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META-ANALYSIS

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Risks and Benefits of Multimodal Esophageal Cancer Treatments: A Meta-Analysis

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Esophageal cancer has traditionally been associated with very poor outcomes. A number of therapies are available for the treatment and palliation of esophageal cancer, but little systematic evidence compares the efficacy of different treatment strategies. This meta-analysis aimed to investigate whether treatments in addition to radiotherapy could provide better efficacy and safety.

Material/Methods: We identified a total of 12 eligible studies with 18 study arms by searching PubMed, the Cochrane Library, EMBASE, and Clinical Trials.gov without time or language restrictions. The final search was conducted on 17 August 2016. We calculated mean differences (MD) and risk ratios (RR) with 95% confidence intervals (CI) for continuous and dichotomous data, respectively. Heterogeneity was calculated and reported using Tau^2, Chi^2, and I^2 analyses.

Results: Twelve studies with 18 study arms were included in the analysis. Addition of surgery to chemo-radiotherapy resulted in improved median survival time (p=0.009) compared with chemo-radiotherapy alone, but all other outcomes were unaffected. Strikingly, and in contrast with patients with squamous cell carcinomas, the subset of patients with adenocarcinoma who received therapies in addition to radiotherapy showed a significant improvement in median survival time (p<0.0001), disease-free survival (p=0.007), 2-year survival rates (p=0.002), and 3-year survival rates (p=0.01). The incidence of adverse effects increased substantially with additional therapies.

Conclusions: This meta-analysis reveals stark differences in outcomes in patients depending on the type of carcinoma. Patients with squamous cell carcinoma should be educated about the risks and benefits of undergoing multiple therapies.

MeSH Keywords: Adenocarcinoma • Carcinoma, Squamous Cell • Esophageal Neoplasms • Radiotherapy

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Background

The incidence of carcinoma of the esophagus as well as the gastro-esophageal junction is increasing around the world [1]. According to the American Cancer Society (ACS), there are about 17 000 new cases of esophageal cancer diagnosed around the world each year [2]. Among those diagnosed with esophageal cancer, most are men [2], and they accounted for approximately 12 720 of the 15 690 deaths caused by esophageal cancer so far in 2016 [2]. The diagnosis of most esophageal cancers happens at an advanced stage in most patients. This fact makes the best intervention strategy for the advanced cases of esophageal cancer palliative care rather than curative treatment [3,4]. The most predominant symptom found in many patients is dysphagia, which is characterized by pain experienced when swallowing food or beverages.

Squamous cell carcinoma is the most common type of esophageal cancer among African Americans, while Caucasians are affected more by adenocarcinoma [5]. It is notable that although esophageal cancer accounts for only 1% of cancers detected in the US, it is much more common among other countries such as China, India, Africa, Pakistan, and Iran [2].

Radiotherapy has been commonly used in the treatment of esophageal cancer. It results in improvement in 50–85% of the patients diagnosed with esophageal cancer at an advanced stage. However, the rate of recovery and response of the patients can be very slow [4]. The addition, in recent years, adding chemotherapy to radiotherapy has been hailed as a potential cure for esophageal cancers that would previously have been considered fatal [6]. Surgery, mostly esophagectomy, is often carried out in an attempt at curative treatment, especially in early esophageal cancer, but it has a high complication rate, both during and after the procedure [7].

Despite the existence of so many esophageal cancer patients around the world, there is little systematic evidence that highlights the best intervention strategies. Although systematic reviews exist that examine the roles of chemotherapy [8] and surgery [9,10], there is no systematic review that focuses on the role of radiotherapy and whether its combination with other interventions could enhance the efficacy of esophageal cancer treatment. Our study investigated the efficacy and adverse effects of therapies added to radiotherapy, such as radiotherapy+chemotherapy (RT *vs.* RT+CT), radiotherapy+surgery (RT *vs.* RT+Surgery), RT+CT+surgery (RT+CT *vs.* RT+CT+surgery), and RT+immune therapy (RT *vs.* RT+immune therapy). In order to determine the effect of treatments in addition to radiotherapy, we only included studies that directly compared these 2 treatment modalities. We also performed subgroup meta-analyses by the type of cancer as well as by the type of intervention.

Material and Methods

The current study was carried out in accordance with the 2015 PRISMA guidelines [11].

PICOT

We identified the following PICOT for our study: **Population**: adults with localized or advanced esophageal cancer; **Intervention:** radiotherapy plus other interventions**; Comparator:** radiotherapy without additional interventions or with fewer interventions; **Outcomes:** median survival time, disease-free survival time, 1-year survival rate, 2-year survival rate, 3-year survival rate, response rate, presence of dysphagia, adverse events; **Time**: At least 1 year following treatment.

Data sources and search strategies

Searches were carried out using PubMed, the Cochrane Library, EMBASE, and Clinical Trials.gov without time or language restrictions. The final search was conducted on 17 August 2016. The keywords used were (esophageal cancer OR oesophageal cancer) AND (radiotherapy OR chemotherapy OR surgery OR chemo-radiotherapy). Search results were uploaded into EppiReviewer 4 [12] to determine their eligibility.

Selection standards

Studies were included if they met the following criteria: 1) the participants had primary esophageal cancer; 2) the article was a randomized controlled trial (RCT), a cohort study or a retrospective analysis; 3) the study had a control group; 4) the treatment included radiotherapy and at least 1 additional treatment option; 5) the control included radiotherapy; and 6) the study included at least 1 of the outcomes listed in the PICOT above. We excluded studies that did not measure the effect of additional therapy added to radiotherapy (e.g., chemo-radiotherapy plus surgery *vs.* surgery alone was excluded).

Study selection

The initial search resulted in 387 abstracts (Figure 1). After removal of duplicates, 303 abstracts were subjected to the inclusion criteria. Two authors examined the abstracts, excluding those that did not match the inclusion criteria. This resulted in 28 studies. We obtained the full-text articles and applied the same inclusion criteria. This resulted in 12 studies remaining. Eighteen study arms from these 12 studies were included in the final analysis.

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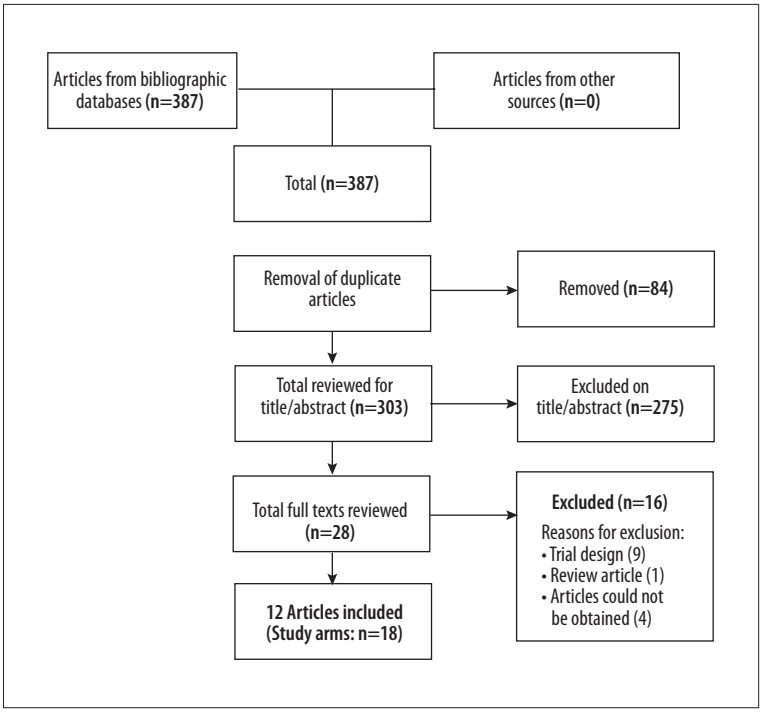

Figure 1. PRISMA diagram of included studies.

