,14,15,16,17]	observational studies	serious [a]	not serious	not serious	serious [d]	publication bias strongly suspected [f]	316/1196 (26.4%)	173/729 (23.7%)	**OR 1.20** (0.95 to 1.51)	**35 more per 1,000** (from 9 fewer to 82 more)	⨁◯◯◯ VERY LOW	

Febrile neutropenia

4 [5,11,12,15]	observational studies	very serious [a,b]	not serious	not serious	very serious [c,d]	none	2/97 (2.1%)	12/105 (11.4%)	**OR 0.35** (0.07 to 1.75)	**71 fewer per 1,000** (from 105 fewer to 70 more)	⨁◯◯◯ VERY LOW	

Neutropenia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
3 [5,11,15]	observational studies	very serious [a,b]	not serious	not serious	very serious [c,d]	none	23/46 (50.0%)	33/70 (47.1%)	**OR 1.31** (0.43 to 3.98)	**67 more per 1,000** (from 194 fewer to 309 more)	⨁◯◯◯ VERY LOW	

Anemia

4 [5,11,12,15]	observational studies	very serious [a,b]	not serious	not serious	very serious [c,d]	none	4/97 (4.1%)	5/105 (4.8%)	**OR 0.81** (0.20 to 3.22)	**9 fewer per 1,000** (from 38 fewer to 91 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
Thrombocytopenia												
4 [5,11,12,15]	observational studies	very serious [a,b]	not serious	not serious	serious [c]	none	17/97 (17.5%)	6/105 (5.7%)	**OR 4.70** (1.59 to 13.89)	**165 more per 1,000** (from 31 more to 400 more)	⨁◯◯◯ VERY LOW	
Nausea/vomiting												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
2 [5,15]	observational studies	very serious [a,b]	not serious	not serious	serious [c]	none	1/36 (2.8%)	26/53 (49.1%)	**OR 0.05** (0.01 to 0.31)	**445 fewer per 1,000** (from 481 fewer to 261 fewer)	⨁◯◯◯ VERY LOW	

Mucositis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	MVAC	Relative (95% CI)	Absolute (95% CI)		
2 [5,15]	observational studies	very serious [a,b]	not serious	not serious	very serious [c,d]	none	0/36 (0.0%)	7/53 (13.2%)	**OR 0.24** (0.02 to 2.50)	**97 fewer per 1,000** (from 129 fewer to 144 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

Explanations

a. outcome assessment

b. comparability

c. Optimal Information Size (OIS) criterion is not met and/or the number of events is small

d. confidence interval includes substantial benefits and harms

e. substantial heterogeneity

f. asymmetric funnel plot with statistically significant Egger's test

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Table s5) Summery of Findings Table: GC vs dd-MVAC for MIBC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	dd-MVAC	Relative (95% CI)	Absolute (95% CI)		
All−cause mortality (follow up: longest)												
4 [1,2,3,4]	observational studies	serious [a,b]	not serious	not serious	not serious	none	197/507 (38.9%)	148/440 (33.6%)	**OR 1.68** (1.23 to 2.28)	**124 more per 1,000** (from 48 more to 200 more)	⨁◯◯◯ VERY LOW	
pCR												
5 [1,2,4,5,6]	observational studies	very serious [a,b]	not serious	not serious	serious [c]	none	130/557 (23.3%)	145/501 (28.9%)	**OR 0.85** (0.54 to 1.33)	**32 fewer per 1,000** (from 109 fewer to 62 more)	⨁◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	dd-MVAC	Relative (95% CI)	Absolute (95% CI)		
pCR												
1 [7]	randomised trials	serious [d]	not serious	not serious	serious [e]	none	71/245 (29.0%)	84/248 (33.9%)	**OR 0.80** (0.54 to 1.17)	**48 fewer per 1,000** (from 122 fewer to 36 more)	⨁⨁◯◯ LOW	
Downstaging												
5 [1,2,4,5,6]	observational studies	very serious [a,b]	not serious	not serious	not serious	none	-/557	-/501	**OR 0.72** (0.54 to 0.97)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	
Downstaging												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	dd-MVAC	Relative (95% CI)	Absolute (95% CI)		
1 [7]	randomised trials	serious [d]	not serious	not serious	not serious	none	98/245 (40.0%)	126/248 (50.8%)	**OR 0.65** (0.45 to 0.92)	**106 fewer per 1,000** (from 191 fewer to 21 fewer)	⨁⨁⨁◯ MODERATE	

Febrile neutropenia

1 [5]	observational studies	very serious [a,f]	not serious	not serious	very serious [c,e]	none	0/51 (0.0%)	6/80 (7.5%)	**OR 0.11** (0.01 to 2.02)	**66 fewer per 1,000** (from 74 fewer to 66 more)	⨁◯◯◯ VERY LOW	

Febrile neutropenia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	dd-MVAC	Relative (95% CI)	Absolute (95% CI)		
1 [7]	randomised trials	serious [d]	not serious	not serious	serious [e]	none	6/245 (2.4%)	16/248 (6.5%)	**OR 0.36** (0.14 to 0.95)	**40 fewer per 1,000** (from 55 fewer to 3 fewer)	⊕⊕◯◯ LOW	

Neutropenia

1 [7]	randomised trials	serious [d]	not serious	not serious	serious [e]	none	113/245 (46.1%)	97/248 (39.1%)	**OR 1.33** (0.93 to 1.91)	**70 more per 1,000** (from 17 fewer to 160 more)	⊕⊕◯◯ LOW	

Anemia

1 [5]	observational studies	very serious [a,f]	not serious	not serious	very serious [c,e]	none	1/51 (2.0%)	2/80 (2.5%)	**OR 0.78** (0.07 to 8.83)	**5 fewer per 1,000** (from 23 fewer to 160 more)	⊕◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	dd-MVAC	Relative (95% CI)	Absolute (95% CI)		
Anemia												
1 [7]	randomised trials	serious [d]	not serious	not serious	serious [e]	none	19/245 (7.8%)	54/248 (21.8%)	**OR 0.32** (0.18 to 0.54)	**136 fewer per 1,000** (from 170 fewer to 87 fewer)	⨁⨁◯◯ LOW	
Thrombocytopenia												
1 [5]	observational studies	very serious [a,f]	not serious	not serious	very serious [c,e]	none	0/51 (0.0%)	2/80 (2.5%)	**OR 0.30** (0.01 to 6.48)	**17 fewer per 1,000** (from 25 fewer to 117 more)	⨁◯◯◯ VERY LOW	
Thrombocytopenia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GC	dd-MVAC	Relative (95% CI)	Absolute (95% CI)		
1 [7]	randomised trials	serious [d]	not serious	not serious	very serious [c,e]	none	41/245 (16.7%)	49/248 (19.8%)	**OR 0.82** (0.52 to 1.29)	**30 fewer per 1,000** (from 84 fewer to 43 more)	⊕◯◯◯ VERY LOW	

Cardiac toxicity

1 [7]	randomised trials	serious [d]	not serious	not serious	very serious [c,e]	none	17/245 (6.9%)	16/248 (6.5%)	**OR 1.08** (0.53 to 2.19)	**5 more per 1,000** (from 29 fewer to 67 more)	⊕◯◯◯ VERY LOW	

Nausea/vomiting

1 [7]	randomised trials	serious [d]	not serious	not serious	serious [e]	none	7/245 (2.9%)	24/248 (9.7%)	**OR 0.27** (0.12 to 0.65)	**69 fewer per 1,000** (from 84 fewer to 32 fewer)	⊕⊕◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Comparability

b. Unclear risk of bias due to lack of info (abstracts)

c. Confidence interval includes substantial benefits and harms

d. Randomization

e. Optimal Information Size (OIS) criterion is not met and/or the number of events is small

f. Outcome assessment

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Figure s1) GC vs MVAC, all-cause mortality at 1 year.

