SCIENTIFIC REPORTS

OPEN

SUBJECT AREAS: RISK FACTORS PROGNOSTIC MARKERS

> Received 31 October 2014

Accepted 4 February 2015

> Published 22 April 2015

Correspondence and requests for materials should be addressed to H.T.W. (wht1972@ 126.com; peterrock2000@126. com)

Prognostic value of pretreatment serum lactate dehydrogenase level in patients with solid tumors: a systematic review and meta-analysis

Jiao Zhang^{1,2,3}, Yan-Hong Yao^{1,3}, Bao-Guo Li^{1,2,3}, Qing Yang^{1,4}, Peng-Yu Zhang^{1,5} & Hai-Tao Wang^{1,3}

¹Department of Interventional Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China, ²Research Group of Evidence-based Clinical Oncology, Tianjin, China, ³Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin, China, ⁴Department of Urologic Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China, ⁵Department of Laboratory Medicine, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China.

Although most studies have reported that high serum lactate dehydrogenase (LDH) levels are associated with poor prognosis in several malignancies, the consistency and magnitude of the impact of LDH are unclear. We conducted the first comprehensive meta-analysis of the prognostic relevance of LDH in solid tumors. Overall survival (OS) was the primary outcome; progression-free survival (PFS) and disease-free survival (DFS) were secondary outcomes. We identified a total of 68 eligible studies that included 31,857 patients. High LDH was associated with a HR for OS of 1.48 (95% CI = 1.43 to 1.53; P < 0.00001; I² = 93%), an effect observed in all disease subgroups, sites, stages and cutoff of LDH. HRs for PFS and DFS were 1.70 (95% CI = 1.44 to 2.01; P < 0.00001; I² = 13%) and 1.86(95% CI = 1.15 to 3.01; P = 0.01; I² = 88%), respectively. Analysis of LDH as a continuous variable showed poorer OS with increasing LDH (HR 2.11; 95% CI = 1.35 to 3.28). Sensitivity analyses showed there was no association between LDH cutoff and reported HR for OS. High LDH is associated with an adverse prognosis in many solid tumors and its additional prognostic and predictive value for clinical decision-making warrants further investigation.

ancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries¹. In the United States, a total of 1,660,290 new cancer cases and 580,350 cancer deaths were projected to occur in 2013². In Europe, there were an estimated 3.45 million new cases of cancer (excluding non-melanoma skin cancer) and 1.75 million deaths from cancer in 2012³. Furthermore, the global burden of cancer continues to increase, largely because of population growth and increased life-expectancy³. Invasion and metastasis are two important hallmarks of cancer and are responsible for the majority of cancer deaths⁴. Although much effort has been devoted to the diagnosis and therapy of cancers, the overall prognosis is still unsatisfactory. A lack of knowledge of molecular biomarkers in cancer has limited the development of personalized therapies and improvements in survival. Therefore, there is an urgent need for universal, effective, readily available and inexpensive biomarkers in solid tumors to identify patients with a poor prognosis so that novel treatments can be initiated earlier.

The metabolism of cancer cells differs from that of normal cells. This is largely because cancer cells exhibit metabolic alterations that are frequently associated with reprogramming. Unlike normal cells, cancer cells preferentially metabolize glucose by glycolysis to generate sufficient energy for the demands of rapid proliferation, even in the presence of adequate $oxygen^5$. This phenomenon is known as the Warburg effect and is one of the predominant metabolicalterations that occur during malignant transformation. In this process, transcriptional programs regulated by oncogenes stabilize hypoxia-inducible factor 1 alpha (HIF-1 α). HIF-1 α contributes to the upregulation of most enzymes involved in the glycolytic pathway, including lactate dehydrogenase (LDH). In the final step of aerobic glycolysis, LDH converts pyruvate tolactate, which is coupled with the oxidation of NADH to NAD+. These metabolic changes are reflected by an elevated serum LDH level⁶(hereinafter LDH).

Elevated LDH has been recognized as a poor prognostic indicator in cancer for many years⁷⁻¹⁰. LDH has also been incorporated in prognostic scores for several types of cancer¹¹. However, the consistency and magnitude of

the prognostic impact of LDH are unclear¹²⁻¹⁴. The aim of this study was to review published studies and use standard meta-analytic techniques to quantify the prognostic value of LDH in various solid tumors.

Methods

Data sources and searches. This analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines¹⁵. PubMed was searched for studies evaluating the LDH and survival in solid tumors from 1978 to 2014. We used various medical subject heading terms, including "I-lactate dehydrogenase", "prognosis", "multivariate analysis" and "proportional hazard model". Title/abstract words included "lactate dehydrogenase", "prognose", "prognostic", "multivariate analysis", "proportional hazard model". Title/abstract words included "lactate dehydrogenase", "proportional hazard model", "COX proportional hazard model" and "COX models". The full search strategy is described in the Supplementary Methods (available online).

Study selection. Inclusion criteria for the primary analysis were as follows: 1) studies of people with solid tumors reporting on the prognostic impact of LDH; 2) prospective or retrospective cohort design with a clearly defined source population and justifications for all excluded eligible cases; 3) sample size greater than 200; 4) statistical analysis using multivariate proportional hazards modeling that adjusted for clinical prognostic factors; and 5) reporting of the resultant adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) or a P value for overall survival (OS). For the secondary analyses, studies providing a HR for cancer-specific survival (CSS), progression-free survival (PFS), disease-free survival (DFS), or recurrence-free survival (RFS) were included as well.

Data extraction. OS was the primary outcome of interest. CSS, PFS, and DFS were secondary outcomes. Two authors (J.Z. and H.W.) independently extracted information using predefined data abstraction forms. The following details were extracted: name of first author, year of publication, number of patients included in analysis, disease site, disease stage (non-metastatic, metastatic, mixed [both non-metastatic and metastatic]), study type (prospective or retrospective), cutoff defining high LDH, and HRs and associated 95% confidence intervals for OS, PFS, DFS, or RFS as applicable. HRs were extracted preferentially from multivariate analyses where available. Where several HR values were given in an article, the value adjusted for most confounders was used.

Data synthesis. The meta-analysis was conducted initially for all included studies for each of the endpoints of interest. Subgroup analyses were conducted for predefined parameters such as disease site, disease stage and LDH cutoff, and all data were limited to multivariate analyses. Disease site subgroups were generated if at least three studies on that site were available; the remaining studies were pooled in a subgroup termed "other." LDH cutoff subgroups were < 250 U/L, 250–300 U/L, 301–400 U/L, and >400 U/L. In three studies, the effect of LDH was reported as a continuous variable; we pooled those studies separately. Univariate meta-regression model analysis was performed to evaluate the relationship between covariates (LDH cutoff) and the HR for OS.

Statistical analyses. The meta-analysis was performed with RevMan 5.2 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Estimates of HRs were weighted and pooled using the generic inverse-variance and random-effect model¹⁶. Analyses were conducted for all studies, and differences between the subgroups were assessed using methods described by Deeks et al.¹⁷. Publication bias was assessed by visual inspection of the funnel plot. Heterogeneity was assessed using Cochran Q and I² statistics. Meta-regression analysis was conducted using Stata12.0 software. All statistical tests were two-sided, and statistical significance was defined as P less than 0.05. No correction was made for multiple testing.

Results

Description of studies. Sixty-eight studies were included in the meta-analysis. The selection process for the systematic review is shown in Figure S1 and the characteristics of the included studies are shown in Table 1. A total of 31,857 patients were included and the median trial sample size was 363.

Overall survival. Sixty-three studies comprising 29,620 patients reported HRs for OS. All studies analyzed LDH as a dichotomous variable. The studies have clearly shown that upper limit of normal (ULN) remains common for high LDH. The median cutoff for high LDH was 250U/L (range = 200-1000).

Two of the 63 eligible studies (3.2%) reported a non-statistically significant HR. A forest plot of all studies is presented in Figure 1. Overall, LDH greater than the cutoff was associated with a HR for OS of 1.48 (95% CI = 1.43 to 1.53; P < 0.00001). As the heterogeneity among studies was significant (P < 0.00001; I² = 93%),

a random-effects model was applied. To explore potential sources of heterogeneity, we performed subgroup analysis in the following subgroups: disease site, tumor stage, and LDH subdivided by predefined cutoffs.

The effect of LDH on OS among disease subgroups is shown in Figure 2. The prognostic effect of LDH was highest in renal cell carcinoma (HR = 1.84, 95% CI = 1.35 to 2.51), followed by naso-pharyngeal carcinoma (HR = 1.82, 95% CI = 1.48 to 2.24), sarcoma (HR = 1.79, 95% CI = 1.30 to 2.47), melanoma (HR = 1.76, 95% CI = 1.56 to 1.98), prostate cancer (HR = 1.55, 95% CI = 1.06 to 2.26), colorectal cancer (HR = 1.52, 95% CI = 1.29 to 1.79), and lung cancer (HR = 1.50, 95% CI = 1.27 to 1.78). The HR for the subgroup of other unselected solid tumors was 1.69 (95% CI = 1.44 to 2.00). For the eight disease-site subgroups analyzed, there was statistically significant heterogeneity between disease sites (P < 0.00001), but no significant differences in the prognostic values of LDH between the subgroups (P for subgroup difference = 0.68).

The effect of LDH on OS among different disease stages is shown in Figure 3. The HRs were 1.54 (95% CI = 1.32 to 1.80) for nonmetastatic disease, 1.70 (95% CI = 1.59 to 1.82) for metastatic disease, and 1.20 (95% CI = 1.16 to 1.24) for a mixed group consisting of studies that included both metastatic and non-metastatic patients. There was statistically significant heterogeneity between disease stages (P < 0.00001). The prognostic value of LDH also varied significantly between different disease stages (P for subgroup difference < 0.00001).

The effect of LDH on OS among different cutoffs for LDH is shown in Figure 4. The HRs were 1.71 (95% CI = 1.38 to 2.12) for LDH cutoff < 250 U/L, 1.67(95% CI = 1.52 to 1.84) for LDH cutoff 250 to 300U/L, 1.69 (95% CI = 1.27 to 2.24) for LDH cutoff 301 to 400U/L, and 1.72(95% CI = 1.45 to 2.05) for LDH cutoff > 400 U/L. There was no statistically significant heterogeneity between the different cutoffs for LDH (P for subgroup difference = 0.99).

The scatter plot for the univariate meta-regression analysis is shown in Figure 5.A total of 63 studies was included in the metaregression analysis. Overall, there was no statistically significant association between LDH cutoff and the HR for OS (P = 0.614).

There was evidence of publication bias, with fewer small studies reporting negative results than would be expected (Supplementary Figure S2).

Three studies, comprising 1,766 patients, analyzed LDH as a continuous variable and reported HRs for OS. The pooled summary HR of these studies was 2.11 (95% CI, 1.35–3.28; P = 0.0003; $I^2 = 84\%$) per incremental LDH unit (Supplementary Figure S5).

Progression-free survival. Six studies, comprising 2,451 patients, reported HRs for PFS. Overall, LDH greater than the cutoff was associated with a HR for PFS of 1.70 (95% CI = 1.44 to 2.01; P < 0.00001; $I^2 = 13\%$). A forest plot is presented as Figure S3.

Disease-free (Recurrence-free) survival. A total of five trials, comprising 1,992 patients, reported HRs for DFS. Overall, LDH greater than the cutoff was associated with a HR for the endpoints of 1.86 (95% CI = 1.15 to 3.01; P = 0.01; $I^2 = 88\%$). A forest plot is presented in Figure S4.

Discussion

This is the first comprehensive meta-analysis of the prognostic relevance of LDH in solid tumors and it is based on a large pool of clinical studies (31,857 patients). We found a consistent effect of an elevated LDH on OS (HR = 1.48, 95%CI = 1.43 to 1.53) across all disease subgroups and stages. In addition, there is a trend toward a stronger prognostic value of LDH in metastatic disease compared with non-metastatic disease, which may reflect greater tumor burden. The prognostic impact of LDH on PFS and DFS (or RFS) is also robust. Interestingly, different cutoffs of LDH for different disease

Tabl	e 1 Baseline Ch	aracteris	tics of Incl	luded Studies								
Å	Fist Author	Year	Sample Size	LDH (High/Low)	Site	Stage	Cutoff (UI/L)	Outcome	Study type	Follow-up Time(mo)	Risk of Bias	Adjusted Variable
- 0	Laurie ⁴¹ Motzer ⁷	2007 2013	210 1059	109/47 NA	SCLC RCC	z₹	ULN 1.5ULN	OS PFS/OS	ር አ	A A A		Gender, ECOG PS, Anemia grade Ethnic origin, ECOG PS, Time from diagnosis to treatment, Bone metastases, Hb, Ca, Neutrophils, C. J. 11:00
ო	Polee ³²	2003	350	296/54	Esophageal	N + X	NIN	SO	R	٩N	_	Cytokine WHO Performance, Extent of disease, Paclitaxel
4	Han ³¹	2003	383	232/151	Many kinds	N + M	NIN	SO	Я	٩N	т	PS(WHO), White blood count, Hb, Number of sites of
5	Atzpodien ³⁰	2003	425	330/95	or cancer RCC	٤	220	SO	2	20 +	_	metastases Neutrophil counts, CRP, Time from diagnosis of tumour to metastatic disease, Number of metastatic sites, Bone
Ŷ	Bidard ⁵⁶	2012	267	121/99	Breast cancer	٤	ULN	PFS	۲	14.9	_	Triple negative, PS, Number of metastatic sites, CTC, 715-05-05-05-05-05-05-05-05-05-05-05-05-05
\sim	Culp ⁴⁷	2010	566	107/366	RCC	٤	618	SO	٩	20	_	CALD-5, CTFKA ZL-1, CEA,ALF, CHNDEA Albumin, ALP, Hb, Metastasectomy at any time, Liver metastasis, Clinical tumor classification, Fuhrman nuclear grade, No. of metastatic sites at CN, Sarcomatoid dedifferentiation, Clear cell histology,
ω	Pierga ²⁸	2001	1336	1039/ 297	Breast cance	٤	NIN	SO	٩	AN	_	treatment Karnofsky index, Disease free interval, No. of metastatic sites, Liver involvement, Adjuvant
6	Cook ³⁷	2006	635	566/69	HRPC	٤	454	SO	ъ	٩N	_	chemonterapy Age, PSA, Hb, Albumin, Analgesics, ECOG, NTx, Age v
10	Wan ⁸	2013	400	367/33	Nasopharyngeal	z	245	DFS/OS	R	NA	_	bar Age, Tumor stage, Node stage
Ξ	Mekenkamp°	2012	1010	637/365	Colorectal cancer	٤	NIN	SO	ĸ	NA	_	Diameter, Invasion depth, Lymph node status, Number lymph nodes, Number positive lymph nodes, MMR
12	Sougioultzis ⁵⁴	2011	311	137/173	Gastric carcinoma	٤	225	SO	2	AN	<u>ب</u>	status, KKAS mutation status, BKAF mutation status Palliative gastrectomy, Chemotherapy, Liver metastasis, Abdominal/Peritoneal metastasis, Histological grade, CA72–4, Weight loss, Blood
13	Zhou ⁶¹	2012	465	424/31	Nasopharyngeal	N + X	245	DFS/OS	Я	44.7	_	nansusions N category, T category, Age
14	Lagerwaard ²³	1999	1292	1081/ 211	carcinoma Many kinds of cancer	z	NIN	SO	R	AN	_	PS, Number and distribution of brain metastases, Site of primary tumor, Histology, Interval between primary tumor and brain metastess, Systemic tumor activity,
15	Aoe ³⁵	2005	309	448/157	Lung cancer	Ν + Υ	450	SO	Ъ	ΑN	т	Anemia, TNM stage ECOG PS, Sex, Histologic type,
16	Bacci ³⁸	2007	742	464/278	Ewing's sarcoma	N + N	NIN	SO	R	AN	_	Age Pelvis, Other sites, Interval symptoms to diagnosis, Fevore
1	Armstrong ⁵⁵	2012	404	264/140	RCC	٤	NIN	OS	R	٩N	т	Treatment, Interaction term, KPS, Prior nephrectomy,
18	Gripp ⁴⁰	2007	205	130/75	Many kinds	N + N	240	SO	۹.	٩N	_	No. or metastatic sites, Corrected catcium, rip VBC, Dyspnear, Morphine, KPS, Brain metastasis, Colocoted
19	Giaccone ³⁶	2005	216	AA	SCLC	z	NIN	OS	۲	AN	т	Contractor, preus Sex, Chest radiotherapy, PCI, Platelets



Table 1 | Continued

Adjusted Variable	Kamofsky PS, Hb, Calcium, Time from initial RCC diaanosis to start of interferon-alpha therapy	Sex, Age, Fever, Anemia, Axial location, Raj attion therary only for local control. Type of chemotherary	regimen, Chemotherargy-induced necrosis KPS, Hb, Ca, Prior nephrectomy.	ECOG PS, TTD, Albumin, Lymphocytes	No 50% decline within 12 wk, Hb, Age ECOG PS, Number of metastatic sites, Time from	nephrectomy to metastatic disease, ALP, Ca PS, Stage, ALP, CEA, Sex	Age, Sex, PS, No. sites, Liver involvement, Primitive tumor. Time to metastasis. Adjuvant CT, ALP, CEA	ECOG PS, Skin rash Recurrence vs. metastasis. KPS. Liver metastasis	Peritoneal metastasis, ALP, CRP KPS. Pleural fluid alucose level. CRP. Pleural effusion.	Pleural thickening on chest CT, Platelet count	Platelet count, INM stage, ECOG PS, Sex, Histologic type Ane	North Sector And Sector National Number of traditional technology and the sector of th	Anorexis, mercanic programmer and the second s	Other sites, Interval symptoms to diagnosis, Treatment	Age, performance status, clinical presentation, disease localization, pathologic findings, PSA, PSA/ PAP ratio. CEA. AIP CRP	Erythrocyte sedimentation rate, Hb, ALP, GGT, Creatinine, Albumin	MYCN oncogene amplification, Abdominal tumor, Stage, VanillyImandelic (VMA) urinary excretion, Ferritin Neuron-seacific enclose (NSF)	ACC T category, AJCC N category, Age	Sex, Age, Metastasis at presentation, Lung metastasis, Post-treatment S-LDH level, Drug number of chemotherapy, Number of involved sites, Liver	menusus, pone menusus, Age, T classification, N classification	Age, Sex, PS, Histopathology, smoking status, Response after 1-line CT, First-line CT, PFS after 1-line	CI, secona-line CI ECOG-PS, Extensive disease, NLR
Risk of Bias	_	_	<u>ب</u>	т	т –	Т	_	тт	: т	: :	I	т	т	_	-	т	-	т	_	-	-	_
Follow-up Time(mo)	46	126	33	NA	A A A A	AN	AN	₹ Z Z	A Z		AN	AN	AN	NA	31	NA	AN	AN	AA	51.5	ΑN	NA
Study type	۲	ጽ	2	<u>م</u>	ድ ዋ	2	R	~~~~	: ~	: 1	×	አ	Ъ	R	ъ	2	2	ĸ	2	Ъ	2	R
Outcome	os	SO	SO	OS	S S	SO	SO	S O S O	os o		ŝ	SO	SO	SO	SO	OS	OS	SO	SO	DFS/OS	SO	SO
Cutoff (UI/L)	1.5 UIN	NIN	1.5ULN	AN	230 1.5ULN	NIN	NIN	ULN 220	500		450	500	502	240	400	400	1000	240	245	225	ULN	240
Stage	N + X	z	Z + X	× ×	Z + ₹₹	× N N	٤	Z Z + + \$ \$	Z +		Z + X	N + X	× ×	X + X	٤	× N N	X + X	× N ×	٤	Z	× ×	M + M
Site	RCC	Ewing's sarcoma	RCC	Many kinds of cancer	CRPC RCC	scic	Colorectal Cancer	NSCLC Pancreatic cancer	Pleural	mesothelioma	Lung Cancer	NSCLC	Many kinds of cancer	Osteosarcoma	Prostate Cancer	Bladder Cancer	Neuroblastoma	Nasopharyngeal	carcinoma carcinoma	Nasopharyngeal	NSCIC	SCIC
LDH (High/Low)	AA	238/121	٩Z	AN	164/90 222/52	147/137	283/252	A A N	₹Z		AN	177/45	94/115	1116/ 305	AA	٩N	162/106	ΝA	379/310	٩N	154/175	75/39
Sample Size	463	357	670	406	254 300	284	535	257 326	363		0	245	209	1421	241	202	246	533	689	601	329	499
Year	2002	2000	666 l	2011	1999 2007	1997	2011	2010 2009	2010		2004	2012	2010	2004	2007	1993	1997	2012	2013	2014	2013	2014
Fist Author	Motzer ²⁹	Bacci ²⁶	Motzer ²⁴	Feliu	Scher ²⁵ Escudier ³⁹	Kawahara ¹⁹	Chibaudel ⁵²	Kim ⁴⁸ Hashimoto ⁴⁶	Tanrikulu ⁵⁰	2 2 2	Ace	Giroux ¹⁰	Suh ⁴⁹	Bacci ³⁴	Saito ⁴²	Hannisdal ¹⁸	Tonini ²⁰	Li ⁵⁸	Jin ⁶⁵	Wei ⁷⁵	Sau ¹⁴	$Wang^{74}$
z	20	21	22	23	24 25	26	27	28 29	i OS			32	33	34	35	36	37	38	39	40	41	42



Tabl	e 1 Continued											
Ž	Fist Author	Year	Sample Size	LDH (High/Low)	Site	Stage	Cutoff (UI/L)	Outcome	Study type	Follow-up Time(mo)	Risk of Bias	Adjusted Variable
43	Yamaguchi ^z ₅	2014	206	AN	Neuroendocrine carcinoma of the	× ×	NIN	SO	2	ΝA	т	Age, Sex, PS, Primary site, Liver metastasis, First-line chemotherapy, Prior surgery
44	Halabi ^{zo}	2014	1050	565/482	aigestive system CRPC	٤	UIN	SO	Я	ΝA	_	ECOG PS, Disease site, Opioid analgesic use,
45	$Templeton^{73}$	2014	357	AA	CRPC	٤	1.2 ULN	SO	ъ	AN	т	Autonimit, rtb, r-2A,Aut Age, ECOG PS, Number of comorbidities, Gleason sum score. Lymph node metastatic only. Bone
												metastasis, Visceral metastasis, Liver metastasis, Hb, Albumin, ALP, PSA, PSA-doubling time, NLR
46	Du ⁶²	2013	286	197/89	RCC	N + N	1.5 ULN	DFS/OS	R	AN	_	Fibrinogen, Hb, Ca, T stage, Fuhrman grade, Tumor
47	Shinohara ⁶⁷	2013	473	388/34	RCC	٤	1.5 ULN	SO	R	NA	_	Time from initial diagnosis to metastasis, Hb, Ca, CRP, Liver metastasis, Bone metastasis, Lymph node
48	Poprach ⁷²	2014	319	285/34	RCC	Z	1.5 ULN	PFS/OS	R	15	 :	metastasts Time from diagnosis to TKI, Neutrophils, ECOG PS
50 50	Powles ^{oo} van Kessel ^{os}	2013 2013	204 290	52/55 152/138	Seminoma Colorectal Cancer	Z + ₹₹	1.5 ULN ULN	PFS OS	<u>ک</u> کر	A A A A	т –	Age, IPFSG score Gender, Age, Number of first line cycles, Metastases, Resettion prim. Tumour, Study-arm, Response
51	Giessen ⁶⁴	2013	215	270/201	Colorectal Cancer	٤	250	OS	R	55.4	_	caregory Liver-limited disease, N-stage of primary, KPS, ALP
52	Weide ⁶⁹	2013	372	263/175	Melanoma	٤	ULN	OS	Я	27	_	S100B, Cerebral metastases, First systemic therapy
53	Meckbach ⁷¹	2014	215	131/63	Melanoma	٤	NIN	SO	2	46		Brain metastasis
54	Durnali°3	2013	240	101/81	Osteosarcoma	Z + ¥	ULN	RFS/OS	R	51		Gender, ALP, Histological subtype, Metastasis at discussis Sussiand massian Tumor postasis rate
												aragnosis, ougroar margins, rumor necrosis rare, Postoperative chemotherapy, Surgery after recurrence, Chemotherapy after recurrence,
55	He ¹³	2013	239	154/82	Colorectal Cancer	٤	NIN	PFS/OS	R	AN	т	Age, Gender, Lines of chemotherapy,CEA,CA19-9, GGT AIP
56	Weide∞	2012	855	502/228	Melanoma	٤	NIN	SO	Я	AN		S100B, Time interval between initial diagnosis and stage IV diagnosis, Site of distant metastasis, Number
57	Shinohara ⁵⁹	2012	361	299/23	RCC	٤	1.5ULN	SO	R	21.5	_	of involved distant sites Time from initial diagnosis to treatment, Hb, Prognostic
58	Jakob ⁵⁷ Podition51	2012	677	263/97	Melanoma	٤2	NIN	Soc	2	12		Age, Gender, M1 Category, Mutation
۲ ۲	Dealklan	107	140	6/7/004	Melanoma	X		3	Ł		-	Age, Crientoresponse, Abornin, M-stage, Locarion of primary melanoma
60	Neuman ⁴⁵	2008	589	246/125	Melanoma	٤	200	SO	۵_	Ϋ́́	_	Sex, Age at diagnosis of stage IV disease, Antecedent stage, DFI, Site of disease, No. of organs involved, No. of materiore
61 62	Schmidt ⁴³ Bedikian ⁴⁴	2007 2008	363 616	317/46 358/258	Melanoma Melanoma	22	2ULN 618	PFS/OS OS	ሌ ሌ	50.4 NA		Sex, Site, ECOG PS, Leukocytes, Neutrophils ECOG PS, Disease stage, Metastatic sites, Visceral motorhand, Albumin Donana A trantant
63	Viganó ²⁷	2000	227	142/85	Many kinds of cancer	Z + ¥	ó18	SO	Z	AN	_	Primary tumor, Liver metastasis, Comorbility, Weight Primary tumor, Liver metastasis, Comorbidity, Weight Joss, ECOG PS, Nausea, Clinical estimation of survival, Albumin, Lymphocyte count



5

Ŷ	Fist Author	Year	Sample Size	LDH (High/Low)	Site	Stage	Cutoff (UI/L)	Outcome	Study type	Follow-up Time(mo)	Risk of Bias	Adjusted Variable
64	Tamura ²²	1998	253	NA	SCLC	Z + ≮	NIN	SO	Z	AN	т	Extent of disease, Number of metastatic sites, Albumin, Weicht loss
65	Eton O ²¹	1998	318	٩N	Melanoma	٤	225	SO	2	٩N	т	Albumin, Soft tissue and/or single visceral organ metastases (especially lung), Sex, Enrollment late in the decade
66	D'AMICO ⁷⁷	2005	494	AN	HRPC	٤	74- 2077	SO	2	15.6- 16.8	_	Hb, Age, ECOG PS, ALP, Treatment, PSA response duration, PSA
67	Halabi ^{z8}	2003	760	ΑN	HRPC	٤	173- 437	SO	R	ΑN	т	PS, Gleason, ALP, PSA, Visceral disease, Hb
68	Schellhammer ⁷⁹	2013	512	AN	CRPC	٤	84- 1662	SO	<u>م</u>	ΑN	_	PSA, Hb, ECOG, ALP, Gleason score
Abbr disea Lactic Ivmph	eviations: SCLC: small-cell1 se-free survival; RFS: recurr : dehydrogenas; ALP: alkali tocvtes: CRP: C-reaction pr	lung cancer; rence-free su ine phospha rotein: IPFSC	NSCLC: non-s rvival; M: met tase; PSA: pro itternational	mall-cell lung cancer astatic; N: non-meta: state specific antiger I Proanostic Factors 3	;RCC: renal cell carcinoma; H static; M + N: mixed (non-me n; Hb: hemoglobin; Ca: calci Study Group; CA19.9: carb	HRPC: hormone stastatic and m um; PS: Perforr ohvdrate antia	→refractory pros etastatic); R: ret mance Status; Ei en 19-9; CEA; (tate cancer; CRP rospective; P: pro COG PS: Easterr carcinoembryoni	C: castration refra ospective; L : low r Cooperative Onc ic antiaen: GGT: c	ctory prostate can isk; High: high risl cology Group Perf aamma-alutamyl tr	cer; ULN: up k; NA: not av ormance Sto anspeptidas	ae Ilimit of normal; OS: overall survival; PFS: progression-free survival; DFS aialable, PS: performance score, KPS: Karnofsky performance score ; LDH tus ; ALP: alkaline phosphatase; CTC: circulating tumor; NLR: neurophils, c. DFI: disasserfee interval

sites were reported in the included studies. However, the result of subgroups analysis for LDH cutoff showed that there was no association between LDH cutoff and reported HR for OS. This result was confirmed by meta-regression of LDH cutoff and HR for OS. Moreover, LDH was also related to poor prognosis in solid tumors when analyzed as a continuous variable. Our conclusions are supported by the fact that our selected studies were confined to those that used proportional hazards modeling to adjust for clinical prognostic factors and where the sample size was greater than 200.