Study quality

The quality of the studies was determined using the Cochrane Collaboration risk of bias assessment tool for randomized controlled trials [13]. This tool examines each study for risk of bias in 7 categories: random sequence generation, allocation concealment, blinding or participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The non-randomized studies were assessed using the Newcastle-Ottawa scale for assessing the quality of non-randomized studies in meta-analyses [14]. This scale allows the assessment of the quality of non-RCT studies using the following criteria: selection, comparability, and outcome/exposure. There are separate scales for cohort studies and case-control studies.

Data extraction

Two authors independently extracted the data from studies into electronic forms and crossed-checked them. The extracted data included: the study characteristics (country, type of cancer, stage of cancer, number in intervention/control, type of therapy used, study design); outcome data; and adverse effects data. Depending on the outcome, we either extracted means and standard deviations or rates (as number of events out of total number in the study arm). If standard errors were given, these were converted to standard deviations by multiplying the standard error by the square root of the number in the study arm.

Statistical analysis

Study data were copied into Review Manager 5.3 (Cochrane Collaboration) [15]. Risk ratios with 95% confidence intervals (CI) were used for dichotomous outcomes, and mean differences with 95% CIs were calculated for continuous outcomes. Meta-analysis was carried out with a random effects model, inverse variance calculation, with $p<0.05$ as the test for statistical significance. Heterogeneity was given as Tau^2, Chi^2, and I^2. *A priori* subgroup analyses were planned by cancer type and treatment modality. Sensitivity analyses were planned for study design, tumor stage, and type of chemotherapy used.

Results

Search results and study characteristics

Table 1 shows the characteristics of all included study arms. Only 4 of the included 12 studies were RCTs [16–19]. Four studies were prospective but non-randomized trials [20–23], 3 were retrospective case-control studies [24–26], and 1 reported on a sequential, non-randomized phase II trial [27]. In terms of interventions, 4 studies compared radiotherapy plus chemotherapy with radiotherapy alone [16,17,24,25]. Three studies compared radiotherapy plus surgery with radiotherapy alone [17,24,25]. Nine studies compared radiotherapy plus chemotherapy plus surgery with radiotherapy and chemotherapy alone [17,19–24,26,27]. A single study compared radiotherapy plus immunotherapy with radiotherapy alone [18].

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Table 1. Studies included in the meta-analysis.

Study ID	Country/ ethnicity	Type of cancer	Stage of cancer	Number of patients (intervention/ control)		Intervention		Control		Study design
						Type	Dose of radiation/ chemotherapy	Type	Dose of radiation/ chemotherapy	
Agronovich 2008-1	Canada/ Not stated	Any	T1, 2, 3, X	16	77	RT+ surgery	≥40 Gy (15 fractions)	RT	≥40 Gy (15 fractions)	Retrospective case-control
Agronovich 2008-2	Canada/ Not stated	Any	T1, 2, 3, X	26	77	RT+CT	≥40 Gy (15 fractions); 5-FU 1000 mg/m^2/day + cisplatin 25 mg/m^2/day	RT	≥40 Gy (15 fractions)	Retrospective case-control
Agronovich 2008-3	Canada/ Not stated	Any	T1, 2, 3, X	12	26	RT+CT+ surgery	≥40 Gy (15 fractions); 5-FU 1000 mg/m^2/day + cisplatin 25 mg/m^2/day	RT+CT	≥40 Gy (15 fractions); 5-FU 1000 mg/m^2/day + cisplatin 25 mg/m^2/day	Retrospective case-control
Algan 1995	USA/ Not stated	Adenoca-rcinoma	I, IIA, IIB	12	12	RT+CT+ surgery	60 Gy (over 6 wks); 5-FU 1000 mg/m^2/ day + mitomycin C 10 mg/m^2 (single bolus)	RT+CT	60 Gy (over 6 wks); 5-FU 1000mg/m^2/day + mitomycin C 10 mg/m^2 (single bolus).	Sequential, non-randomized
Burmeister 1995	Australia/ Not stated	Any	I, IIA, IIB	78	137	RT+CT+ surgery	60 Gy (30 fractions); CDDP 80 mg/m^2 + 5-FU 800 mg/m^2/day	RT+CT	60 Gy (30 fractions); CDDP 80 mg/m^2 + 5-FU 800 mg/m^2/day	Prospective, non-randomized
Cordice 1990-1	USA/ Mixed	Any	Not stated	34	52	RT+ surgery	Not stated	RT	Not stated	Retrospective case-control
Cordice 1990-2	USA/ Mixed	Any	Not stated	13	52	RT+CT	Not stated	RT	Not stated	Retrospective case-control
Hainsworth 2007	USA/ Not stated	Any	I, II, III	97	50	RT+CT+ surgery	45 Gy (25 fractions); 5-FU 225 mg/m^2 + carboplatin AUC 6.0 + paclitaxel 200 mg/ m^2 (PC)	RT+CT	45 Gy (25 fractions); 5-FU 225 mg/m^2 + carboplatin AUC 6.0 + paclitaxel 200 mg/m^2 then radiation to 64.8 Gy + 1 additional dose of PC	Prospective, non-randomized
Herskovic 1992	USA/ Mixed	Any	T1, 2, 3, NX, 0, 1	61	60	RT+CT	50 Gy (25 fractions); 5-FU 1000 mg/m^2/day + cisplatin 75 mg/m^2	RT	64 Gy (32 fractions)	RCT
Hihara 2014	Japan/ Japanese	Squamous (26), carcino-sarcoma (1)	T4N0M0, T4N1M1, T4N1M1a, T4N1M1b	17	10	RT+CT+ surgery	50–66 Gy (25 fractions); CDDP 3–70 mg/m^2, 5-FU 250–700 mg/m^2 OR docetaxel 7.5 mg/m^2 + 5-FU 250 mg/m^2	RT+CT	50–66 Gy (25 fractions); CDDP 3–70 mg/m^2, 5-FU 250–700 mg/m^2 OR docetaxel 7.5 mg/m^2 + 5-FU 250mg/m^2	Prospective, non-randomized
Mukaida 1998	Japan/ Japanese	Not stated	T1, 2, 3, 4 N0, N1 M0, M1 IIA, IIB, III, IV	19	19	RT+CT	40 to 60 Gy; CDDP 50 mg/m^2 + 5-FU 500 mg/ m^2 + VP-16 60 mg/m^2	RT	40 to 60 Gy	Prospective, non-randomized
Shridhar 2014	USA/ Not stated	Adenoca-rcinoma	T1, 2, 3, 4 N0, N1 M0, M1 IIA, IIB, III, IV	94	60	RT+CT+ surgery	Mixed protocols	RT+CT	Mixed protocols	Retrospective case-control
Smith 1998-1	USA/ Not stated	Squamous cell carcinoma	I, II	24	32	RT+ surgery	Maximum 40 Gy	RT	Maximum 60 Gy;	RCT
Smith 1998-2	USA/ Not stated	Squamous cell carcinoma	I, II	21	37	RT+CT+ surgery	Maximum 40 Gy; 5-FU 1000 mg/m^2 + bolus mitomycin C 10 mg/m^2	RT+CT	Maximum 40 Gy; 5-FU 1000 mg/m^2 + bolus mitomycin C 10mg/m^2	RCT
Smith 1998-3	USA/ Not stated	Squamous cell carcinoma	I, II	37	32	RT+CT	Maximum 60 Gy; 5-FU 1000 mg/m^2 + bolus mitomycin C 10 mg/m^2	RT	Maximum 60 Gy	RCT

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Table 1 continued. Studies included in the meta-analysis.