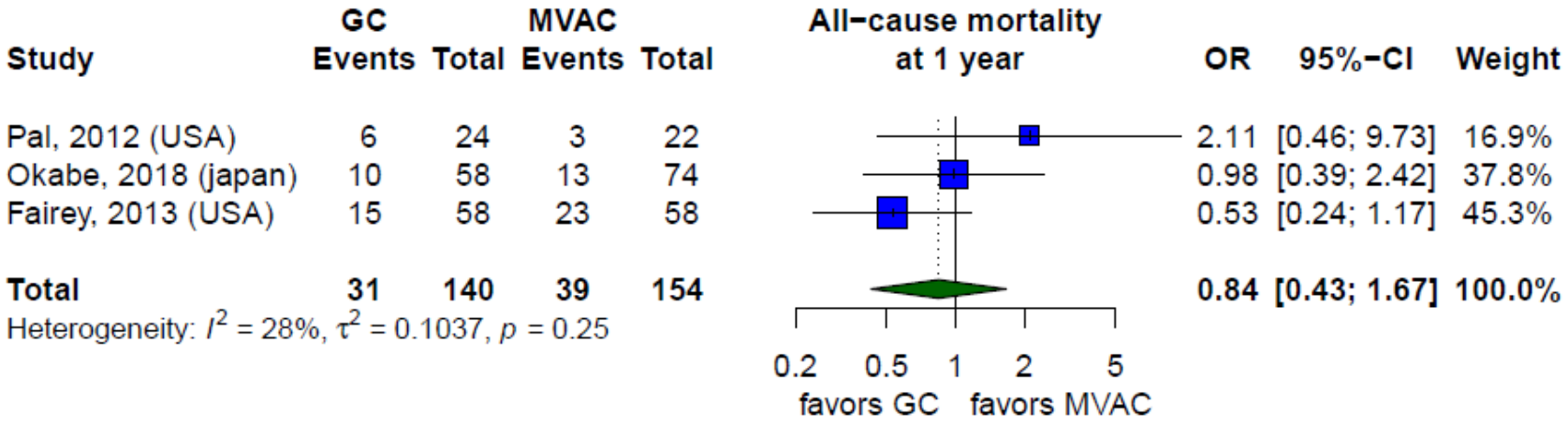

Figure s2) GC vs MVAC, all-cause mortality at 2 year.

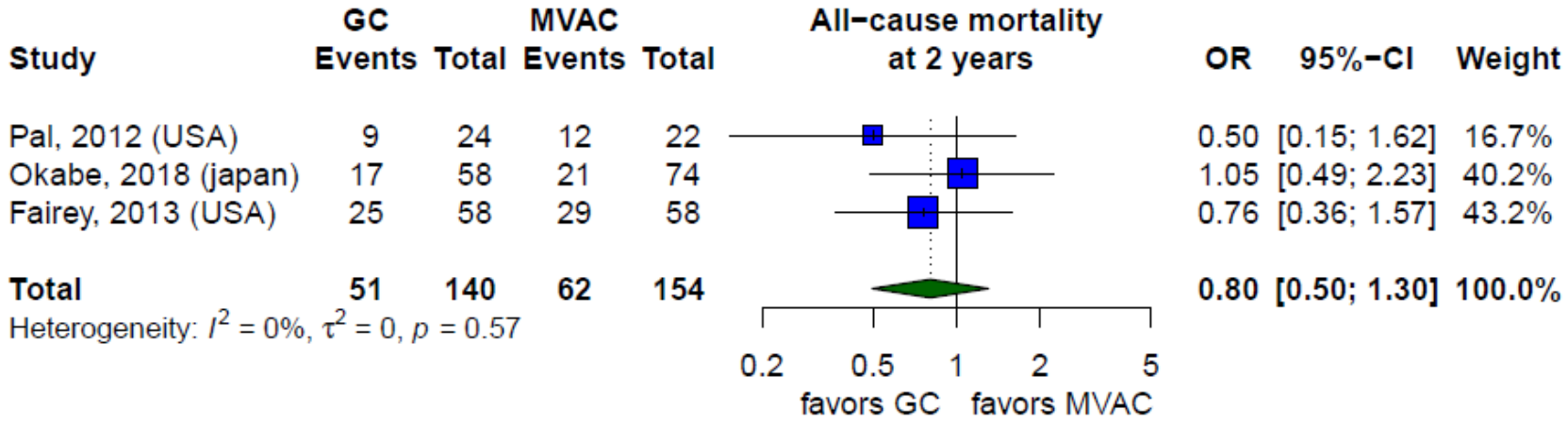

Figure s3) GC vs MVAC, all-cause mortality at longest follow-up.

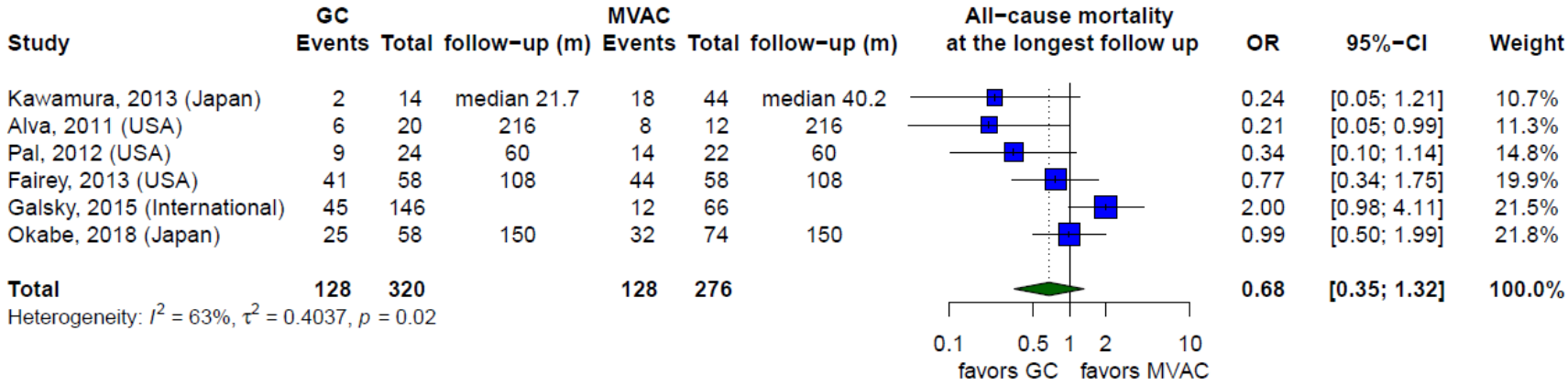

Figure s4) GC vs dd- MVAC, all-cause mortality at longest follow-up.

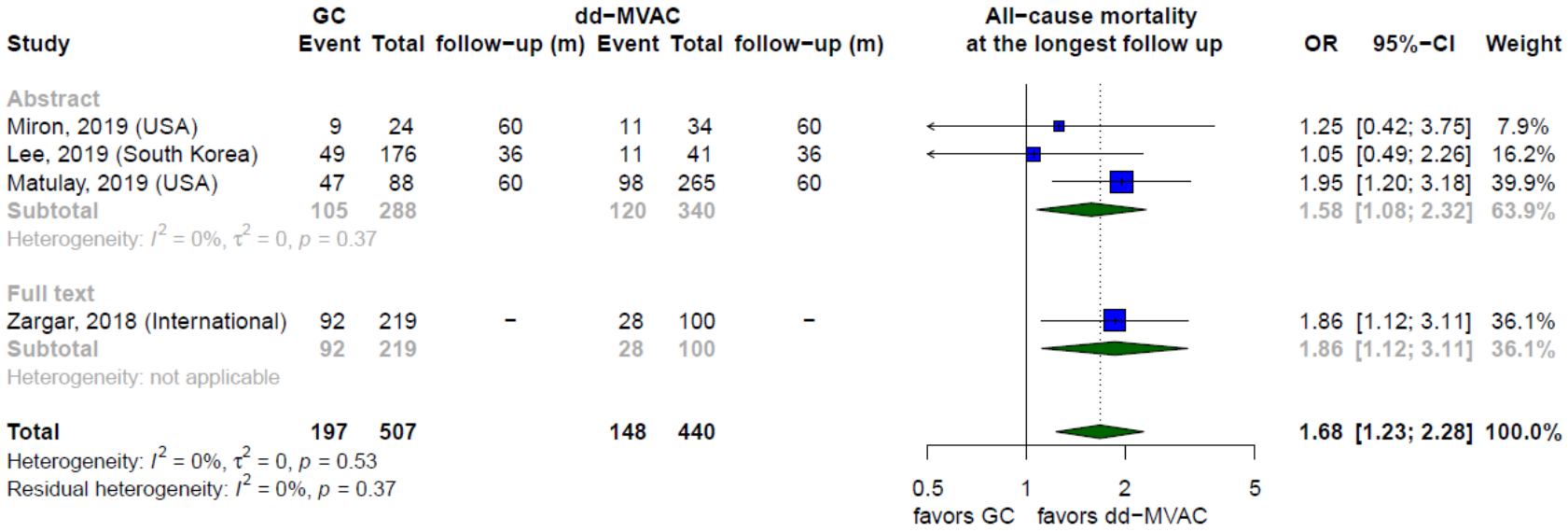

Figure s5) GC vs MVAC, pathologic complete response.