There is a good biologic rationale for the use of LDH as a prognostic marker for cancer patients; however, the exact mechanism is not understood. One potential mechanism may be an association between LDH and the well-established phenomenon of oncogenicanaerobic glycolysis, or the Warburg effect⁵. This metabolic reprogramming is regulated by HIF-1 α , as well as myc, through the transcriptional activation of key genes encoding metabolic enzymes; these include LDH, which converts pyruvate to lactate. This process is closely associated with an increased risk of invasion, metastasis, and patient death⁷⁷.

These analyses have several important implications. First, they show that a high LDH is associated with worse outcome, which suggests that LDH may be a useful biomarker to direct therapeutic selection78,79. This is because LDH is under the translational control of HIF-1 α , as well as myc, and thus is regulated by key oncogenic processes, such as the phosphatidylinositol 3-kinase/Akt/TORC1/ hypoxia-inducible factor (PI3K/Akt/TORC1/HIF) pathway⁸⁰⁻⁸². A recent study has demonstrated that the TORC1 inhibitor, temsirolimus, could provide therapeutic benefit in patients with RCC and high LDH⁷⁹. Further work to investigate the predictive value of pretreatment LDH in other solid tumors may provide a more general insight into which patients derive benefit from TORC1 inhibition. Second, they show that increased LDH may be interpreted as reflecting high tumor burden or tumor aggressiveness. This suggests that dynamic changes of LDH level may be useful for predicting the prognosis in cancer patients after a primary operation, adjuvant chemotherapy, hormonal therapy, or radiotherapy⁶⁵. Third, LDH allows the identification of a subgroup of tumors with a worse outcome. It is essential in the treatment of cancer to distinguish between low- and high-risk patients, thereby allowing stratification for standard or intensified treatment protocols. It has been shown that LDH can be used as an effective biomarker to guide the selection of regorafenib in patients with colorectal cancer; patients with high LDH may not be optimal candidates for regorafenib⁸³.To adequately address these issues and dissect the complex relationship between LDH and cancer, future studies should be conducted within tumor- and stagespecific cohorts.

The strengths of this meta-analysis include the large sample size, estimation of HR using multivariate proportional hazards modeling that adjusted for clinical prognostic factors, and analysis of a massive dataset comprising a large pool of clinical studies. LDH is also likely to be a cancer-specific biomarker, given that it is rarely increased in patients without cancer⁸⁴. Thus, LDH may be a universal prognostic marker in cancer. To improve research in this area, studies with a more specific focus, such as those that address the impact of an individual LDH level on the prognosis of a homogeneous population of cancer patients (i.e., patients with the same cancer stage and sub-type), would likely be more informative.

These analyses have limitations. One of the main limitations is the significant heterogeneity between studies, although we used randomeffects models when pooling subgroup data. The heterogeneity in these studies could be explained by different patient characteristics or study designs. To facilitate interpretation, we grouped the patients by tumor type and tumor stage. Another limitation is that this is a literature-based analysis. It is compromised by the potential for publication bias, in which there is a tendency for predominantly positive results to have been published, thus inflating our estimate for the



				Hazard Ratio	Hazar	d Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% C	I IV, Rando	om, 95% Cl
Aoe 2004	0.3436	0.1085	1.9%	1.41 [1.14, 1.74]		-
Aoe 2005	0.3148	0.1074	2.0%	1.37 [1.11, 1.69]		-
Armstrong 2012	1.0332	0.1709	0.9%	2.81 [2.01, 3.93]		
Atzpodien 2003	0.2624	0.1339	1.4%	1.30 [1.00, 1.69]		.
Bacci 2000	0.3293	0.0923	2.5%	1.39 [1.16, 1.67]		
Bacci 2004	0.5676	0.2009	0.6%	1.00 [1.20, 2.70]		-
Bedikian 2008	0.0471	0.0948	2.4%	1.57 [1.43, 2.43]		-
Bedikian 2011	0.4357	0.1225	1.6%	1.55 [1.22, 1.97]		-
Chibaudel 2011	0.5878	0.1103	1.9%	1.80 [1.45, 2.23]		-
Cook 2006	0.7372	0.1558	1.1%	2.09 [1.54, 2.84]		
Culp 2010	0.5068	0.1407	1.3%	1.66 [1.26, 2.19]		-
Du 2013	0.005	0.0025	9.1%	1.01 [1.00, 1.01]		•
Durnali 2013	2.1988	0.7249	0.1%	9.01 [2.18, 37.32]		
Escudier 2007	0.5194	0.1888	0.7%	1.68 [1.16, 2.43]		
Eton 1998	0.5878	0.166	0.9%	1.80 [1.30, 2.49]		
Ciaccono 2005	0.1190	0.0322	0.9%	1.13 [1.06, 1.20]		-
Giessen 2013	0.000	0.1019	2.1%	1 27 [1 04 1 55]		-
Giroux 2012	0.6931	0.2005	0.7%	2.00 [1.35, 2.96]		
Gripp 2007	0.8755	0.2101	0.6%	2.40 [1.59, 3.62]		
Halabi 2014	0.3365	0.0959	2.3%	1.40 [1.16, 1.69]		+
Han 2003	0.4318	0.1359	1.3%	1.54 [1.18, 2.01]		-
Hannisdal 1993	0.4055	0.1582	1.0%	1.50 [1.10, 2.05]		
Hashimoto 2009	0.5977	0.1818	0.8%	1.82 [1.27, 2.60]		
He 2013	-0.0336	0.2162	0.6%	0.97 [0.63, 1.48]	_	
Jakob 2012	1.0116	0.1995	0.7%	2.75 [1.86, 4.07]		
Jin 2013	0.4669	0.0806	3.0%	1.60 [1.36, 1.87]		
Kawanara 1997 Kim 2010	0.6729	0.1433	1.2%	1.96 [1.48, 2.60]		
Lagenwaard 1000	0.7657	0.292	2.9%	2.19[1.24, 3.69]		-
Laurie 2007	0.4005	0.002	2.3%	1.36 [1.12, 1.65]		-
Li 2012	0.5068	0.2465	0.5%	1.66 [1.02, 2.69]		
Meckbach 2014	0.8329	0.1852	0.8%	2.30 [1.60, 3.31]		
Mekenkamp 2012	0.6152	0.1139	1.8%	1.85 [1.48, 2.31]		-
Mekenkamp2 2012	0.5008	0.1296	1.4%	1.65 [1.28, 2.13]		-
Motzer 1999	0.9002	0.1245	1.5%	2.46 [1.93, 3.14]		
Motzer 2002	1.1725	0.1726	0.9%	3.23 [2.30, 4.53]		
Motzer 2013	0.4517	0.1805	0.8%	1.57 [1.10, 2.24]		<u> </u>
Rieraa 2001	0.3507	0.1257	2.0%	2 00 [1 70 2 35]		÷
Polee 2003	0.0351	0.0023	1.0%	1 50 [1.10, 2.05]		
Poprach 2014	0.8242	0.2274	0.5%	2.28 [1.46, 3.56]		
Saito 2007	0.4818	0.2357	0.5%	1.62 [1.02, 2.57]		— —
Sau 2013	-0.2058	0.1259	1.5%	0.81 [0.64, 1.04]	-	+
Scher 1999	0.003	0.001	9.1%	1.00 [1.00, 1.00]		t
Schmidt 2007	0.7885	0.1625	1.0%	2.20 [1.60, 3.03]		
Shinohara 2012	0.6329	0.2519	0.4%	1.88 [1.15, 3.09]		
Shinohara 2013	0.47	0.1912	0.7%	1.60 [1.10, 2.33]		
Sougiouitzis 2011	0.5423	0.1289	1.5%	1.72 [1.34, 2.21]		_
Juli 2010	0.5499	0.1770	0.0%	1.73 [1.22, 2.40]		-
Tanrikulu 2010	0.8065	0.1765	0.8%	2.24 [1.58, 3.17]		
Templeton 2014	0.9243	0.213	0.6%	2.52 [1.66, 3.83]		
Tonini 1997	1.4061	0.6316	0.1%	4.08 [1.18, 14.07]		<u> </u>
van Kessel 2013	0.4028	0.1298	1.4%	1.50 [1.16, 1.93]		-
Viganó 2000	0.5878	0.2069	0.6%	1.80 [1.20, 2.70]		
Wan 2013	0.9658	0.3053	0.3%	2.63 [1.44, 4.78]		
Wang 2014	0.5939	0.1138	1.8%	1.81 [1.45, 2.26]		<u> </u>
Wei 2014	0.5446	0.176	0.8%	1.72 [1.22, 2.43]		1
vveide 2012	0.47	0.1059	2.0%	1.60 [1.30, 1.97]		_
Vvelue 2013 Vamaguchi 2014	0.47	0.1059	∠.U% 1 10/	1.00 [1.30, 1.97]		
ramayuuni ∠014 Zhou 2012	0.4318	0.149	1.1% 0.3%	1.04 [1.10, 2.06] 3.04 [1.63, 5.65]		<u> </u>
	1.1112	0.017	0.070	0.04 [1.00, 0.00]		
Total (95% CI)	00.063.000.70	u - 00 (5	100.0%	1.48 [1.43, 1.53]	II	
Test for overall effect: 2	Z = 22.95 (P < 0.000)	א) נס – וג 1)	- < 0.0000	17, 1~ = 93%	0.01 0.1 Favours I DH≪ cutoff	1 10 100 Favours LDH > cutoff

Figure 1 | Forest plots showing HR for OS for LDH greater than or less than the cutoff. HRs for each study are represented by the squares, the size of the square represents the weight of the study in the meta-analysis, and the horizontal linecrossing the square represents the 95% confidence interval (CI). All statistical tests were two-sided.