Study ID	Country/ ethnicity	Type of cancer	Stage of cancer	Number of patients (intervention/ control)		Intervention		Control		Study design
						Type	Dose of radiation/ chemotherapy	Type	Dose of radiation/ chemotherapy	
Yan 2014	China/ Chinese	Squamous cell carcinoma	I, II, III, IV	34	34	RT+ immu-no-the-rapy	60–66 Gy (30–33 fractions); 1×10^9 CIK cells/day + 1×10^7 DC cells/day for 5 days	RT	60–66 Gy (30–33 fractions)	RCT
Yoon 2015	Republic of Korea/ Korean	Squamous (95), adenoca-rcinoma (2)	II, III, IVa	47	50	RT+CT+ sur-gery+ induc-tion CT	Oxaliplatin 130 mg/ m^2 + S1 40 mg/m^2 – 2 cycles followed by 46 Gy (23 fractions) plus concurrent oxaliplatin 130 mg/m^2 + S1 30 mg/m^2	RT+CT+ surgery	46 Gy (23 fractions) plus concurrent oxaliplatin 130 mg/m^2 + S1 30 mg/m^2 (no induction)	RCT

RT – radiotherapy; CT – chemotherapy; RCT – randomized controlled trial; FU – fluorouracil, CDDP – cisplatin, S1: combination of tegafur, gimeracil, oteracil potassium. Staging scores: TNM – T1: cancer is growing into tissue under the epithelium; T2: cancer is growing into the muscularis mucosa; T3: cancer is growing into the adventitia; T4: cancer is growing into the pleura, the pericardium, the diaphragm, the trachea, the aorta, the spine, or other crucial structures; TX: primary tumor cannot be assessed. N0: cancer has not spread to lymph nodes; N1: cancer has spread to 1 or 2 nearby lymph nodes; NX: nearby lymph nodes cannot be assessed. M0: no metastasis to distant organs or lymph nodes; M1: cancer has metastasized to distant lymph nodes or other organs. Stage I, II, III, IV – combinations of TNM and cancer grade (46).

Although most studies enrolled patients with any type of esophageal cancer [16,20,21,24,25], 4 studies included only patients with squamous cell carcinoma or had a majority of squamous cell carcinomas [17–19,22], and only 2 studies focused only on patients with adenocarcinomas [26,27].

Quality of studies

We evaluated the risk of bias in the 4 RCTs using the Cochrane Collaboration tool [13] and the 8 non-randomized studies were assessed using the Newcastle-Ottawa scale [14]. Overall, the risk of bias in the RCTs was mostly acceptable (Figure 2A). None of the studies suffered from reporting bias, and only 1 study [17] lost more than 10% of patients to follow-up. No other obvious bias was present. None of the 4 RCTs undertook blinding of participants or personnel, and blinding of outcome assessors was unclear. Allocation concealment was not reported in any of these studies, and only 2 studies provided a method of randomization.

The quality of the non-randomized studies was poor (Figure 2B). Using the scoring methodology as suggested by the authors [14], only 1 study [23] obtained the score of "good" and the other studies were all rated as "poor", mostly due to their lack of comparability. To investigate whether this had an influence on study outcomes, we undertook a sensitivity analysis of the RCTs.

Median survival times

To determine whether additional therapies added to radiotherapy improve survival times, we undertook 2 subgroup meta-analyses (Figure 3). To investigate whether different kinds of interventions produced different results, we did a subgroup analysis of median survival time by treatment type (Figure 3A). Comparing RT with RT+CT showed no significant increase in median survival time (MD 3.31months, 95% CI: –0.48, 7.11, p=0.85, I^2=0%); similarly, addition of surgery to RT also showed no significant improvement in median survival time (MD 6.20 months, 95% CI: –7.51, 19.92, p=0.05, I^2=75%). In contrast, when surgery was added to RT and CT, a significant increase in median survival times was observed (MD 13.13 months, 95% CI: 3.32, 22.95, p=0.009, I^2=64%). However, this did not differ significantly from either of the other 2 interventions (subgroup difference p=0.18).

We also examined differences in survival time by type of cancer (Figure 3B). In the 2 studies in patients with adenocarcinoma, adding further treatments to radiotherapy resulted in a significant increase in median survival time (MD=23.16 months, 95% CI: 12.31, 34.00, p<0.0001). In contrast, the 2 studies in patients with squamous cell carcinoma did not gain any advantage with the addition of further treatments to radiotherapy (MD=4.67 months, 95% CI: –2.35, 11.70, p=0.19). Neither subgroup had any heterogeneity. The studies that did not select patients based on cancer type (subgroup "All carcinomas") did show an overall increase in median survival time (MD 5.23 months (95% CI: 0.67, 9.79, p=0.02, I^2=42%), although this was significantly smaller than in adenocarcinoma (subgroup difference p=0.003).

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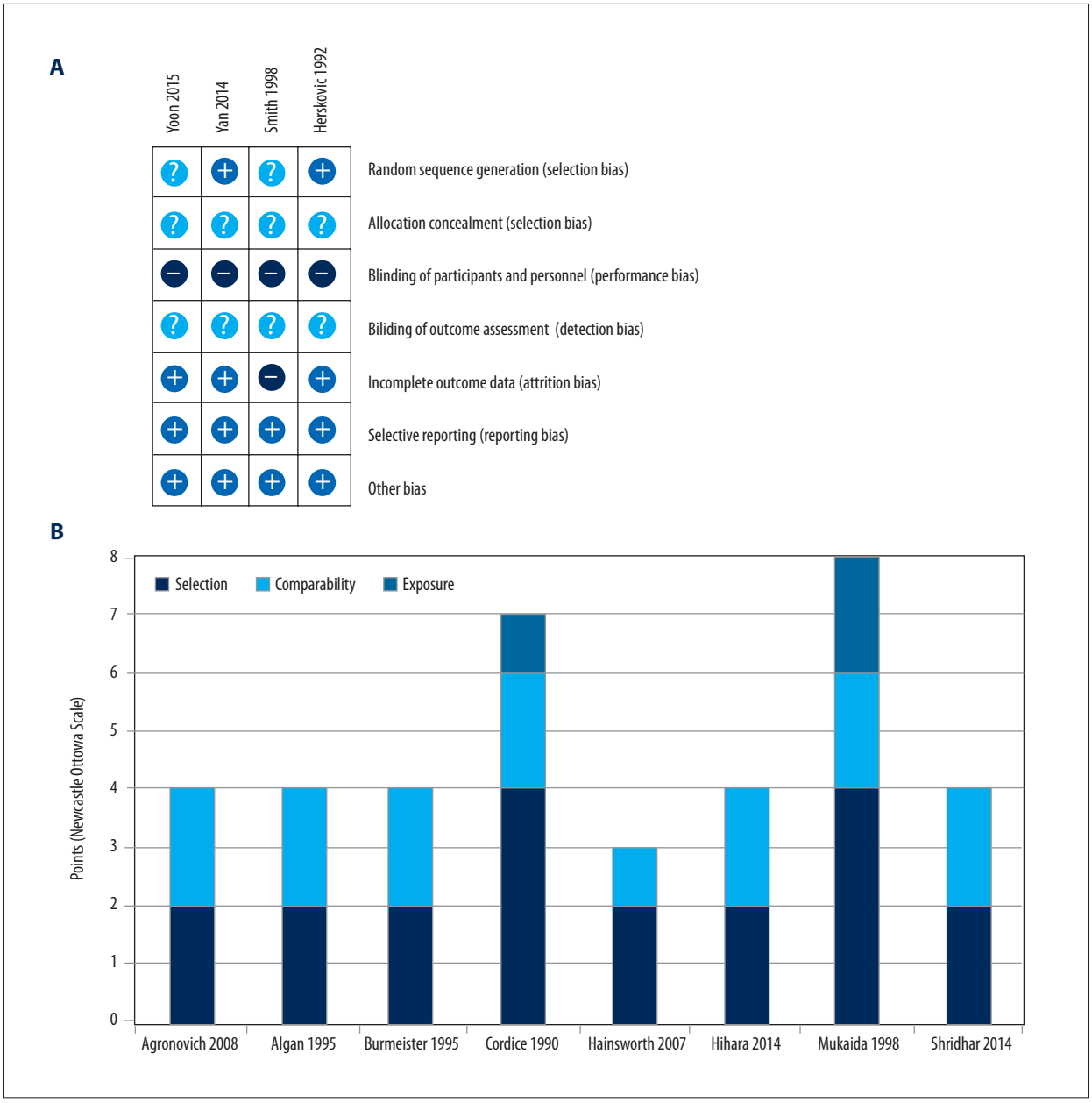