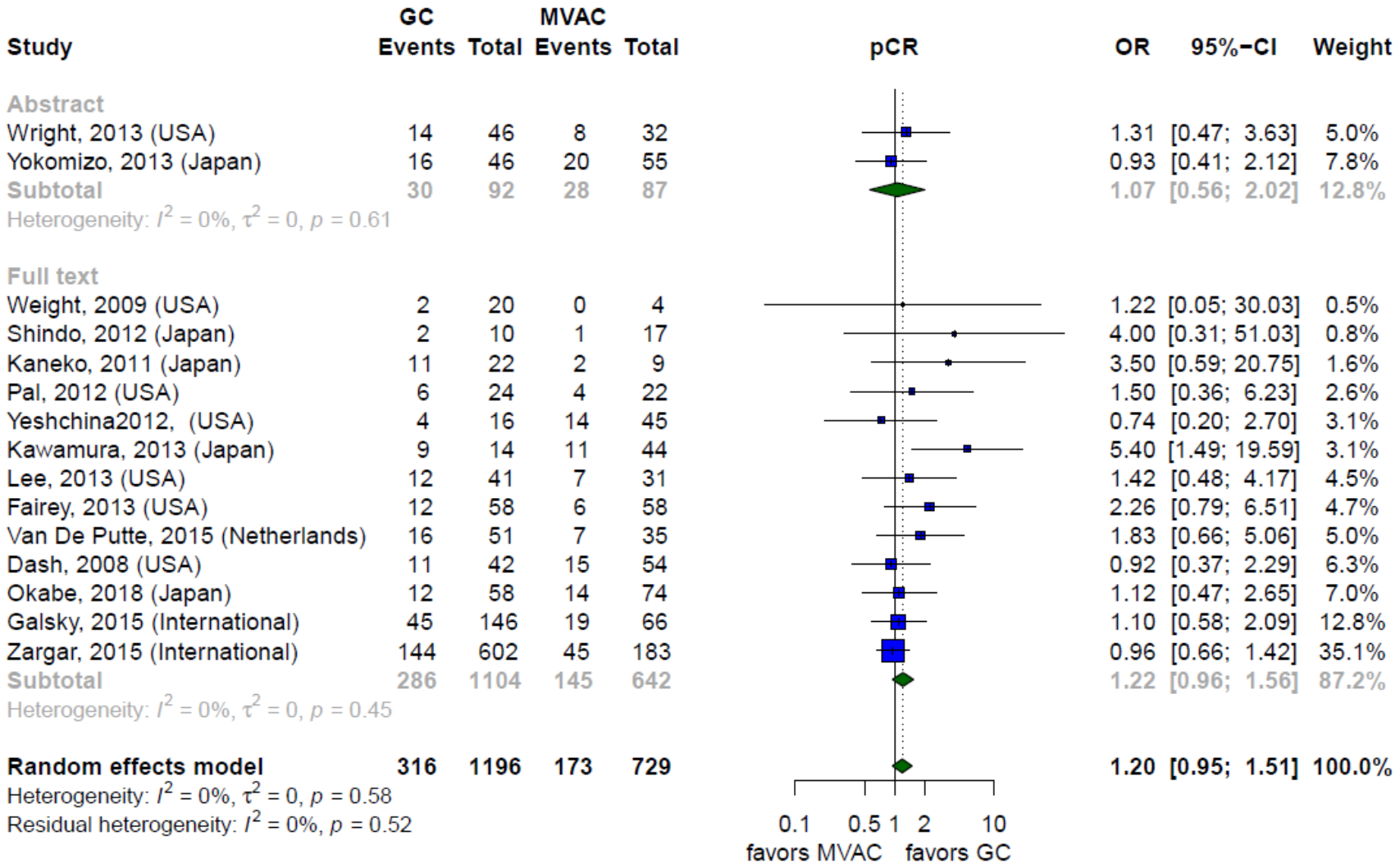

Figure s6) GC vs dd-MVAC, pathologic complete response.

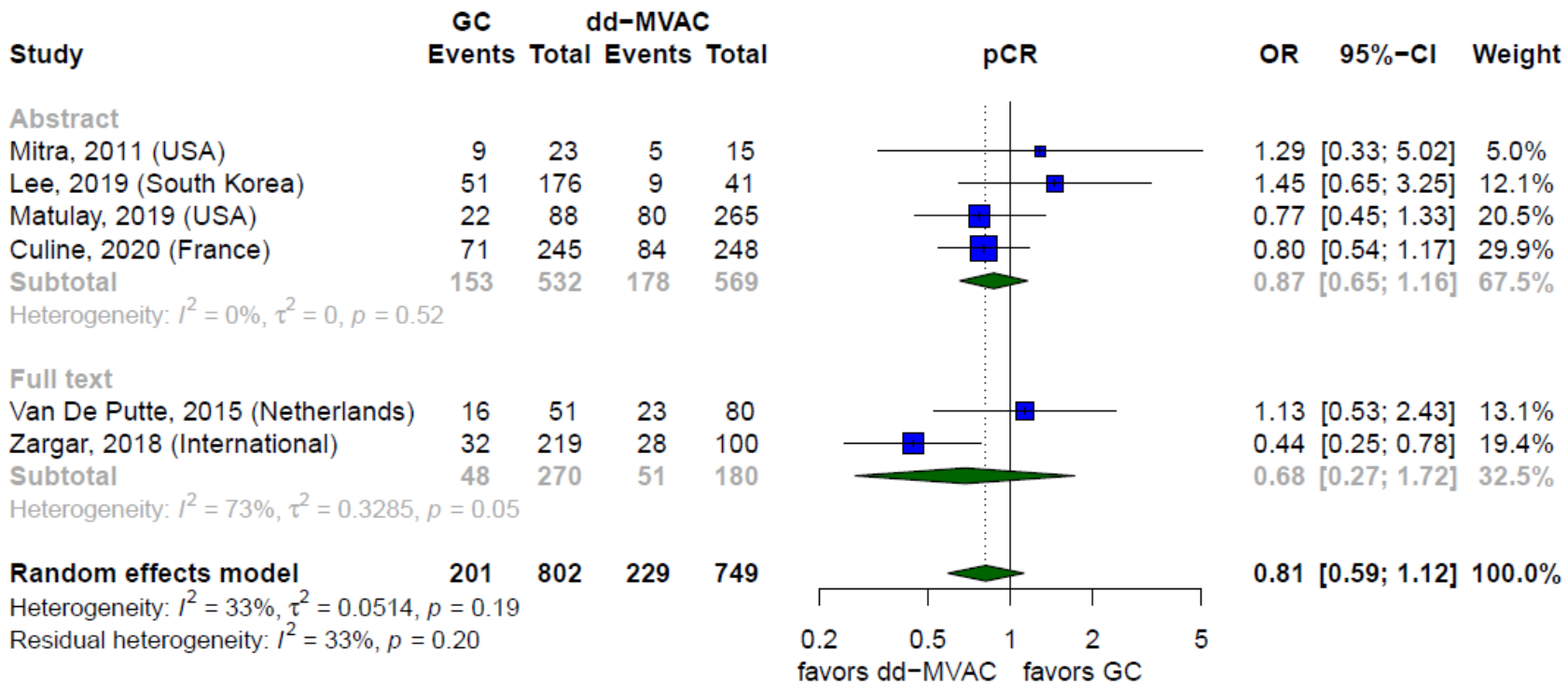

Figure s7) GC vs dd-MVAC, pathologic complete response, subgroup analysis of RCT vs retrospective cohort.