1.1.4 Read	Study or Subaroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio	Hazaro IV Rando	d Ratio
Amestering 2012 1 0032 0 1700 0 0% 2 28 [0.0.389]	1.7.1 Renal		52	weight	10, Randolli, 3376 C	I IV, Rande	111, 35 % CI
Algooden 0.2824 0.138 1.48 1.30 10.10 10.10 Exacute: 2007 0.514 0.6202 0.71 1.66 11.02 10.10 McCar: 1090 0.0002 0.71 1.66 11.02 10.10 10.10 McCar: 2002 1.725 0.726 0.95 3.20 12.44 1.55 1.66 11.05 1.66 11.05 1.66 1.05 1.66 1.05 1.66 1.05 1.05 1.05 1.05 1.05 1.06	Armstrong 2012	1.0332	0.1709	0.9%	2.81 [2.01, 3.93]		-
Lule_2010 0.008 0.109 1.00	Atzpodien 2003	0.2624	0.1339	1.4%	1.30 [1.00, 1.69]		
$\begin{aligned} \sum_{k=0}^{k=0} 0007 & 0.9134 & 0.0486 & 0.048 & 0.176 & 0.186 & 1.18 & 2.49 \\ Moder 1600 & 0.0022 & 0.1726 & 0.786 & 0.95 & 3.28 & 12.94 & 13.94 \\ Moder 2020 & 1.725 & 0.726 & 0.95 & 3.28 & 12.94 & 13.94 \\ Moder 2020 & 0.47 & 0.912 & 0.75 & 0.95 & 3.28 & 12.94 & 13.94 \\ Moder 2020 & 0.47 & 0.912 & 0.75 & 0.95 & 3.28 & 12.94 & 13.94 \\ Moder 2020 & 0.47 & 0.912 & 0.75 & 0.95 & 3.28 & 12.94 & 13.94 \\ Moder 2020 & 0.47 & 0.912 & 0.75 & 0.95 & 3.28 & 12.94 & 10.91 & 10.23 \\ Moder 2010 & 0.47 & 0.912 & 0.75 & 1.061 & 10.2 & 0.0001 \\ Moder 2010 & 0.4368 & 0.1085 & 1.95 & 1.41 & 11.41 & 1.74 \\ Meac 2005 & 0.148 & 0.106 & 1.95 & 1.41 & 11.41 & 1.74 \\ Meac 2005 & 0.148 & 0.106 & 1.95 & 1.41 & 11.41 & 1.74 \\ Meac 2005 & 0.148 & 0.106 & 1.95 & 1.11 & 10.5 & 2.29 \\ Moder 2010 & 0.3468 & 0.1085 & 1.95 & 1.21 & 11.5 & 2.20 \\ Moder 2010 & 0.078 & 0.228 & 0.295 & 2.19 & 12.3 & 3.80 \\ Moder 2010 & 0.078 & 0.228 & 0.039 & 1.28 & 1.12 & 10.5 & 1.20 \\ Moder 2010 & 0.078 & 0.228 & 0.039 & 1.28 & 1.12 & 1.65 & 1.04 \\ Meac 2005 & 0.044 & 0.028 & 0.128 & 1.58 & 1.26 & 1.27 & 1.28 & 1.2$	Culp 2010	0.5068	0.1407	1.3%	1.66 [1.26, 2.19]		
$\begin{aligned} \begin{aligned} & Decay and points of the set of the$	Du 2013 Ecoudior 2007	0.005	0.0025	9.1%	1.01 [1.00, 1.01]		
Notices 2020 11725 0.1726 0.5% 1.22 2.20 4.5% Popush 2014 0.8242 0.221 1.4% 1.57 1.1% 1.1% 1.5% Popush 2014 0.8242 0.221 0.4% 1.8% 1.5% 1.4% 1.5% 1.4% 1.5% 1.4% 1.5% 1.4% 1.5% 1.4% 1.5% 1.4% 1.5% 1.4% 1.5% 1.5% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.5% 1.5% 1.5% 1.1% 1.0% 1.1%	Motzer 1999	0.9002	0.1000	1.5%	2 46 [1 93 3 14]		-
Access 2015 0.4617 0.1685 1.27 [11:0.224] Bincham 2012 0.6328 0.2214 0.6% 1.08 [11:0.223] Bincham 2012 0.6328 0.2214 0.6% 1.08 [11:0.224] Bincham 2012 0.6328 0.2214 0.6% 1.08 [11:0.224] Bincham 2012 0.6328 0.2214 0.6% 1.08 [11:0.226] Finance 2001 0.6328 0.1024 1.002 0.00001) I* = 55%. Tare for ownall effect. 2 = 3.8 (P = 0.00001) 1.255 1.255 1.255 1.255 Bincham 2012 0.0001 2.056 1.256 1.251 1.251 1.251 Bincham 2012 0.0001 2.785 1.251 1	Motzer 2002	1 1725	0.1726	0.9%	3 23 [2 30 4 53]		-
Pergrand: 2014 0.8242 0.2274 0.5% 1.28 [14.3.56] Shoubar 2013 0.47 0.1912 0.7% 1.80 [15.2.33] Shoubar 2013 0.47 0.1912 0.7% 1.80 [15.2.33] Shoubar 2013 0.47 0.1912 0.7% 1.80 [15.2.33] The for overall effect 2 = 3.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 3.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 3.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 3.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 3.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 3.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 3.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 05. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 75. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 40. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 40. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 40. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 40. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 40. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 40. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 30. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 30. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 30. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 30. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 30. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 30. The for overall effect 2 = 0.8 (<i>P</i> = 0.0001): <i>P</i> = 30. Th	Motzer 2013	0.4517	0.1805	0.8%	1.57 [1.10, 2.24]		
Shouhan 2012 0.6228 0.2519 0.4% 1.88 [115, 2.09] Shouhan 2012 0.7% 1.00 7.0191 0.7% 1.08 [115, 2.09] Shouhan 2012 0.7% 1.00 7.0 0.0001; I = 255 Test for consult stort: 2 = 3.5 (P = 0.001) T.2 Lung Ace 2000 0.348 0.1085 1.09% 1.41 [1.4, 1.74] Ace 2000 0.3486 0.1085 1.09% 1.42 [1.5, 1.09] Consult of the consult stort: 2 = 3.5 (P = 0.001) T.2 Lung Ace 2000 0.3486 0.1085 1.09% 1.41 [1.4, 1.52] The consult stort: 2 = 3.5 (P = 0.001) The consult stort: 2 = 4.5 (P = 0.001) The consult stort: 2	Poprach 2014	0.8242	0.2274	0.5%	2.28 [1.46, 3.56]		
Sheahan 2013 0.47 1.00	Shinohara 2012	0.6329	0.2519	0.4%	1.88 [1.15, 3.09]		
Subtable (1995; C) 18.3% 1.4.1.39, 2.51 Test for convall affect: Z = 3.33, P = 0.00001) 1.4.1.93, 2.51 1.4.1.93, 2.51 Advectory and the decision of the second affect of the second af	Shinohara 2013	0.47	0.1912	0.7%	1.60 [1.10, 2.33]		-
Heterogenety: Tur ¹ = 0.25; Ch ¹ = 188.37, df = 10 (P < 0.00001); l ² = 95% Field roward infect 2 = 3.81 (P = 0.0001) 17.2 Lung Aes 2005 0.058 0.058 0.198 0.139 1.39; 1.31 [1.11, 1.6] Sincone 2005 0.058 0.058 0.198 0.139; 1.31 [1.11, 1.6] Sincone 2005 0.058 0.058 0.198 0.139; 1.31 [1.11, 1.6] Sincone 2005 0.058 0.058 0.159 0.15% 0.027 0.027 0.027 0.028 0.128 1.28; 1.31 [1.12, 1.6] Sincone 2007 0.027 0.027 0.028 0.128 1.29; 1.31 [1.12, 1.6] Sincone 2007 0.027 0.028 0.138 1.29; 1.31 [1.12, 1.6] Sincone 2007 0.027 0.028 0.138 1.29; 1.31 [1.12, 1.6] Sincone 2007 0.027 0.028 0.138 1.29; 1.31 [1.12, 1.6] Sincone 2007 1.32 [1.12, 1.13] Sincene 2007 1.32 [1.12, 1.2] 1.33 [1.12, 1.6] Sincone 2007 1.32 [1.12, 1.2] 1.33 [1.12, 1.6] Sincene 2007 1.32 [1.12, 1.2] 1.33 [1.12, 1.6] Sincene 2007 1.32 [1.12, 1.2] 1.34 [1.12, 1.2] 1	Subtotal (95% CI)			18.3%	1.84 [1.35, 2.51]		•
Tes for consult effect: Z = 3.83 (P = 0.0001) 1.72 Lung Ava: 2004 0.3436 0.1058 0.159 1.3% 1.41 [1.14, 1.74] Ava: 2005 0.3436 0.1074 2.0% 1.37 [1.11, 1.0] Glaccome 2005 0.0348 0.1074 2.0% 1.37 [1.11, 1.0] Glaccome 2005 0.0348 0.1074 2.0% 1.20 [1.8, 2.69] Test for consult effect: Z = 0.830 0.108 0.108 0.108 0.200 0.178 Sin 2010 0.0720 0.143 1.2% 1.99 [1.4, 2.69] Test for consult effect: Z = 0.0001; I ⁺ = 75% Sin 2013 0.0208 0.159 1.5% 0.81 [0.6, 1.0] Hearogenety: Tau ⁺ = 0.05, Ch ⁺ = 38.06, d ⁻ = 9 (P = 0.0001; I ⁺ = 75% Sin 2013 0.0208 0.159 1.5% 0.81 [1.1, 1.2] Test for consult effect: Z = 4.78 (P = 0.0001; I ⁺ = 75% Sin 2013 0.0459 0.156 0.168 0.4% 1.20 [1.2, 1.77] Hearogenety: Tau ⁺ = 0.05, Ch ⁺ = 38.06, d ⁻ = 9 (P = 0.001; I ⁺ = 40% Test for consult effect: Z = 4.78 (P = 0.0001; I ⁺ = 75% Sin 2013 0.047 0.1598 0.159 1.1% 2.049 Test for consult effect: Z = 4.78 (P = 0.0001; I ⁺ = 40% Test for consult effect: Z = 6.83 (P < 0.0001) T.2 Metanoma Beckkina 2007 0.0785 0.1626 0.0% 1.20 [1.0, 3.0] Test for consult effect: Z = 6.83 (P < 0.0001) T.4 Metaopharyngeal in 2013 0.047 0.1599 2.0% 1.20 [1.50, 1.57] Test for consult effect: Z = 6.83 (P < 0.0001) T.4 Metaopharyngeal in 2013 0.0468 0.0468 0.056 0.30% 1.60 [1.50, 1.87] Test for consult effect: Z = 6.83 (P < 0.0001) T.4 Metaopharyngeal in 2013 0.047 0.1598 2.03% 1.26 [1.62, 2.26] Test for consult effect: Z = 5.70 (P = 0.000); I ⁺ = 35% Test for consult effect: Z = 5.70 (P = 0.000); I ⁺ = 35% Test for consult effect: Z = 5.70 (P = 0.000); I ⁺ = 35% Test for consult effect: Z = 2.58 (P = 0.000) T.4 Metaopharyngeal in 2013 0.0478 0.1169 1.59; 1.27 [1.0, 1.16, 1.69] Solution (19% C) T.4 Colorectal T.4 Colorectal Test for consult effect: Z = 2.58 (P = 0.000) T.7 Solution T.7 Solution T.7 Solution T.7 Solution T.7 Solution T.7 Solution T.7 A Colorectal T.7 Solution T.7 A Colorectal T.7 Solution T.7 Solution T.7 Solution T.7 Solution T.7 Solution T.7 Solution T.7 Solution T.7 Solution T.7 Solution	Heterogeneity: Tau ² =	0.25; Chi ² = 188.37, c	if = 10 (F	> < 0.0000	01); I ² = 95%		
1.72 Lung have 2005 0.3446 0.1085 1.9% 1.41 (1.14, 1.74) 1.44 (1	Test for overall effect:	Z = 3.83 (P = 0.0001)					
Ace 2005 0 4340 0 1074 2 0% 1 41 114, 174 0 482 205 0 4585 0 1399 1 3% 1 71 113, 2 29 0 453 0 1265 0 139 1 3% 1 71 113, 2 29 0 453 0 1265 0 126 0 43 0 457 0 1262 0 433 1 2% 1 96 1 43, 269 0 4130 0 0 417 0 2026 0 27% 1 91 143, 269 0 4130 0 0 417 0 2026 0 27% 1 91 143, 269 0 4130 0 0 417 0 428 0 248 1 144, 269 0 4130 0 0 417 1 40 [104, 114, 124] 0 417 1 40 [104, 114, 124] 0 4180 0 0 418 0 248 1 448 1 448 1 448, 269 0 4130 0 0 419 0 0385 0 5197 1 1.1% 1 40 [104, 114, 124] 0 4180 0 0 418 0 048 0 24% 1 49 [12, 17, 17] 1 400 0 0 114 0 0048 0 24% 1 49 [12, 17] 1 400 0 0 114 0 048 0 24% 1 49 [12, 17] 1 400 0 0 114 0 048 0 24% 1 52 [12, 17] 1 400 0 0 114 0 048 0 24% 1 52 [12, 17] 1 400 0 0 114 0 048 0 140 0 140 1 140, 124, 143 1 400 124, 111, 145, 229 1 400 0 0 114 0 048 0 24% 1 52 [12, 17] 1 400 0 0 114 0 048 0 140 0 140 1 140, 124 1 400 0 0 114 0 048 0 140 0 140 0 140 0 140 0 140 0 140 0 140 1 400 0 140 0 140 0 048 0 140 0	1.7.2 Lung						
beb 2005 0.0514 0.074 2.0% 1.37 11.11, 1.69 Discourse 2005 0.0558 0.256 0.7% 2.00 1.35, 2.64 Discourse 2007 0.0375 0.0376 0.0316 0.266 0.133, 1.24, 1.63 Discourse 2007 0.0375 0.0391 0.2385 0.159 1.5% 1.04 Discourse 2007 0.0375 0.159 1.5% 1.04 1.04 1.88 Mang 2014 0.0358 0.159 1.5% 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.40 1.1% 1.55 1.2 1.1% 1.5% 1.5% 1.2% 1.1% 1.5% 1.2% 1.1% 1.5% 1.2% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2% 1.1% 1.2%	Aoe 2004	0.3436	0.1085	1.9%	1.41 [1.14, 1.74]		-
Glacobe 2005 0.2885 0.1399 1.3% 1.71 1.30, 2.29 Knowhan 1997 0.0720 0.143 1.2% 1.26 1.48, 2.69 The second	Ace 2005	0.3148	0.1074	2.0%	1.37 [1.11, 1.69]		-
$ \begin{array}{c} \text{Bicus 2012} \\ \text{Grave 2012} \\ \text{Grave 2012} \\ \text{Grave 2017} \\ \text{Or 285} \\ Or 2$	Giaccone 2005	0.5365	0.1399	1.3%	1.71 [1.30, 2.25]		-
Swaham 1967 0.0720 0.143 1.2% 1.66 [1.48, 2.60]	Giroux 2012	0.6931	0.2005	0.7%	2.00 [1.35, 2.96]		-
$ \begin{array}{c} \mbox{Grave} 2007 & 0.0765 & 0.295 & 0.295 & 0.1124 & 0.899 \\ \mbox{Sub 2013} & 0.0266 & 0.156 & 0.157 & 1.14 & 1.40 & 1.04 & 1.04 & 1.04 \\ \mbox{Sub 2013} & 0.0266 & 0.157 & 1.14 & 1.04 & 1.04 & 1.04 & 1.04 \\ \mbox{Sub 2013} & 0.0500 & 0.113 & 1.06 & 1.04 & 1.04 & 1.04 & 1.04 \\ \mbox{Sub 2013} & 0.0500 & 0.113 & 1.06 & 1.04 & 1.04 & 1.04 & 1.04 \\ \mbox{Sub 2013} & 0.0500 & 0.113 & 1.06 & 1.05 & 1.25 & 1.25 & 1.25 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 2.4\% & 1.52 & 1.26 & 1.28 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 2.4\% & 1.52 & 1.26 & 1.28 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 2.4\% & 1.52 & 1.26 & 1.28 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 0.7\% & 2.75 & 1.08 & 4.07 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 0.7\% & 2.25 & 1.168 & 4.07 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 0.168 & 0.9\% & 1.20 & 1.10 & 1.00 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 0.168 & 0.9\% & 1.20 & 1.10 & 1.00 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 0.168 & 0.9\% & 1.20 & 1.10 & 1.00 \\ \mbox{Sub 2012} & 0.0149 & 0.0648 & 0.168 & 0.9\% & 1.20 & 1.00 & 1.00 \\ \mbox{Sub 2012} & 0.017 & 0.168 & 0.07\% & 1.20 & 1.00 & 1.00 \\ \mbox{Sub 201} & 0.057 & 0.168 & 0.0\% & 1.60 & 1.10 & 1.07 \\ \mbox{Sub 201} & 0.057 & 0.0500 & 0.050 & 0.056 & 0.5\% & 1.60 & 1.00 & 1.00 \\ \mbox{Sub 201} & 0.057 & 0.0500 & 0.056 & 0.5\% & 1.60 & 1.10 & 1.00 \\ \mbox{Sub 201} & 0.056 & 0.056 & 0.05\% & 1.26 & 1.10 & 1.20 & 0.000 \\ \mbox{Sub 201} & 0.056 & 0.056 & 0.05\% & 1.26 & 1.10 & 1.20 & 0.000 \\ \mbox{Sub 201} & 0.056 & 0.056 & 0.05\% & 1.26 & 1.10 & 1.20 & 0.000 \\ \mbox{Sub 201} & 0.056 & 0.056 & 0.056 & 0.25\% & 1.60 & 1.02 & 2.60 \\ \mbox{Sub 201} & 0.056 & 0.056 & 0.056 & 0.25\% & 1.60 & 1.02 & 2.60 \\ \mbox{Sub 201} & 0.050 & 0.032 & 0.010 & 1.1\% & 1.00 & 1.00 & 1.00 \\ \mbox{Sub 201} & 0.050 & 0.026 & 0.057 & 0.200 & 1.15 & 1.00 & 1.00 & 1.00 \\ \mbox{Sub 201} & 0.050 & 0.026 & 0.057 & 0.200 & 1.15 & 1.20 & 0.15 \\ \mbox{Sub 201} & 0.050 & 0.027 & 0.0500 & 1.25\% & 1.20 & 1.10 & 1.20 & 0.000 \\ \mbox{Sub 201} & 0.050 & 0.027 & 0.0500 & 1.25\% & 1.20 & 1.10 & 1.00 & 1.00 & 1.00 & 1.00 \\ $	Kawahara 1997	0.6729	0.1433	1.2%	1.96 [1.48, 2.60]		-
Lastie 2007 0.307 0.0981 2.2% 1.38 [1:12, 1.65] Size 2013 0.2368 0.1519 1.5% 0.61 [0.44, 1.64] Farmun 1968 0.336.0 0.158 1.5% 1.64 [1.64, 2.66] Wang 2014 0.056.0 0.97 $+ 0.00001$); $t^1 = 75%$. 1.65 [1.64, 2.66] Hancragnenity, Tua' = 0.05; 0.07 $+ 0.256$; 1.65 [1.22, 1.57] 1.55 [1.22, 1.67] 1.55 [1.22, 1.67] Beckkin 2011 0.457 0.1225 1.56 [1.22, 1.67] 1.56 [1.22, 1.67] Econ 1968 0.587 0.1225 1.56 [1.22, 1.67] 1.56 [1.22, 1.67] Schwidz 2007 0.776 0.1698 2.20 [1.66, 0.30]	Kim 2010	0.7857	0.292	0.3%	2.19 [1.24, 3.89]		
Sau 2013	Laurie 2007	0.3075	0.0991	2.2%	1.36 [1.12, 1.65]		-
Tarum 1988 0.386 0.1517 1.1% 1.40 [1.04, 1.88] Wang 2014 0.559 0.1138 1.45 [1.45, 2.26] Subtoal [95% C] 1.40% 1.50 [1.27, 1.78] Subtoal [95% C] 1.40% 1.50 [1.27, 1.78] Beckkin 2008 0.4149 0.048 2.4% 1.52 [1.26, 1.83] Seckkin 2008 0.4149 0.048 2.4% 1.52 [1.22, 1.83] Seckkin 2010 0.4149 0.048 2.4% 1.52 [1.22, 1.83] Seckkin 2010 0.4149 0.048 2.4% 1.52 [1.22, 1.87] Seckkin 2010 0.4576 0.1262 1.5% 1.22 [1.68, 4.07] The start or overall effect 2 = 4.76 [P < 0.0001] Weckbach 2012 0.07 0.1287 1.5% 1.42 [1.11, 1.82] The start of the start 2.2 (1.11, 1.82] Schwid 2007 0.768 0.1282 1.5% 1.22 [1.61, 3.03] Henrogravely, Tau' = 0.02; Ch' = 16 2.75 (1.64, 4.47] Henrogravely, Tau' = 0.02; Ch' = 16 2.75 (1.64, 2.48) Henrogravely, Tau' = 0.02; Ch' = 16 2.75 (1.64, 2.44) Henrogravely, Tau' = 0.02; Ch' = 16 0.466 0.05% 1.60 [1.36, 1.87] Li 2012 0.44 0.544 0.176 0.8% 1.72 [1.22, 2.43] Henrogravely, Tau' = 0.02; Ch' = 16 0.26; H = 49%. Test for overall effect: Z = 8.30 [P < 0.0001] 1.74 Henrogravely, Tau' = 0.02; Ch' = 60 2.4f = 4 (P = 0.20); H = 34%. Test for overall effect: Z = 5.70 (P < 0.00001) 1.75 Protate Cock 2006 0.7372 0.1568 1.1% 2.09 [1.54, 2.84] Henrogravely, Tau' = 0.02; Ch' = 60 2.4f = 4 (P = 0.20); H = 34%. Test for overall effect: Z = 5.70 (P < 0.00001) 1.75 Protate Cock 2006 0.7372 0.1568 1.1% 2.09 [1.54, 2.84] Henrogravely, Tau' = 0.02; Ch' = 60 2.4f = 4 (P = 0.20); H = 34%. Test for overall effect: Z = 5.70 (P < 0.00001) 1.75 Protate Cock 2006 0.7372 0.1568 1.1% 2.09 [1.54, 2.84] Henrogravely, Tau' = 0.02; Ch' = 60 2.4f = 4 (P = 0.20); H = 34%. Test for overall effect: Z = 5.70 (P < 0.00001) 1.75 Protate Cock 2006 0.7372 0.1568 1.1% 2.09 [1.54, 2.84] Henrogravely, Tau' = 0.02; Ch' = 60 2.4f = 4 (P = 0.20); H = 35%. Test for overall effect: Z = 2.86 (P < 0.00001) 1.75 Protate Cock 2006 0.7578 0.2098 0.6% 1.80 [1.42, 2.23] Henrogravely, Tau' = 0.02; Ch' = 15.4, 4 (P < 0.00001); H = 95%. Test for overall effect: Z = 3.86 (P < 0.00001) 1.75 Protate Deckalotal (29%, C) .00;	Sau 2013	-0.2058	0.1259	1.5%	0.81 [0.64, 1.04]	-	
$\begin{split} & \text{Marg} 2014 & 0.553 & 0.133 & 1.86 & 1.81 [1.45, 2.26] & 1.40 & 0.50 & 0.74 & 0.80 & 0.74 & 0.0001); P = 75\% & Fact for overall affect 2 = 4.7 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 7.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 7.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 7.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 7.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 7.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 7.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 75\% & \text{Fact for overall affect 2 = 0.8 & (P < 0.0001); P = 93\% & \text{Fact for overall affect 2 = 0.7 & (P < 0.0001); P = 93\% & \text{Fact for overall affect 2 = 0.7 & (P < 0.0001); P = 93\% & \text{Fact for overall affect 2 = 0.7 & (P < 0.0001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.0001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.0001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.0001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & \text{Fact for overall affect 2 = 2.5 & (P = 0.010); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & \text{Fact for overall affect 2 = 7.0 & (P < 0.00001); P = 93\% & $	Tamura 1998	0.3365	0.1517	1.1%	1.40 [1.04, 1.88]		-
Subtrain (19% C) 140% C) 140% C) 120% C) 120% C) 120% C) 1277 C) 127% C	Wang 2014	0.5939	0.1138	1.8%	1.81 [1.45, 2.26]		T
$\begin{aligned} relation operating the 2 0.05, 0.11 = 0.05, 0.11 = 0.0001); 1.12 = 0.05, 0.11 = 0.05, 0.11 = 0.00001) \\ 1.13 = 0.05, 0.00001 = 0.05, 0.15, 0.00001) \\ 1.13 = 0.05, 0.00001 = 0.05, 0.15, 0$	Subtotal (95% CI)			14.0%	1.50 [1.27, 1.78]		•
$ \begin{array}{c} 1.3 \text{ Melanoma} \\ \begin{array}{c} \text{Berlikin} 2010 \\ \text{Berlikin} 2011 \\ 0.457 \\ 0.125 \\ 1.01 \\ 0.157 \\ 0.125 \\ 0$	Heterogeneity: 1 au ^e = Test for overall effect:	0.05; Chi* = 36.06, df Z = 4.78 (P < 0.0000*	=9(P< I)	0.0001);	I* = 75%		
14 metanoma Bedikan 2001 0.4194 0.0948 2.4% 1.52 [1.26, 1.83] Bedikan 2011 0.4357 0.1225 1.6% 1.55 [1.22, 1.57] Bedikan 2011 0.4357 0.125 1.6% 1.55 [1.22, 1.57] Bedikan 2011 0.4357 0.125 1.6% 1.55 [1.22, 1.57] Mackbach 2014 0.8329 0.1825 0.6% 2.30 [1.60, 1.30] 1.7 Weide 2012 0.47 0.199 2.0% 1.60 [1.30, 1.57] 1.7 Weide 2013 0.47 0.199 2.0% 1.60 [1.30, 1.57] 1.7 Traft for overall effect: 2 = 8.83 (P < 0.0006		,					
Demandary core is a set of the s	1.7.3 Melanoma	o ·	0.0015	0.404	4 50 14 00 4 777		-
$\begin{aligned} \begin{aligned} & \text{permanur } u_1 & \text{u}_{437} & \text{u}_{1225} & \text{l}_{578} & \text{l}_{158} & \text{l}_{122} & \text{l}_{217} & \text{l}_{158} & \text{l}_{122} & \text{l}_{137} & \text{l}_{158} & \text{l}_{123} & \text{l}_{158} & l$	Bedikian 2008	0.4194	0.0948	2.4%	1.52 [1.26, 1.83]		l÷
$\begin{aligned} \begin{array}{c} \label{eq:constraint} & 0.0000 & 0.00000 & 0.0000 & 0.0000 & 0.00000 & 0.00000 & 0.0000 & 0.0000 & 0.0$	peuikian ∠011 Eton 1999	0.4357	0.1225	1.6%	1.00 [1.22, 1.97]		-
$\begin{aligned} \begin{array}{c} \label{eq:constraint} & 1 & 01 & 00 & 01 & 00 & 01 & 01 & 00 & 01 & 01 & 00 & 01 & 00 &$	Lion 1990 Jakob 2012	0.58/8	0.100	0.9%	2 75 [1 86 / 071		
Neuman 2008 -3267 -1267 1267 1268 -1261 120 -2019 Note 2012 0.7865 0.1267 1267 1268 120	Meckbach 2014	0.8320	0.1852	0.8%	2.30 [1.00, 4.07]		
Semial 2007 0.7825 0.1825 1.055 2.20 [$\pm 60.3.03$] whick 2013 0.47 0.1039 2.0% 1.60 [± 30.167] whick 2013 0.47 0.1039 2.0% 1.60 [± 30.167] whick 2013 0.47 0.1099 2.0% 1.60 [± 30.167] which 2013 0.47 0.1099 2.0% 1.60 [± 30.167] which 2013 0.47 0.1099 2.0% 1.60 [± 30.167] the corporate fact: $Z = 8.83 (P < 0.0001)$ 1.7.1 A Nasopharyngeal in 2013 0.4669 0.0806 3.0% 1.60 [± 36.187] which 2012 0.5068 0.2465 0.5% 1.66 [± 22.69] which 2012 0.5068 0.2465 0.5% 1.66 [± 22.69] which 2012 0.5068 0.2465 0.5% 1.66 [± 22.69] which 2012 0.507 ($P < 0.0001$) 2.1012 0.558 1.1% 2.09 [$\pm 4.2.44$] which 2014 0.3355 0.059 2.3% 1.40 [± 16.169] Subtotal (95% C) 1.4.9% 1.82 [$\pm 1.48, 2.24$] 4.16erogeneity: Tax ² = 0.02; Ch ² = 6.02; df = 4 (P < 0.0001); P = 93%. Test for overall effect: $Z = 2.59 (P = 0.010)$ 1.7.6 Colorectal Challenge 1.102 0.5578 0.1103 1.9% 1.80 [$\pm 4.2.24$] 4.16erogeneity: Tax ² = 0.16; Ch ² = 5.7.3; df = 4 (P < 0.0001); P = 93%. Test for overall effect: $Z = 2.59 (P = 0.010)$ 1.7.7 Golorectal Challenge 0.0328 0.0592 2.5% 1.39 [$\pm 0.51, 1.51, 2.23$] 4.1697 ($\pm 0.33, 0.0528 0.14\%$ 1.55 [$\pm 1.28, 2.13$] 4.1697 ($\pm 0.33, 0.0528 0.1596 1.130 1.16, 1.507$] 3.80 total (95% C) 4.028 0.1289 1.14\% 1.55 [$\pm 1.28, 2.13$] 4.1697 ($\pm 0.33, 0.0528 0.0528 0.25\% 1.39 [1.16, 1.53]$ 3.80 total (95% C) 4.028 0.1289 1.139 [1.16, 1.67] 3.80 total (95% C) 4.028 0.1289 1.139 [1.16, 1.67] 3.80 total (95% C) 4.028 0.1289 1.139 [1.16, 1.67] 3.80 total (95% C) 4.028 0.128 1.139 [1.16, 1.67] 3.80 total (95% C) 4.028 0.128 1.139 [1.16, 1.67] 3.80 total (95% C) 4.028 0.129 [$\pm 0.02, 1^{+} = 2.5\%$ [$\pm 0.02, 1^{+} = 2.5\%$ Test for overall effect: $Z = 3.00 (P = 0.0003)$ 1.7.7 Stream 3.80 total (95% C) 4.028 0.128 1.139 [1.16, 1.20] 4.7.8 total 1.10 0.1196 0.0322 0.9% 1.50 [1.20, 2.70] 4.7.8 total 1.10 0.433 0.022 2.9% 1.55 [Neuman 2008	0.3507	0.1257	1.5%	1,42 [1.11, 1.82]		-
Works 2012 0.47 0.1059 2.0% 1.60 1.30 1.97 Subtotal (95% CI) 0.7 0.150 1.2.9% 1.73 1.53 1.95 Subtotal (95% CI) 0.73 0.150 1.2.9% 1.65 1.73 1.55 Test for overall effect: Z = 8.83 (P < 0.00001)	Schmidt 2007	0.7885	0.1625	1.0%	2.20 [1.60. 3.03]		-
Wede 2013 0.47 0.1059 2.0% 160 [1.30, 1.97] Subtotal (95% C1) 12.9% 1.72 [1.53, 1.95] Heterogeneity: Tau ² = 0.02; Ch ² = 15.67, dF = 6 (P = 0.05); P = 49%. Test for overall effect: Z = 8.83 (P < 0.00001) L7.1 A Nasopharymgal Jin 2013 0.4669 0.0806 3.0% 160 [1.36, 1.87] L2012 0.5068 0.2466 5.5% 1.66 [1.02, 2.69] Wan 2013 0.9658 0.3053 0.3% 2.63 [1.44, 7.8] Wa 2014 0.5446 0.176 0.8% 1.72 [1.22, 2.43] Zhou 2012 1.1112 0.317 0.3% 3.04 [1.63, 5.66] Subtotal (95% C1) 4.9% 1.82 [1.48, 2.24] Heterogeneity: Tau ² = 0.02; Ch ² = 6.02, df = 4 (P = 0.20); P = 34% Test for overall effect: Z = 5.70 (P < 0.00001) L7.5 Prostate Cock 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Heterogeneity: Tau ² = 0.01, 0.1100 1.00, 1.00] Templeton 2014 0.3285 0.0359 2.23% 1.40 [1.16, 1.69] Subtotal (95% C1) 1.3.5% 1.60 [1.12, 2.28] Heterogeneity: Tau ² = 0.01, 0.010 L7.6 Colorectal Chabado 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Subtotal (95% C1) 1.3.52 0.1139 1.8% 1.85 [1.48, 2.31] Heterogeneity: Tau ² = 0.04, 0.028 0.1296 1.4% 1.65 [1.28, 2.13] And Keashamp 2012 0.5008 0.1296 1.4% 1.65 [1.28, 2.13] Heterogeneity: Tau ² = 0.04, 0.129 0.109 1.1% 1.80 [1.45, 2.23] Subtotal (95% C1) 9.3% 1.52 [1.19] 1.8% 1.85 [1.48, 2.31] Heterogeneity: Tau ² = 0.0428 0.1298 1.4% 1.65 [1.28, 2.13] Heterogeneity: Tau ² = 0.0428 0.1298 1.4% 1.55 [1.28, 1.79] Heterogeneity: Tau ² = 0.0471 0.1267 1.5% 1.99 [1.40, 2.45] Subtotal (95% C1) 4.7% 1.77 [1.30, 2.47] Heterogeneity: Tau ² = 0.06; Ch ² = 10.29; I ² = 62% Test for overall effect: Z = 4.98 (P < 0.00001) H.7.6 Other Test for overall effect: Z = 4.98 (P < 0.00001) H.7.6 Other Test for overall effect: Z = 4.98 (P < 0.00001) H.7.7 Sin 1.91 [1.40, 2.45] Durnal 2013 0.438 0.0622 0.9% 1.80 [1.02, 2.05] Tau 4.0000 0.5878 0.2101 0.5% 2.40 [1.50, 3.62] Tau 4.0000 0.5878 0.2101 0.5% 2.40 [1.50, 3.62] Tau 4.0000 0.5878 0.2101 0.5% 2.40 [1.50, 3.62] Tau 4.00000 0.5878 0.2101 0.5% 2.40 [1.50, 3.62] Tau 4.0000 0.5878 0.2101 0.5% 2.40 [1.50, 3.62] Tau 4.0000 0.5878 0	Weide 2012	0.47	0.1059	2.0%	1.60 [1.30, 1.97]		-
Subtotal (95% CI) 12.9% 1.72 [1.53, 1.95] Heterogeneity: Tau" = 0.02; Ci+ 257, df = 6 (P = 0.05); P = 49% Test for overall effect: Z = 8.83 (P < 0.0001) 1.7.4 Nasopharyngeal Jin 2013 0.4669 0.0806 3.0% 1.60 [1.36, 1.87] L2012 0.5068 0.2465 0.5% 1.66 [1.02, 2.69] Wen 2013 0.9568 0.3053 0.3% 2.63 [1.44, 4.78] Wen 2013 0.9568 0.3053 0.3% 2.63 [1.44, 4.78] Wen 2014 0.5446 0.76 0.8% 1.72 [1.22, 2.43] Subtotal (95% CI) 4.02, df = 4 (P = 0.20); P = 34% Test for overall effect: Z = 5.70 (P < 0.0001) 1.7.5 Prostate Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Test for overall effect: Z = 5.70 (P < 0.00001) 1.7.5 Prostate Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Test for overall effect: Z = 5.71 (P < 0.00001); P = 93% Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Coorectal Chabadel 2014 0.3365 0.0459 2.3% 1.40 [1.62, 1.58] Subtotal (95% CI) 13.6% 2.52 [1.66, 3.83] Subtotal (95% CI) 13.0% 1.00 [1.05, 1.16] 1.36% 1.50 [1.45, 2.23] Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Colorectal Chabadel 2013 0.239 0.1019 2.1% 1.27 [1.04, 1.55] Test for overall effect: Z = 4.84 (P < 0.00001); P = 93% Test for overall effect: Z = 4.84 (P < 0.00001) 1.7.6 Colorectal Chabadel 2013 0.239 0.1019 2.1% 1.25 [1.28, 1.79] Heterogeneity: Tau" = 0.03; Ch ² = 13.14, df = 5 (P = 0.02); P = 62%. Test for overall effect: Z = 4.84 (P < 0.00001) 1.7.7 Sarcom Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 2.20] Heterogeneity: Tau" = 0.03; Ch ² = 13.14, df = 5 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Heterogeneity: Tau" = 0.00; Ch ² = 0.29; df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Heterogeneity: Tau" = 0.00; Ch ² = 0.29; df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Heterogeneity: Tau" = 0.00; Ch ² = 0.29; df = 3 (P = 0.00	Weide 2013	0.47	0.1059	2.0%	1.60 [1.30, 1.97]		+