Figure 2. Quality of included studies. The randomized controlled trials were subjected to the Cochrane Collaboration's risk of bias analysis (**A**). The non-randomized trials were analyzed with the Newcastle-Ottawa Scale (**B**).

Disease-free survival times

Very few studies reported disease-free survival times [21,26,27] (Figure 4). Whereas the single study reporting this outcome in patients with any type of carcinoma showed no significant difference with additional treatments, those with adenocarcinoma did respond better to adding treatments to radiotherapy (MD=15.71 months, 95% CI: 4.29, 27.12, p=0.007, I^2=36%). Coincidentally, all 3 studies reporting this outcome compared chemo-radiotherapy with chemo-radiotherapy plus surgery. Overall, adding surgery to chemo-radiotherapy did not result in any significant difference in disease-free survival times (MD=8.88 months, 95% CI: −5.36, 23.12, p=0.22, $I2$=82%).

One-year survival rates

One-year survival rates were largely unaffected by addition of other treatments to radiotherapy (Figure 5). When viewed by type of treatment (Figure 5A), the only improvement in 1-year survival rates was seen in patients undergoing chemo-radiotherapy plus surgery (RR=1.13, 95% CI: 1.02, 1.26, p=0.02, I^2=21%), although this was a minimal difference. When grouped

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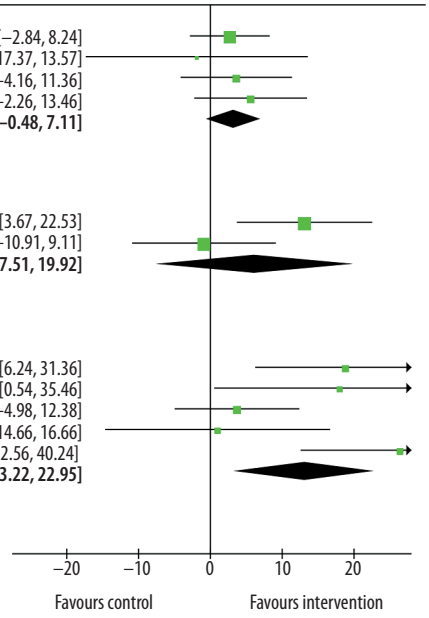
A

Study or subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
1.2.1 RT vs. RT+CT								
Agronovich 2008-2	14.5	13.9	26	11.8	6.6	77	46.8%	2.70 [−2.84, 8.24]
Cordice 1990-2	6.5	27.6	13	8.4	13.8	52	6.0%	−1.90 [−17.37, 13.57]
Herskovic 1992	12.5	27.6	61	8.9	13.8	60	23.9%	3.60 [−4.16, 11.36]
Smith 1998	14.8	27.6	59	9.2	13.8	60	23.3%	5.60 [−2.26, 13.46]
Subtotal (95% CI)			**159**			**249**	**100.0%**	**3.31 [−0.48, 7.11]**
Heterogeneity: Tau²=0.00; Chi²=0.81, df=3 (P=0.85); I²=0%								
Test for overall effect: Z=1.71 (P=0.09)								
1.2.2 RT vs. RT+surgery								
Agronovich 2008-1	24.9	19	16	11.8	6.6	77	50.7%	13.10 [3.67, 22.53]
Cordice 1990-1	7.5	27.6	34	8.4	13.8	52	49.3%	−0.90 [−10.91, 9.11]
Subtotal (95% CI)			**50**			**129**	**100.0%**	**6.20 [−7.51, 19.92]**
Heterogeneity: Tau²=73.40; Chi²=3.98, df=1 (P=0.05); I²=75%								
Test for overall effect: Z=0.89 (P=0.38)								
1.2.3 RT+CT vs. RT+CT+surgery								
Agronovich 2008-3	33.3	20.1	12	14.5	13.9	26	21.1%	18.80 [6.24, 31.36]
Algan 1995	33	27.6	12	15	13.8	12	15.9%	18.00 [0.54, 35.46]
Hainsworth 2007	29.3	29.3	97	25.6	23.2	50	25.7%	3.70 [−4.98, 12.38]
Hihara 2014	9.7	27.6	17	8.7	13.8	10	17.7%	1.00 [−14.66, 16.66]
Shridhar 2014	49.2	64.4	94	22.8	18.6	60	19.6%	26.40 [12.56, 40.24]
Subtotal (95% CI)			**232**			**158**	**100.0%**	**13.13 [3.22, 22.95]**
Heterogeneity: Tau²=77.86; Chi²=11.11, df=4 (P=0.03); I²= 64%								
Test for overall effect: Z=2.62 (P=0.009)								
Test for subgroup differences: Chi²= 3.40, df= 2 (P= 0.18), I²= 41.2%								