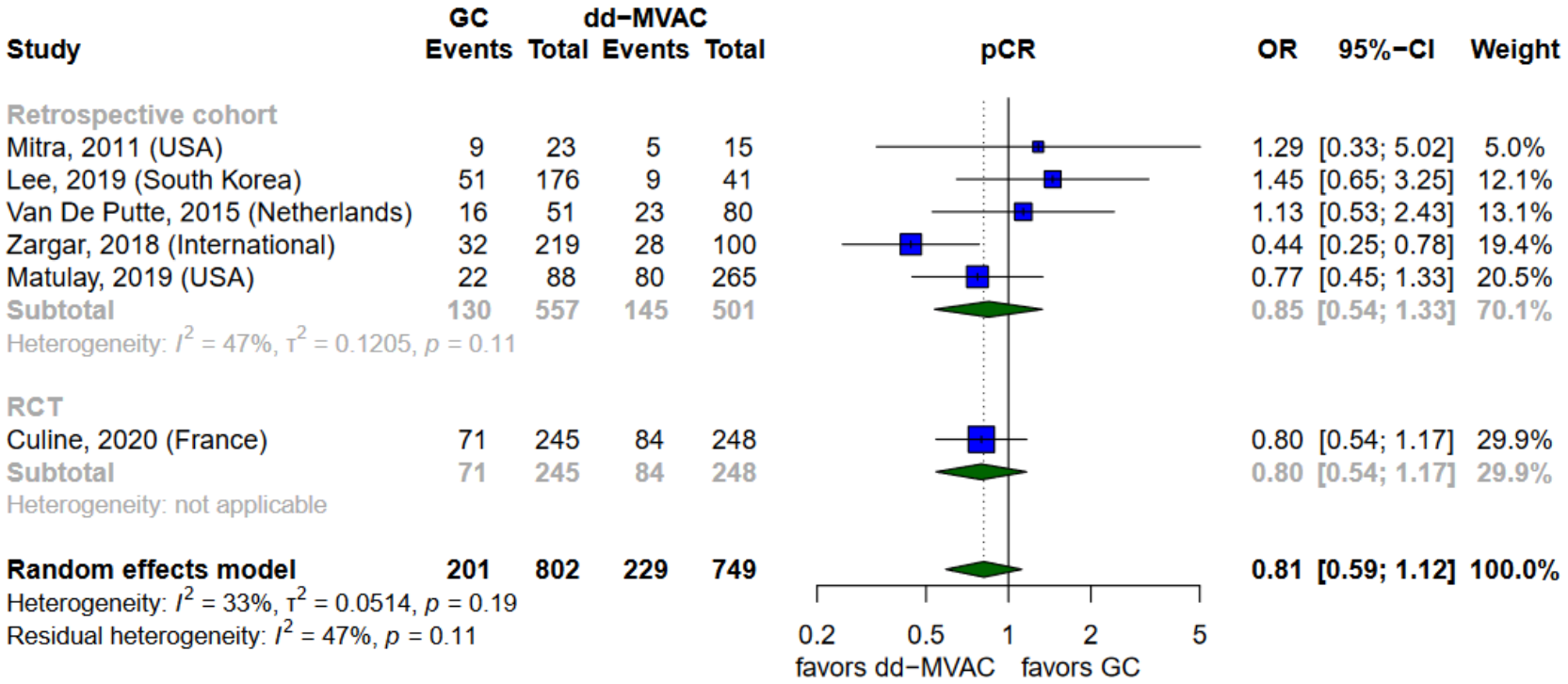

Figure s8) GC vs MVAC, downstaging.

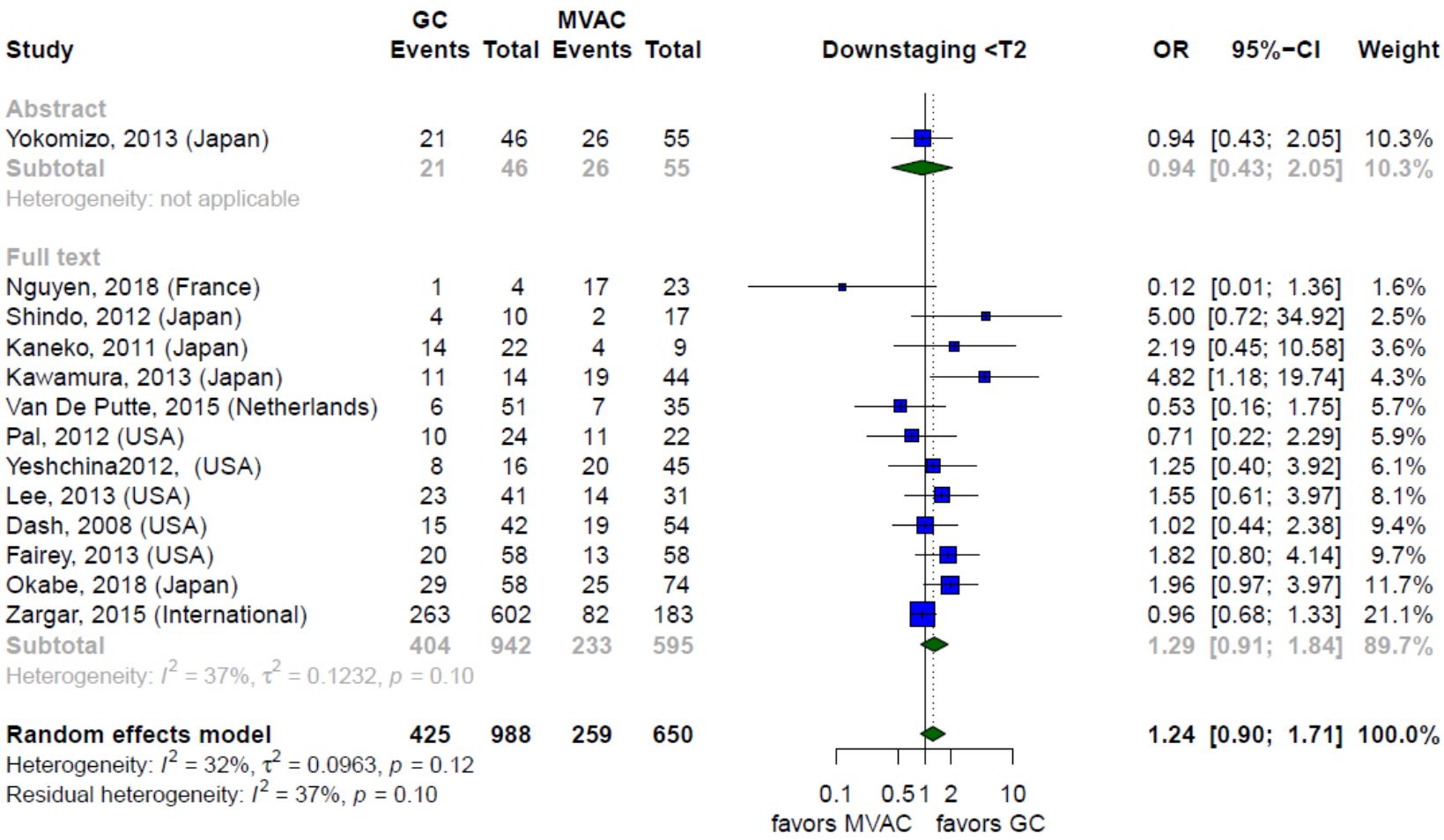

Figure s9) GC vs dd-MVAC, downstaging.

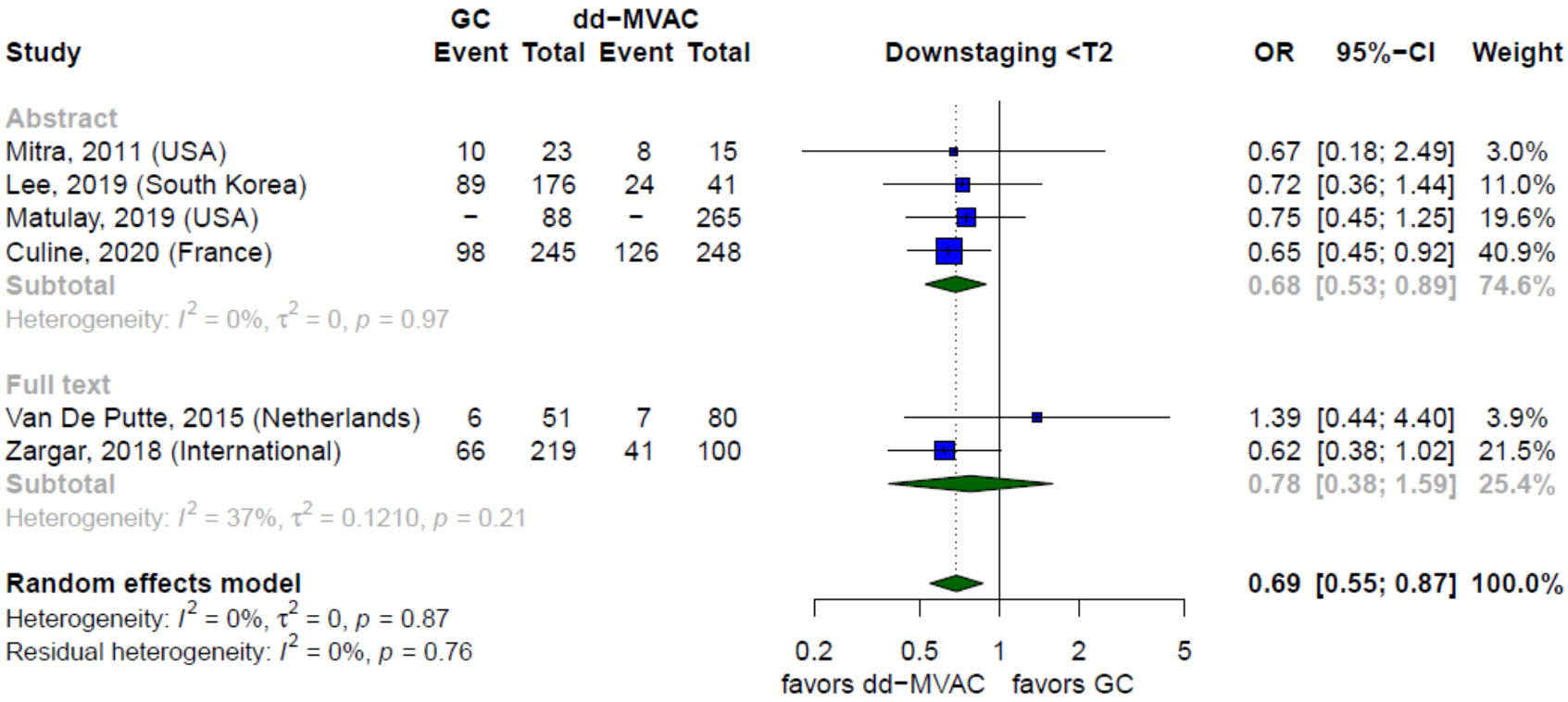

Figure s10) GC vs dd-MVAC, downstaging, subgroup analysis of RCT vs retrospective cohort.