Heterogeneity: Tau ² = 0.02; Ch ² = 15.67, df = 8 (P = 0.05); P = 49%, Test for overall effect: Z = 8.83 (P < 0.00001) 17.4 Nasophyrrygel Jin 2013 0.4669 0.0806 3.0% 160 [1.36, 1.87] Li 2012 0.5068 0.2465 0.5% 161 (10.2.269] Wan 2013 0.9658 0.3053 0.3% 2.63 [1.44, 78] Wa 2014 0.5446 0.176 0.8% 1.72 (1.22, 2.43] Zhou 2012 1.1112 0.317 0.3% 3.04 [1.63, 5.65] Subtotal (9%, C) 1.7.5 Prostate Cox 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Heterogeneity: Tau ² = 0.02; Ch ² = 6.02, df = 4 (P = 0.20); P = 34%, Test for overall effect: Z = 5.70 (P < 0.00001) 1.7.6 Colorectal Charlen 2014 0.5355 0.0959 2.3% 1.40 [1.16, 1.69] Sato 2007 0.4818 0.2357 0.5% 1.60 [1.62, 2.57] Sato 2007 0.4818 0.2357 0.5% 1.60 [1.60, 1.00] Empleton 2014 0.9244 0.21 1.8% 1.50 [1.63, 2.82] Sato 2007 0.4818 0.2357 0.5% 1.66 3.838] Sato 2007 0.4818 0.2357 0.5% 1.66 3.838] Sato 2013 0.239 0.1019 2.1% 1.20 [1.63, 1.48] Heterogeneity: Tau ² = 0.14; Ch ² = 57.13, df = 4 (P < 0.00001); P = 83% Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Colorectal Chabadel 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Heterogeneity: Tau ² = 0.04; Ch ² = 57.13, df = 4 (P < 0.00001); P = 83% Test for overall effect: Z = 2.88 (P = 0.0001) 1.7.7 Sarcoma Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.9 [1.48, 2.45] Unitarial 2.5, 2.498 (P < 0.0001) 1.7.7 Sarcoma Bacci 2000 0.3293 0.0923 2.5% 1.9 [1.49, 2.45] Subtotal (9%, C) 1.7.8 Other Feat for overall effect: Z = 3.80 (P = 0.002); P = 71% Test for overall effect: Z = 4.98 (P < 0.0003) 1.7.8 Other Feat 2.000 0.5478 0.2069 0.5% 1.91 [1.48, 2.45] Subtotal (9%, C) 1.7.9 Sarcoma Bacci 2000 0.5478 0.2069 0.5% 1.95 [1.10, 2.07] Heterogeneity: Tau ² = 0.05; Ch ² = 10.29, df = 3 (P < 0.02); P = 71% Test for overall effect: Z = 3.80 (P = 0.0003) 1.7.8 Other Feat for overall effect: Z = 3.80 (P = 0.0003) 1.7.9 Sarcoma Bacci 2000 0.6378 0.2069 6.5% 1.59 [1.10, 2.07] 1.7 	Subtotal (95% CI)			12.9%	1.73 [1.53, 1.95]		•
Let for overall effect $Z = 8.83 (P < 0.0001)$ 1.7.4 Nasopharyngeal in 2013 0.4669 0.0806 3.0% 1.60 [1.36, 1.67] 12.012 0.5068 0.2465 0.5% 1.66 [1.02, 2.69] Wan 2013 0.9668 0.3050 3.3% 2.63 [1.44, 4.78] Wan 2014 0.5446 0.076 0.8% 1.72 [1.22, 2.43] Theorements Trail = 0.02; Pi = 6.02; df = 4 (P = 0.20); P = 34% Test for overall effect: $Z = 5.70 (P < 0.00001)$ 1.7.5 Prostate Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Heatergoneity: Trail = 0.02; Chi = 6.02; df = 4 (P = 0.20); P = 34% Test for overall effect: Z = 5.70 (P < 0.00001); P = 93% Test for overall effect: Z = 5.71 (J = 6 + 0.00001); P = 93% Test for overall effect: Z = 0.11; D = 57.13, df = 4 (P < 0.00001); P = 93% Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Colorectal Chibaud 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Subtotal (95% CI) 0.0339 0.0109 2.1% 1.27 [1.04, 1.55] Heterogeneity: Trail = 0.01; OL280 1.128 1.4% 1.65 [1.28, 2.13] wat Kessel 2013 0.0239 0.1019 1.1% 1.80 [1.45, 2.23] Subtotal (95% CI) 9.0339 0.1019 2.1% 1.27 [1.04, 1.55] Heterogeneity: Trail = 0.03; OL280 1.298 1.4% 1.65 [1.82, 2.13] wat Kessel 2013 0.0238 0.1296 1.4% 1.65 [1.28, 2.13] wat Kessel 2013 0.0280 1.298 1.4% 1.65 [1.56, 1.33] Subtotal (95% CI) 9.3% 1.52 [1.29, 1.79] Heterogeneity: Tau' = 0.08; Chi'' = 10.29, df = 3 (P = 0.02); P = 62% Test for overall effect: Z = 4.98 (P < 0.00001) 1.7.7 Sarcona Bacci 2000 0.3283 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3283 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2004 0.6878 0.2069 0.6% 1.80 [1.20, 2.70] Feator overall effect: Z = 3.60 (P = 0.003) 1.7.8 Other Feator overall effect: Z = 3.60 (P = 0.003) 1.7.8 Other Feator overall effect: Z = 4.98 (P < 0.00001) 1.7.8 Other Feator overall effect: Z = 3.60 (P = 0.002); P = 71% To an 1.79 (D = 0.438 0.1559 1.13 [1.06, 1.20] Tauhimota 2000 0.5478 0.2069 0.6% 1.50 [1.10, 2.05] Subtotal (95% CI) 2.2.3 [1.56, 1.17, 2.26] Tauhimota 2000 0.5478 0.2069 0.6% 1.50 [1.10, 2.05] To an 1.78 (D = 0.07; Chi'' = 83.25, df = 13 (P < 0.00001); P = 85% Test	Heterogeneity: Tau ² =	0.02; Chi ² = 15.67, df	= 8 (P =	0.05); l ² =	= 49%		
1.7.4 Nasopharyngel ii 2013 0.4660 0.0006 3.0% 1.60 [1.36, 1.87] ii 2012 0.5068 0.365 0.5% 1.66 [1.02, 2.69] Wan 2013 0.9668 0.376 0.3% 2.63 [1.44, 4.76] Wan 2012 1.1112 0.317 0.3% 3.04 [1.63, 5.65] Stabutal (95% CI) 4.9% 1.82 [1.48, 2.43] Test for overall effect: Z = 5.70 (P < 0.00001)	l est for overall effect:	Z = 8.83 (P < 0.0000)				
Jin 2013 0.4660 0.0006 3.0% 1.60 [1.36, 1.87] J2012 0.5060 0.2466 0.5% 1.66 [1.02, 2.69] Wan 2013 0.9668 0.3065 0.3% 2.63 [1.44, 4.78] Wan 2014 0.5446 0.176 0.8% 1.72 [1.22, 2.43] Zhou 2012 1.1112 0.317 0.3% 3.04 [1.63, 5.65] Subtotal (95% C1) 4.9% 1.32 [1.48, 2.24] Heterogeneity: Tau ² = 0.02; ChF = 6.02, df = 4 (P = 0.20); P = 34% Test for overall effect: Z = 5.70 (P < 0.0001) 1.7.5 Prostate Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Tampieton 2014 0.3366 0.0699 2.3% 1.40 [1.16, 1.619] Subtotal (95% C1) 1.3.6% 1.66 [1.12, 2.257] Scher 1999 0.003 0.001 9.1% 1.00 [1.00, 1.00] Templeton 2014 0.29243 0.213 0.6% 2.55 [1.66, 3.83] Subtotal (95% C1) 1.3.6% 1.66 [1.12, 2.28] Heterogeneity: Tau ² = 0.14; ChF = 57.13, df = 4 (P < 0.0001); P = 93% Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Concretal Heterogeneity: Tau ² = 0.03; ChF = 50.1103 1.9% 1.80 [1.45, 2.23] Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Concretal Heterogeneity: Tau ² = 0.03; ChF = 13.14, df = 5 (P = 0.02); P = 62% Test for overall effect: Z = 4.98 (P < 0.0001) 1.7.7 Scher 199 0.033 0.2126 0.5% 0.97 [0.63, 1.48] Weterkmapp 2012 0.5088 0.1296 1.4% 1.56 [1.28, 2.13] Test for overall effect: Z = 4.98 (P < 0.0001) 1.7.7 Scher 190 0.322 0.9% 1.39 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Heterogeneity: Tau ² = 0.06; ChF = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 4.98 (P < 0.0001) 1.7.7 Scher Felu 2011 0.1196 0.0322 6.9% 1.13 [106, 1.20] Test for overall effect: Z = 4.08 (ChF = 0.02); P = 0.02; P = 71% Test for overall effect: Z = 4.08 (ChF = 0.02); P = 0.02; P = 71% Test for overall effect: Z = 0.00001) 1.7.8 Cher Felu 2011 0.1586 0.1586 1.10% 1.50 [1.10, 2.05] Test for overall effect: Z = 0.40 (ChF = 0.02); P = 0.02; P = 71% Test for overall effect: Z = 0.40	1.7.4 Nasopharyngea	d					
$ \begin{array}{c} 12012 \\ (12012 \\ (12012 \\ (12013 \\ (12014 \\ (1201$	Jin 2013	0.4669	0.0806	3.0%	1.60 [1.36, 1.87]		*
Wan 2013 0.9658 0.3053 0.3% 2.68 [1.44, 4.78] Wei 2014 0.5446 0.176 0.8% 1.72 [1.22, 2.43] Zhou 2012 1.1112 0.317 0.3% 3.04 [1.63, 5.65] Subtotal (95% CI) 4.9% 1.82 [1.48, 2.24] Heterogeneity: Tau ² = 0.02; Ch ² = 6.02, df = 4 (P = 0.20); P = 34% Test for overall effect: Z = 5.70 (P < 0.00001) 1.7.5 Prostate Cook 2006 0.7372 0.1568 1.1% 2.09 [1.54, 2.84] Heterogeneity: Tau ² = 0.02; OH = 5.713, df = 4 (P = 0.20); P = 34% Test for overall effect: Z = 5.70 (P < 0.00001) 1.7.6 Colorectal Chabudo 2014 0.9243 0.213 0.6% 2.52 [1.66, 3.83] Subtotal (95% CI) 1.3.6% 1.60 [1.12, 2.87] Test for overall effect: Z = 5.80 (P = 0.010) 1.7.6 Colorectal Chabudo 2011 0.5676 0.1103 1.9% 1.80 [1.45, 2.23] Heterogeneity: Tau ² = 0.41; Ch ² = 57.13, df = 4 (P < 0.00001); P = 93% Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Colorectal Chabudo 2011 0.5676 0.1103 1.9% 1.80 [1.45, 2.23] Heterogeneity: Tau ² = 0.03; Ch ² = 0.139 1.3% 1.86 [1.48, 2.31] Wetenkimg 2012 0.6152 0.139 1.4% 1.56 [1.28, 2.13] Test for overall effect: Z = 4.98 (P < 0.00001) 1.7.7 Sarcoma Bacci 2000 0.2293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.2393 0.0123 4.5% 1.80 [1.20, 2.70] 5.000 1.7.7 Sarcoma Bacci 2000 0.2393 0.0023 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.2393 0.0023 2.5% 1.39 [1.18, 0.10] 1.7.7 Sarcoma Bacci 2000 0.2393 0.0023 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.5677 0.1618 0.3% 1.80 [1.20, 2.70] 1.7.6 There Feitor overall effect: Z = 3.80 (P = 0.002); P = 71% Test for overall effect: Z = 3.80 (P = 0.0003) 1.7.6 Other Feitor 2001 0.6549 0.15% 1.77 [1.34, 2.41] 1.7.6 Test for overall effect: Z = 6.24 (P < 0.00001); P = 85% Test for overall effect: Z = 6.24 (P < 0.00001); P = 85% Test for over	Li 2012	0.5068	0.2465	0.5%	1.66 [1.02, 2.69]		-
Wei 2014 0.544 0.776 0.8% 1.72 [1.22, 2.43] Subtotal (95% CI) 1.112 0.317 0.3% 3.00 [1.63, 5.65] Subtotal (95% CI) 1.112 0.317 0.3% 3.00 [1.63, 5.65] Subtotal (95% CI) 1.12 0.20; $H = 4 (P = 0.20; P = 34\%$ Test for overall effect: $Z = 5.70 (P < 0.00001)$ 17.5 Prostate Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Halab 2014 0.3365 0.0659 2.3% 1.40 [1.16, 16, 16] Subtotal (95% CI) 1.3.6% 1.62 [1.02, 2.57] Subtotal (95% CI) 1.3.6% 1.60 [1.12, 2.28] Heterogeneity: Tau" = 0.14; Ch ² = 57.13, df = 4 (P < 0.00001); P = 93% Test for overall effect: $Z = 2.58 (P = 0.010)$ 17.6 Colorectal Chibaud 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Heterogeneity: Tau" = 0.03; Ch ² = 13, 14, df = 5 (P = 0.02); P = 62% Test for overall effect: $Z = 4.98 (P < 0.00001)$ 17.7 Sarcona Bacci 2000 0.3293 0.0023 2.5% 1.38 [1.16, 16.7] Bacci 2000 0.3293 0.0023 2.5% 1.38 [1.16, 16.7] Bacci 2000 0.3293 0.0023 2.5% 1.38 [1.16, 1.67] Bacci 2000 0.3293 0.0023 2.5% 1.38 [1.18, 1.37, 2] Heterogeneity: Tau" = 0.08; Ch ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 4.98 (P < 0.00001) 1.7.8 Other Fealu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Tashotal (1993 0.4055 0.1582 1.0% 1.59 [1.10, 2.67] Heterogeneity: Tau" = 0.08; Ch ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.02); P = 0.02; P = 71% Test for overall effect: Z = 3.60 (P = 0.02); P = 0.02; P = 71% Test for overall effect: Z = 3.60 (P = 0.0001) 1.7.8 Other Test for overall effect: Z = 0.40 (P < 0.00001) Test for overall effect: Z = 0.40 (P < 0.00001) Test for overall effect: Z = 0.40 (P < 0.00001); P = 85% Test for overall effect: Z = 0.40 (P < 0.00001) Test for overall effect: Z = 0.40 (P < 0.00001) Test for o	Wan 2013	0.9658	0.3053	0.3%	2.63 [1.44, 4.78]		
The 2012 1.1112 0.317 0.3% 3.04 [1.63, 5.65] Subtotal (95% CI) 4.9% 1.32 [1.48, 2.24] Heterogeneity: Tau ² = 0.02; ChF = 6.02, df = 4 (P = 0.20); P = 34% Test for overall effect: Z = 5.70 (P < 0.0001) 1.7.5 Prostate Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Habia 2014 0.3365 0.0659 2.3% 1.40 [1.16, 1.69] Salto 2007 0.4418 0.2357 0.5% 1.62 [1.02, 2.57] Salto 2007 0.4418 0.2357 0.5% 1.62 [1.02, 2.57] Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Colorectal Chabudo 2011 0.5678 0.1103 1.9% 1.80 [1.45, 2.23] Wekenkamp2 2012 0.6152 0.1139 1.8% 1.65 [1.48, 2.31] Wekenkamp2 2012 0.6152 0.1139 1.8% 1.56 [1.48, 2.31] Wekenkamp2 2012 0.5038 0.1236 1.4% 1.55 [1.28, 2.13] Saltotal (9% CI) 1.7.7 Sarcoma Bacci 2000 0.2329 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.2329 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.2329 0.0923 1.5% 1.59 [1.49, 2.45] Unimal 2013 0.4657 0.2069 0.6% 1.80 [1.20, 2.70] Saltotal (9% CI) 1.7.7 Sarcoma Bacci 2000 0.2329 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.2393 0.0923 2.5% 1.39 [1.18, 2.01] 1.7.8 Other Feat for overall effect: Z = 3.60 (P = 0.0003) 1.7.4 Other Feat for overall effect: Z = 3.60 (P = 0.0003) 1.7.4 Other Feat for overall effect: Z = 0.60 ChF = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 0.40 (ChF = 0.020) 1.7.9 (1.48, 1.40, 2.01) 1.7.9 (1.40, 2.42) 1.7.9 (1.40, 2	Wei 2014	0.5446	0.176	0.8%	1.72 [1.22, 2.43]		
Subtotal (95% CI) 4.29 , 1.32 [1.48, 2.24] Heterogeneity: Tau ² = 0.02; Ch ² = 6.02, df = 4 (P = 0.20); P = 34% Test for overall effect: $Z = 5.70$ (P < 0.00001) 17.5 Prostate Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Halabi 2014 0.3366 0.0959 2.3% 1.40 [1.16, 16.9] Subtotal (95% CI) 0.9243 0.213 0.6% 2.52 [1.66, 3.83] Subtotal (95% CI) 0.9243 0.213 0.6% 2.52 [1.66, 3.83] Subtotal (95% CI) 0.9243 0.213 0.6% 2.52 [1.66, 3.83] Subtotal (95% CI) 1.05876 0.1103 1.9% 1.80 [1.45, 2.23] Heterogeneity: Tau ² = 0.13; Ch ² = 7.13, df = 4 (P < 0.00001); P = 93% Test for overall effect: Z = 2.58 (P = 0.010) 17.6 Colorectal Chibaudel 2011 0.5876 0.1103 1.9% 1.80 [1.45, 2.23] Heterogeneity: Tau ² = 0.03; Ch ² = 13.14, df = 5 (P = 0.2); P = 62% Test for overall effect: Z = 4.98 (P < 0.00001) 17.7 Sarcoma Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Heterogeneity: Tau ² = 0.03; Ch ² = 10.29; H = 0.02); P = 71% Test for overall effect: Z = 4.39 (P < 0.00001) 1.7.7 Sarcoma Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Heterogeneity: Tau ² = 0.03; Ch ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Thanishold 1993 0.4435 0.138 1.3% 1.58 [1.18, 2.01] Heterogeneity: Tau ² = 0.03; Ch ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Feliu 2011 0.5439 0.128 1.3% 1.58 [1.18, 2.01] Thanishold 1993 0.4455 0.158 2.10% 1.59 [1.10, 2.05] Thanishold 1993 0.4455 0.158 2.10% 1.59 [1.10, 2.05] Than	Zhou 2012	1.1112	0.317	0.3%	3.04 [1.63, 5.65]		
17.5 Prostate Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.84] Habbi 2014 0.3365 0.0859 2.3% 1.40 [1.16, 1.69] Salo 2007 0.4418 0.2357 0.5% 1.62 [1.02, 2.57] Salot 2007 0.4418 0.2324 0.213 0.6% 2.52 [1.66, 3.83] Subtotal (95% CI) 1.3.8% 1.60 [1.12, 2.28] 1.66 [1.12, 2.28] Test for overall effect: $Z = 2.58 (P = 0.010)$ 1.3.8% 1.60 [1.12, 2.28] 17.6 Colorectal Ent overall effect: $Z = 2.58 (P = 0.010)$ 1.27 [1.04, 1.55] 1.27 [1.04, 1.55] 17.6 Colorectal Ent overall effect: $Z = 2.58 (P = 0.02)$; $P = 62%$ 1.38 [1.48, 2.31] 1.52 [1.28, 1.73] Wekenkamp2 2012 0.5050 0.1296 1.4% 1.65 [1.28, 2.13] 1.52 [1.29, 1.79] Heterogeneity: Tau" = 0.03; Ch= 1.3.1.4, df = 5 (P = 0.02); P = 62% 1.38 [1.46, 1.67] 1.56 [1.28, 2.73] 1.52 [1.29, 1.79] Bacci 2001 0.5279 0.269 6.6% 1.80 [1.20, 2.70] 1.78 [1.40, 2.45] 1.78 [1.40, 2.70] Bacci 2004 0.5770 0.269 0.6% 1.80 [1.20, 2.70] 1.78 [1.30, 2.47] 1	Heterogeneity: Tau ² = Test for overall effect:	0.02; Chi ² = 6.02, df = Z = 5.70 (P < 0.0000)	= 4 (P = 0 I)	0.20); l² =	34%		
Cook 2006 0.7372 0.1558 1.1% 2.09 (15.4.2.44) Halai 2014 0.3365 0.0959 2.3% 1.40 (1.16, 1.69) Sato 2007 0.4818 0.2357 0.5% 1.62 [1.02, 2.57] Sator 1999 0.030 0.001 9.1% 1.00 [1.00, 1.00] Tampleton 2014 0.29243 0.213 0.6% 2.52 [1.68, 3.83] Subtotal (95% CI) 1.3.6% 1.60 [1.12, 2.28] Heterogenetity. Tau ² = 0.14; ChP ² = 57.13, df = 4 ($P < 0.00001$); P = 93% Test for overall effect: $Z = 2.58$ ($P = 0.010$) 1.7.6 Colorectal Mekenkamp 2012 0.6152 0.1103 1.9% 1.80 [1.45, 2.23] Giessen 2013 0.239 0.1019 2.1% 1.27 [1.04, 1.55] Heterogenetity. Tau ² = 0.03; ChP ² = 13.14, df = 5 ($P = 0.02$); P = 62% Test for overall effect: $Z = 4.98$ ($P < 0.00001$) 1.7.7 Sarcoma Bacci 2000 0.3283 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3283 0.0923 2.5% 1.39 [1.16, 1.67] Heterogenetity. Tau ² = 0.06; ChP ² = 10.29, df = 3 ($P = 0.02$); P = 71% Test for overall effect: $Z = 3.60$ ($P = 0.0003$) 1.7.8 Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Gripp 2007 0.6575 0.210 6.5% 2.40 [1.58, 1.32, 1.28] Perega 2010 0.6583 0.082 2.9% 2.017.0, 2.55] Tankhub 2019 0.4583 0.082 2.9% 1.50 [1.10, 2.05] Takahimoto 2009 0.5577 0.181 0.8% 1.82 [1.27, 2.60] Takahimoto 2009 0.5577 0.181 0.8% 1.82 [1.27, 2.60] Takahimoto 2009 0.5577 0.181 0.8% 1.82 [1.27, 2.60] Takahimoto 2009 0.5577 0.181 0.8% 1.50 [1.10, 2.05] Takahimoto 2009 0.5577 0.181 0.8% 1.52 [1.38, 2.18] Perega 2001 0.6587 0.298 0.299 0.2971, 2.181, 2.24 [1.58, 3.17] Tomin 1997 1.4061 0.6316 0.15% 4.06 [1.61, 1.407] Yamaguchi 2014 0.4587 0.196 0.8% 1.77 [1.34, 2.21] Takahimoto 2009 0.5578 0.2060 0.65% 1.80 [1.20, 2.70] Yamaguchi 2014 0.5478 0.2600 0.05878 0.20	1.7.5 Prostate						
Halai 2014 0.3365 0.0659 2.3% 1.40 [11.6, 1.69] Templeton 2014 0.2277 0.5% 1.62 [10.2, 2.57] Templeton 2014 0.9243 0.213 0.6% 2.52 [1.66, 3.63] Subtotal (95% C) 1.3.6% 1.60 [1.12, 2.28] Heterogeneity. Tau" = 0.14; CH ² = 57.13, df = 4 (P < 0.00001); P = 93% Test for overall effect: $Z = 2.56 (P = 0.010)$ 17.6 Colorectal Chibaudo 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Mekenkamp 2012 0.6152 0.1139 1.8% 1.85 [1.48, 2.31] Mekenkamp 2012 0.6152 0.1139 1.8% 1.85 [1.48, 2.31] Mekenkamp 2012 0.6152 0.129 1.4% 1.55 [1.16, 1.53] Subtotal (95% C) 9.0229 1.4% 1.55 [1.16, 1.53] Subtotal (95% C) 9.0329 0.00001) 17.7 Sarcoma Bacci 2000 0.3293 0.0923 2.5% 1.38 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.38 [1.16, 1.67] Bacci 2004 0.5576 0.2069 0.6% 1.80 [1.20, 2.70] Bacci 2004 0.5577 0.181 0.28% 1.27 [1.3, 1.79 [1.30, 2.47] Heterogeneity. Tau" = 0.03; ChF = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.00001) 17.8 Other Fellu 2011 0.1196 0.0322 6.9% 1.13 [1.16, 1.20] Fellu 2011 0.1196 0.0322 6.9% 1.13 [1.0, 2.47] Heterogeneity. Tau" = 0.06; ChF = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.00003) 17.8 Other Fellu 2010 0.6471 0.1259 1.3% 1.58 [1.18, 2.01] Tahashmoto 2009 0.4350 0.1882 1.0% 1.59 [1.10, 2.65] Test for overall effect: Z = 3.60 (P = 0.00001) 17.8 Other Fellu 2010 0.6471 0.1269 1.5% 1.77 [1.30, 2.47] Heterogeneity. Tau" = 0.06; ChF = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.00003) 17.78 0.8% 1.73 [1.22, 2.46] Test for overall effect: Z = 3.60 (P = 0.00001) 17.8 Other Fellu 2010 0.6493 0.0822 2.9% 2.00 [1.70, 2.55] Test for overall effect: Z = 3.60 (P = 0.00001) Test for overall effect: Z = 0.24 (P < 0.00001) Test for overall effect: Z = 0.24 (P < 0.00001) Test for overall effect: Z = 0.24 (P < 0.00001) Test for overall effect: Z = 0.24 (P < 0.00001) Test for overall effect: Z = 0.24 (P < 0.00001) Test for overall effect: Z = 0.24 (P < 0.00001) Test for overall effect: Z = 0.	Cook 2006	0.7372	0.1558	1.1%	2.09 [1.54, 2.84]		-
Salb 2007 0.4618 0.2357 0.5% 1.62 [1.02, 2.57] Solber 1999 0.003 0.001 9.1% 1.00 [1.00, 1.00] Templeton 2014 0.9243 0.213 0.6% 2.52 [1.66, 3.83] Subbta [95%, C1) 1.3.6% 1.60 [1.12, 2.28] Heterogeneity. Tau ² = 0.14; Chi ² = 57.13, df = 4 (P < 0.00001); P = 93% Test for overall effect: $Z = 2.58 (P = 0.010)$ 1.7.6 Colorectal Chibauda 2011 0.5876 0.1103 1.9% 1.80 [1.45, 2.23] Mekenkamp.2012 0.6152 0.1139 1.8% 1.56 [1.46, 2.23] Mekenkamp.2012 0.6152 0.1139 1.8% 1.56 [1.46, 2.31] Mekenkamp.2012 0.6152 0.1139 1.8% 1.56 [1.46, 2.31] Mekenkamp.2012 0.6152 0.1139 1.8% 1.56 [1.46, 2.31] Mekenkamp.2012 0.6508 0.1236 1.4% 1.55 [1.46, 2.31] Mekenkamp.2012 0.6576 0.00030 1.7.7 Sarcoma Bacci 2000 0.3283 0.0223 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.5877 0.169 0.74% 1.57 [1.39, 2.47] Heterogeneity. Tau ² = 0.06; Chi ² = 10.29, df = 3 (P = 0.02); P = 62% Test for overall effect: $Z = 3.60 (P = 0.0003)$ 1.7.7 Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Grip 2007 0.8675 0.2101 0.6% 2.40 [1.59, 3.62] Thanisold 1993 0.4055 0.1582 1.0% 1.55 [1.10, 2.05] Heterogeneity. Tau ² = 0.06; Chi ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: $Z = 3.60 (P = 0.0003)$ 1.7.8 Other Feliu 2011 0.1196 0.0522 6.9% 1.51 [1.10, 2.05] Grip 2007 0.8675 0.2101 0.6% 2.40 [1.59, 3.62] Thanisold 1993 0.4055 0.1582 1.0% 1.55 [1.10, 2.05] Thanisold 1993 0.4055 0.1582 1.0% 1.55 [1.10, 2.05] Thanisold 1993 0.4055 0.1582 1.0% 1.52 [1.20, 2.70] Subtotal (95% C1) Thanisold 1995 0.1438 0.1452 1.72 [1.34, 2.1] Thanisold 1995 0.4438 0.1582 1.77 [1.34, 2.21] Thanisold 1995 0.4438 0.1582 1.77 [1.34, 2.21] Thanisold 1995 0.4455 0.158 0.150 [1.10, 2.05] Thanisold 1995 0.4528 0.1284 1.6% 1.68 [1.42, 2.00] Thanisold 1995 0.4528 0.1284 1.6% 1.68 [1.42, 2.00] Thanisold 1995 0.4455 0.158 0.200 (1.77, 2.35] Thanisold 1995 0.100 0.5499 0.778 0.8% 1.73 [1	Halabi 2014	0.3365	0.0959	2.3%	1.40 [1.16, 1.69]		-
Scher 1999 0.003 0.001 9.1% 1.00 [1.00, 1.00] Templeton 2014 0.243 0.213 0.6% 2.52 [1.65, 3.83] Subtotal (95%, CI) 4.27 [1.04, 1.55] Test for overall effect: $2 = 2.58 (P = 0.010)$ 1.7.6 Colorectal Chibaudel 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Giessen 2013 0.239 0.1019 2.1% 1.27 [1.04, 1.55] Giessen 2013 0.239 0.1262 0.6% 0.97 [0.63, 1.46] Metenkamp2 2012 0.5060 0.1260 1.4% 1.65 [1.48, 2.31] Metenkamp2 2012 0.5060 0.1260 1.4% 1.65 [1.48, 2.13] Metenkamp2 2012 0.5060 0.1269 1.4% 1.65 [1.48, 2.13] Metenkamp2 2012 0.5060 0.129 1.4% 1.56 [1.16, 1.67] Bacci 2000 0.3293 0.0223 2.5% 1.39 [1.16, 1.67] Heterogeneity: Tau ² = 0.03; Ch ² = 10.29, d ² = 0.02); P = 71% Test for overall effect: 2 = 3.60 (P = 0.0003) 1.7.8 Other Failu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Fritu 2011 0.158 0.1582 1.0% 1.56 [1.10, 2.05] Fritu 2011 0.5489 0.1778 0.8% 1.54 [1.18, 2.01] Fritu 2010 0.6583 0.1682 2.0% 2.00 [1.70, 2.55] Pice 2003 0.4456 0.1582 1.0% 1.56 [1.10, 2.05] Fritu 2010 0.6583 0.1682 2.9% 2.00 [1.70, 2.55] Fritu 2010 0.6583 0.1682 1.0% 1.56 [1.10, 2.05] Fritu 2010 0.6583 0.1682	Saito 2007	0.4818	0.2357	0.5%	1.62 [1.02, 2.57]		
Templeton 2014 0.9243 0.213 0.6% 2.52 [1.66, 3.83] Subtotal (95% C1) 1.3.6% 1.60 [1.12, 2.28] Heterogeneity: Tau ² = 0.14; ChF = 57.13, df = 4 (P < 0.00001); P = 93% Test for overall effect: Z = 2.58 (P = 0.010) 1.7.6 Colorectal Chibaude 2011 0.5678 0.1103 1.9% 1.80 [1.45, 2.23] Giessen 2013 0.239 0.1019 2.1% 1.27 [1.04, 1.55] He 2013 0.0328 0.0102 1.4% 1.56 [1.48, 2.13] Mekenkamp2 2012 0.5068 0.1296 1.4% 1.56 [1.48, 2.13] Mekenkamp2 2012 0.5068 0.1296 1.4% 1.56 [1.48, 2.13] Mekenkamp2 2012 0.5068 0.1296 1.4% 1.56 [1.48, 2.13] Mekenkamp2 2012 0.5076 0.1298 1.4% 1.50 [1.16, 1.93] Subtotal (95% C1) 9.3% 1.52 [1.29, 1.79] Heterogeneity: Tau ² = 0.03; Ch ² = 10, 24, f = 5 (P = 0.02); P = 62% Test for overall effect: Z = 4.98 (P < 0.00001) 1.7.7 Sarcoma Bacci 2000 0.3293 0.0232 2.5% 1.39 [1.16, 1.67] Subtotal (95% C1) 4.7% 1.79 [1.30, 2.47] Heterogeneity: Tau ² = 0.06; Ch ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.003) 1.7.8 Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Gripp 2007 0.8757 0.198 1.3% 1.51 [1.18, 2.01] 1.7.8 Other Feliu 2011 0.1196 0.0322 6.9% 1.50 [1.10, 2.05] Heterogeneity: Tau ² = 0.06; Ch ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Feliu 2010 0.6433 0.0822 2.9% 2.00 [1.70, 2.35] 7.9 Polee 2003 0.44350 0.1582 1.0% 1.52 [1.10, 2.05] 7.9 Polee 2003 0.44550 0.156 0.8% 1.72 [1.32, 2.46] 7.9 Polee 2003 0.44550 0.156 0.8% 1.72 [1.32, 2.46] 7.9 Polee 2003 0.44550 0.156 0.8% 1.72 [1.32, 2.46] 7.9 Polee 2003 0.44550 0.156 0.8% 2.24 [1.58, 3.77] 7.9 Polee 2003 0.44550 0.156 0.8% 1.72 [1.32, 2.46] 7.9 Polee 2003 0.44550 0.156 0.8% 1.72 [1.32, 2.46] 7.9 7.9 Polee 2000 0.05470 0.126 0.8% 1.72 [1.34, 2.00] 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7.9 7.9	Scher 1999	0.003	0.001	9.1%	1.00 [1.00, 1.00]		
