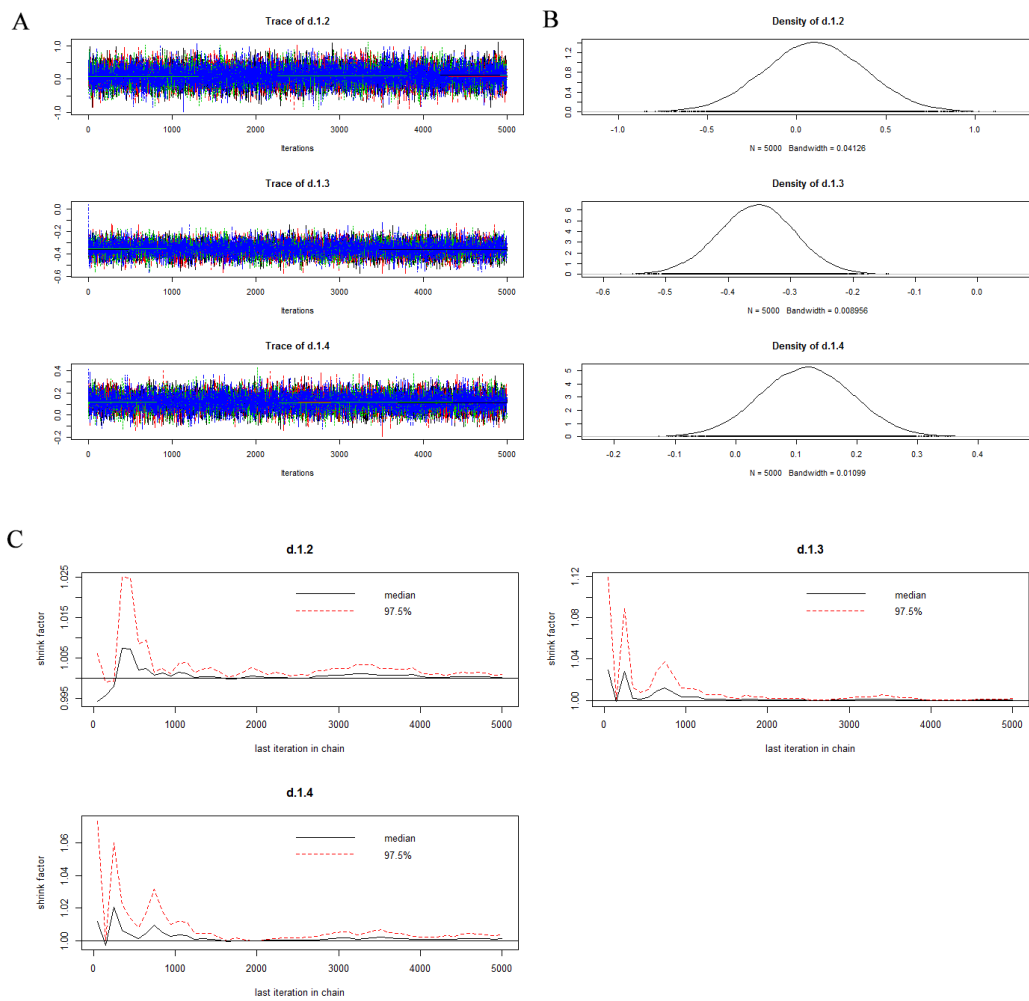
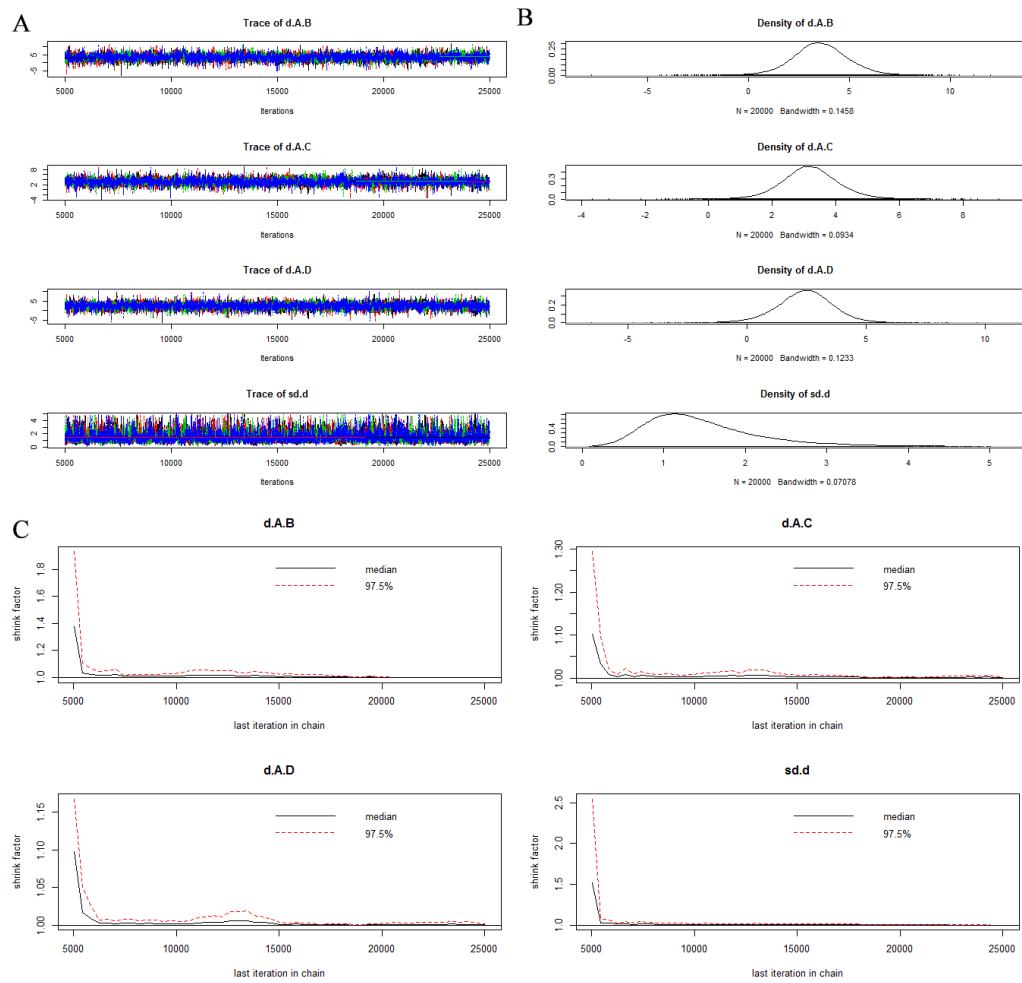