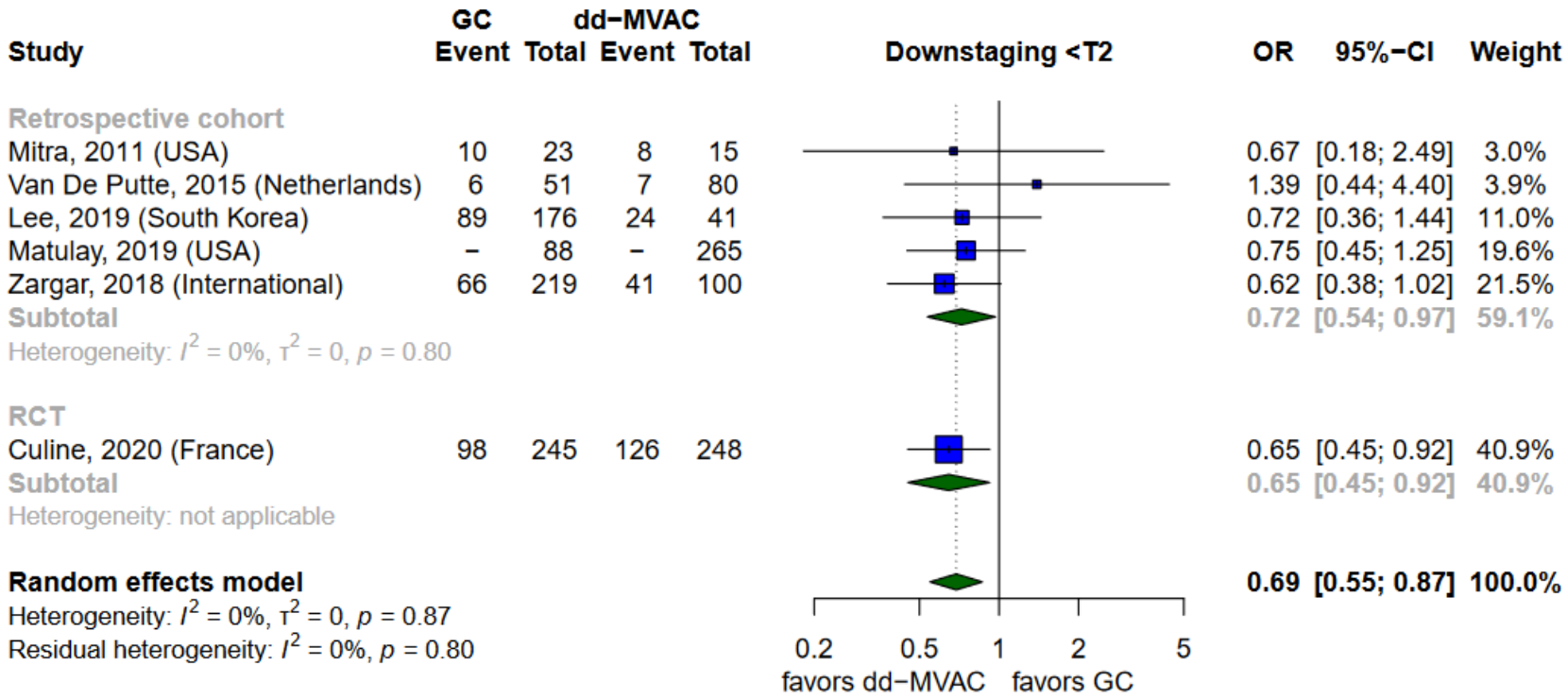

Figure s11) GC vs MVAC, recurrence at 1 year.

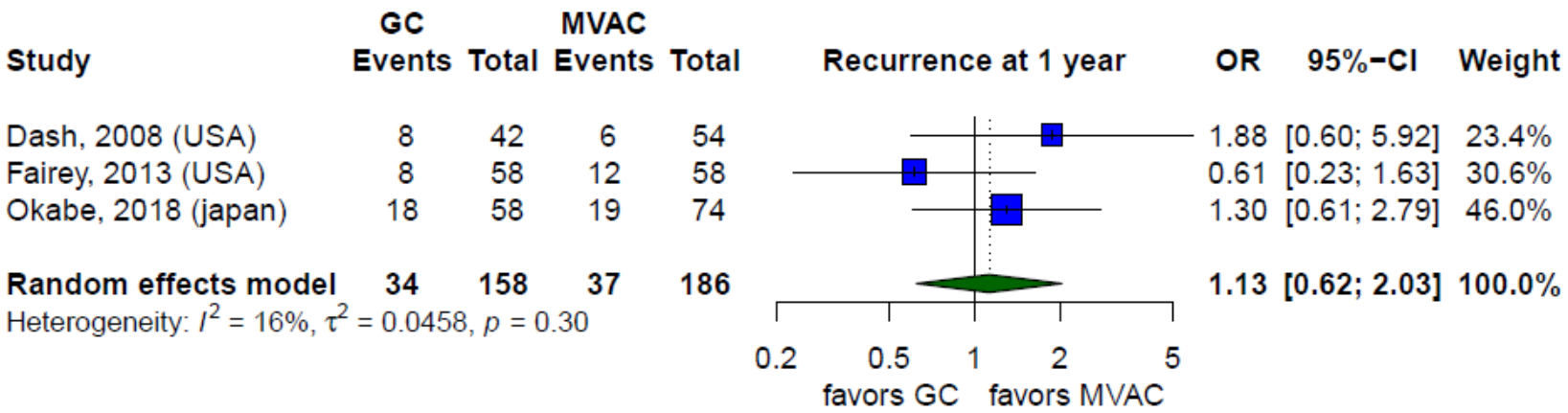

Figure s12) GC vs MVAC, recurrence at 2 year.

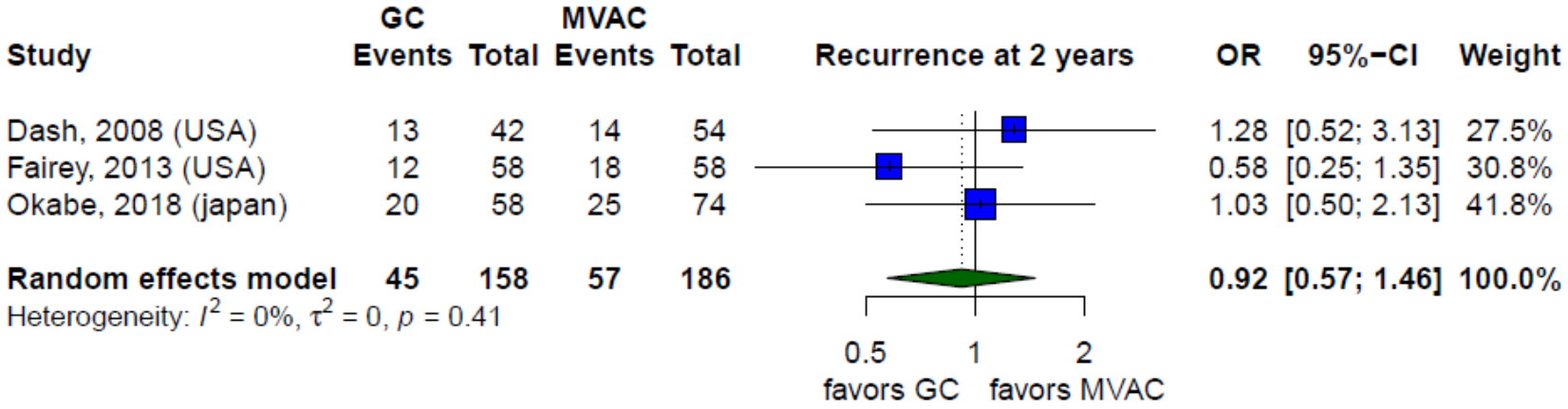

Figure s13) GC vs MVAC, recurrence at longest follow up.