Subtrail (95% Cl) Heterogeneity: Tau ² = 0.42; Ch ² = 5.7.13, df = 4 ($P < 0.0001$); $P = 93\%$ Test for overall effect: $Z = 2.58$ ($P = 0.010$) 1.7.6 Colorectal Chibaudel 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Giessen 2013 0.239 0.1019 2.1% 1.27 [1.04, 1.55] Heterogeneity: Colorectal Mekenkamp 2012 0.6152 0.6158 0.1103 1.9% 1.80 [1.45, 2.23] Wekenkamp 2012 0.6152 0.6158 0.1103 1.9% 1.80 [1.46, 2.31] Wekenkamp 2012 0.6152 0.6184 1.65 [1.28, 2.13] Vara Kessel 2013 0.4028 0.1298 1.4% 1.50 [1.16, 1.63] 9.3% 1.52 [1.29, 1.79] Heterogeneity: Tau ² = 0.03; Ch ² = 13.14, df = 5 ($P = 0.02$); $P = 62\%$ Test for overall effect: $Z = 4.39$ ($P < 0.00001$) 1.7.7 Sarcoma Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Ferlia 2011 0.17 8 Tau ² = 0.06; Ch ² = 10.29, df = 3 ($P = 0.02$); $P = 71\%$ Test for overall effect: $Z = 3.60$ ($P = 0.0003$) 1.7.7 8 there ret tor overall effect: $Z = 3.60$ ($P = 0.0003$) 1.7.8 Other Feliu 2011 0.198 0.0455 0.1582 1.0% 1.50 [1.10, 2.05] Test for overall effect: $Z = 3.60$ ($P = 0.0003$) 1.7.8 Other Feliu 2011 0.1582 0.1582 1.0% 1.50 [1.10, 2.05] Test for overall effect: $Z = 3.60$ ($P = 0.0003$) 1.7.8 Other Feliu 2010 0.6587 0.1582 1.0% 1.50 [1.10, 2.05] Test for overall effect: $Z = 3.60$ ($P = 0.0003$) 1.7.8 Other Feliu 2011 0.5422 0.1280 1.5% 1.77 (1.34, 2.21] 1.5% 2010 0.5587 0.268 0.68% 1.88 [1.20, 2.70] 1.5% 1.77 (1.34, 2.21] 1.5% 1.5% (1.10, 0.5578 0.268 0.68% 1.68 [1.20, 2.70] 1.5% 1.5% (1.10, 0.5578 0.268 0.68% 1.68 [1.20, 2.70] 1.5% 1.5% (1.10, 0.5578 0.268 0.68% 1.68 [1.20, 2.70] 1.5% 1.5% (1.10, 0.5578 0.268 0.68% 1.68 [1.40, 2.70] 1.5% 1.5% (1.10, 0.5578 0.268 0.68% 1.68 [1.40, 2.70] 1.5% 1.5% (1.10, 0.55	Templeton 2014	0.9243	0.213	0.6%	2.52 [1.66, 3.83]		
The degraphicity in the result of the counce of the counc	Subtotal (95% CI) Heterogeneity: Tau ² =	0 14: Cbi2 = 57 13. df	= 1 (P <	13.6%	1.60 [1.12, 2.28] 12 = 03%		•
1.7.6 Colorectal Chibaudo 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Siessen 2013 0.238 0.1019 2.1% 1.27 [1.04, 1.55] 14e 2013 0.0380 0.2162 0.6% 0.97 [0.63, 1.48] Mekenkamp2 2012 0.5060 0.1296 1.4% 1.65 [1.48, 2.31] Mekenkamp2 2012 0.5060 0.1296 1.4% 1.50 [1.16, 1.93] Subtotal (95% CI) 9.3% 1.52 [1.29, 1.79] Heterogeneity: Tau ² = 0.03; Ch ² = 10.29, dF = 3 (P = 0.02); P = 62% Test for overall effect: Z = 4.98 (P < 0.00001)	Test for overall effect:	Z = 2.58 (P = 0.010)		0.00001)	1 - 3576		
1.7.0 Surfactal Displayed 2011 0.5878 0.1103 1.9% 1.80 [1.45, 2.23] Giessen 2013 0.239 0.1019 2.1% 1.27 [1.04, 1.55] He 2013 0.0388 0.216 0.6% 0.97 [0.63, 1.48] Mekenkamp 2012 0.6152 0.478 1.85 [1.48, 2.31] mark Kessel 2013 0.4028 0.1298 1.4% 1.56 [1.16, 1.83] subtotal (85% Cl) 9.3% 1.52 [1.28, 1.79]	176 Colorastal						
$\begin{array}{c} \text{Linear Details} \\ \text{decension 12} \\ \text{decension 2013} \\ \text{decension 2013} \\ \text{decension 2012} \\ \text{decension 2013} \\ \text{decension 2013} \\ \text{decension 2012} \\ \text$	Chibaudel 2014	0 5070	0 1102	1 0.0/	1 80 11 / = 0.001		-
$\begin{array}{c} \text{Jarcessent 2015} & \text{Locas} 0 \\ L$	Giorgen 2012	0.5878	0.1103	1.9%	1.80 [1.45, 2.23]		-
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Jiessen ZU13 He 2013	0.239	0.1019	2.1%	1.27 [1.04, 1.55]	_	L
$\begin{array}{c} \text{Helenkamp 2012} \\ \text{O} 0.0000 0.0000 1.4\% 0.65 [1.28, 2.13] \\ \text{ran Kossel 2013} \\ \text{O} 4028 0.1298 1.4\% 1.50 [1.16, 1.6.3] \\ \text{ran Kossel 2013} \\ \text{O} 4028 0.1298 1.4\% 1.50 [1.16, 1.6.3] \\ \text{ran Kossel 2013} \\ \text{O} 4028 0.1298 1.4\% 1.50 [1.16, 1.6.7] \\ \text{ran Kossel 2013} \\ \text{rat for overall effect: Z = 4.98 (P < 0.00001) \\ \text{Helerogeneity: Tau2 = 0.03; Chi2 = 13, 14, d = 5 (P = 0.02); P = 62\% \\ \text{Test for overall effect: Z = 4.98 (P < 0.00001) \\ \text{Helerogeneity: Tau2 = 0.05; Chi2 = 0.577 0.2690 0.6\% 1.38 [1.16, 1.67] \\ \text{Bacci 2000} \\ \text{Bacci 2000} \\ \text{Bacci 2000} \\ \text{O} 3293 0.0923 2.5\% 1.38 [1.16, 1.67] \\ \text{Bacci 2000} \\ \text{Bacci 2000} \\ \text{Bacci 2000} \\ \text{O} 5377 0.2690 0.6\% 1.88 (0.120, 2.70] \\ \text{Bacci 2001} \\ \text{O} 6587 0.2690 0.6\% 1.88 (0.120, 2.70] \\ \text{Bacci 2001} \\ \text{Comparison 1} \\ \text{Helerogeneity: Tau2 = 0.06; Chi2 = 10.29, df = 3 (P = 0.02); P = 71\% \\ \text{Test for overall effect: Z = 3.60 (P = 0.0003) \\ \text{I.7.8 Other} \\ \text{Felu 2011} \\ \text{O} 1193 0.0435 0.0522 0.9\% 1.13 [1.06, 1.20] \\ \text{Transition 2009} \\ \text{O} 5977 0.1816 0.8\% 1.82 (1.27, 2.60] \\ \text{Hanisodal 1993} \\ \text{O} 4055 0.1582 1.0\% 1.55 (1.10, 2.05] \\ \text{Hanisodal 1993} \\ \text{O} 4055 0.1582 1.0\% 1.55 (1.10, 2.05] \\ \text{Tarkhulz 2010} \\ \text{O} 6587 0.2680 0.6\% 1.58 1.72 [1.38, 1.71] \\ \text{Tork in 1997} \\ \text{Holes 2003} \\ \text{O} 4055 0.1582 1.0\% 1.72 [1.34, 2.21] \\ \text{Subtotal (95\% Ch)} \\ \text{Est for overall effect: Z = 6.44 (P < 0.00001) \\ \text{Tork in 1997} \\ \text{Helerogeneity: Tau2 = 0.07; Chi2 = 82.8, df = 53 (P < 0.0001); P = 85\% \\ \text{Test for overall effect: Z = 6.44 (P < 0.00001) \\ \text{Tork in 1997} \\ Helerogeneity: Tau2 = 0.00; Chi2 = 962.28 (df = 53 (P < 0.00001); P = 93\% \\ \hline 0.01 0.1 1 0 \\ \hline 0.1 0 \\ 10 \\ \hline 0.1 0 \\ \hline 0.1 0 \\ \hline 0.1 0 \\ \hline 0.1 \\ \hline $	Mokenkame 2012	-0.0336	0.2102	0.0%	0.57 [0.03, 1.48] 1.85 [1.49, 2.24]		-
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Mekenkamp 2012	0.0152	0.1296	1.0%	1.65 [1.46, 2.31]		-
Subted (95% CI) Subted (95% CI) 1.32 (1.26, 1.79] Heterogeneity: Tau" = 0.03; Ch" = 13.14, df = 5 (P = 0.02); P = 62% Test for verall effect: Z = 4.98 (P < 0.00001) 1.7.7 Sarcoma Sacci 2000 0.3293 0.0233 2.5% 1.39 [1.16, 1.67] Sacci 2000 0.6677 0.0627 1.5% 1.91 [1.49, 2.45] Subted (95% CI) 1.7.8 Cher Felix 2011 0.196 0.724 0.1% 9.01 [2.16, 37.32] Subted (95% CI) 1.7.8 Other Felix 2011 1.7.9 (1.30, 2.47] Heterogeneity: Tau" = 0.06; Ch" = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Felix 2011 1.7.9 (1.30, 2.47] Heterogeneity: Tau" = 0.06; Ch" = 10, 29, df = 3 (P = 0.02); H = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Felix 2011 1.7.8 Other Felix 2011 1.7.8 Other Felix 2011 1.7.8 Other Felix 2010 1.7.8 Other Felix 2011 1.7.8 Other Felix 2010 1.7.8 Other Felix 2011 1.7.8 Other Felix 2010 1.7.8 Other Felix 2010 1.7.8 Other Felix 2010 1.7.8 Other Felix 2011 1.7.8 Other Felix 2010 1.7.8 Other Felix 2011 1.7.8 Other Felix 2010 1.7.8 Other Felix 2.2.4 (Fill 2.2.2.46] 1.7.8 Other Felix 2.2.4 (Fill 2.3.17) 1.7.8 Other Felix 2.2.4 (Fill 2.4.2.00] 1.7.8 Other Felix 2.2.4 (Fill 2.4.2.00] 1.7.8 Other 1.7.8 Ot	van Kessel 2013	0.5008	0.1298	1.4%	1.50 [1.20, 2.13]		-
Heterogeneity: Tau ² = 0.03; Chi ² = 13.14, df = 5 (P = 0.02); P = 62% Test for overall effect: Z = 4.98 (P < 0.0001) 1.7.7 Sarcoma Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2000 0.5878 0.2069 0.6% 1.80 [1.20, 2.70] Bacci 2001 0.6471 0.1267 1.5% 1.91 [1.49, 2.45] Durnali 2013 2.1988 0.724 0.1% 9.01 [2.18, 37.32] Subtotal (95% Ct) 4.7% 1.77 [1.30, 2.47] Heterogeneity: Tau ² = 0.06; Chi ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Gripp 2007 0.6755 0.2101 0.6% 2.46 [1.59, 3.62] Hannisdal 1903 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Hansindar 1993 0.4353 0.082 2.9% 1.55 [1.32, 1.82] Pregra 2001 0.6581 0.082 2.9% 1.50 [1.10, 2.05] Hashimoto 2009 0.5977 0.1815 0.8% 1.82 [1.27, 2.60] Pregra 2001 0.6581 0.082 2.9% 2.01(7.0, 2.55] Pregra 2001 0.6583 0.082 2.9% 1.50 [1.10, 2.05] Tankiulu 2010 0.5678 0.2069 0.65% 1.80 [1.50, 2.10] Tankiulu 2010 0.5678 0.2069 0.65% 1.81 0.152, 2.46] Tankiulu 2010 0.5678 0.2069 0.65% 1.80 [1.50, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankiulu 2010 0.5678 0.2069 0.65% 1.80 [1.20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankiulu 2010 0.5678 0.2069 0.65% 1.80 [1.20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankiulu 2010 0.5678 0.2069 0.65% 1.80 [1.20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankiulu 2010 0.05678 0.2069 0.65% 1.80 [1.20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankiulu 2010 0.05678 0.2069 0.65% 1.80 [1.20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankiulu 2010 0.05678 0.2069 0.65% 1.80 [1.20, 2.70] Yamaguchi 2014 0.0000(1) FP = 85% Test for overall effect: Z = 0.4 (P < 0.00001); P = 85%	Subtotal (95% CI)	0.4020		9.3%	1.52 [1.29, 1.79]		•
Tast for overall effect: Z = 4.98 (P < 0.00001)	Heterogeneity: Tau ² =	0.03; Chi ² = 13.14, df	= 5 (P =	0.02); l ² :	= 62%		
1.7.7 Sarcoma Bacci 2000 0.3293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2004 0.5677 0.2669 0.6% 1.80 [1.20, 2.70] Bacci 2004 0.6677 0.1267 1.5% 1.91 [1.49, 2.45] Dumail 2013 2.1988 0.724 0.1% 9.01 [2.18, 37.32] Subtotal (95% CI) 4.7% 1.77 [1.30, 2.47] Heterogeneity: Tau ² = 0.06; Ch ² = 10.29, df = 3 (P = 0.02); l ² = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 17.8 Other Felu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Grip 2007 0.8755 0.2101 0.6% 2.40 [1.59, 3.62] Hannisda 1993 0.4055 0.1582 1.0% 1.56 [1.10, 2.05] Hannisda 1993 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Pelega 2001 0.6831 0.682 2.9% 2.00 [1.70, 2.35] Pelega 2001 0.5830 0.682 2.9% 2.00 [1.72, 2.36] Pelega 2001 0.586 0.176 0.8% 1.73 [1.22, 2.46] Tomin 1997 1.4061 0.516	Test for overall effect:	Z = 4.98 (P < 0.00001	I)				
Bacci 2000 0.2293 0.0923 2.5% 1.39 [1.16, 1.67] Bacci 2004 0.5678 0.2069 0.6% 1.80 [1.20, 2.70] Bacci 2007 0.6471 0.1267 1.5% 1.91 [1.49, 2.45] Durmal 2013 2.1988 0.7249 0.1% 9.01 [2.18, 37.32] Bacci 2007 0.6471 0.1267 1.5% 1.91 [1.49, 2.45] Durmal 2013 2.1988 0.7249 0.1% 9.01 [2.18, 37.32] Test for overall effect: Z = 3.60 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Gripp 2007 0.6755 0.2101 0.6% 2.40 [1.59, 3.62] Hannisdul 1903 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Hannisdul 1903 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Hannisdul 1903 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Hashimoto 2009 0.5577 0.1818 0.8% 1.82 [1.27, 2.60] Perga 2001 0.6493 0.0292 2.9% 1.55 [1.32, 1.82] Perga 2001 0.6493 0.0292 2.9% 1.55 [1.32, 1.82] Primer 2003 0.4055 0.1582 1.5% 1.72 [1.34, 2.21] Sun 2010 0.5678 0.2069 0.6% 1.80 [1.50, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.66] Tornin 1997 1.4061 0.6316 0.1% 4.06 [1.81, 14.07] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.66] Fest for overall effect: Z = 0.67, Chir = 88.25, df = 53 (P < 0.0001); P = 85% Test for overall effect: Z = 0.42 (P < 0.00001) Test for overall effect: Z = 0.42 (P < 0.00001); P = 93%	1.7.7 Sarcoma						
Bacci 2004 0.5677 0.2069 0.6% 1.80 [1.20, 2.70] Bacci 2007 0.6471 0.157 1.5% 1.91 1.49, 2.45] Durmali 2013 2.1988 0.7249 0.1% 9.01<[2.18, 37, 32]	Bacci 2000	0.3293	0.0923	2.5%	1.39 [1.16, 1.67]		-
Bacic 2007 0.6471 0.1267 1.5% 1.91 [1.4.9, 2.45] Durmail 2013 2.1988 0.7249 0.1% 9.01 [2.18, 37.32] Subtotal (95% CI) 4.7% 1.79 [1.30, 2.47] Heterogeneity: Tau* = 0.06; Chi* = 10.29, df = 3 (P = 0.02); P = 71% Test for overal effect: Z = 3.00 (P = 0.003) 17.8 Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Tannisdal 1993 0.4055 1.33 1.54 [1.18, 2.01]	Bacci 2004	0.5878	0.2069	0.6%	1.80 [1.20, 2.70]		
Durnal 2013 2.1988 0.7249 0.1% 9.01 [218.37.32] Subtotal (95% CI) 4.7% 1.79 [1.30, 2.47] Heterogeneity: Tau ² = 0.06; Chi ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.030) Tr.8. Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.08, 3.62] Feliu 2011 0.4315 0.1359 1.3% 1.54 [1.18, 2.01] Hannisodi 1993 0.4055 0.1682 1.0% 1.59 [1.10, 2.05] Hannisodi 1993 0.4055 0.1582 1.0% 1.59 [1.10, 2.05] Poleg 2001 0.6893 0.0822 2.9% 2.01 [7.0, 3.5] Poleg 2003 0.4055 0.1582 1.0% 1.59 [1.10, 2.05] Tankikul 2010 0.5499 0.1778 0.8% 1.73 [1.22, 2.46] Tankikul 2010 0.5498 0.1778 0.8% 1.73 [1.22, 2.46] Tankikul 2010 0.5498 0.1778 0.8% 1.73 [1.22, 2.46] Tankikul 2010 0.5498 0.066 0.176 0.8% 2.24 [1.58, 3.17] Tonin 1997 1.4061 0.6316 0.1% 4.08 [1.81, 14.07] Viganó 2000 0.55478 0.2600 0.6% 1.80 [1.20, 2.70] Vamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankikul 2010 0.247 (Chi = 88.25, df = 13 (P < 0.00001); P = 85% Test for overall effect: Z = 6.24 (P < 0.00001); P = 93% Poleg 0.000 0.1 196 (2.0001) Poleg 0.000 0.1 148 [1.43, 1.53] Heterogeneity: Tau ² = 0.00; Chi = 962.78, df = 63 (P < 0.00001); P = 93%	Bacci 2007	0.6471	0.1267	1.5%	1.91 [1.49, 2.45]		-
Subtotal (95% Cl) 4.7% 1.79 [1.30, 2.47] Heterogeneity: Tau ² = 0.06; Ch ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 6.60 (P = 0.0003) 1.7.8 Other Felu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Tanisdal 1993 0.4318 0.1559 1.3% 1.54 [1.18, 2.01] Tanisdal 1993 0.4455 0.1522 1.0% 1.55 [1.12, 2.05] Tashinoto 2009 0.5977 0.1818 0.8% 1.82 [1.27, 2.60] Tashinoto 2009 0.5977 0.1818 0.8% 1.82 [1.27, 2.60] Tashinoto 2009 0.5977 0.1818 0.8% 1.82 [1.27, 2.60] Tankuluz 2011 0.6453 0.0829 2.9% 2.00 [1.70, 2.35] Tankuluz 2011 0.5423 0.1269 1.5% 1.72 [1.34, 2.21] Subote 2003 0.4318 0.1765 0.8% 1.24 [1.58, 1.71] Tankuluz 2010 0.5499 0.1778 0.8% 1.72 [1.24, 2.246] Tankuluz 2010 0.5687 0.2060 0.6% 1.80 [1.2, 0.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankuluz 2010 0.05676 0.260 0.6% 1.80 [1.20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Tankuluz 2010 0.00001) Test for overall effect: Z = 6.24 (P < 0.00001); P = 85% Test for overall effect: Z = 6.24 (P < 0.00001); P = 93%	Durnali 2013	2.1988	0.7249	0.1%	9.01 [2.18, 37.32]		·
Heterogeneity: Tau ² = 0.06; Ch ² = 10.29, df = 3 (P = 0.02); P = 71% Test for overall effect: Z = 3.60 (P = 0.0003) 1.7.8 Other Feliu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Feliu 2011 0.196 0.0322 6.9% 1.13 [1.06, 1.20] Han 2003 0.4018 0.1359 1.3% 1.54 [1.18, 2.01] Hannisdal 1903 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Hannisdal 1903 0.4055 0.1582 2.9% 1.55 [1.32, 1.82] Pregra 2001 0.6581 0.082 2.9% 1.50 [1.10, 2.05] Pregra 2001 0.6581 0.082 2.9% 1.50 [1.10, 2.05] Pregra 2001 0.6581 0.082 2.9% 1.50 [1.10, 2.05] Pregra 2001 0.6581 0.082 2.9% 2.01 [.70, 2.35] Pregra 2001 0.5683 0.082 2.9% 2.01 [.70, 2.35] Prece 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Prece 2003 0.4055 0.1582 1.0% 1.52 [1.32, 2.46] Prece 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Prece 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Prece 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Prece 2003 0.4055 0.1582 1.0% 1.73 [1.22, 2.46] Prece 2003 0.4055 0.1582 0.08% 1.73 [1.22, 2.46] Prece 2003 0.4055 0.1582 0.08% 1.73 [1.22, 2.46] Prece 2003 0.5578 0.2060 0.6% 1.80 [1.50, 1.70] Prece 2003 0.05578 0.2060 0.6% 1.80 [1.50, 2.70] Prece 2003 0.0578 0.2060 0.6% 1.80 [1.20, 2.70] Prece 2003 0.0576 0.206 0.6% 1.50 [1.40, 7.70] Prece 2003 0.0576 0.206 0.6% 1.56 [1.40, 7.70] Prece 2003 0.0576 0.206 0.6% 1.50 [1.50, 2.70] Prece 2003 0.0576 0.206 0.6% 1.50 [1.50, 2.70] Prece 2003 0.0576 0.206 0.5% 1.50 [1.50, 2.60] Prece 2	Subtotal (95% CI)			4.7%	1.79 [1.30, 2.47]		♥
1.7.8 Other Fellu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] 570p 2007 0.8755 0.2101 0.6% 2.40 [1.59, 3.62] Han 2003 0.4318 0.1359 1.3% 1.54 [1.18, 2.01] Hansidad 1993 0.4055 0.1582 1.0% 1.55 (1.10, 2.05] Hashimoto 2009 0.5977 0.1818 0.8% 1.82 [1.27, 2.60] Lageward 1999 0.4333 0.0822 2.9% 5.5 [1.32, 1.82] Pierga 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.05] Sougoutzia 2011 0.5423 0.1289 1.5% 1.72 [1.34, 2.21] Sougoutzia 2011 0.5429 0.177 0.8% 1.77 [1.34, 2.21] Sougoutzia 2010 0.5697 0.260 0.8% 1.80 [1.20, 2.70] Yaamayohi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Subtobal (95% Cl) 2.24 [1.68, 1.407] 1.406 [1.48, 1.407] 1.406 [1.48, 1.407] Yaamayohi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] 1.406 [1.48, 1.407] Yaamayohi 2014 0.4318	Heterogeneity: Tau ² = Test for overall effect:	0.06; Chi ² = 10.29, df Z = 3.60 (P = 0.0003)	= 3 (P =	0.02); l ² :	= 71%		
Glu 2011 0.1196 0.0322 6.9% 1.13 [1.06, 1.20] Grip 2007 0.8755 0.2101 0.8% 2.40 [1.59, 3.62] Hannisda 1993 0.4055 0.138 1.54 [1.18, 2.01] Hannisda 1993 0.4055 0.1582 1.0% 1.59 [1.10, 2.05] Heanistad 1993 0.4055 0.1582 2.9% 2.00 [1.70, 2.35] Pelega 2001 0.6931 0.682 2.9% 2.00 [1.70, 2.35] Pankud 2010 0.6493 0.152 1.5% 1.77 [1.34, 2.21] Tankuku 2010 0.6495 0.158 1.78 [1.18, 1.07] Toplas Subjooltiz 2011 0.5423 0.128 1.5% 1.77 [1.34, 2.21] Tankuku 2010 0.6495 0.1576 0.8% 1.73 [1.52, 2.46] Tonini 1997 1.4061 0.6316 0.1% 4.08 [1.81, 14.07] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Yamaguchi 2010 0.6376 0.209 6.8% 1.69 [1.44, 2.00] Yamaguchi 2014 0.4318	1.7.8 Other						
Control Ontrol Output Outpu	Feliu 2011	0.1106	0.0322	6.0%	1 13 [1 06 1 20]		-
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Gripp 2007	0.1190	0.2101	0.6%	2.40 [1.59, 3.62]		
Hannisdal 1993 0.4055 0.1582 1.0% 1.50 [1:10, 2.05] Hashimoto 2009 0.5977 0.1816 0.8% 1.82 [1:27, 2.60] Plega 2001 0.6937 0.082 2.9% 1.55 [1:32, 1.82] Plega 2001 0.6931 0.0822 2.9% 2.00 [1:70, 2.35] Plega 2001 0.6931 0.0822 1.9% 1.50 [1:10, 2.05] Soujeoutiza 2011 0.5432 0.1282 1.0% 1.78 [1:22, 2.66] Tarnikulu 2010 0.8065 0.1576 0.8% 2.24 [1:58, 3.17] Tohini 1997 1.4061 0.6316 0.1% 4.08 [1:48, 1.407] Vigand 22000 0.5878 0.2069 0.6% 1.80 [1:20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1:15, 2.06] Vigand 2000 0.5878 0.2069 0.6% 1.80 [1:42, 0.00] Vigand 20201 0.5878 0.2069 0.6% 1.80 [1:42, 0.00] Vietorigeneity: Tau ² = 0.07; Chi ² = 88.25, df = 13 (P < 0.00001); P = 85%	Han 2003	0.4318	0.1359	1.3%	1.54 [1.18, 2.01]		-
$\label{eq:constraints} \begin{array}{c c c c c c c c c c c c c c c c c c c $	Hannisdal 1993	0.4055	0.1582	1.0%	1.50 [1.10, 2.05]		
Lagenvard 1999 0.4383 0.082 2.9% 1.55 [1.32, 1.82] Pilerga 2001 0.6893 0.082 2.9% 2.00 [1.70, 2.35] Sougioutizs 2011 0.5423 0.1289 1.5% 1.72 [1.34, 2.21] Sougioutizs 2011 0.5429 0.17% 0.8% 1.73 [1.22, 2.46] Tanrikulu 2010 0.8066 0.1765 0.8% 2.24 [1.58, 3.17] Tanrikulu 2010 0.5499 0.17% 0.8% 1.73 [1.22, 2.46] Tanrikulu 2010 0.5498 0.17% 0.8% 1.80 [1.10, 1.407] Viganó 2000 0.5578 0.2069 0.6% 1.80 [1.20, 2.70] transpective 1.24 (P < 0.00001); P = 85% Tato averall effect: Z = 6.24 (P < 0.00001); P = 85% Test for overall effect: Z = 6.24 (P < 0.00001); P = 93% 0.01 0.1 10	Hashimoto 2009	0.5977	0.1818	0.8%	1.82 [1.27, 2.60]		
Pierga 2001 0.6931 0.0829 2.9% 2.00 [17.0, 2.5] Pierga 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.6] Sougioultzia 2011 0.5429 0.15% 1.72 [1.34, 2.21] Sin 2010 0.5499 0.1776 0.8% 1.72 [1.34, 2.21] Tarnklul 2010 0.5695 0.1765 0.8% 1.72 [1.34, 2.21] Tarnklul 2010 0.5696 0.1765 0.8% 1.72 [1.32, 2.46] Tornin 1997 1.4061 0.516 0.1% 4.06 [1.16, 1.407] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Yamaguchi 2010 0.45876 0.2600 0.6% 1.30 [1.20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Yamaguchi 20107 Chi 24, (1.40, [1.40, [1.40, [1.40, 1.00] Image: 1.20 (1.10, 1.00) Image: 1.20 (1.10, 1.00) Heterogeneity: Tau ² = 0.00; Chi = 82.5, df = 13 (P < 0.00001); P = 85%	Lagerwaard 1999	0.4383	0.082	2.9%	1.55 [1.32, 1.82]		-
Polee 2003 0.4055 0.1582 1.0% 1.50 [1.10.2.05] Sougioultzis 2011 0.5423 0.1289 1.5% 1.72 [1.34, 2.21] Sougioultzis 2010 0.5499 0.1778 0.8% 1.73 [1.22, 2.46] Tarnikluu 2010 0.8065 0.1765 0.8% 2.24 [1.58, 3.17] Viganó 2000 0.5878 0.2069 0.6% 1.80 [1.20, 2.70] Yiganó 2000 0.5878 0.2069 0.6% 1.80 [1.20, 2.70] Fielderogeneity: Tau ² = 0.07; Chi ² = 88.25, df = 13 (P < 0.00001); P = 85% Test for overall effect: Z = 6.24 (P < 0.00001) Total (95% CI) 100.0% 1.48 [1.43, 1.53] Helerogeneity: Tau ² = 0.00; Chi ² = 962.78, df = 63 (P < 0.00001); P = 93% 0.01 0.1 1 10	Pierga 2001	0.6931	0.0829	2.9%	2.00 [1.70, 2.35]		-
Sougioutizs 2011 0.5429 0.15% 1.72 [1.34, 2.21] Tarnikulu 2010 0.5499 0.17% 0.8% 7.3 [1.22, 2.46] Tarnikulu 2010 0.8065 0.1765 0.8% 2.24 [1.58, 3.17] Tonini 1997 1.4061 0.6316 0.1% 4.08 [1.81, 14.07] Viganó 2000 0.5878 0.2069 0.5% 1.80 [1.20, 2.70] Varianguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Subtotal (95% C1) 2.24% 1.406 [1.40, 1.407] 1.406 [1.40, 1.407] Heterogeneity: Tau² = 0.07; Ch² = 88.25, dr = 13 (P < 0.00001); P = 85%	Polee 2003	0.4055	0.1582	1.0%	1.50 [1.10, 2.05]		
Sun 2010 0.5499 0.1778 0.8% 1.73 [1.22, 2.46] Tannikulu 2010 0.8065 0.1756 0.8% 2.24 [1.58, 3.77] Tonin 1997 1.4061 0.6316 0.1% 4.06 [1.18, 14.07] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Subtotal (9% c1) 2.24% 1.06 [1.44, 2.00] Heterogeneity: Tau ² = 0.07; Chi ² = 88.25, di = 13 (P < 0.00001); P = 85% Test for overall effect: Z = 6.24 (P < 0.00001) Heterogeneity: Tau ² = 0.00; Chi ² = 962.78, df = 63 (P < 0.00001); P = 93% Heterogeneity: Tau ² = 0.00; Chi ² = 962.78, df = 63 (P < 0.00001); P = 93%	Sougioultzis 2011	0.5423	0.1289	1.5%	1.72 [1.34, 2.21]		-
Tanrikulu 2010 0.8065 0.8765 0.8% 2.24 [1.58, 3.17] Tomini 1997 1.4061 0.6316 0.1% 4.06 [1.18, 1.407] Viganó 2000 0.5878 0.2089 0.6% 1.80 [1.20, 2.70] Yamaguchi 2014 0.43518 0.149 1.54 [1.15, 2.06] Subtotal (195% CI) 22.4% 1.08 [1.44, 4.00] Heterogeneity: Tau² = 0.07; Ch² = 88.25, df = 13 (P < 0.00001); P = 85%	Suh 2010	0.5499	0.1778	0.8%	1.73 [1.22, 2.46]		-
Tonin 1997 1.4061 0.6316 0.1% 4.08 [1.8, 14.07] Viganó 2000 0.5878 0.2060 0.6% 1.80 [1.20, 2.70] Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Subtotal (95% C1) 22.4% 1.69 [1.44, 2.00] • Heterogenetiy: Tau' = 0.07; Chi" = 88.25, df = 13 (P < 0.00001); P = 85%	Tanrikulu 2010	0.8065	0.1765	0.8%	2.24 [1.58, 3.17]		
Viganà 2000 0.5878 0.2069 0.6% 1.80 [1.20, 2.70] Viganà 2000 0.45878 0.2069 0.6% 1.80 [1.20, 2.70] Viamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Subtotal (95% Cl) 22.4% 1.69 [1.44, 2.00] Heterogeneity: Tau ² = 0.07; Chi ² = 88.25, df = 13 (P < 0.00001); P = 85% Total (95% Cl) 100.0% 1.48 [1.43, 1.53] Heterogeneity: Tau ² = 0.00; Chi ² = 962.78, df = 63 (P < 0.00001); P = 93% Heterogeneity: Tau ² = 0.00; Chi ² = 962.78, df = 63 (P < 0.00001); P = 93%	Tonini 1997	1.4061	0.6316	0.1%	4.08 [1.18, 14.07]		
Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06] Subtotal (95% Ct) 22.4% 1.06 [1.44, 2.00] • Heterogeneity: Tau ² = 0.07; Chi ² = 88.25, df = 13 (P < 0.00001); P = 85%	Viganó 2000	0.5878	0.2069	0.6%	1.80 [1.20, 2.70]		
Subtotal (95% CI) 22.4% 1.69 [1.44, 2.00] Heterogeneity: Tau ² = 0.07; Chi ² = 88.25, df = 13 (P < 0.00001); P = 85% Total (95% CI) 100.0% 1.48 [1.43, 1.53] Heterogeneity: Tau ² = 0.00; Chi ² = 962.78, df = 63 (P < 0.00001); P = 93% 0.01 0.1 100	Yamaguchi 2014	0.4318	0.149	1.1%	1.54 [1.15, 2.06]		T
Heterogeneity: 1au ² = 0.07; Chi ² = 88.25, df = 13 (P < 0.00001); P = 85% Test for overall effect: Z = 6.24 (P < 0.00001) Test for overall effect: Z = 6.24 (P < 0.00001) Heterogeneity: Tau ² = 0.00; Chi ² = 962.78, df = 63 (P < 0.00001); P = 93% Heterogeneity: Tau ² = 0.00; Chi ² = 962.69 (2.00001); P = 93% 0.01 0.1 1 10	Subtotal (95% CI)			22.4%	1.69 [1.44, 2.00]		•
Total (95% Cl) 100.0% 1.48 [1.43, 1.53] 1 Heterogeneity: Tau? = 0.00; Ch? = 962.78, df = 63 (P < 0.00001); l² = 93% 0.01 0.1 1 10	Heterogeneity: Tau ² =	0.07; Chi ² = 88.25, df	= 13 (P	< 0.00001); I ^z = 85%		
Total (95% CI) 100.0% 1.48 [1.43, 1.53]	rest for overall effect:	د – ۲.24 (P < 0.0000°	9				
Heterogeneity: Tau ² = 0.00; Chi ² = 962.78, df = 63 (P < 0.00001); l ² = 93%	Total (95% CI)			100.0%	1.48 [1.43, 1.53]		1
Test for suprell effect: 7 = 22.05 (P < 0.00001) U.U.U.U.U.U.U.U.U.U.U.U.U.U.U.U.U.U.U.	Heterogeneity: Tau ² =	0.00; Chi ² = 962.78, c	if = 63 (F	<pre>> < 0.0000</pre>	01); l² = 93%	0.01 0.1	1 10 1
rescrut overall eneod: Z = 22.95 (P < 0.00001) Eavours LDH < cutoff Eavoure LDH >	Fest for overall effect:	Z = 22.95 (P < 0.0000	01)			Favours LDH < cutoff	Favours I DH > outr