B

Study or subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
1.1.1 Adenocarcinoma								
Algan 1995	33	27.6	12	15	13.8	12	38.6%	18.00 [0.54, 35.46]
Shridhar 2014	49.2	64.4	94	22.8	18.6	60	61.4%	26.40 [12.56, 40.24]
Subtotal (95% CI)			**106**			**72**	**100.0%**	**23.16 [12.31, 34.00]**
Heterogeneity: Tau²=0.00; Chi²=0.55, df=1 (P=0.46); I²=0%								
Test for overall effect: Z=4.18 (P<0.0001)								
1.1.2 Squamous cell carcinoma								
Hihara 2014	9.7	27.6	17	8.7	13.8	10	20.1%	1.00 [−14.66, 16.66]
Smith 1998	14.8	27.6	59	9.2	18.8	60	79.9%	5.60 [−2.26, 13.46]
Subtotal (95% CI)			**76**			**70**	**100.0%**	**4.67 [−2.35,11.70]**
Heterogeneity: Tau²=0.00; Chi²=0.26, df=1 (P=0.61); I²=0%								
Test for overall effect: Z=1.30 (P=0.19)								
1.1.3 All carcinomas								
Agronovich 2008-1	24.9	19	16	11.8	6.6	77	14.1%	13.10 [3.67, 22.53]
Agronovich 2008-2	14.5	13.9	26	11.8	6.6	77	23.2%	2.70 [−2.84, 8.24]
Agronovich 2008-3	33.3	20.1	12	14.5	13.9	26	9.6%	18.80 [6.24, 31.36]
Cordice 1990-1	7.5	27.6	347	8.4	13.8	52	13.1%	−0.90 [−10.91, 9.11]
Cordice 1990-2	6.5	27.6	13	8.4	13.8	52	7.0%	−1.90 [−17.37, 13.57]
Hainsworth 2007	29.3	29.3	97	25.6	23.2	50	15.5%	3.70 [−4.98, 12.38]
Herskovic 1992	12.5	27.6	61	8.9	13.8	60	17.55%	3.60 [−4.16, 11.36]
Subtotal (95% CI)			**259**			**394**	**100.0%**	**5.23 [0.67, 9.79]**
Heterogeneity: Tau²=15.31; Chi²=10.42, df=6 (P=0.11); I²=42%								
Test for overall effect: Z=2.25 (P=0.02)								
Test for subgroup differences: Chi²=9.52, df=2 (P=0.009), I²=79.0%								

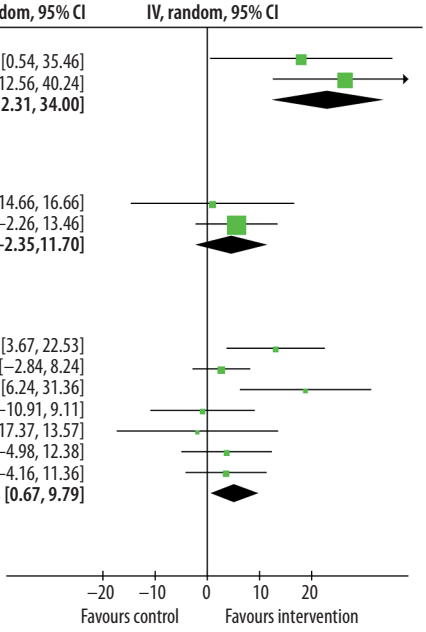


Figure 3. Subgroup meta-analysis of median survival times after treatment by type of intervention (**A**) or type of cancer (**B**). The interventions included radiotherapy plus chemotherapy, radiotherapy plus surgery, and radiotherapy plus chemotherapy plus surgery. The control groups were radiotherapy alone, or radiotherapy plus chemotherapy.

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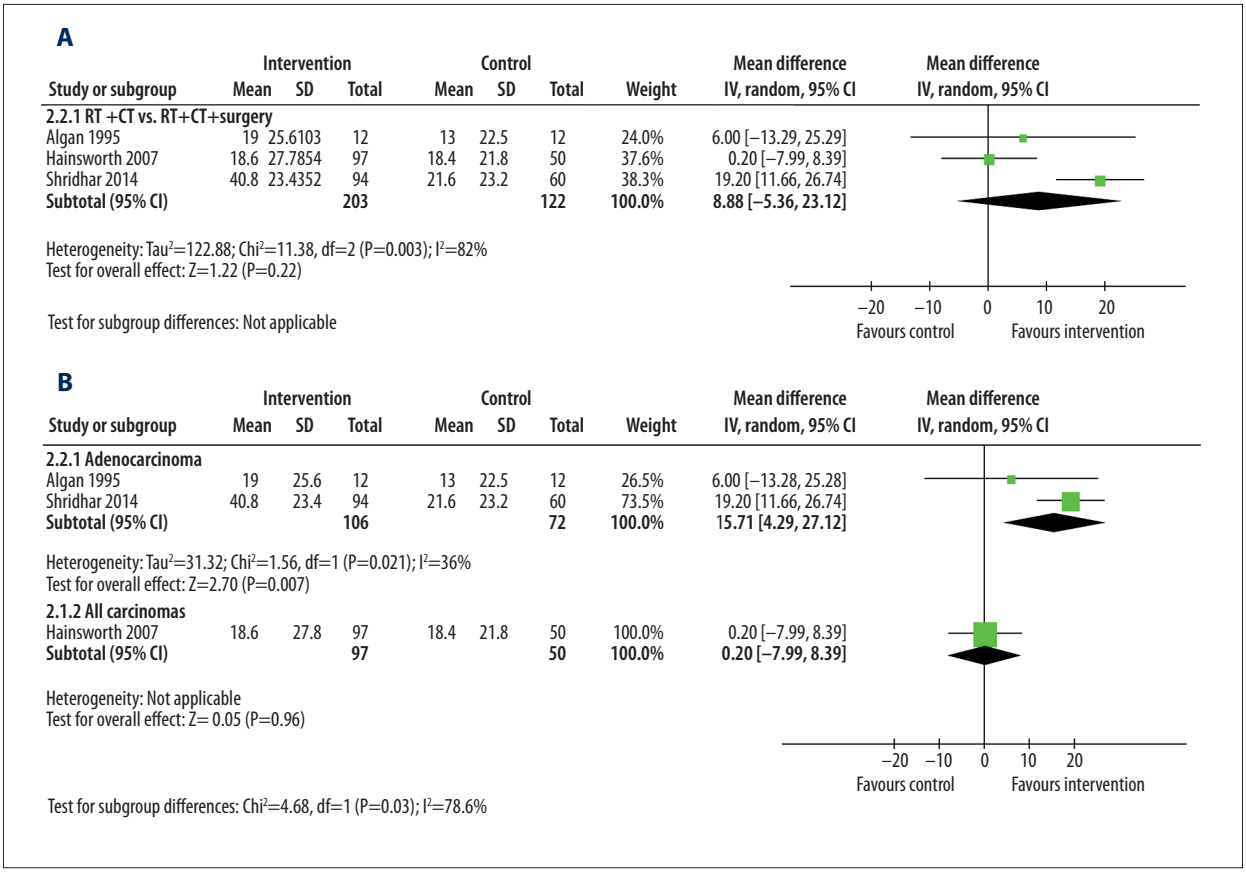

Figure 4. Subgroup meta-analysis of median disease-free survival times after treatment by type of intervention (**A**) or of cancer (**B**). In all 3 studies, the intervention was radiotherapy plus chemotherapy and surgery. The control group was radiotherapy plus chemotherapy without surgery.

by cancer type, the only group that experienced an increased survival rate was the "all carcinomas" group (RR=1.29, 95% CI: 1.08, 1.54, p=0.005). Neither patients with only adenocarcinoma nor only squamous cell carcinoma had a greater chance of surviving to 1 year (Figure 5B).

Two-year survival rates

When grouped by the type of intervention (Figure 6A), none of the treatments added to radiotherapy affected survival rates at 2 years. In contrast, when grouped by cancer type, the results for the 2-year survival rates were similar to the 1-year rates (Figure 6B). The exception was that patients with adenocarcinoma improved their chances of surviving to 2 years by adding surgery to chemo-radiotherapy (RR=1.50, 95% CI: 1.15, 1.95, p=0.002, I^2=0%). The magnitude of this effect was similar to that seen with the "All carcinomas" group (test for subgroup differences, p=0.86).