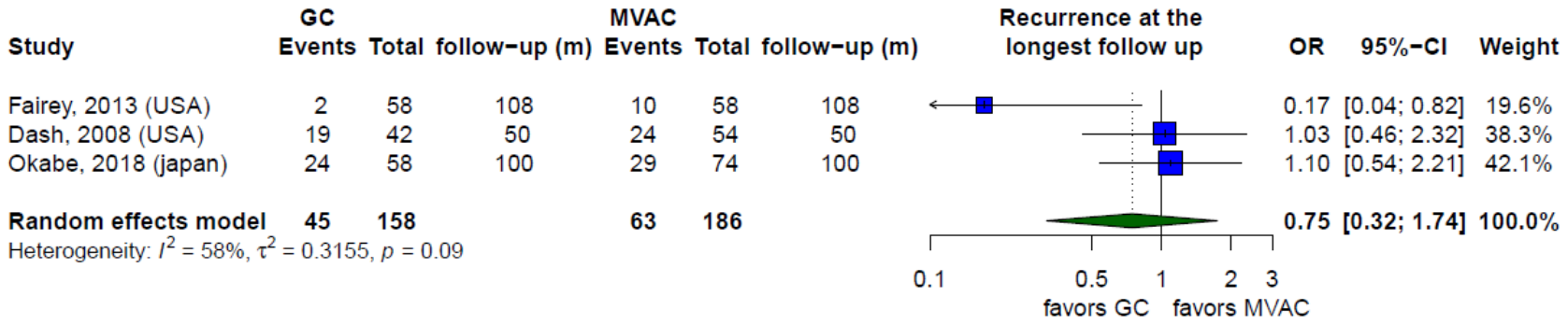

Figure s14) GC vs MVAC, febrile neutropenia.

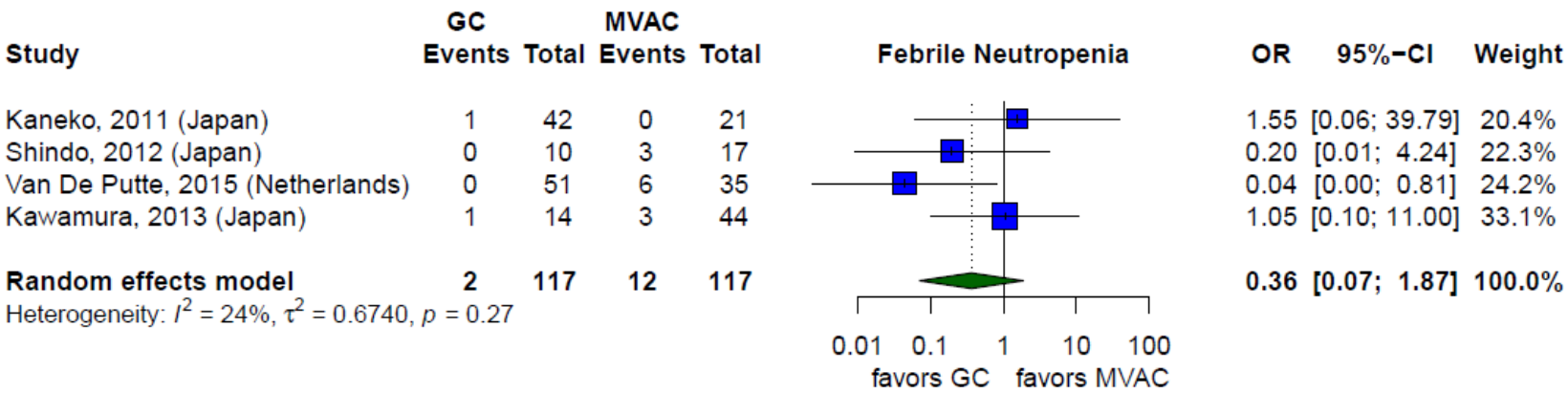

Figure s15) GC vs dd-MVAC, febrile neutropenia.

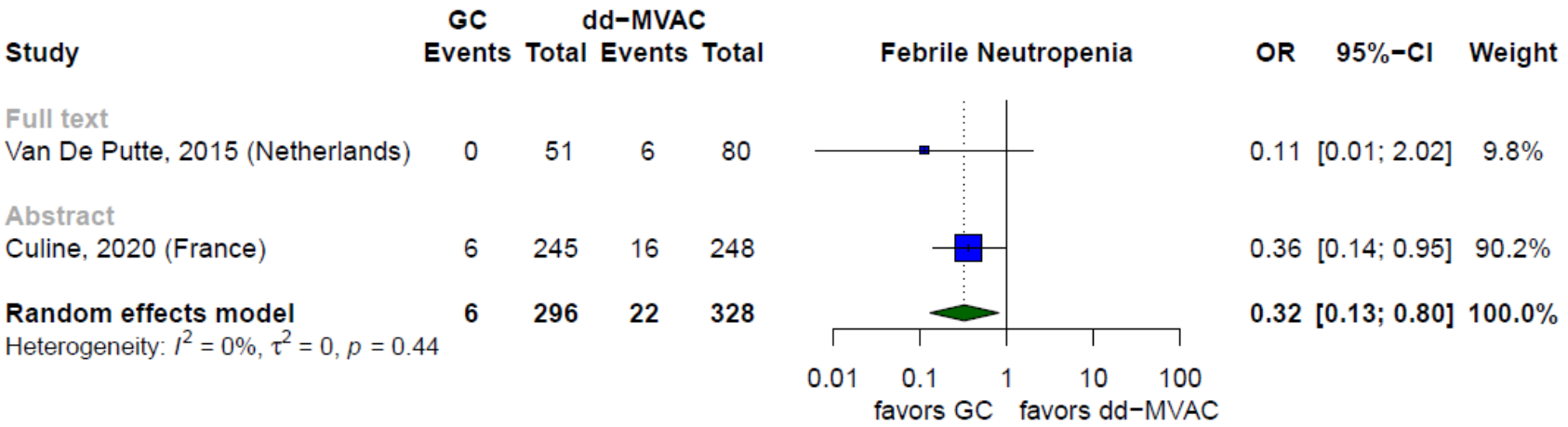

Figure s16) GC vs MVAC, thrombocytopenia.

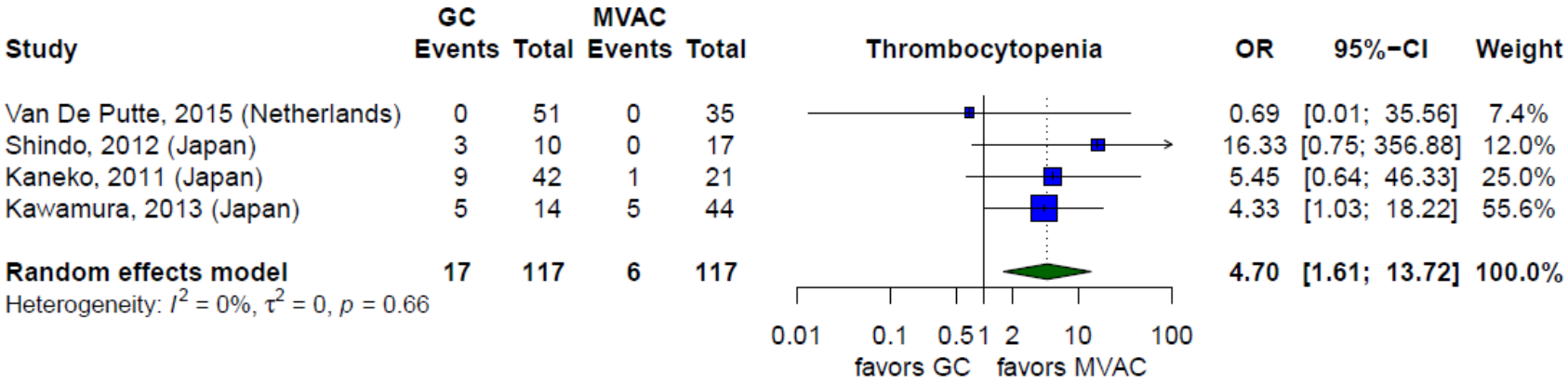

Figure s17) GC vs dd-MVAC, thrombocytopenia.

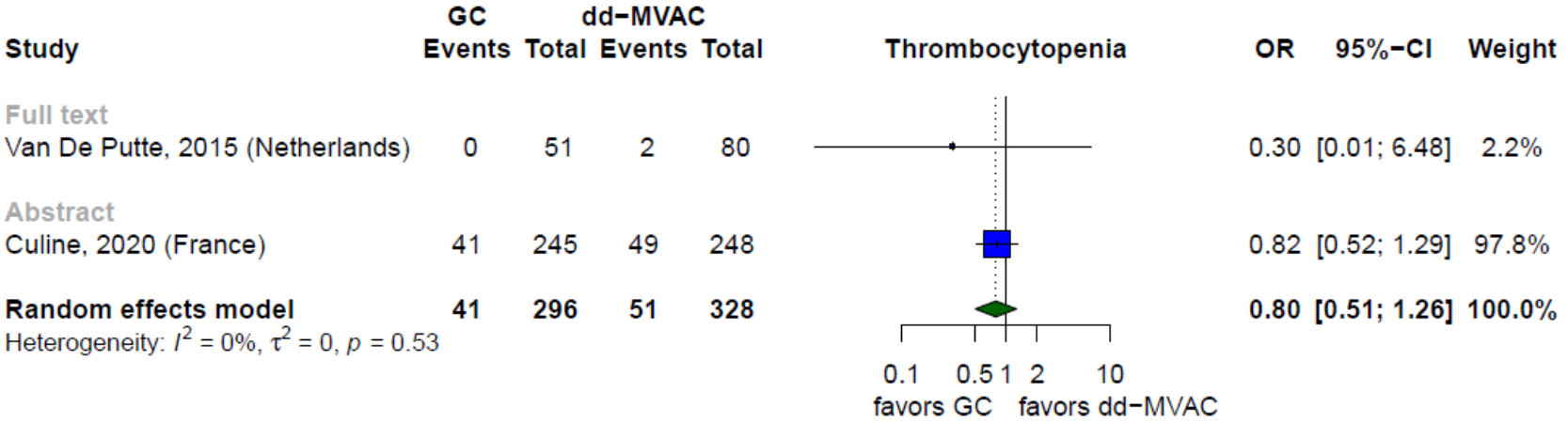

Figure s18) GC vs MVAC, anemia.