Figure 2 | Forest plots showing HRs by disease subgroups.

association between LDH and outcome. Our strict inclusion criteria (study size greater than 200, the requirement for HRs, and a requirement for a 95% CI or P value) may have introduced selection bias. Most of the included studies were retrospective, which may have introduced reporting bias. Finally, different cutoffs used to assess high LDH level in these studies might also have contributed to the

heterogeneity because it is possible that more false-positive cases were obtained with a cutoff of < 300 U/L than with a cutoff of >300 U/L. However, there is no accepted and validated absolute LDH level above which high LDH can be assigned. Instead, we used a cutoff of ULN. This may have introduced substantial heterogeneity, which may not have been fully accounted for by our use of sensitive



tudy or Subgroup .5.1 Non metastatic acci 2000	Ion[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
acci 2000					
	0.3293	0.0923	2.5%	1.39 [1.16, 1.67]	-
Jiaccone 2005	0.5365	0 1399	1.3%	1 71 [1 30 2 25]	-
aurie 2007	0.0000	0.1000	2.2%	1 36 [1 12 1 65]	-
dune 2007	0.0075	0.0991	2.2/0	2.62 [1.12, 1.03]	
van 2013	0.9658	0.3053	0.3%	2.03 [1.44, 4.78]	
Vei 2014	0.5446	0.176	0.8%	1.72 [1.22, 2.43]	
Subtotal (95% CI)			7.1%	1.54 [1.32, 1.80]	•
leterogeneity: Tau ² = 0.	01; Chi ² = 6.52, df =	= 4 (P = (1)	0.16); l ² =	39%	
	0.00 (1 - 0.0000	''			
.5.2 Mixed (Non meta:	static and metasta 0 3436	tic) 0 1085	1.9%	1 41 [1 14 1 74]	-
00 2004	0.3430	0.1003	2.00/	1 27 [1 11 1 60]	
	0.5140	0.1074	2.0 /0	1.07 [1.11, 1.09]	
	0.0070	0.2009	0.0%	1.00 [1.20, 2.70]	
acci 2007	0.6471	0.1267	1.5%	1.91 [1.49, 2.45]	
u 2013	0.005	0.0025	9.1%	1.01 [1.00, 1.01]	T
Jurnali 2013	2.1988	0.7249	0.1%	9.01 [2.18, 37.32]	
eliu 2011	0.1196	0.0322	6.9%	1.13 [1.06, 1.20]	
Giroux 2012	0.6931	0.2005	0.7%	2.00 [1.35, 2.96]	
Gripp 2007	0.8755	0.2101	0.6%	2.40 [1.59, 3.62]	
lan 2003	0.4318	0.1359	1.3%	1.54 [1.18, 2.01]	
lannisdal 1993	0.4055	0.1582	1.0%	1.50 [1.10, 2.05]	
lashimoto 2009	0.5977	0.1818	0.8%	1.82 [1.27, 2.60]	
awahara 1997	0.6729	0.1433	1.2%	1.96 [1.48, 2.60]	
(im 2010	0.7857	0.292	0.3%	2.19 [1.24, 3.89]	
i 2012	0 5068	0.2465	0.5%	1.66 [1.02 2.69]	⊢
lotzer 1999	0 0000	0.1245	1.5%	2 46 [1 93 3 14]	-
Antzer 2002	1 1705	0 1726	0.0%	2.70 [1.00, 0.14]	
101201 2002	0.4055	0.1720	1 00/	1 50 [4.00, 4.00]	
0100 2003	0.4055	0.1082	1.0%	1.00 [1.10, 2.05]	-
au 2013	-0.2058	0.1259	1.5%	0.01 [0.04, 1.04]	1
cher 1999	0.003	0.001	9.1%	1.00 [1.00, 1.00]	Ī
5uh 2010	0.5499	0.1778	0.8%	1.73 [1.22, 2.46]	
amura 1998	0.3365	0.1517	1.1%	1.40 [1.04, 1.88]	
anrikulu 2010	0.8065	0.1765	0.8%	2.24 [1.58, 3.17]	
	1.4061	0.6316	0.1%	4.08 [1.18, 14.07]	
onini 1997	0 5070	0 2060	0 60/	1 80 [1 20 2 70]	
onini 1997 ′iganó 2000	0.0070	0.2069	0.0 %	1.00 [1.20, 2.70]	
onini 1997 ⁄iganó 2000 Vang 2014	0.5939	0.2069	1.8%	1.81 [1.45, 2.26]	-
onini 1997 ′iganó 2000 Vang 2014 ′amaguchi 2014	0.5939 0.4318	0.2089 0.1138 0.149	1.8% 1.1%	1.81 [1.45, 2.26] 1.54 [1.15, 2.06]	- -
ionini 1997 Yiganó 2000 Vang 2014 Yamaguchi 2014 Yhou 2012	0.5939 0.4318 1.1112	0.2069 0.1138 0.149 0.317	0.0% 1.8% 1.1% 0.3%	1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibuo 2012 iubtotal (95% CI) leterogeneity: Tau ² = 0. est for overall effect: Z	0.5939 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000 ⁻	0.2069 0.1138 0.149 0.317 df = 27 (F	0.0% 1.8% 1.1% 0.3% 49.2% P < 0.0000	1.80 [1.26, 2.76] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93%	
ionini 1997 figanó 2000 Vang 2014 famaguchi 2014 hou 2012 Jubtotal (95% CI) leterogeneity: Tau ² = 0. jest for overall effect: Z .5.3 Metastatic Irmstrong 2012	0.5939 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000 ⁻	0.2069 0.1138 0.149 0.317 df = 27 (F 1)	0.0% 1.8% 1.1% 0.3% 49.2% P < 0.0000	1.80 [1:45, 2:26] 1.81 [1:45, 2:26] 1.54 [1.15, 2:06] 3.04 [1:63, 5:65] 1.20 [1.16, 1.24] 1); l ² = 93%	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibuotal (95% CI) leterogeneity: Tau ² = 0. rest for overall effect: Z .5.3 Metastatic rmstrong 2012 tzondian 2003	0.5339 0.4318 1.1112 00; Chi ² = 366.19, c = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624	0.2069 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339	0.8% 1.8% 1.1% 0.3% 49.2% P < 0.0000 0.9% 1.4%	1.80 [1:45, 2:26] 1.81 [1:45, 2:26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69]	
onini 1997 (ganó 2000 Vang 2014 (amaguchi 2014 hou 2012 subtotal (95% CI) leterogeneity: Tau ² = 0 jest for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 iedikien 2009	0.5379 0.5339 0.4318 1.1112 00; Chi ² = 366.19, c = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624	0.2069 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339	0.8% 1.8% 1.1% 0.3% 49.2% P < 0.0000 0.9% 1.4% 2.4%	1.80 [1.24,5,2.26] 1.84 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 4.82]	
ionini 1997 iganó 2000 Vang 2014 'amaguchi 2014 hou 2012 subtotal (95% CI) leterogeneity: Tau ² = 0, est for overall effect: Z .5.3 Metastatic urmstrong 2012 tzpodien 2003 ledikina 2008	0.5379 0.5399 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194	0.2069 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948	0.8% 1.8% 1.1% 0.3% 49.2% P < 0.0000 0.9% 1.4% 2.4%	1.80 [1:45, 2:26] 1.81 [1:45, 2:26] 3.04 [1:63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2:01, 3.93] 1.30 [1:00, 1.69] 1.52 [1:26, 1.83] 4.55 (1:20, 2:77]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 iubtotal (95% CI) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 ledikian 2008 ledikian 2011	0.3578 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194 0.4357 	0.12069 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225	0.3% 1.8% 1.1% 0.3% 49.2% P < 0.0000 0.9% 1.4% 2.4% 1.6%	1.80 [1:45, 2:26] 1.81 [1:45, 2:26] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); I ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic .tr.mstrong 2012 .tzpodien 2003 iedikian 2008 iedikian 2011 hibaudel 2011	0.5379 0.5339 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194 0.4357 0.5878	0.12069 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103	0.8% 1.8% 0.3% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9%	1.80 [1.22, 2.70] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.22, 1.97] 1.80 [1.45, 2.23] 0.81 [1.51, 2.23]	
onini 1997 (ganó 2000 Vang 2014 'amaguchi 2014 hou 2012 subtotal (95% CI) leterogeneity: Tau ² = 0 iest for overall effect: Z .5.3 Metastatic urmstrong 2012 tzpodien 2003 ledikian 2008 ledikian 2011 chibaudel 2011 cock 2006	0.5379 0.5339 0.4318 1.1112 00; Chi ² = 366.19, ¢ = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372	0.12059 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558	0.8% 1.8% 0.3% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.9%	1.80 [1.22, 2.70] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84]	
onini 1997 (iganó 2000 Vang 2014 'amaguchi 2014 hou 2012 subtotal (95% CI) leterogeneity: Tau ² = 0 est for overall effect: Z .5.3 Metastatic urmstrong 2012 tzpodien 2003 tedikian 2008 tedikian 2011 hibaudel 2011 cook 2006 2010	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, = 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068	0.12059 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407	0.8% 1.8% 0.3% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3%	1.80 [1.24, 2.26] 1.81 [1.45, 2.26] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19]	
onini 1997 iganó 2000 Vang 2014 amaguchi 2014 ibuotal (95% CI) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 tedikian 2011 bibaudel 2011 bibaudel 2011 bibaudel 2011 bibaudel 2010 soudier 2007	0.3578 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194	0.1069 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888	0.8% 1.8% 0.3% 49.2% 9 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3% 0.7%	1.80 [1.22, 2.70] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic .trmstrong 2012 .tzpodien 2003 .tedikian 2008 .tedikian 2011 ibiaudel 2011 .biaudel 2011 .cook 2006 .culp 2010 .scudier 2007 .ton 1998	0.5379 0.5339 0.4318 1.1112 00; Chi ² = 366.19, c = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.166	0.9% 1.8% 1.1% 0.3% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3% 0.7% 0.9%	1.80 [1.22, 2.70] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49]	
onini 1997 (ganó 2000 Vang 2014 'amaguchi 2014 ibu 2012 bubtotal (95% CI) leterogeneity: Tau ² = 0. čest for overall effect: Z .5.3 Metastatic urmstrong 2012 tzpodien 2003 leedikian 2008 leedikian 2011 Chibaudel 2011 Cok 2006 Lulp 2010 iscudier 2007 tion 1998 Siessen 2013	0.5379 0.5399 0.4318 1.1112 00; Chi ² = 366.19, c = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.166 0.1019	0.0% 1.8% 1.1% 0.3% 49.2% 2 < 0.0000 0.9% 1.4% 1.6% 1.9% 1.1% 1.3% 0.9% 2.1%	1.80 [1.22, 2.70] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ihou 2012 iubtotal (95% Cl) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 ledikian 2014 chibaudel 2011 cok 2006 culp 2010 iscudier 2007 iton 1998 lessen 2013 lalabi 2014	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.3365	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.160 0.1019 0.0959	0.9% 1.8% 1.1% 0.3% 49.2% 9 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3% 0.7% 0.9% 2.1% 2.3%	1.80 [1.24, 2.26] 1.81 [1.45, 2.26] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic trmstrong 2012 tzpodien 2003 iedikian 2011 hibaudel 2011 ibudel 2011 isook 2006 iulp 2010 iscudier 2007 iton 1998 iiessen 2013 lalabi 2014 le 2013	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5879 0.3865 -0.0336	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.166 0.1019 0.0959 0.2162	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.3% 0.7% 0.9% 2.1% 2.3% 0.6%	1.80 [1.22, 2.70] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.6, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic .rmstrong 2012 .tzpodien 2003 .edikian 2008 .edikian 2011 Chibaudel 2011 Cook 2006 .eulp 2010 .scudier 2007 .iton 1998 Diessen 2013 Ialabi 2014 Ie 2013 akob 2012	0.5379 0.5339 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194 0.4357 0.5678 0.7372 0.5668 0.5194 0.5878 0.239 0.3365 -0.0336 1.0116	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1528 0.1407 0.1888 0.166 0.1019 0.0959 0.2162 0.1995	0.0% 1.8% 1.1% 0.3% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.6% 1.9% 1.1% 1.3% 0.7% 0.9% 2.1% 2.3% 0.9% 0.9% 2.1% 0.9% 0.7%	1.80 [1.45, 2.26] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibu 2012 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic urmstrong 2012 tzpodien 2003 iedikian 2008 iedikian 2011 Chibaudel 2011 Cok 2006 Culp 2010 iscudier 2007 tion 1998 Siessen 2013 lalabi 2014 le 2013 akob 2012 in 2013	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5678 0.7372 0.5068 0.7365 0.7365 0.7365 0.7365 0.7365 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7365 0.7365 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7365 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.7365 0.7372 0.7365 0.7372 0.7365 0.7372 0.7365 0.7372 0.7365 0.7372 0.7365 0.7372 0.7365 0.7372 0.7365 0.7372 0.7372 0.7365 0.7372 0.7365 0.7372 0.7365 0.7372 0.	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1255 0.1103 0.1558 0.1407 0.1888 0.1407 0.1888 0.169 0.2162 0.1995 0.2192 0.2955 0.2192 0.2955 0.2192 0.2955 0.2192 0.2955 0.2195 0.2195 0.21558 0.11339 0.21558 0.1105 0.11339 0.21558 0.1105 0.1105 0.11339 0.21558 0.1105 0.1055 0.1005 0.0055 0.0055 0.00566 0.00566 0.00566 0.00566 0.00566 0.00566 0.05	0.0% 1.8% 1.1% 0.3% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3% 0.7% 0.9% 2.1% 2.3% 0.6% 0.7% 0.3%	1.80 [1.22, 2.70] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ihou 2012 iubtotal (95% Cl) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 ledikian 2008 ledikian 2014 chibaudel 2011 cok 2006 culp 2010 iscudier 2007 iton 1998 jiessen 2013 lalabi 2014 le 2013 akob 2012 in 2013 agerwaart 1999	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.55878 0.239 0.3365 -0.0336 1.0116 0.4669 0.4383	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.1407 0.1888 0.166 0.01019 0.0959 0.2162 0.1995 0.0806 0.082	0.9% 1.8% 1.1% 0.3% 49.2% 49.2% 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3% 0.7% 0.9% 2.1% 0.6% 0.7% 3.0% 2.9%	$\begin{array}{c} 1.83 \ [1.245, 2.26] \\ 1.54 \ [1.15, 2.06] \\ 3.04 \ [1.63, 5.65] \\ 1.20 \ [1.16, 1.24] \\ 1.20 \ [1.16, 1.24] \\ 1.21 \ [1.22, 1.20] \\ 1.22 \ [1.26, 1.83] \\ 1.30 \ [1.00, 1.69] \\ 1.52 \ [1.22, 1.97] \\ 1.80 \ [1.45, 2.23] \\ 2.09 \ [1.54, 2.84] \\ 1.66 \ [1.26, 2.19] \\ 1.68 \ [1.16, 2.43] \\ 1.80 \ [1.30, 2.49] \\ 1.27 \ [1.04, 1.55] \\ 1.40 \ [1.16, 1.69] \\ 0.97 \ [0.63, 1.48] \\ 2.75 \ [1.86, 4.07] \\ 1.60 \ [1.36, 1.87] \\ 1.55 \ [1.32, 1.82] \end{array}$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% Cl) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic trmstrong 2012 .tzpodien 2003 iedikian 2011 hibaudel 2011 ibubadel 2011 ibubadel 2011 ibubadel 2011 iscudier 2007 iton 1998 Biessen 2013 Ialabi 2014 Iei 2013 akob 2012 in 2013 agerwaard 1999 Ieckbach 2014	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5678 0.7372 0.5668 0.5194 0.5878 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.166 0.0959 0.2162 0.1995 0.0806 0.0822 0.1852	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.3% 0.7% 0.9% 2.1% 2.3% 0.6% 0.7% 3.0% 2.9% 0.8%	1.80 $[1.26, 2.76]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.6, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.86, 4.07]$ 1.60 $[1.32, 1.82]$ 2.30 $[1.30, 3.31]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) ieterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic urmstrong 2012 .tzpodien 2003 iedikian 2011 Chibaudel 2011 Cook 2006 Culp 2010 Sicsudier 2007 iton 1998 Diessen 2013 Ialabi 2014 le 2013 akob 2012 in 2013 agerwaard 1999 Meckbach 2014 Mekenkamp 2012	0.5379 0.5339 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.000) 1.0332 0.2624 0.4194 0.4357 0.5678 0.7372 0.5668 0.5194 0.5878 0.239 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1528 0.1407 0.1888 0.166 0.0195 0.2162 0.1995 0.0806 0.082 0.1852 0.11852	0.0% 1.8% 1.1% 0.3% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.6% 1.9% 1.3% 0.7% 0.9% 2.1% 2.3% 0.9% 2.1% 0.9% 1.4% 1.8% 1.8% 1.1% 1.8% 1.1% 1.8% 1.1% 1.8% 1.1% 1.8% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.1% 1.2% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.3% 0.9% 1.4% 1.4% 1.3% 0.9% 1.4% 1.3% 1.4% 1.3% 1.3% 1.3% 1.4% 1.3%	1.80 [1.45, 2.26] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87] 1.55 [1.32, 1.82] 2.30 [1.60, 3.31] 1.88 [1.48, 2.31]	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibu 2012 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic urmstrong 2012 tzpodien 2003 iedikian 2008 iedikian 2011 chibaudel 2011 cok 2006 culp 2010 iscudier 2007 iton 1998 Siessen 2013 lalabi 2014 le 2013 akob 2012 in 2013 agerwaard 1999 leckbach 2014 lekenkamp 2012	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1255 0.1103 0.1558 0.1407 0.1888 0.1407 0.1888 0.166 0.1019 0.0959 0.2162 0.0826 0.0826 0.0822 0.1852 0.1139 0.1256	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.6% 1.1% 1.3% 0.7% 0.9% 2.3% 0.6% 0.7% 0.8% 1.4% 2.3% 0.6% 0.7% 0.8% 1.1% 1.1% 1.4%	1.80 [1.24, 2.26] 1.81 [1.45, 2.26] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1); l ² = 93% 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.66 [1.36, 1.87] 1.55 [1.32, 1.82] 2.30 [1.60, 3.31] 1.85 [1.48, 2.31] 1.66 [1.28, 2.13]	
onini 1997 iganó 2000 Vang 2014 amaguchi 2014 ibuotal (95% Cl) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic trmstrong 2012 tzpodien 2003 iedikian 2011 ihibaudel 2011 ibibaudel 2011 ibibaudel 2011 isock 2006 iulp 2010 iscudier 2007 iton 1998 isessen 2013 alabi 2014 le 2013 akob 2012 in 2013 agerwaard 1999 ieckbach 2014 lekenkamp 2012 iekenkamp 2012 iekenkamp 2012 iekenkamp 2013	0.5878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4387 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1528 0.1407 0.1888 0.166 0.0195 0.2162 0.1995 0.0959 0.2162 0.1995 0.0959 0.2162 0.1995 0.0959 0.2162 0.1995 0.0806 0.0825 0.1139 0.1296 0.0806 0.0825 0.1139 0.1296 0.1295 0.0806 0.0825 0.1139 0.1295 0.0959 0.2162 0.1995 0.0959 0.2162 0.1995 0.0806 0.0806 0.0805 0.0805 0.1139 0.0959 0.2162 0.1995 0.0959 0.2162 0.1995 0.0959 0.2162 0.1995 0.0959 0.2162 0.0806 0.0806 0.0805 0.0805 0.0805 0.0805 0.1139 0.0959 0.0959 0.0959 0.0959 0.0959 0.0959 0.0959 0.0959 0.0959 0.0959 0.0959 0.0959 0.0959 0.0806 0.0806 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0805 0.0855 0.0805 0.08555 0.08555 0.08555 0.085555 0.08555555 0.0855555555555555555555	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3% 0.7% 0.9% 2.1% 0.6% 0.7% 3.0% 2.3% 0.6% 0.7% 3.0% 2.9% 0.8% 1.8% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 1.4% 0.7% 0.9% 0.8% 0.8% 0.8% 0.7% 0.8%	1.80 $[1.24, 2.26]$ 1.84 $[1.45, 2.26]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1.20 $[1.16, 1.24]$ 1.21 $[1.22, 1.22]$ 1.22 $[1.26, 1.83]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.36, 1.48]$ 2.75 $[1.86, 4.07]$ 1.65 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.22, 1.24]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic trmstrong 2012 .tzpodien 2003 iedikian 2011 hibaudel 2011 bibaudel 2011 bibaudel 2011 bibaudel 2011 iscoutier 2007 iton 1998 Biessen 2013 alabi 2014 le 2013 agerwaard 1999 feckbach 2014 Mekenkamp 2012 Mekenkamp 2012 Motzer 2013 leterona 2008	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5879 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.3607	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1528 0.1407 0.1888 0.166 0.0959 0.2162 0.0955 0.0806 0.0822 0.1852 0.1805 0.1296	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2 < 0.0000 0.9% 1.4% 1.6% 1.9% 1.6% 1.9% 1.3% 0.7% 0.9% 2.3% 0.9% 2.3% 0.9% 1.4% 2.3% 0.9% 1.4% 2.3% 0.9% 1.4% 2.4% 1.6% 1.9% 1.8% 1.1% 0.9% 1.4% 1.6% 1.9% 1.8% 1.8% 1.6% 1.9% 1.8% 1.8% 1.8% 1.4% 1.6% 1.9% 1.4% 1.6% 1.9% 1.4% 1.8% 1.8% 1.8% 1.6% 1.8% 1.4% 1.8% 1.4% 1.8% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.5% 1.4% 1.5% 1.4% 1.5% 1.4% 1.5% 1.4% 1.5%	1.80 $[1.26, 2.76]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.30, 2.49]$ 1.68 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.36, 1.87]$ 1.60 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.24, 2.13]$ 1.65 $[1.22, 2.13]$ 1.65 $[1.24, 2.13]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic urmstrong 2012 .tzpodien 2003 iedikian 2011 Chibaudel 2011 Cook 2006 Culp 2010 Siccudier 2007 iton 1998 Diessen 2013 Ialabi 2014 le 2013 akob 2012 in 2013 agerwaard 1999 Meckbach 2014 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp 2012 Mekenkamp 2012 Mekenkam	0.5379 0.5339 0.4318 1.1112 00; Chi ² = 366.19, c = 9.92 (P < 0.000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5668 0.5194 0.5878 0.239 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.5608 0.4528 0.5088 0.4517 0.5608 0.4517 0.5608 0.4517 0.5608 0.4517 0.5608 0.4529 0.66152 0.5088 0.4517 0.5608 0.4517 0.5608 0.4517 0.5608 0.4529 0.66152 0.5088 0.4517 0.5608 0.4529 0.66152 0.5088 0.4517 0.5608 0.5618	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.0339 0.0948 0.1225 0.1103 0.1588 0.1407 0.1888 0.1407 0.1888 0.166 0.0195 0.2162 0.1995 0.0826 0.082 0.1852 0.11296 0.1296 0.1295 0.1296 0.1296 0.1295 0.1296 0.1296 0.1296 0.1296 0.1296 0.1296 0.1295 0.1296 0.1296 0.1295 0.1296 0.1295 0.1296 0.1297 0.0826 0.0826 0.0826 0.0826 0.1296 0.0826 0.0866 0.0866 0.0866 0.0866 0.0866 0.0866 0.0866 0.0866 0	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.3% 0.9% 2.1% 2.3% 0.9% 2.1% 2.3% 0.9% 2.1% 0.9% 1.4% 1.8% 1.8% 1.8% 1.8% 1.8% 1.4% 0.8% 1.8% 1.4% 0.8% 1.4% 0.9% 0.9% 1.4% 0.9%	1.80 $[1.2, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.86, 4.07]$ 1.65 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.57 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.55]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ihou 2012 iubtotal (95% Cl) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 ledikian 2001 ichibaudel 2011 cok 2006 culp 2010 iscudier 2007 iton 1998 isessen 2013 lalabi 2014 le 2013 akob 2012 in 2013 agerwaard 1999 feckbach 2014 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lotzer 2013 leuman 2008 leuman 2008 leuman 2004	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5088 0.7372 0.5068 0.7372 0.5068 0.5194 0.5878 0.239 0.3655 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.5008 0.4518 0.4519 0.4518 0.4518 0.4519 0.4518 0.4519 0.4518 0.4518 0.4519 0.4518 0.4518 0.4519 0.4518 0.4519 0.4518 0.4519 0.4518 0.4519 0.4518 0.4519 0.4518 0.4517 0.5008 0.4517 0.5008 0.4517 0.4699 0.4517 0.5008 0.4517 0.5017 0.	0.2069 0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1130 0.1558 0.1407 0.1588 0.1407 0.1888 0.166 0.0959 0.2162 0.1995 0.2062 0.1852 0.1295 0.1295 0.0820 0.1805 0.1257 0.0821 0.2274	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2< 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 2.4% 1.6% 1.9% 2.3% 0.6% 0.7% 0.8% 1.8% 1.4% 2.9% 0.8% 1.8% 1.4% 0.8% 1.5% 2.9%	1.80 $[1.2, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.36, 1.48]$ 2.75 $[1.86, 4.07]$ 1.66 $[1.36, 1.48]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.67 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$	