Three-year survival rates

At 3 years, when analyzed by type of treatment, none of the treatment subgroups showed any advantage over less invasive treatment (Figure 7A). In contrast, patients with adenocarcinoma again clearly gained an advantage by adding surgery to RT and CT (Figure 7B). Patients with adenocarcinoma who underwent surgery in addition to chemo-radiotherapy had a 57% greater rate of survival compared with those who had chemo-radiotherapy alone (RR=1.57, 95%CI: 1.10, 2.25, p=0.01, I^2=0%). Patients with squamous cell carcinoma (p=0.29) and "All carcinomas" (p=0.12) did not see significantly longer rates of survival.

Response rates

Only 5 studies reported response rates [16,18,19,22,23] (Figure 8). Subgroup analysis of response by treatment type was hampered by a lack of studies (Figure 8A). Only 1 treatment type had more than 1 study to analyze (Figure 8A). Of this limited analysis, a study comparing radiotherapy with chemo-radiotherapy [16] showed a significant difference in response (RR 2.5 95% CI: 1.24, 5.37, p=0.01).

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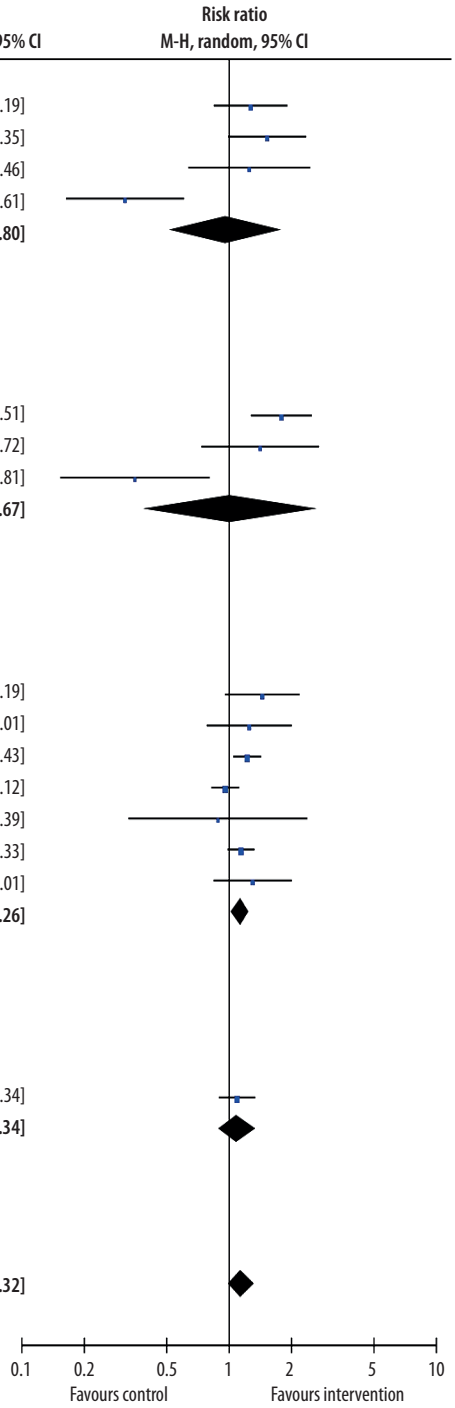
A

Study or subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
3.2.1 RT vs. RT+CT						
Agronovich 2008-2	15	26	35	77	6.6%	1.27 [0.84, 1.19]
Herskovic 1992	31	61	20	60	6.2%	1.52 [0.99, 2.35]
Mukaida 1998	10	19	8	19	3.5%	1.25 [0.63, 2.46]
Smith 1998-3	8	37	22	32	3.6%	0.31 [0.16, 0.61]
Subtotal (95% CI)		**143**		**188**	**19.8%**	**0.96 [0.51, 1.80]**
Total events	64		85			
Heterogeneity: Tau^2=0.33; Chi^2=17.09, df=3 (P=0.0007); I^2=82%						
Test for overall effect: Z=0.12 (P=0.91)						
3.2.2 RT vs. RT+surgery						
Agronovich 2008-1	13	16	35	77	7.8%	1.79 [1.27, 2.51]
Cordice 1990-1	12	34	13	52	3.6%	1.41 [0.73, 2.72]
Smith 1998-1	5	24	19	32	2.5%	0.35 [0.15, 0.81]
Subtotal (95% CI)		**74**		**161**	**14.0%**	**1.01 [0.38, 2.67]**
Total events	30		67			
Heterogeneity: Tau^2=0.63; Chi^2=16.10, df=2 (P=0.0003); I^2=88%						
Test for overall effect: Z=0.03 (P=0.98)						
3.2.3 RT+CT vs. RT+CT+surgery						
Agronovich 2008-3	10	12	15	26	6.5%	1.44 [0.95, 2.19]
Algan 1995	10	12	8	12	5.6%	1.25 [0.78, 2.01]
Burmeister 1995	64	78	92	137	11.7%	1.22 [1.04, 1.43]
Hainsworth 2007	78	97	42	50	11.7%	0.96 [0.82, 1.12]
Hihara 2014	6	17	4	10	1.9%	0.88 [0.33, 2.39]
Shridhar 2014	84	94	47	60	11.8%	1.14 [0.98, 1.33]
Smith 1998-3	14	21	19	37	6.2%	1.30 [0.84, 2.01]
Subtotal (95% CI)		**331**		**332**	**55.4%**	**1.13 [1.02, 1.26]**
Total events	266		227			
Heterogeneity: Tau^2=0.00; Chi^2=7.57, df=6 (P=0.27); I^2=21%						
Test for overall effect: Z=2.34 (P=0.02)						
3.2.4 RT+CT+surgery vs. RT+CT+surgery+Induction CT						
Yoon 2015	39	47	38	50	10.8%	1.09 [0.89, 1.34]
Subtotal (95% CI)		**47**		**50**	**10.8%**	**1.09 [0.89, 1.34]**
Total events	39		38			
Heterogeneity: Not applicable						
Test for overall effect: Z=0.85 (P=0.40)						
Total (95%)		**595**		**731**	**100.0%**	**1.14 [0.99, 1.32]**
Total events	399		417			
Heterogeneity: Tau^2=0.04; Chi^2=39.92, df=14 (P=0.0003); I^2=65%						
Test for overall effect: Z=1.77 (P=0.08)						
Test for subgroup differences: Chi^2=0.37, df=3 (P=0.095); I^2=0%						