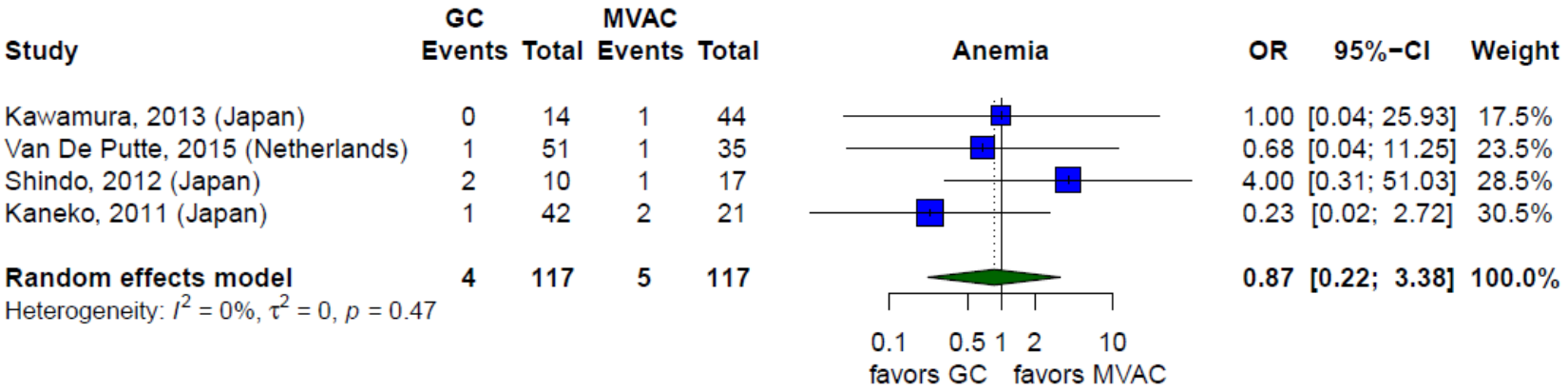

Figure s19) GC vs dd-MVAC, anemia.

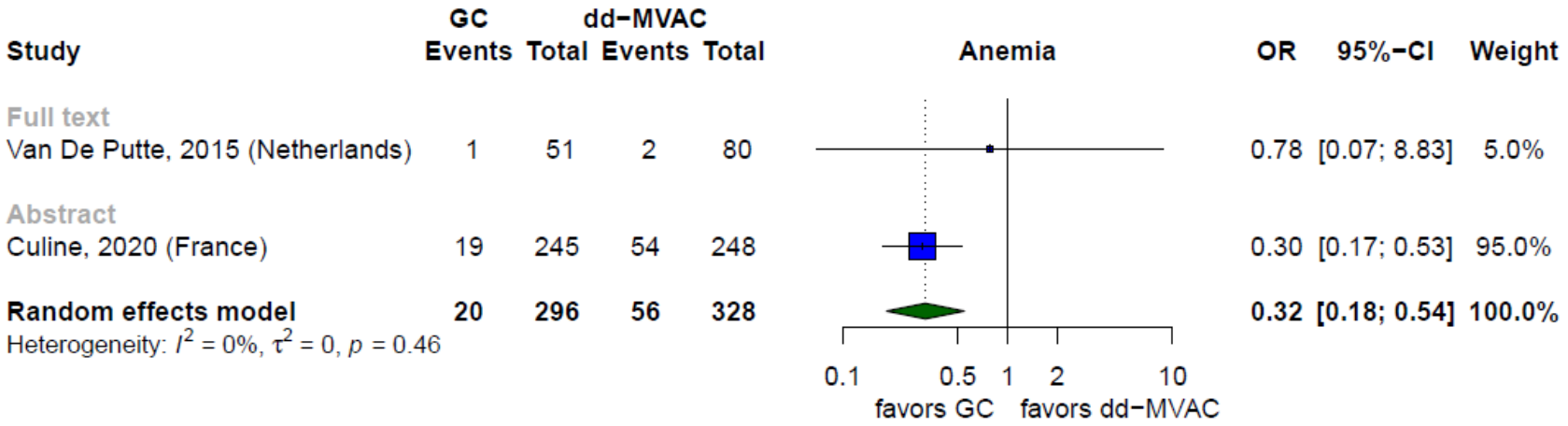

Figure s20) GC vs MVAC, nausea/vomiting.

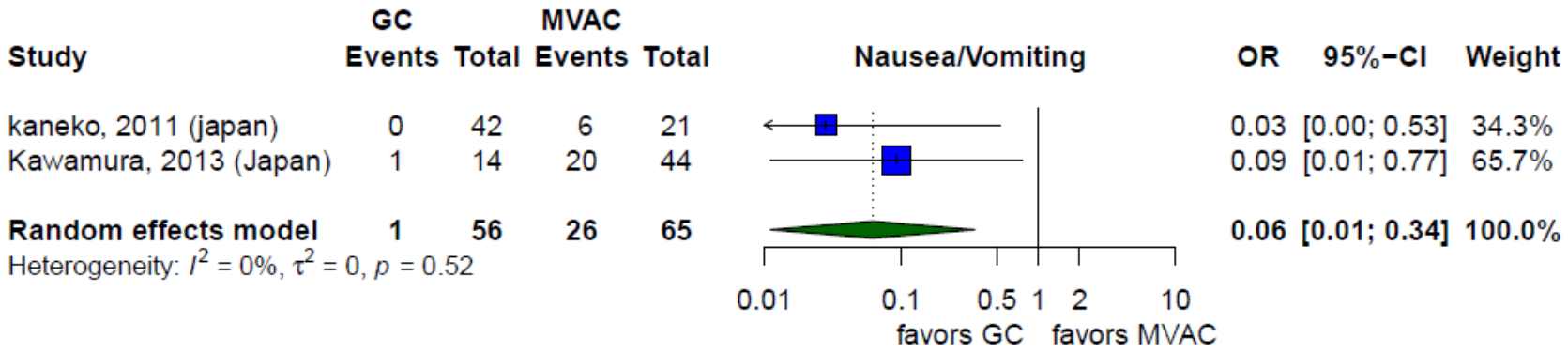

Figure s21) GC vs MVAC, mucositis.

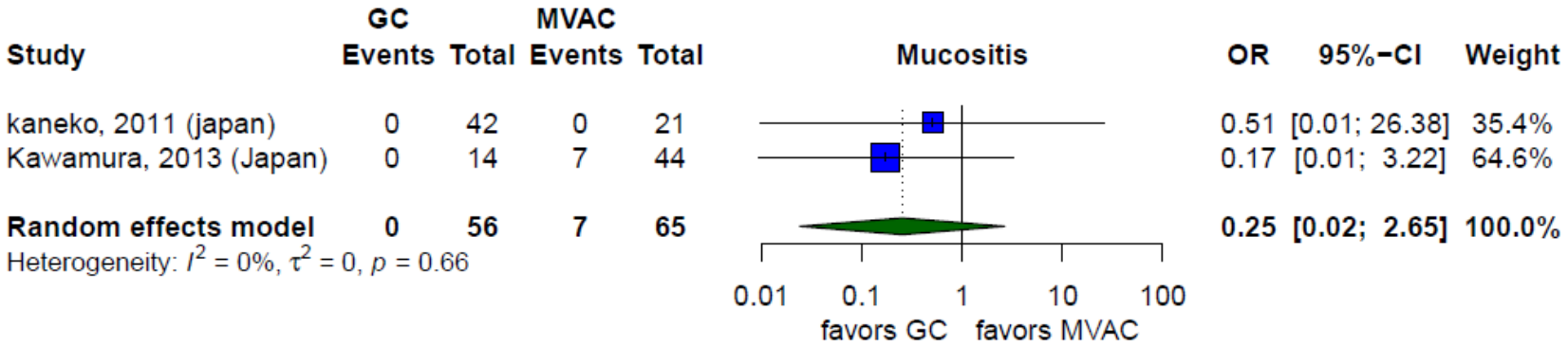

Figure s22) GC vs MVAC, neutropenia.