onini 1997 iganó 2000 Vang 2014 amaguchi 2014 ibuotal (95% Cl) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic trmstrong 2012 tzpodien 2003 iedikian 2011 ibibaudel 2013 akob 2012 in 2013 agerwaard 1999 leckbach 2014 lekenkamp2 2012 letzer 2013 leuman 2008 ibirga 2001 ioprach 2014 iaito 2007	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4387 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.3665 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.3507 0.6931 0.8242 0.4619	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1528 0.1407 0.1888 0.166 0.0959 0.2162 0.1995 0.0959 0.2162 0.1995 0.0862 0.1852 0.1139 0.1296 0.1852 0.1296 0.1296 0.1297 0.2274 0.2274 0.2274	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3% 0.7% 0.9% 2.1% 0.6% 0.7% 3.0% 2.3% 0.6% 0.7% 3.0% 2.9% 0.8% 1.8% 1.8% 1.4% 0.5%	1.80 $[1.24, 2.26]$ 1.81 $[1.45, 2.26]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1.20 $[1.16, 1.24]$ 1.21 $[1.22, 1.22]$ 1.20 $[1.22, 1.22]$ 1.20 $[1.22, 1.22]$ 1.20 $[1.22, 1.22]$ 1.20 $[1.22, 1.22]$ 1.20 $[1.24, 2.23]$ 2.09 $[1.54, 2.23]$ 2.09 $[1.54, 2.23]$ 2.09 $[1.54, 2.24]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.36, 1.48]$ 2.75 $[1.32, 1.48]$ 2.75 $[1.32, 1.48]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.22, 1.32]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.57 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.28 $[1.40, 3.56]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% Cl) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic rrmstrong 2012 .tzpodien 2003 iedikian 2011 hibaudel 2011 bibaudel 2011 bibaudel 2011 bibaudel 2011 bibaudel 2011 bibaudel 2011 bibaudel 2011 bibaudel 2011 bibaudel 2013 akob 2012 in 2013 agerwaard 1999 Heckbach 2014 Hekenkamp 2012 Hekenkamp 2012 Hekenkamp 2012 Hekenkamp 2012 Hekenkamp 2012 Hekenkamp 2012 Hekenkamp 2012 Hekenkamp 2012 Hotzer 2013 Joprach 2014 Joprach 2014 Joprach 2014 Joprach 2007 Joprach 2007	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4357 0.6931 0.8671 0.8671 0.6931 0.8672 0.6931 0.8722 0.8752 0.6931 0.8752 0.8752 0.9752	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.166 0.0959 0.2162 0.1995 0.2162 0.1995 0.2162 0.1139 0.2162 0.2162 0.2162 0.2162 0.2125 0.2162 0.2125 0.2125 0.2125 0.2125 0.225 0.225 0.225 0.0829 0.2257 0.262 0.2257 0.262 0.2257 0.262 0.262 0.2257 0.262 0.262 0.262 0.2257 0.262 0.262 0.262 0.262 0.2257 0.262 0.262 0.262 0.262 0.262 0.262 0.2257 0.262 0.262 0.262 0.262 0.262 0.262 0.2257 0.262 0.262 0.262 0.262 0.262 0.262 0.262 0.2257 0.262 0.262 0.262 0.262 0.262 0.2257 0.262 0.	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 0.9% 1.4% 2.4% 1.6% 1.9% 1.4% 0.9% 2.1% 2.3% 0.6% 0.7% 3.0% 2.9% 0.8% 1.4% 0.8% 1.4% 0.8% 1.4% 0.8% 1.4% 0.8% 1.4% 0.5%	1.80 $[1.22, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 4.15]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.82, 1.82]$ 2.30 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.75 $[1.28, 1.28]$ 1.75 $[1$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic urmstrong 2012 .tzpodien 2003 iedikian 2008 iedikian 2011 Chibaudel 2011 Cook 2006 2019 2010 Siccudier 2007 iton 1998 Diessen 2013 Ialabi 2014 Ie 2013 akob 2012 in 2013 agerwaard 1999 Meckbach 2014 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2014 Mekenkamp	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5678 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.4357 0.4569 0.4383 0.8329 0.6152 0.5008 0.4517 0.5008 0.4522 0.4818 0.7855 0.5008 0.4517 0.5008 0.4517 0.5008 0.4522 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5007 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4522 0.4517 0.5008 0.4517 0.5007 0.5008 0.4517 0.5007 0.5008 0.4517 0.5007 0.5008 0.4517 0.5007 0.5008 0.4517 0.5007 0.5008 0.4517 0.5007 0.5008 0.4517 0.5007 0.5007 0.5007 0.5007 0.5008 0.4517 0.5007 0.	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1255 0.1103 0.1558 0.1407 0.1888 0.1407 0.1888 0.166 0.1019 0.0959 0.2162 0.199 0.2162 0.1852 0.1852 0.1852 0.1852 0.1257 0.1829 0.2274 0.2257 0.6557 0.65577 0.65577 0.65577 0.65577 0.655777 0.6557777 0.65577777777777777777777777777777777777	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 0.7% 0.9% 1.1% 1.3% 0.7% 0.9% 1.4% 2.3% 0.6% 0.7% 0.8% 1.4% 2.9% 0.8% 1.4% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.4% 0.4% 0.5% 0.5% 0.5% 0.4% 0.5%	1.80 $[1.2, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.86, 4.07]$ 1.66 $[1.36, 1.48]$ 2.75 $[1.36, 1.48]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.57 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.28 $[1.46, 3.56]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ihou 2012 iubtotal (95% Cl) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic urmstrong 2012 tzpodien 2003 tedikian 2008 tedikian 2011 chibaudel 2011 cook 2006 iulp 2010 iscudier 2007 iton 1998 Siessen 2013 lalabi 2014 le 2013 akob 2012 in 2013 akob 2012 in 2013 akob 2012 lekenamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2013 leuman 2008 Horpach 2014 Iei 2013 leuman 2008 Horpach 2014 Iei 2013 Iei 2014 Iei 2013 Iei 2013 Iei 2014 Iei 2013 Iei 2014 Iei 2013 Iei 2014 Iei 2013 Iei 2014 Iei 2013 Iei 2014 Iei 2013 Iei 2014 Iei 2015 Iei 2014 Iei 2015 Iei 2014 Iei 2015 Iei 20	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.4383 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.3507 0.6931 0.8242 0.4818 0.7885 0.6324	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.166 0.025 0.2162 0.1995 0.2162 0.1995 0.2162 0.1257 0.8029 0.2274 0.2357 0.22519 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.1655 0.25519 0.1655 0.1655 0.25519 0.1655 0.1655 0.25519 0.1655 0.1655 0.1655 0.25519 0.1655 0.1655 0.1655 0.25519 0.1655 0.1655 0.1655 0.25519 0.1655 0.1655 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.1655 0.25519 0.2551	0.9% 1.8% 1.1% 0.3% 49.2% 49.2% 2 < 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 1.3% 0.7% 0.9% 2.1% 0.9% 2.3% 0.6% 0.9% 2.3% 0.6% 0.9% 1.8% 1.8% 1.5% 2.9% 0.8% 1.5% 2.9% 0.5%	1.80 $[1.2, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.36, 1.48]$ 2.75 $[1.86, 4.07]$ 1.65 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.57 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.28 $[1.46, 3.56]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibubtal (95% Cl) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic trmstrong 2012 .tzpodien 2003 iedikian 2011 coldikian 2012 coldikian 2013 agerwaard 1999 leckbach 2014 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 coldita 2007 chimohara 2013 coldikian 2013 coldikian 2013 coldikian 2007 chimohara 2013 coldikian 2014 coldikian 2014 coldikian 2015 coldikian 2014 coldikian 2014 coldikian 2014 coldikian 2014 coldikian 2014 coldikian 2015 coldikian 2014 coldikian 2014 coldikian 2014 coldikian 2014 coldikian 2015 coldikian 2014 coldikian 2014 coldikian 2014 coldikian 2015 coldikian 2014 coldikian 2015 coldikian 2015 cold	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.3655 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.3507 0.6931 0.8242 0.4818 0.7885 0.6329 0.4785 0.6329 0.6452 0.5944 0.8785 0.5974 0.5975 0.5976 0.5976 0.5976 0.5976 0.5976 0.5976 0.5976 0.5976 0.59777 0.59777 0.59777 0.597777 0.59777777777777777777777777777777777777	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1558 0.1407 0.1888 0.166 0.0959 0.2162 0.1995 0.0959 0.2162 0.1895 0.0806 0.0822 0.1852 0.1852 0.1852 0.1852 0.1257 0.0829 0.2274 0.2274 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1257 0.1625 0.2519 0.1625 0.2519 0.1257 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0.2519 0.1625 0	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2.00000 0.9% 1.4% 2.4% 1.6% 1.9% 1.1% 0.7% 0.9% 2.1% 0.9% 2.3% 0.6% 0.7% 0.9% 1.8% 1.8% 1.8% 1.5% 2.9% 0.5% 0	1.80 $[1.22, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1.20 $[1.16, 1.24]$ 1.21 $[1.22, 1.22]$ 1.20 $[1.22, 1.22]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.36, 1.48]$ 2.75 $[1.86, 4.07]$ 1.60 $[1.36, 1.87]$ 1.65 $[1.22, 2.13]$ 1.65 $[1.22, 2.13]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.10, 2.33]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. est for overall effect: Z 5.3 Metastatic trmstrong 2012 tzpodien 2003 tedikian 2011 hibaudel 2011 cook 2006 culp 2010 iscoudier 2007 iton 1998 biessen 2013 lalabi 2014 le 2013 agerward 1999 Meckbach 2014 Mekenkamp 2012 Mekenkamp 2012	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.2599 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.5078 0.4383 0.8329 0.6152 0.5008 0.4517 0.5078 0.4383 0.8299 0.4517 0.5678 0.6391 0.8242 0.4818 0.7885 0.6329 0.47 0.5423	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1103 0.1588 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.125 0.0959 0.2162 0.0959 0.2162 0.1995 0.0822 0.1139 0.1257 0.0829 0.2274 0.2357 0.625 0.2519 0.1289 0.21289	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2< 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.3% 0.9% 2.1% 2.3% 0.9% 2.1% 2.3% 0.9% 2.1% 2.3% 0.9% 1.4% 0.9% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 1.4% 0.9% 0.9% 0.9% 1.4% 0.9% 0.5%	1.80 $[1.22, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.86, 4.07]$ 1.60 $[1.36, 1.87]$ 1.55 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.57 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.10, 2.33]$ 1.72 $[1.34, 2.21]$	
onini 1997 iganó 2000 Vang 2014 amaguchi 2014 ibubtal (95% Cl) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic urmstrong 2012 tzpodien 2003 ledikian 2008 ledikian 2011 cok 2006 culp 2010 iscudier 2007 iton 1998 jessen 2013 lalabi 2014 le 2013 akob 2012 in 2013 agerwaard 1999 feckbach 2014 lekenkamp2 2012 dekenkamp2 2012 lekkenkamp2 2012 lekkenkamp2 2012 letzer 2013 leuman 2008 leigag 2001 ioprach 2014 iaito 2007 ichmidt 2007 ichmidt 2007 ichmidt 2013 isionhara 2014 isionhara 2015 isionhara 2015 isionhara 2015 isionhara 2014 isionhara 2015 isionhara 2015	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5088 0.7372 0.5068 0.7372 0.5068 0.5194 0.5878 0.239 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.3507 0.6931 0.8242 0.4188 0.7885 0.6329 0.47 0.5423 0.9243	$\begin{array}{l} 0.2069\\ 0.1138\\ 0.149\\ 0.317\\ \text{df}=27\ (\text{F})\\ 0.1709\\ 0.1339\\ 0.0948\\ 0.1225\\ 0.1339\\ 0.0948\\ 0.1225\\ 0.1103\\ 0.1558\\ 0.1407\\ 0.1888\\ 0.1407\\ 0.1888\\ 0.1407\\ 0.1888\\ 0.160\\ 0.0959\\ 0.2162\\ 0.1950\\ 0.0820\\ 0.1852\\ 0.1852\\ 0.1852\\ 0.1852\\ 0.1257\\ 0.0829\\ 0.2274\\ 0.2357\\ 0.1625\\ 0.2274\\ 0.2357\\ 0.1625\\ 0.2274\\ 0.2357\\ 0.1625\\ 0.2274\\ 0.2357\\ 0.1625\\ 0.2213\\ 0.1289\\ 0.213\\ 0.213\\ 0.213\\ 0.213\\ 0.213\\ 0.213\\ 0.128\\ 0.213\\$	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2< 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 0.7% 0.9% 2.1% 2.3% 0.6% 0.7% 0.8% 1.8% 1.4% 2.9% 0.8% 1.8% 1.5% 2.9% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 0.6% 0.5%	1.83 $[1.45, 2.26]$ 1.84 $[1.45, 2.26]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.36, 1.48]$ 2.75 $[1.86, 4.07]$ 1.66 $[1.28, 2.13]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.67 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.28 $[1.46, 3.56]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.10, 2.23]$ 1.72 $[1.34, 2.21]$ 2.52 $[1.66, 3.83]$	
onini 1997 iganó 2000 Vang 2014 amaguchi 2014 ibutotal (95% Cl) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic trmstrong 2012 tzpodien 2003 iedikian 2011 ibibaudel 2013 akob 2012 in 2013 agerwaard 1999 feckbach 2014 Hekenkamp 2012 Hekenkamp 2012 Hekenkamp 2012 Idekenkamp 2012 ibicar 2013 ibiga 2001 ioprach 2014 iaito 2007 ibinohara 2012 ibinohara 2013 ibiougioultzis 2011 iempleton 2014 an Kessel 2013	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.3655 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.5078 0.4517 0.5072 0.6931 0.8242 0.4818 0.7825 0.6329 0.47 0.5423 0.5425 0.5425 0.5425 0.5425 0.5425 0.5425 0.5425 0.5425 0.5	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1133 0.1528 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.0959 0.2162 0.1995 0.0802 0.1139 0.1296 0.0822 0.1295 0.2162 0.1295 0.2274 0.2357 0.1625 0.2519 0.1228 0.2128	0.9% 1.8% 1.1% 0.3% 49.2% 49.2% 49.2% 0.9% 1.4% 2.4% 1.6% 1.9% 0.7% 0.9% 2.1% 0.7% 0.9% 2.3% 0.6% 0.7% 0.8% 1.8% 1.8% 1.8% 1.8% 1.8% 1.9% 0.9% 2.9% 0.5	1.83 $[1.45, 2.26]$ 1.84 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.36, 1.87]$ 1.55 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.22, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.57 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.28 $[1.46, 3.56]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.10, 2.33]$ 1.72 $[1.34, 2.21]$ 2.52 $[1.66, 3.83]$ 1.50 $[1.16, 1.93]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% Cl) leterogeneity: Tau ² = 0. iest for overall effect: Z 5.3 Metastatic trmstrong 2012 tzpodien 2003 ledikian 2011 coldikian 2011 coldikian 2011 coldikian 2011 coldikian 2011 coldikian 2011 coldikian 2011 coldikian 2013 lalabi 2014 le 2013 agerwaard 1999 feckbach 2014 Mekenkamp 2012 Mekenkamp 2012 Mekenkamp 2012 Motzer 2013 leuman 2008 cierga 2001 toprach 2014 cischnidt 2007 cischnidt 2007 cischnidt 2007 cischnidt 2007 cischnidt 2007 cischnidt 2007 cischnidt 2007 cischnidt 2013 an Kessel 2013 Veide 2013 Veide 2013 Veide 2013	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8229 0.6152 0.5008 0.4517 0.5807 0.6931 0.8242 0.4818 0.7885 0.6329 0.47 0.5423 0.9243 0.4028 0.47	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.0948 0.1225 0.1103 0.1588 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1995 0.0959 0.2162 0.0806 0.0822 0.1852 0.1852 0.1852 0.1257 0.2257 0.2257 0.2257 0.2257 0.2257 0.2257 0.2213 0.2213 0.1298 0.2213 0.1298 0.1295 0.2213 0.1298 0.1295 0.2213 0.1295 0.1295 0.2213 0.1295 0.1295 0.2213 0.1295 0.1295 0.2519 0.2130 0.1295 0.1295 0.2519 0.2130 0.1295 0.1295 0.1295 0.2519 0.2519 0.1295 0.2519 0.2130 0.1295 0.1295 0.1295 0.2519 0.2519 0.2130 0.1295 0.1295 0.2519 0.2519 0.2130 0.1295 0.1295 0.2519	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 49.2% 0.9% 1.4% 1.6% 1.9% 1.4% 0.9% 2.3% 0.6% 0.7% 3.0% 2.3% 0.6% 0.7% 3.0% 2.9% 0.5% 1.6% 1.5% 0.5% 0.5	1.80 $[1.2, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.82, 1.82]$ 2.30 $[1.30, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.10, 2.33]$ 1.72 $[1.34, 2.21]$ 2.52 $[1.66, 3.83]$ 1.50 $[1.16, 1.93]$ 1.60 $[1.30, 1.97]$	
onini 1997 iganó 2000 Vang 2014 iamaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic .rmstrong 2012 .tzpodien 2003 .tedikian 2008 .tedikian 2008 .tedikian 2008 .tedikian 2008 .tedikian 2008 .tedikian 2008 .tedikian 2008 .tedikian 2008 .tedikian 2008 .tedikian 2011 .thibaudel 2011 .took 2006 .too 1998 .tescudier 2007 .tion 1998 .tescudier 2007 .tion 1998 .tescudier 2007 .tion 1998 .tescudier 2013 .telexenkamp 2012 .tekenkamp 2013 .tekenkamp 2013 .tekenkamp 2014 .tekenkamp 2014 .tekenkamp 2014 .tekenkamp 2012 .tekenkamp 2012 .tekenkamp 2012 .tekenkamp 2013 .tekenkamp 2012 .tekenkamp 2013 .tekenkamp 2013 .tekenkamp 2012 .tekenkamp 2012 .tekenkamp 2013 .tekenkamp 2013 .tekenkamp 2012 .tekenkamp 2012	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5688 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.5088 0.7372 0.5088 0.239 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.6931 0.8242 0.4818 0.7885 0.6329 0.47 0.5423 0.9243 0.4028 0.47	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1255 0.1103 0.1558 0.1407 0.1888 0.1407 0.1888 0.166 0.1019 0.0959 0.2162 0.1852 0.1852 0.1852 0.1852 0.1257 0.2274 0.2257 0.1625 0.2274 0.22579 0.1298 0.2273 0.1298 0.2139 0.1298 0.2139 0.1059	0.0% 1.8% 1.1% 0.3% 49.2% 2< 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.4% 2.4% 1.6% 1.9% 0.7% 0.9% 1.4% 2.3% 0.6% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.4% 0.6% 0.7% 0.8% 1.4% 2.4% 0.6% 0.7% 0.8% 1.4% 2.4% 0.6% 0.6% 0.8% 1.4% 2.9% 0.8% 1.4% 2.4% 0.6% 0.7% 0.8% 1.4% 2.3% 0.6% 0.7% 0.8% 1.4% 2.4% 0.6% 0.7% 0.8% 1.4% 2.4% 0.6% 0.6% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.5% 0.6% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 0.6% 0.5% 1.0% 0.5% 0.6% 0.5% 0.6% 0.5% 1.0% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6% 0.5% 0.6% 0.7% 0.6% 0.7% 0.6% 0.7% 0.6% 0.7% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6%	1.80 $[1.2, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $l^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.86, 4.07]$ 1.66 $[1.28, 2.13]$ 1.85 $[1.48, 2.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.67 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.28 $[1.46, 3.56]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$	
onini 1997 iganó 2000 Vang 2014 amaguchi 2014 ibubtal (95% Cl) leterogeneity: Tau ² = 0. iest for overall effect: Z .5.3 Metastatic urmstrong 2012 .tzpodien 2003 iedikian 2011 cibibaudel 2011 .cook 2006 .uip 2010 .iscudier 2007 .ton 1998 Siessen 2013 alabi 2014 le 2013 akob 2012 in 2013 agerwaard 1999 Aeckbach 2014 Aekenkamp 2012 Aekenkamp 2012 Aekenkamp 2012 Aekenkamp 2012 Aekenkamp 2012 Aekenkamp 2012 Aito 2007 .comidt 2007 .c	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.7372 0.5068 0.4383 0.3365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.3507 0.6931 0.8242 0.4818 0.7322 0.4242 0.4418 0.747	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1130 0.1558 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.166 0.0959 0.2162 0.1995 0.0802 0.1852 0.1296 0.1296 0.22519 0.22519 0.22519 0.22519 0.1258 0.2519 0.1288 0.1298 0.1059 0.1298 0.129	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 2< 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 0.7% 0.9% 2.1% 0.6% 0.7% 0.8% 1.8% 1.8% 1.8% 1.8% 1.8% 0.5% 0.6% 0.5%	1.80 $[1.24, 5, 2.26]$ 1.81 $[1.45, 2.26]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $ ^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.86, 4.07]$ 1.65 $[1.32, 1.82]$ 2.30 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 3.11]$ 1.85 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.57 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.28 $[1.46, 3.56]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$	
onini 1997 iganó 2000 Vang 2014 amaguchi 2014 ibutotal (95% CI) leterogeneity: Tau ² = 0. est for overall effect: Z 5.3 Metastatic trmstrong 2012 tzpodien 2003 iedikian 2011 coldikian 2011 coldikian 2011 coldikian 2011 coldikian 2011 coldikian 2011 coldikian 2011 coldikian 2013 iscudier 2007 tion 1998 Siessen 2013 alabi 2014 le 2013 agerwaard 1999 Teckbach 2014 Teckbach 2014 Teckbach 2014 Teckbach 2014 Teckbach 2014 Teckbach 2014 Tekenkamp 2012 Tekenkamp 2012 Totzer 2013 coldi 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2014 an Kessel 2013 veide 2012 veide 2013 veide 2014 ubtotal (95% CI)	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000' 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.3655 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.5507 0.6931 0.8242 0.4818 0.7885 0.6329 0.477 0.5423 0.9243 0.4028 0.47 0.47	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1133 0.1558 0.1407 0.1888 0.166 0.1019 0.0959 0.2162 0.1995 0.0806 0.0852 0.1805 0.1805 0.1257 0.0829 0.1257 0.0829 0.1257 0.0829 0.1257 0.1852 0.1257 0.1852 0.1257 0.1258 0.1257 0.1258 0.1257 0.1258 0.1257 0.1258 0	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 49.2% 0.9% 1.4% 2.4% 1.6% 1.9% 0.7% 0.9% 2.1% 0.7% 0.9% 2.3% 0.6% 0.7% 0.9% 2.3% 0.6% 0.7% 0.8% 1.8% 1.8% 1.8% 1.5% 2.9% 0.5	1.80 [1.45, 2.26] 1.81 [1.45, 2.26] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1.20 [1.16, 1.24] 1.21 [1.22, 1.22] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.65 [1.28, 2.13] 1.55 [1.22, 1.82] 2.30 [1.60, 3.31] 1.85 [1.48, 2.31] 1.65 [1.28, 2.13] 1.57 [1.10, 2.24] 1.42 [1.11, 1.82] 2.00 [1.70, 2.35] 2.28 [1.46, 3.56] 1.62 [1.02, 2.57] 2.20 [1.60, 3.03] 1.88 [1.15, 3.09] 1.60 [1.30, 1.97] 1.60 [1.30, 1.97] 1.60 [1.30, 1.97] 1.60 [1.30, 1.97] 1.60 [1.30, 1.97] 1.69 [1.58, 1.81] ; J ² = 51%	
onini 1997 iganó 2000 /ang 2014 amaguchi 2014 hou 2012 ubtotal (95% CI) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 edikian 2011 hibaudel 2011 ook 2006 ulp 2010 scudier 2007 ton 1998 iessen 2013 alabi 2014 e 2013 alabi 2014 e 2013 agerwaard 1999 leckbach 2014 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lotzer 2013 oprach 2014 aito 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2013 anglez 2013 ougioultzis 2011 empleton 2014 an Kessel 2013 /eide 2013 /eide 2013 /eide 2014 eterogeneity: Tau ² = 0. est for overall effect: Z	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, q = 9.92 (P < 0.0000 ⁻ 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.3655 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.5807 0.6931 0.8242 0.4818 0.7885 0.6329 0.47 0.5423 0.428 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.4028 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.47 0.5423 0.428 0.4785 0.6329 0.47 0.5423 0.428 0.477 0.5423 0.428 0.477 0.5423 0.428 0.477 0.5423 0.428 0.477 0.5423 0.428 0.477 0.5423 0.428 0.477 0.5423 0.428 0.477 0.5423 0.547	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1133 0.1548 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1257 0.0829 0.2274 0.2257 0.1257 0.2257 0.2257 0.2257 0.2257 0.2257 0.2257 0.2257 0.2257 0.2213 0.2213 0.1299 0.2130 0.1299 0.2130 0.1299 0.1299 0.2130 0.1299 0.1299 0.1297	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 49.2% 0.9% 1.4% 2.4% 1.6% 1.9% 1.4% 0.9% 2.3% 0.6% 0.7% 2.3% 0.6% 0.7% 3.0% 2.3% 0.6% 0.7% 3.0% 2.9% 0.5% 1.4% 0.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.5% 1.5% 0.0% 0.5% 0.0% 0.5% 0.0% 0.5% 0.0	1.80 $[1.22, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.82, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.65 $[1.28, 2.13]$ 1.62 $[1.00, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.10, 2.33]$ 1.72 $[1.34, 1.27]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$ 1.69 $[1.58, 1.81]$; $l^2 = 51\%$	
onini 1997 iganó 2000 /ang 2014 amaguchi 2014 hou 2012 ubtotal (95% CI) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 edikian 2011 hibaudel 2011 ook 2006 ulp 2010 scudier 2007 ton 1998 iessen 2013 alabi 2014 e 2013 akob 2012 n 2013 agerward 1999 leckbach 2014 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lekenkamp 2012 lotzer 2013 agurvard 1999 leckbach 2014 aito 2007 chmidt 2007 chmidt 2007 hinohara 2012 ougioultzis 2011 empleton 2014 an Kessel 2013 ubtotal (95% CI) eterogeneity: Tau ² = 0. est for overall effect: Z	0.3678 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.5008 0.4517 0.6931 0.8242 0.4818 0.7885 0.6329 0.47 0.5423 0.9243 0.4028 0.47 0.5423 0.9243 0.47 0.5423 0.9243 0.47 0.5423 0.9243 0.47 0.5423 0.47 0.5423 0.47 0.5423 0.9243 0.47 0.5423 0.5423 0.555 0.555 0.555 0.555 0.555 0.555 0.555 0.555 0.555 0.	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1255 0.1103 0.1558 0.1407 0.1888 0.1407 0.1888 0.166 0.1019 0.0959 0.2162 0.1995 0.2274 0.2857 0.1852 0.1257 0.1852 0.1257 0.2274 0.22579 0.1257 0.2274 0.22579 0.1298 0.2273 0.1298 0.2273 0.1298 0.1059 f = 30 (P 01)	0.0% 1.8% 1.1% 0.3% 49.2% 2< 0.0000 0.9% 1.4% 2.4% 1.6% 1.9% 1.6% 1.9% 0.7% 0.9% 2.3% 0.6% 0.7% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.4% 2.9% 0.8% 1.5% 0.6% 0.5% 1.0% 1.5% 0.6% 0.5% 1.0% 1.5% 0.6% 0.5% 1.0% 0.5% 1.0% 0.6% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 1.0% 0.5% 0.6% 0.5% 0.0% 0.6% 0.5% 1.0% 0.5% 0.6% 0.5% 1.0% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 1.0% 0.5% 0.6% 0.5% 1.0% 0.5% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6% 0.7% 0.6% 0.5% 0.6% 0.6% 0.5% 0.6% 0.6% 0.5% 0.6% 0.6% 0.5% 0.6% 0.6% 0.5% 0.6% 0.7% 0.6%	1.80 [1.2, 2.70] 1.81 [1.45, 2.26] 1.54 [1.15, 2.06] 3.04 [1.63, 5.65] 1.20 [1.16, 1.24] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.65 [1.22, 1.32] 2.30 [1.60, 3.31] 1.85 [1.48, 2.31] 1.65 [1.28, 2.13] 1.65 [1.28, 2.13] 1.65 [1.28, 2.13] 1.65 [1.28, 2.13] 1.57 [1.10, 2.24] 1.42 [1.11, 1.82] 2.00 [1.70, 2.35] 2.28 [1.46, 3.56] 1.62 [1.02, 2.57] 2.20 [1.60, 3.03] 1.88 [1.15, 3.09] 1.60 [1.30, 1.97] 1.60 [1.30, 1.97] 1.60 [1.30, 1.97] 1.69 [1.58, 1.81] ; $l^2 = 51\%$	
onini 1997 iganó 2000 vang 2014 amaguchi 2014 hou 2012 ubtotal (95% Cl) leterogeneity: Tau ² = 0. est for overall effect: Z .5.3 Metastatic rmstrong 2012 tzpodien 2003 edikian 2008 edikian 2011 hibaudel 2011 ook 2006 ulp 2010 scudier 2007 ton 1998 iessen 2013 alabi 2014 e 2013 akob 2012 n 2013 agerwaard 1999 leckbach 2014 lekenkamp 2012 lekkenkamp 2012 lekkenkamp 2012 lekkenkamp 2012 lekkenkamp 2012 lekkenkamp 2012 lekkenkamp 2012 lekkenkamp 2012 lekenkamp 2012 oprach 2014 atio 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2007 chmidt 2013 ugioultzis 2011 empleton 2014 an Kessel 2013 ubtotal (95% Cl) eterogeneity: Tau ² = 0. est for overall effect: Z	0.3878 0.5939 0.4318 1.1112 00; Chi ² = 366.19, (= 9.92 (P < 0.0000 1.0332 0.2624 0.4194 0.4357 0.5878 0.7372 0.5068 0.5194 0.5878 0.239 0.365 -0.0336 1.0116 0.4669 0.4383 0.8329 0.6152 0.5008 0.4517 0.3507 0.6931 0.8242 0.4818 0.7855 0.6229 0.477 0.5423 0.4028 0.47 0.47 0.47 02; Chi ² = 61.37, df = 15.15 (P < 0.0000	0.1138 0.149 0.317 df = 27 (F 1) 0.1709 0.1339 0.0948 0.1225 0.1133 0.1528 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1407 0.1888 0.1255 0.2162 0.1995 0.2162 0.1995 0.2162 0.1267 0.8029 0.2274 0.2357 0.1625 0.2519 0.22519 0.2125 0.22519 0.1257 0.1259 0.22519 0.1265 0.22519 0.1265 0.22519 0.1265 0.22519 0.1298 0.1298 0.1298 0.1298 0.1059 = 30 (P	0.0% 1.8% 1.1% 0.3% 49.2% 49.2% 49.2% 0.9% 1.4% 2.4% 1.6% 1.9% 0.7% 0.9% 2.1% 0.9% 2.3% 0.6% 0.7% 3.0% 0.8% 1.8% 1.8% 1.8% 1.8% 1.5% 2.9% 0.8% 1.8% 1.8% 1.8% 1.6% 1.9% 0.9% 2.1% 0.9% 1.4% 2.4% 1.6% 1.9% 0.9% 2.1% 0.9% 1.4% 2.4% 1.6% 1.9% 0.9% 2.1% 0.9% 1.4% 2.4% 1.6% 1.9% 0.9% 2.1% 0.9% 1.4% 2.4% 1.6% 1.9% 0.9% 2.1% 0.9% 0.9% 1.4% 2.3% 0.6% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.6% 0.4% 0.5% 0.5% 0.5% 0.5% 0.6% 0.4% 0.5% 0.6% 0.5% 0.6% 0.4% 0.5% 0.6% 0.5% 0.5% 0.6% 0.5% 0.6% 0.5% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.5% 0.6% 0.4% 0.5% 0.6% 0.6% 0.6% 0.5% 0.6% 0.6% 0.6% 0.6% 0.6% 0.5% 0.6% 0.6% 0.6% 0.6% 0.6% 0.6% 0.6% 0.6% 0.6% 0.6% 0.6% 0.0% 0.6% 0.6% 0.0% 0.6% 0.0	1.80 $[1.26, 2.70]$ 1.81 $[1.45, 2.26]$ 1.54 $[1.15, 2.06]$ 3.04 $[1.63, 5.65]$ 1.20 $[1.16, 1.24]$ 1); $ ^2 = 93\%$ 2.81 $[2.01, 3.93]$ 1.30 $[1.00, 1.69]$ 1.52 $[1.26, 1.83]$ 1.55 $[1.22, 1.97]$ 1.80 $[1.45, 2.23]$ 2.09 $[1.54, 2.84]$ 1.66 $[1.26, 2.19]$ 1.68 $[1.16, 2.43]$ 1.80 $[1.30, 2.49]$ 1.27 $[1.04, 1.55]$ 1.40 $[1.16, 1.69]$ 0.97 $[0.63, 1.48]$ 2.75 $[1.86, 4.07]$ 1.60 $[1.36, 1.87]$ 1.55 $[1.32, 1.82]$ 2.30 $[1.60, 3.31]$ 1.85 $[1.48, 2.31]$ 1.65 $[1.28, 2.13]$ 1.57 $[1.10, 2.24]$ 1.42 $[1.11, 1.82]$ 2.00 $[1.70, 2.35]$ 2.28 $[1.46, 3.56]$ 1.62 $[1.02, 2.57]$ 2.20 $[1.60, 3.03]$ 1.88 $[1.15, 3.09]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$ 1.60 $[1.30, 1.97]$ 1.69 $[1.58, 1.81]$; $ ^2 = 51\%$	

Figure 3 | Forest plots showing HRs by stage subgroups.