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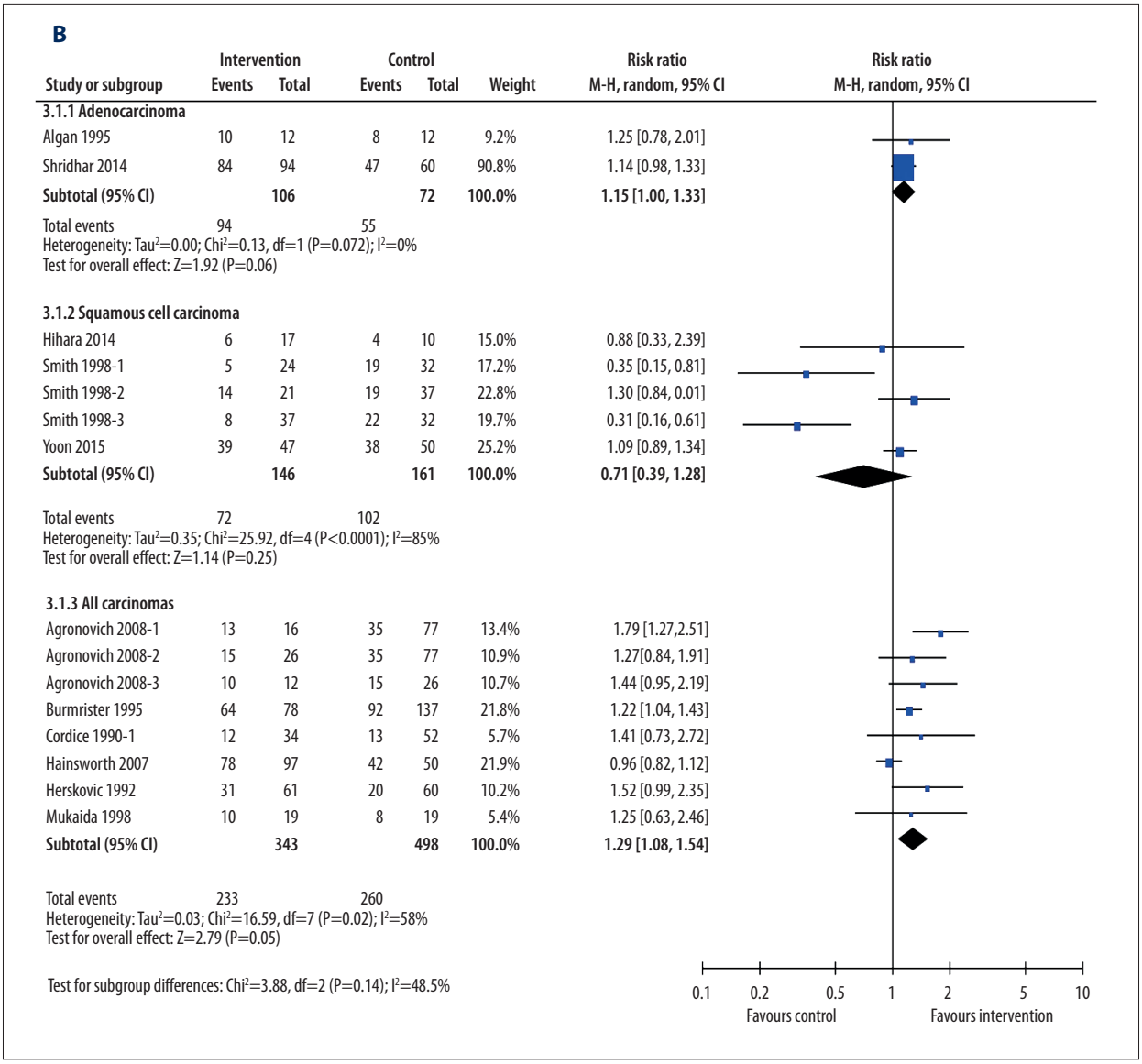

Figure 5. Subgroup meta-analysis of 1-year survival rates after treatment by type of intervention (**A**) or type of cancer (**B**). The interventions included radiotherapy plus chemotherapy, radiotherapy plus surgery, radiotherapy plus chemotherapy plus surgery, and radiotherapy plus chemotherapy plus surgery plus induction chemotherapy. The control groups were radiotherapy alone, radiotherapy plus chemotherapy, or radiotherapy plus chemotherapy plus surgery.

The analysis by the type of cancer was similarly restricted. None of the studies reported response rates for patients with adenocarcinoma. Surprisingly, 3 studies [18,19,22] that reported response rates for patients with squamous cell carcinoma indicated a poor response with additional treatments (Figure 8A), although this was not statistically significant (RR=0.71, 95% CI: 0.51, 0.99, p=0.05, I^2=0%). The 2 studies that reported response rates for patients grouped under the "All carcinoma" subgroup also failed to show any significant difference in their response with additional treatments (Figure 8B).

Dysphagia

Although dysphagia is one of the most debilitating symptoms of esophageal cancer, only 3 studies examined differences in this outcome. These studies compared RT+CT+surgery with RT+CT [27], RT+CT with RT alone [16], or adding induction CT to RT+CT+surgery [19] (Figure 9). None of the studies showed a significant improvement in dysphagia with treatments in addition to radiotherapy, and the meta-analysis of these studies was similarly neutral (RR=0.99, 95% CI: 0.67, 1.48, p=0.97, I^2=41%).

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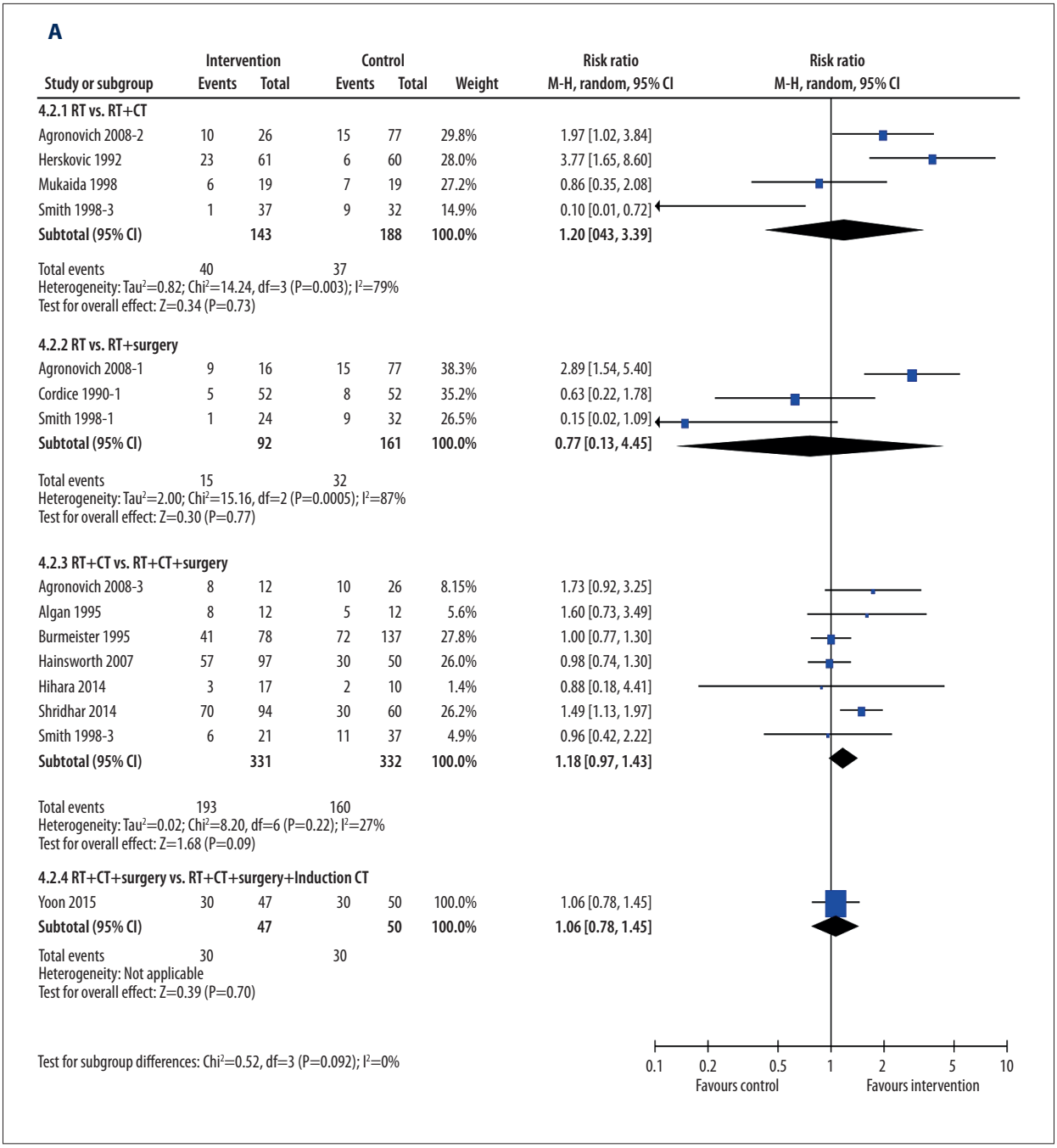