Supplemental material



Supplemental Figure 1 trace plot (A), density plot (B) and Brooks-Gelman-Rubin diagnosis plot (C) of overall survival



Supplemental Figure 2 trace plot (A), density plot (B) and Brooks-Gelman-Rubin diagnosis plot (C) of overall toxicity

Supplemental Table1. Quality assessment of randomized control studies

	random sequen ce generat ion	allocatio n conceal ment	blinding of particip ants and personn el	blinding of outcom e assessm ent	Incompl ete outcom e data	selecti ve reporti ng	oth er bia s
Casadei 2015	L	L	L	H	L	L	L
Golcher 2015	?	?	L	L	L	L	L
Oettle 2007	L	L	L	L	L	L	L
Kosuge 2006	?	L	L	L	L	L	L
Ueno 2009	?	L	L	L	L	L	L
Bakke old 1993	L	L	L	L	L	L	L
Smeenk 2007	L	?	L	L	L	L	L
Kalser 1985	L	L	L	L	L	L	L
Van 2010	?	?	L	L	L	L	L
ESPAC -1 2001	L	?	L	L	L	L	L

ESPEC	L	?	L	L	L	L	L
-1 plus							
2004							
ESPEC	L	?	L	L	L	L	L
-3 (V1)							
2009							

+: Low risk of bias; -: High risk of bias; ?: unclear risk of bias

supplemental Table2. Baseline Demographic and Disease Characteristics of Included studies

Study	Arms	N	Period	country	Age, median (range)	Primary tumor stage T1/T2/T3/T4	Nodal status N0/N1/N2	Grading G1/G2/G3/unknown
Casadei, R et al 2015	NCR+S	18	2007- 2014	Italy	71.5 (51- 78)	2/6/10/0	4/14/0	2/10/3/3
	Surgery	20			67.5 (48- 79)	1/0/19/0	4/16/0	6/11/1/2
Golcher, H et al 2015	NCR+S	33	2003- 2009	Germany, Switzerland	62.5 (33- 76)	1/15/16/1	22/11/0	na
	Surgery	33			65.1 (46- 73)	1/15/17/0	30/3/0	na
Oettle, H. et al 2007, 2013	S+AC	179	1998- 2004	Germany, Austrian	62.0 (34- 82)	7/18/146/8	52/126/1	10/103/63/3
	Surgery	175			62.0 (36- 81)	7/17/146/5	48/124/3	9/96/67/3
Kosuge, T. et al	S+AC	45	1992-	Japan	60.8 ±8.1*	-/-/-/9	23/-/-	na