				Hazard Ratio	Hazard	Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% C	IV, Rando	m, 95% Cl
Atzpodien 2003	በ 2624	0.1339	1 4%	1.30 [1.00 1.60]		.
Bacci 2004	0.5878	0.2069	0.6%	1.80 [1.20, 2.70]		~
Eton 1998	0.5878	0.166	0.9%	1.80 [1.30, 2.49]		-
Gripp 2007	0.8755	0.2101	0.6%	2.40 [1.59, 3.62]		
Hashimoto 2009	0.5977	0.1818	0.8%	1.82 [1.27, 2.60]		-
Li 2012	0.5068	0.2465	0.5%	1.66 [1.02, 2.69]		
Neuman 2008	0.3507	0.1257	1.5%	1.42 [1.11, 1.82]		-
Scher 1999	0.003	0.001	9.1%	1.00 [1.00, 1.00]		
Sougioultzis 2011	0.5423	0.1289	1.5%	1.72 [1.34, 2.21]		
Wang 2014	0.5939	0.1138	1.8%	1.81 [1.45, 2.26]		-
Wei 2014	0.5446	0.176	0.8%	1.72 [1.22, 2.43]		
Zhou 2012	1.1112	0.317	0.3%	3.04 [1.63, 5.65]		
Subtotal (95% CI)	44. 052 - 472.00	4 - 40 (23.1%	1.71 [1.38, 2.12]		•
Test for overall effect: Z	2 = 4.92 (P < 0.0000	1) – 13 (r	- < 0.0000	1), 1 92 %		
4 4 9 959 999						
1.4.2 250-300 Armstrong 2012	1 0222	0 1700	0.0%	2 91 [2 01 2 02]		
Bacci 2000	0.3293	0.0923	2.5%	1.39 [1.16, 1.67]		+
Bacci 2007	0.6471	0.1267	1.5%	1.91 [1.49, 2.45]		~
Bedikian 2011	0.4357	0.1225	1.6%	1.55 [1.22, 1.97]		-
Chibaudel 2011	0.5878	0.1103	1.9%	1.80 [1.45, 2.23]		
Durnali 2013	2.1988	0.7249	0.1%	9.01 [2.18, 37.32]		÷ .
Giessen 2013	0.239	0.1019	2.1%	1.27 [1.04, 1.55]		-
Halabi 2014	0.3365	0.0959	2.3%	1.40 [1.16, 1.69]		-
Han 2003	0.4318	0.1359	1.3%	1.54 [1.18, 2.01]		-
He 2013	-0.0336	0.2162	0.6%	0.97 [0.63, 1.48]	-	
Jakob 2012	1.0116	0.1995	0.7%	2.75 [1.86, 4.07]		- -
Kawanara 1997 Kim 2010	0.6729	0.1433	0.3%	2 19 [1.46, 2.60]		
Lagerwaard 1999	0.4383	0.082	2.9%	1.55 [1.32, 1.82]		-
Laurie 2007	0.3075	0.0991	2.2%	1.36 [1.12, 1.65]		-
Meckbach 2014	0.8329	0.1852	0.8%	2.30 [1.60, 3.31]		_
Mekenkamp 2012 Mekenkamp 2012	0.6152	0.1139	1.8%	1.85 [1.48, 2.31]		÷
Motzer 1999	0.9002	0.1290	1.4 %	2.46 [1.93, 3.14]		-
Pierga 2001	0.6931	0.0829	2.9%	2.00 [1.70, 2.35]		+
Polee 2003	0.4055	0.1582	1.0%	1.50 [1.10, 2.05]		.
Sau 2013	-0.2058	0.1259	1.5%	0.81 [0.64, 1.04]	-	
Tamura 1998	0.3365	0.1517	1.1%	1.40 [1.04, 1.88]		- <u>-</u>
Veide 2012	0.9243	0.213	2.0%	2.52 [1.66, 3.83]		-
Weide 2012 Weide 2013	0.47	0.1059	2.0%	1.60 [1.30, 1.97]		-
Yamaguchi 2014	0.4318	0.149	1.1%	1.54 [1.15, 2.06]		.
Subtotal (95% CI)			41.3%	1.67 [1.52, 1.84]		•
Heterogeneity: Tau ² = 0 Test for overall effect: 7	0.05; Chi² = 106.95, 0 ' = 10.45 (P < 0.000)	df = 27 (F 01)	P < 0.0000	1); l² = 75%		
	10.40 (1 1 0.000)	,				
1.4.3 301-400						
Du 2013 Ecoudios 2007	0.005	0.0025	9.1%	1.01 [1.00, 1.01]		
Hannisdal 1993	0.5194	0.1666	1.0%	1.00 [1.10, 2.43]		
Motzer 2002	1.1725	0.1726	0.9%	3.23 [2.30, 4.53]		-
Motzer 2013	0.4517	0.1805	0.8%	1.57 [1.10, 2.24]		
Poprach 2014	0.8242	0.2274	0.5%	2.28 [1.46, 3.56]		
Saito 2007	0.4818	0.2357	0.5%	1.62 [1.02, 2.57]		<u> </u>
Shinohara 2012 Shinohara 2013	0.6329	0.2519	0.4%	1.66 [1.15, 3.09]		_
van Kessel 2013	0.4028	0.1298	1.4%	1.50 [1.16, 1.93]		.
Subtotal (95% CI)			16.2%	1.69 [1.27, 2.24]		♦
Heterogeneity: Tau ² = 0 Test for overall effect: Z	0.18; Chi² = 104.15, d := 3.62 (P = 0.0003)	df = 9 (P	< 0.00001); I² = 91%		
1.4.4 >400						
Aoe 2004	0.3436	0.1085	1.9%	1.41 [1.14, 1.74]		-
Aoe 2005	0.3148	0.1074	2.0%	1.37 [1.11, 1.69]		-
Bedikian 2008	0.4194	0.0948	2.4%	1.52 [1.26, 1.83]		-
Culp 2010	0.7372	0.1556	1.1%	2.09 [1.54, 2.64]		-
Feliu 2011	0.1196	0.0322	6.9%	1.13 [1.06, 1.20]	1	•
Giroux 2012	0.6931	0.2005	0.7%	2.00 [1.35, 2.96]		-
Schmidt 2007	0.7885	0.1625	1.0%	2.20 [1.60, 3.03]		
Suh 2010 Taprikulu 2010	0.5499	0.1778	0.8%	1.73 [1.22, 2.46]		
rannkulu ∠010 Tonini 1997	0.8065	0.1765	0.8% 0.1%	∠.∠4 [1.58, 3.17] 4 08 [1 18 14 07]		
Viganó 2000	0.5878	0.2069	0.6%	1.80 [1.20, 2.70]		
Subtotal (95% CI)			19.5%	1.69 [1.42, 2.01]		•
Heterogeneity: Tau ² = 0 Test for overall effect: Z	0.07; Chi² = 68.42, df = 5.87 (P < 0.0000	^r = 11 (P 1)	< 0.00001); I² = 84%		
Total (95% CI)			100.0%	1.48 [1.43 1.53]		1
Heterogeneity: Tau ² = 0	.00; Chi² = 962.78, d	df = 63 (F	P < 0.0000	1); l ² = 93%		
Test for overall effect: Z	= 22.95 (P < 0.000	D1) `			Favours LDH <cutoff< td=""><td>Favours LDH>cutoff</td></cutoff<>	Favours LDH>cutoff
Test for subgroup differ	ences: Chi ² = 0.04, o	df = 3 (P	= 1.00), I ²	= 0%		

Figure 4 \mid Forest plots showing HRs by LDH cutoffs.

_



Figure 5 | Study-level (i.e., at the individual publication level) association of the cutoff used to define LDH and the HR for overall survival. Each study is represented by a circle, and the area of the circle proportional to the number of patients enrolled in each study. The gradient of the dashed line represents the results of the meta-regression ($\beta = 1.000138$).

analyses. The use of ULN is less robust; however, this was the only feasible method with the data available. An internationally accepted and validated LDH cutoff is warranted.

In summary, our data suggest that pretreatment LDH is a simple, cost-effective prognostic factor that can be considered as a criterion to consider patients in different prognostic groups. LDH is also a potential predictive marker to guide individual therapy decisions in solid tumors. Further, adequate, multi-center prospective studies are required to explore the clinical utility of LDH in solid tumors.

- Mathers, C., Fat, D. M. & Boerma, J. T. The global burden of disease : 2004 update.1–146 (World Health Organization, Geneva, Switzerland; 2008).
- Siegel, R., Naishadham, D. & Temal, A. Cancer statistics, 2013. CA Cancer J Clin 63, 11–30(2013)..
- Ferlay, J. et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 49, 1374–1403 (2013).
- Fidler, I. J. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 3, 453–458 (2003).
- Hsu, P. P. & Sabatini, D. M. Cancer cell metabolism: Warburg and beyond. *Cell* 134, 703–707 (2008).
- Serganova, I. *et al.* Metabolic imaging: a link between lactate dehydrogenase A, lactate, and tumor phenotype. *Clin Cancer Res* 17, 6250–6261 (2011).
- Motzer, R. J. et al. Prognostic factors for survival in 1059 patients treated with sunitinib for metastatic renal cell carcinoma. Br J Cancer 108, 2470–2477 (2013).
- Wan, X. B. *et al.* High pretreatment serum lactate dehydrogenase level correlates with disease relapse and predicts an inferior outcome in locally advanced nasopharyngeal carcinoma. *Eur J Cancer* 49, 2356–2364 (2013).
- Mekenkamp, L. J. et al. Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer. Eur J Cancer 48, 501–509 (2012).
- Giroux, L. E. et al. Factors associated with long-term survival of patients with advanced non-small cell lung cancer. *Respirology* 17, 134–142 (2012).
- Lorch, A. *et al.* Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. *J Clin Oncol* 28, 4906–4911 (2010).
- Kamiya, N. *et al.* Clinical outcomes by relative docetaxel dose and dose intensity as chemotherapy for Japanese patients with castration-resistant prostate cancer: a retrospective multi-institutional collaborative study. *Int J Clin Oncol* 19, 157–164 (2014).
- He, W. Z. *et al.* Gamma-glutamyl transpeptidase level is a novel adverse prognostic indicator in human metastatic colorectal cancer. *Colorectal Dis* 15, e443–e452 (2013).
- Sau, S., Biswas, A., Roy, A., Sau, S. & Ganguly, S. Retrospective analysis of the clinical and demographic variables on the outcomes after second-line treatment in advanced non-small cell lung cancer. *Indian J Med Paediatr Oncol* 34, 274–279 (2013).
- 15. Liberati, A. *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* **6**, e1000100 (2009).
- Cochrane Handbook for Systematic Reviews of Interventions. DOI:http://www. cochrane.org/training/cochrane-handbook Accessed October 24, 2014 (2011).

- Higgins, J. P. T. & Green, S. (ed.) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). (The Cochrane Collaboration, 2011).
- Hannisdal, E., Fossa, S. D. & Host, H. Blood tests and prognosis in bladder carcinomas treated with definitive radiotherapy. *Radiother Oncol* 27, 117–122 (1993).
- Kawahara, M. et al. Prognostic factors and prognostic staging system for small cell lung cancer. Jpn J Clin Oncol 27, 158–165 (1997).
- Tonini, G. P. *et al.* MYCN oncogene amplification in neuroblastoma is associated with worse prognosis, except in stage 4s: the Italian experience with 295 children. *J Clin Oncol* 15, 85–93 (1997).
- Eton, O. *et al.* Prognostic factors for survival of patients treated systemically for disseminated melanoma. *J Clin Oncol* 16, 1103–1111 (1998).
- Tamura, M. et al. Prognostic factors of small-cell lung cancer in Okayama Lung Cancer Study Group Trials. Acta Med Okayama 52, 105–111 (1998).
- Lagerwaard, F. J. *et al.* Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 43, 795–803 (1999).
- 24. Motzer, R. J. *et al.* Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* **17**, 2530–2540 (1999).
- Scher, H. I. *et al.* Post-therapy serum prostate-specific antigen level and survival in patients with androgen-independent prostate cancer. *J Natl Cancer Inst* **91**, 244–251 (1999).
- Bacci, G. *et al.* Prognostic factors in nonmetastatic Ewing's sarcoma of bone treated with adjuvant chemotherapy: analysis of 359 patients at the Istituto Ortopedico Rizzoli. *J Clin Oncol* 18, 4–11 (2000).
- 27. Vigano, A. *et al.* Clinical survival predictors in patients with advanced cancer. *Arch Intern Med* **160**, 861–868 (2000).
- Pierga, J. Y. et al. Effect of adjuvant chemotherapy on outcome in patients with metastatic breast carcinoma treated with first-line doxorubicin-containing chemotherapy. Cancer 91, 1079–1089 (2001).
- Motzer, R. J., Bacik, J., Murphy, B. A., Russo, P. & Mazumdar, M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 20, 289–296 (2002).
- 30. Atzpodien, J., Royston, P., Wandert, T. & Reitz, M. Metastatic renal carcinoma comprehensive prognostic system. *Br J Cancer* **88**, 348–353 (2003).
- Han, C. et al. Comparison of prognostic factors in patients in phase I trials of cytotoxic drugs vs new noncytotoxic agents. Br J Cancer 89, 1166–1171 (2003).
- Polee, M. B. *et al.* Prognostic factors for survival in patients with advanced oesophageal cancer treated with cisplatin-based combination chemotherapy. *Br J Cancer* 89, 2045–2050 (2003).
- Aoe, K. et al. Thrombocytosis as a useful prognostic indicator in patients with lung cancer. Respiration 71, 170–173 (2004).
- 34. Bacci, G. *et al.* Prognostic significance of serum lactate dehydrogenase in osteosarcoma of the extremity: experience at Rizzoli on 1421 patients treated over the last 30 years. *Tumori* **90**, 478–484 (2004).
- Aoe, K. et al. Serum hemoglobin level determined at the first presentation is a poor prognostic indicator in patients with lung cancer. Intern Med 44, 800–804 (2005).
- 36. Giaccone, G. et al. Phase III study of adjuvant vaccination with Bec2/bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971– 08971B; Silva Study). J Clin Oncol 23, 6854–6864 (2005).
- Cook, R. J. et al. Markers of bone metabolism and survival in men with hormonerefractory metastatic prostate cancer. Clin Cancer Res 12, 3361–3367 (2006).
- Bacci, G. *et al.* Ewing's sarcoma family tumours. Differences in clinicopathological characteristics at presentation between localised and metastatic tumours. *J Bone Joint Surg Br* 89, 1229–1233 (2007).
- Escudier, B. *et al.* Prognostic factors of metastatic renal cell carcinoma after failure of immunotherapy: new paradigm from a large phase III trial with shark cartilage extract AE 941. *J Urol* 178, 1901–1905 (2007).
- Gripp, S. *et al.* Survival prediction in terminally ill cancer patients by clinical estimates, laboratory tests, and self-rated anxiety and depression. *J Clin Oncol* 25, 3313–3320 (2007).
- 41. Laurie, S. A. *et al.* The impact of anemia on outcome of chemoradiation for limited small-cell lung cancer: a combined analysis of studies of the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol* 18, 1051–1055 (2007).
- Saito, T., Hara, N., Kitamura, Y. & Komatsubara, S. Prostate-specific antigen/ prostatic acid phosphatase ratio is significant prognostic factor in patients with stage IV prostate cancer. *Urology* 70, 702–705 (2007).
- 43. Schmidt, H. *et al.* Pretreatment levels of peripheral neutrophils and leukocytes as independent predictors of overall survival in patients with American Joint Committee on Cancer Stage IV Melanoma: results of the EORTC 18951 Biochemotherapy Trial. *J Clin Oncol* 25, 1562–1569 (2007).
- Bedikian, A. Y. *et al.* Prognostic factors that determine the long-term survival of patients with unresectable metastatic melanoma. *Cancer Invest* 26, 624–633 (2008).
- 45. Neuman, H. B. *et al*. A single-institution validation of the AJCC staging system for stage IV melanoma. *Ann Surg Oncol* **15**, 2034–2041 (2008).
- Hashimoto, K. *et al.* Do recurrent and metastatic pancreatic cancer patients have the same outcomes with gemcitabine treatment? *Oncology-Basel* 77, 217–223 (2009).

- 47. Culp, S. H. et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer 116, 3378-3388 (2010).
- 48. Kim, S. T. et al. Prognostic model to predict outcomes in non-small cell lung cancer patients with erlotinib as salvage treatment. Oncology-Basel 79, 78-84 (2010)
- 49. Suh, S. Y. et al. Construction of a new, objective prognostic score for terminally ill cancer patients: a multicenter study. Support Care Cancer 18, 151-157 (2010).
- 50. Tanrikulu, A. C. et al. A clinical, radiographic and laboratory evaluation of prognostic factors in 363 patients with malignant pleural mesothelioma. Respiration 80, 480-487 (2010).
- 51. Bedikian, A. Y. et al. Predictive factors for the development of brain metastasis in advanced unresectable metastatic melanoma. Am J Clin Oncol 34, 603-610 (2011).
- 52. Chibaudel, B. et al. Simplified prognostic model in patients with oxaliplatin-based or irinotecan-based first-line chemotherapy for metastatic colorectal cancer: a GERCOR study. Oncologist 16, 1228-1238 (2011).
- 53. Feliu, J. et al. Development and validation of a prognostic nomogram for terminally ill cancer patients. J Natl Cancer Inst 103, 1613-1620 (2011).
- 54. Sougioultzis, S. et al. Palliative gastrectomy and other factors affecting overall survival in stage IV gastric adenocarcinoma patients receiving chemotherapy: a retrospective analysis. Eur J Surg Oncol 37, 312-318 (2011).
- 55. Armstrong, A. J., George, D. J. & Halabi, S. Serum lactate dehydrogenase predicts for overall survival benefit in patients with metastatic renal cell carcinoma treated with inhibition of mammalian target of rapamycin. J Clin Oncol 30, 3402-3407 (2012)
- 56. Bidard, F. C. et al. Assessment of circulating tumor cells and serum markers for progression-free survival prediction in metastatic breast cancer: a prospective observational study. Breast Cancer Res 14, R29 (2012).
- 57. Jakob, J. A. et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer 118, 4014-4023 (2012).
- 58. Li, G. et al. Increased pretreatment levels of serum LDH and ALP as poor prognostic factors for nasopharyngeal carcinoma. Chin J Cancer 31, 197-206 (2012).
- 59. Shinohara, N. et al. A new prognostic classification for overall survival in Asian patients with previously untreated metastatic renal cell carcinoma. Cancer Sci 103, 1695-1700 (2012).
- 60. Weide, B. et al. Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis. Br J Cancer 107, 422-428 (2012).
- 61. Zhou, G. Q. et al. Baseline serum lactate dehydrogenase levels for patients treated with intensity-modulated radiotherapy for nasopharyngeal carcinoma: a predictor of poor prognosis and subsequent liver metastasis. Int J Radiat Oncol Biol Phys 82, e359-e365 (2012).
- 62. Du, J. et al. High preoperative plasma fibrinogen is an independent predictor of distant metastasis and poor prognosis in renal cell carcinoma. Int J Clin Oncol 18, 517-523 (2013).
- 63. Durnali, A. et al. Prognostic factors for teenage and adult patients with high-grade osteosarcoma: an analysis of 240 patients. Med Oncol 30, 624 (2013).
- 64. Giessen, C. et al. Evaluation of prognostic factors in liver-limited metastatic colorectal cancer: a preplanned analysis of the FIRE-1 trial. Br J Cancer 109, 1428-1436 (2013).
- 65. Jin, Y. et al. Serum lactic dehydrogenase strongly predicts survival in metastatic nasopharyngeal carcinoma treated with palliative chemotherapy. Eur J Cancer 49, 1619-1626 (2013)
- 66. Powles, T., Bascoul-Mollevi, C., Kramar, A., Lorch, A. & Beyer, J. Prognostic impact of LDH levels in patients with relapsed/refractory seminoma. J Cancer Res Clin Oncol 139, 1311-1316 (2013).
- 67. Shinohara, N. et al. Is Memorial Sloan-Kettering Cancer Center risk classification appropriate for Japanese patients with metastatic renal cell carcinoma in the cytokine era? Urol Oncol 31, 1276-1282 (2013).
- 68. van Kessel, C. S. et al. Radiological heterogeneity in response to chemotherapy is associated with poor survival in patients with colorectal liver metastases. Eur J Cancer 49, 2486-2493 (2013).
- 69. Weide, B. et al. Serum S100B, lactate dehydrogenase and brain metastasis are prognostic factors in patients with distant melanoma metastasis and systemic therapy. PLoS One 8, e81624 (2013).
- 70. Halabi, S. et al. Updated prognostic model for predicting overall survival in firstline chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol 32, 671-677 (2014).
- 71. Meckbach, D. et al. BRAF-V600 mutations have no prognostic impact in stage IV melanoma patients treated with monochemotherapy. PLoS One 9, e89218 (2014).
- 72. Poprach, A. et al. Clinical and laboratory prognostic factors in patients with metastatic renal cell carcinoma treated with sunitinib and sorafenib after progression on cytokines. Urol Oncol 32, 488-495 (2014).

- 73. Templeton, A. J. et al. Simple prognostic score for metastatic castration-resistant prostate cancer with incorporation of neutrophil-to-lymphocyte ratio. Cancer 120, 3346-3352 (2014).
- 74. Wang, X., Jiang, R. & Li, K. Prognostic significance of pretreatment laboratory parameters in combined small-cell lung cancer. Cell Biochem Biophys 69, 633-640 (2014).
- 75. Wei, Z., Zeng, X., Xu, J., Duan, X. & Xie, Y. Prognostic value of pretreatment serum levels of lactate dehydrogenase in nonmetastatic nasopharyngeal carcinoma: single-site analysis of 601 patients in a highly endemic area. Onco Targets Ther 7, 739–749 (2014).
- 76. Yamaguchi, T. et al. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. Cancer Sci 105,1176-1181 (2014).
- 77. Halabi, S. et al. Prognostic model for predicting survival in men with hormonerefractory metastatic prostate cancer. J Clin Oncol 21,1232-1237 (2003).
- 78. Schellhammer, P.F. et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. Urology 81,1297-1302 (2013).
- 79. D'Amico, A.V. Chen, M.H. Cox, M.C. Dahut, W. & Figg, W.D. et al. Prostatespecific antigen response duration and risk of death for patients with hormonerefractory metastatic prostate cancer. Urology 66,571-576 (2005).
- 80. Vaupel, P. & Mayer, A. Hypoxia in tumors: pathogenesis-related classification, characterization of hypoxia subtypes, and associated biological and clinical implications. Adv Exp Med Biol 812, 19-24 (2014).
- 81. Scartozzi, M. et al. Pre-treatment lactate dehydrogenase levels as predictor of efficacy of first-line bevacizumab-based therapy in metastatic colorectal cancer patients. Br J Cancer 106, 799-804 (2012).
- 82. Armstrong, A. J., George, D. J. & Halabi, S. Serum lactate dehydrogenase predicts for overall survival benefit in patients with metastatic renal cell carcinoma treated with inhibition of mammalian target of rapamycin. J Clin Oncol 30, 3402-3407 (2012).
- 83. Kim, J. W. & Dang, C. V. Multifaceted roles of glycolytic enzymes. Trends Biochem Sci 30, 142-150 (2005).
- 84. Kim, J. W. & Dang, C. V. Cancer's molecular sweet tooth and the Warburg effect. Cancer Res 66, 8927-8930 (2006).
- 85. Majumder, P. K. et al. mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. Nat Med 10, 594-601 (2004).
- 86. Del Prete, M. et al. LDH serum levels as a predictive factor for global outcome in pretreated colorectal cancer patients receiving regorafenib: Implications for clinical management. J Clin Oncol 32, 2318 (2014).
- 87. Harrison, D. E. et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460, 392-395 (2009).

Acknowledgments

None

Author contributions

Conception and design: J.Z. and H.W. Collection and checking eligible studies included in the meta-analysis: J.Z. and Y.Y. Acquisition of data: J.Z. and Y.Y. Analysis of data: J.Z., Y.Y., B.L., Q.Y., P.Z. and H.W. Statistical analyses: J.Z., Y.Y. and B.L. Writing of manuscript: J.Z. and H.W. Preparation of tables and figures: B.L., Q.Y. and P.Z. All authors reviewed the manuscript.

Additional information

Grant Support None

Supplementary information accompanies this paper at http://www.nature.com/ scientificreports

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Zhang, J. et al. Prognostic value of pretreatment serum lactate dehydrogenase level in patients with solid tumors: a systematic review and meta-analysis. Sci. Rep. 5, 9800; DOI:10.1038/srep09800 (2015).



This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder in order to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/