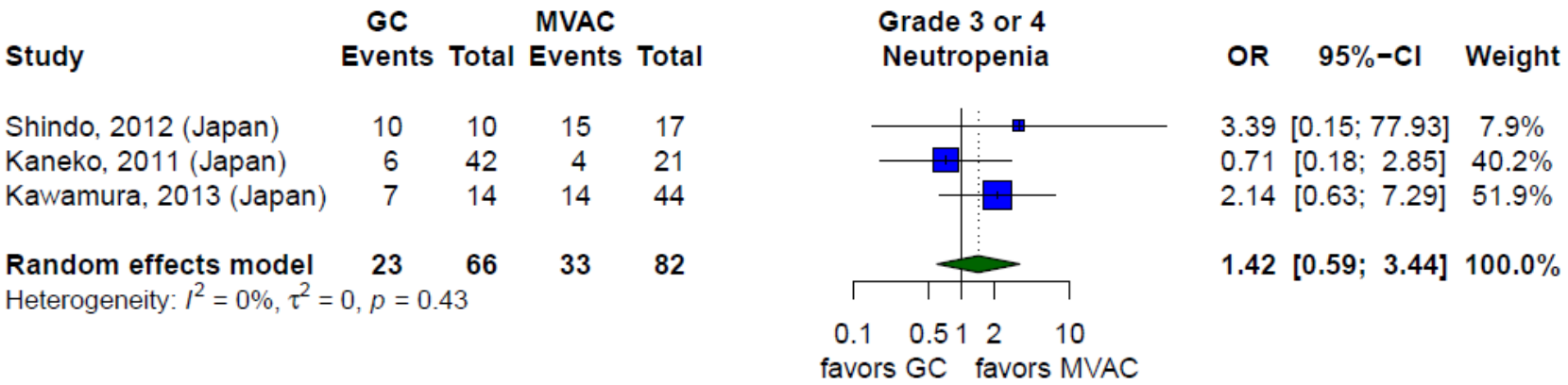

Figure s23) GC vs. MVAC, Funnel plot for publication bias assessment in pCR.

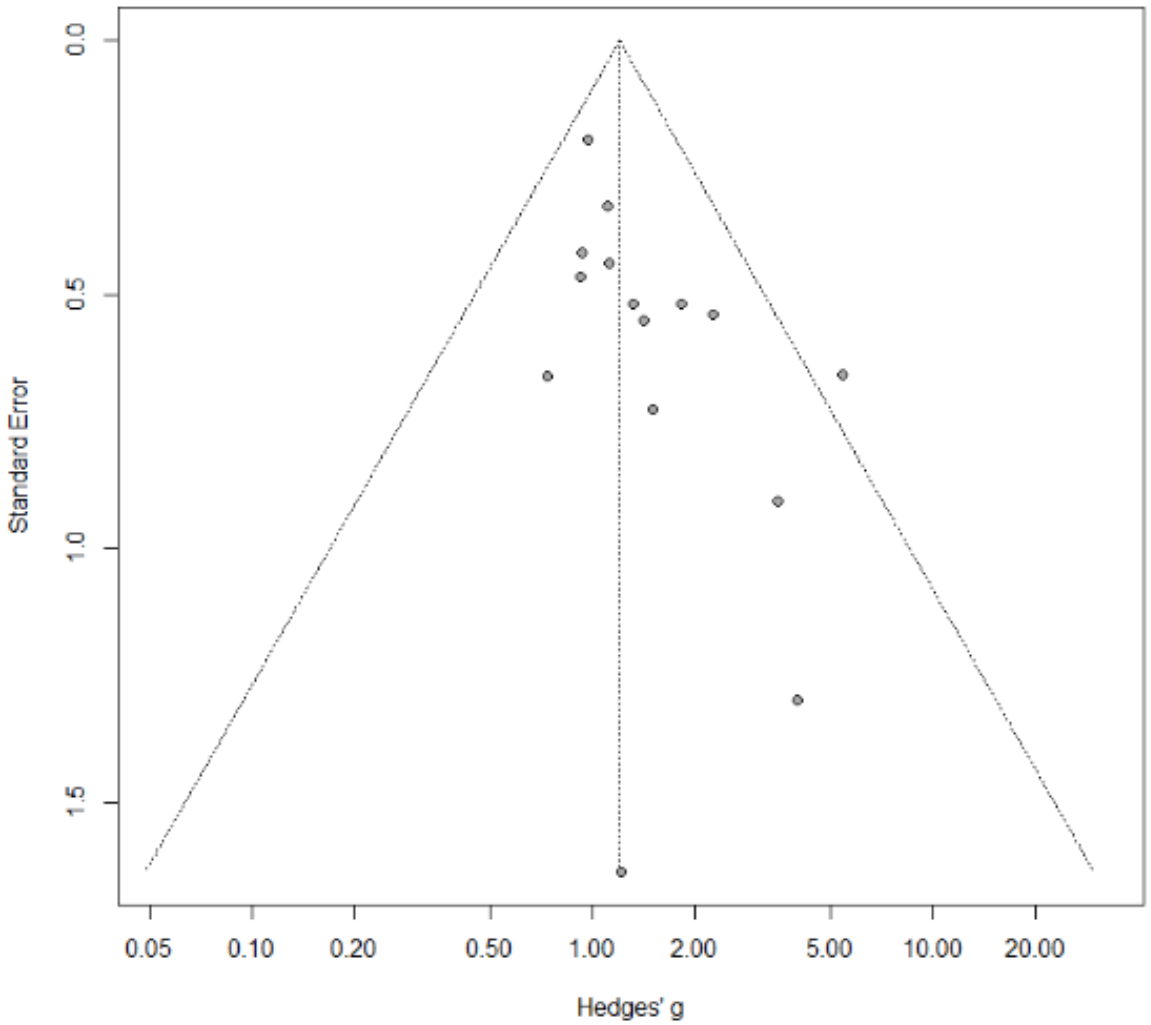

Figure s24) GC vs. MVAC, Funnel plot for publication bias assessment in pCR after running Duval & Tweedie's trim-and-fill procedure.

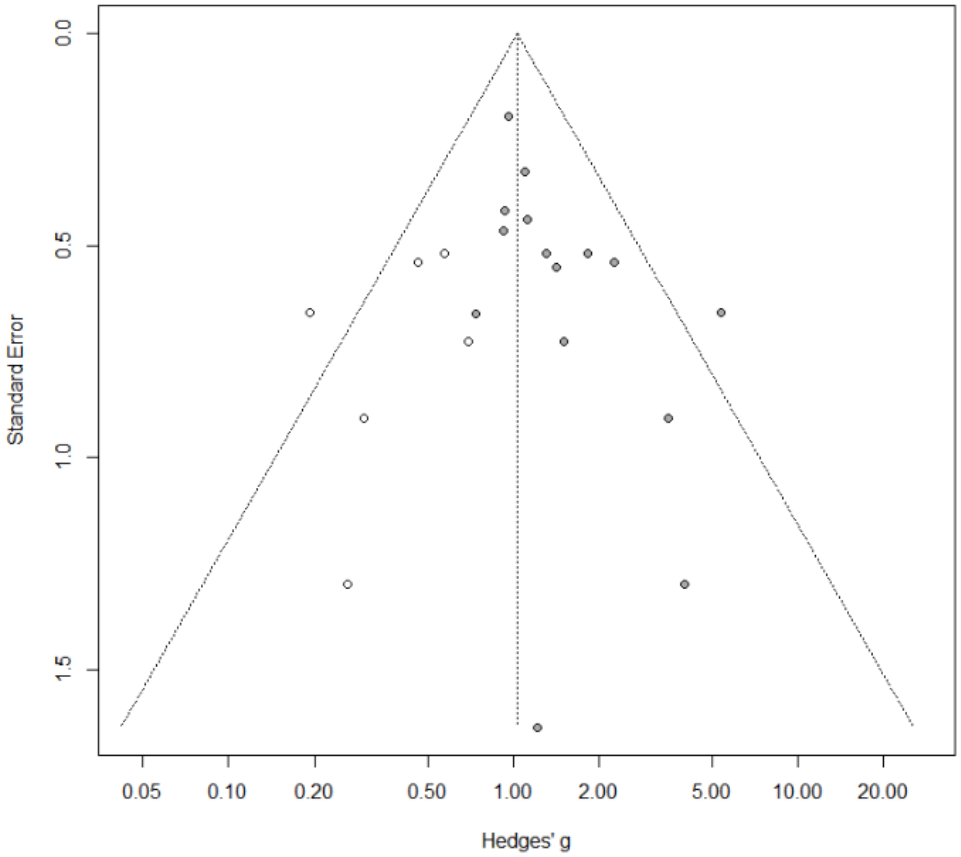

Figure s25) GC vs. MVAC, Funnel plot for publication bias assessment in downstaging.