2006			2000					
	Surgery	44			60.1 ±8.9*	-/-/-/11	35/-/-	na
Ueno, H. et al 2009	S+AC	58	2002- 2005	Japan	65 (41- 74)	6/1/31/20	19/39/0	18/33/5/2
	Surgery	60			64 (36- 74)	6/4/28/22	18/42/0	16/36/4/4
Bakkevold, K. E. et al 1993	S+AC	30	1984- 1987	Norway	66.5 (36- 75)	na	na	na
	Surgery	31			62 (40- 72)	na	na	na
Smeenk, H. G. et al 2007	S+ACD	63	1987- 1995	Europe	na	16/39/6/2	28/23/12	na
Klinkenbijl, J. H. et al 1999	Surgery	57			na40-72	6/48/2/1	26/23/8	na
Kalser, M. H. et al 1985	S+ACD	21	1974- 1982	USA	na	na	na	na
	Surgery	22			na40-72	na40-72	na40-72	na40-72

Van Laethem, J. L. et al 2010	S+ACD	45	2004- 2007	France	61.0 (44- 75)	3/9/32/0	13/31/1	10/20/10/5
	S+AC	45			58.0 (32- 77)	2/8/30/4	14/31/0	12/26/6/1
Neoptolemos, J. et al 2001, 2004, 2009 (ESPAC-1)	S+ACD	73	1994- 2000	Europe	na	na	na	na
	S+AC	75			61 (41- 83)	na	35/36/-	21/28/18/0
	S+AC+ACD	72			na	na	na	na
	Surgery	69			60 (36- 84)	na	25/42/-	12/40/13/0
ESPAC-1 plus	S+ACD	33	1994- 2000	Europe	na	na	na	na
	Surgery	36			na	na	na	na
	S+AC	97			57 (28- 78)	na	48/45/-	18/57/17/0
	Surgery	95			60 (32- na)	na	51/40/-	19/52/22/0

					84)				
ESPAC-3 (V1)	S+AC	61	1994-	Europe	61	(42-	na	18/42/-	11/30/18/1
			2000		80)				
	Surgery	61			62	(33-	na	21/40/-	5/43/12/1
					77)				

NCRT+S: neoadjuvant chemoradiotherapy with surgery; S+ACT: surgery with adjuvant chemotherapy; S+ACRT, surgery with adjuvant chemoradiotherapy; na: not available.

Supplement Table 3. Reported toxicity events of included trails

Study	arms	n	Leukopenia	Thrombopenia	Anemia	Hematological toxicity	Nausea/vomiting	Infection/Fever	Asthenia/Fatigue	Diarrhea	total toxicity
Bakkevold, K. E. et al 1993	S+ACT	31	na	na	na	na	na	na	na	na	na
Casadei, R et al 2015	NRCT +S	20	5	1	0	6	0	na	1	na	7
Golcher, H et al 2015	NRCT +S	33	9	11	2	22	10	5	na	1	38
Kalser, M. H. et al 1985	S+ACR T	22	na	na	na	3	na	na	na	na	na
Kosuge, T. et al 2006	S+ACT	44	2	0	na	2	5	na	na	na	7
ESPAC-1 v1	S+ACT	61	na	na	na	na	na	na	na	na	na
ESPAC-1	S+ACT	75	na	na	na	2	na	na	na	na	2

ESPAC-1	S+ACR	73	na	na	na	0	na	na	na	na	0
	T										
ESPAC-1plus	S+ACT	97	na	na	na	na	na	na	na	na	na
ESPAC-1plus	S+ACR	33	na	na	na	na	na	na	na	na	na
	T										
Oettle, H. et al 2007	S+AC	17	4	6	8	18	11	13	15	16	73
2013		5									
Smeenk, H. G, 2007	S+AC	10	na	na	na	na	na	na	na	na	na
	D	8									
Ueno, H. et al 2009	S+AC	60	14	1	2	17	2	1	1	1	22
Van Laethem, J. L.	S+AC	45	7	1	3	11	2	3	3	1	20
et al 2010	D										
	S+AC	45	6	0	0	6	0	0	2	0	8

NCRT+S, neoadjuvant chemoradiotherapy with surgery; S+ACT, surgery with adjuvant chemotherapy; S+ACRT, surgery with adjuvant chemoradiotherapy; na: not available.