Adverse effects

Only 3 studies directly compared adverse effects between treatment types [16,18,19] (Table 2). Two of these studies were in people with squamous cell carcinoma [18] or predominately squamous cell carcinoma [19]. One study was in people with any type of carcinoma [16]. Our analysis found that additional therapies resulted in additional adverse effects. This was especially the case when chemotherapy was added to radiotherapy [16], or induction chemotherapy added to chemo-radiotherapy with surgery [19]. However, due to the small number of studies, only 1 adverse effect reached statistical significance – hematological abnormalities (RR=2.59, 95% CI: 1.63, 4.11, p<0.0001). Other adverse effects that did not reach statistical significance, but were substantially increased when additional treatments were added, were over-excitation (35% *vs.* 15%), upper aerodigestive tract complications (33% *vs.* 18%), shivering and fever (9% *vs.* 3%), and tracheitis (32% *vs.* 26%).

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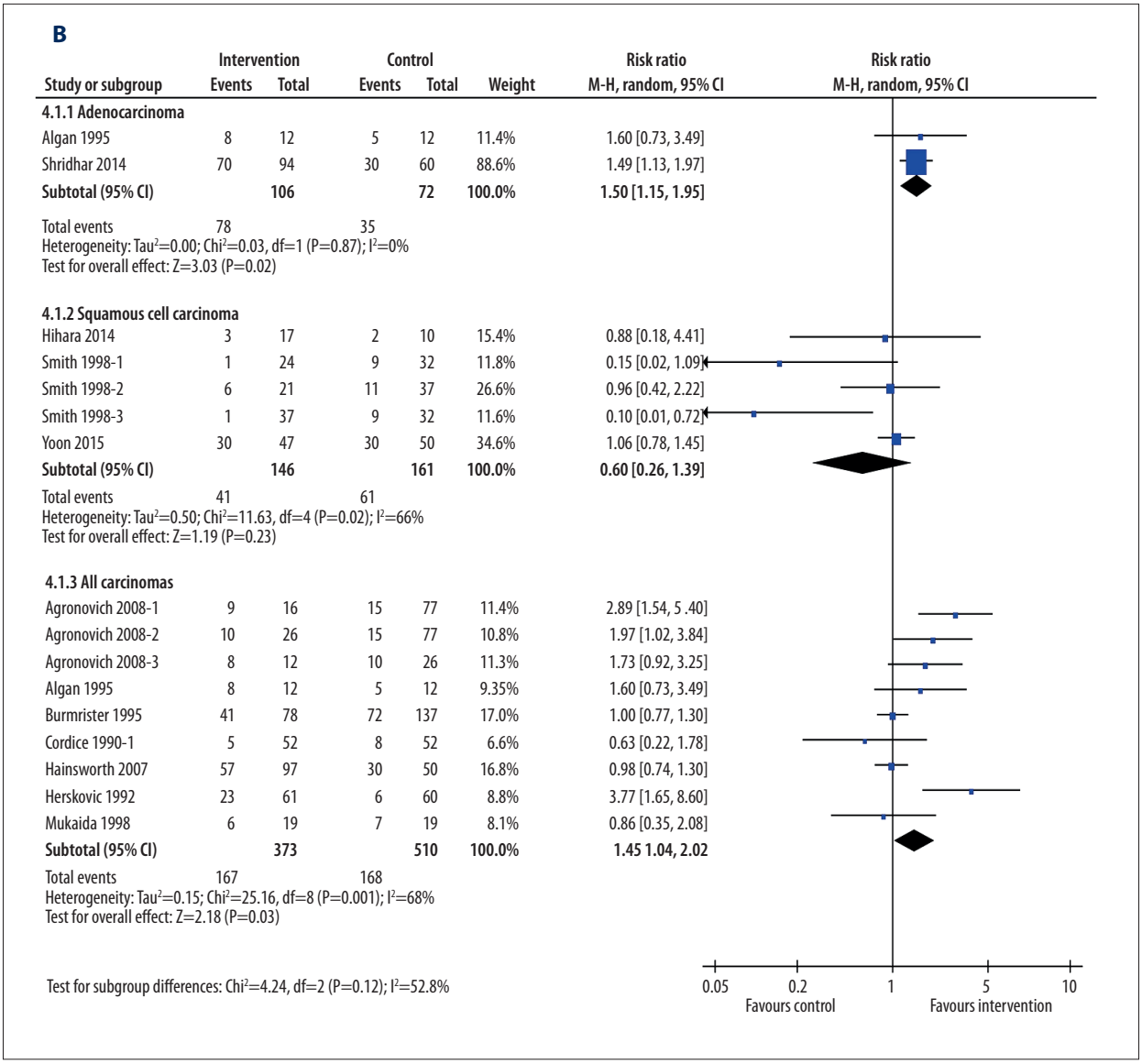

Figure 6. Subgroup meta-analysis of 2-year survival rates after treatment by type of intervention (**A**) or type of cancer (**B**). The interventions included radiotherapy plus chemotherapy, radiotherapy plus surgery, radiotherapy plus chemotherapy plus surgery, and radiotherapy plus chemotherapy plus surgery plus induction chemotherapy. The control groups were radiotherapy alone, radiotherapy plus chemotherapy, or radiotherapy plus chemotherapy plus surgery.

Sensitivity analysis – inclusion of RCTs

We undertook a sensitivity analysis of RCTs alone where possible (Figure 10). Median survival was reported in only 2 RCTs (Figure 10A), 1 in patients with squamous cell carcinoma [17] and 1 in patients with any carcinoma type [16]. Both studies compared RT with RT+CT. Meta-analysis of the 2 studies yielded similar results to the non-randomized trials (MD=4.59 months, 95% CI: –0.93, 10.11, p=0.10). Similarly, meta-analysis of the 5 study arms looking at 1-year survival (Figure 10B) did not differ substantially from the meta-analysis of all trials (RR=0.82, 95% CI: 0.50, 1.36, p=0.45). The same was true for 2-year survival (RR = 0.84, 95% CI: 0.35, 2.02, p=0.70) (Figure 10C) and 3-year survival (RR=0.70, 95% CI: 0.16, 3.03, p=0.64) (Figure 10D), response rates (RR=1.26, 95% CI: 0.45, 3.53, p=0.66) (Figure 10E), or dysphagia (RR=0.97, 95% CI: 0.60, 1.59, p=0.92) (Figure 10F).

Sensitivity analysis – tumor stage

It was possible that the tumor stage of the patients at the beginning of the studies would confound our results. As such, we undertook an *a priori* sensitivity analysis by tumor stage (Figure 11). As seen in Table 1, many studies included patients

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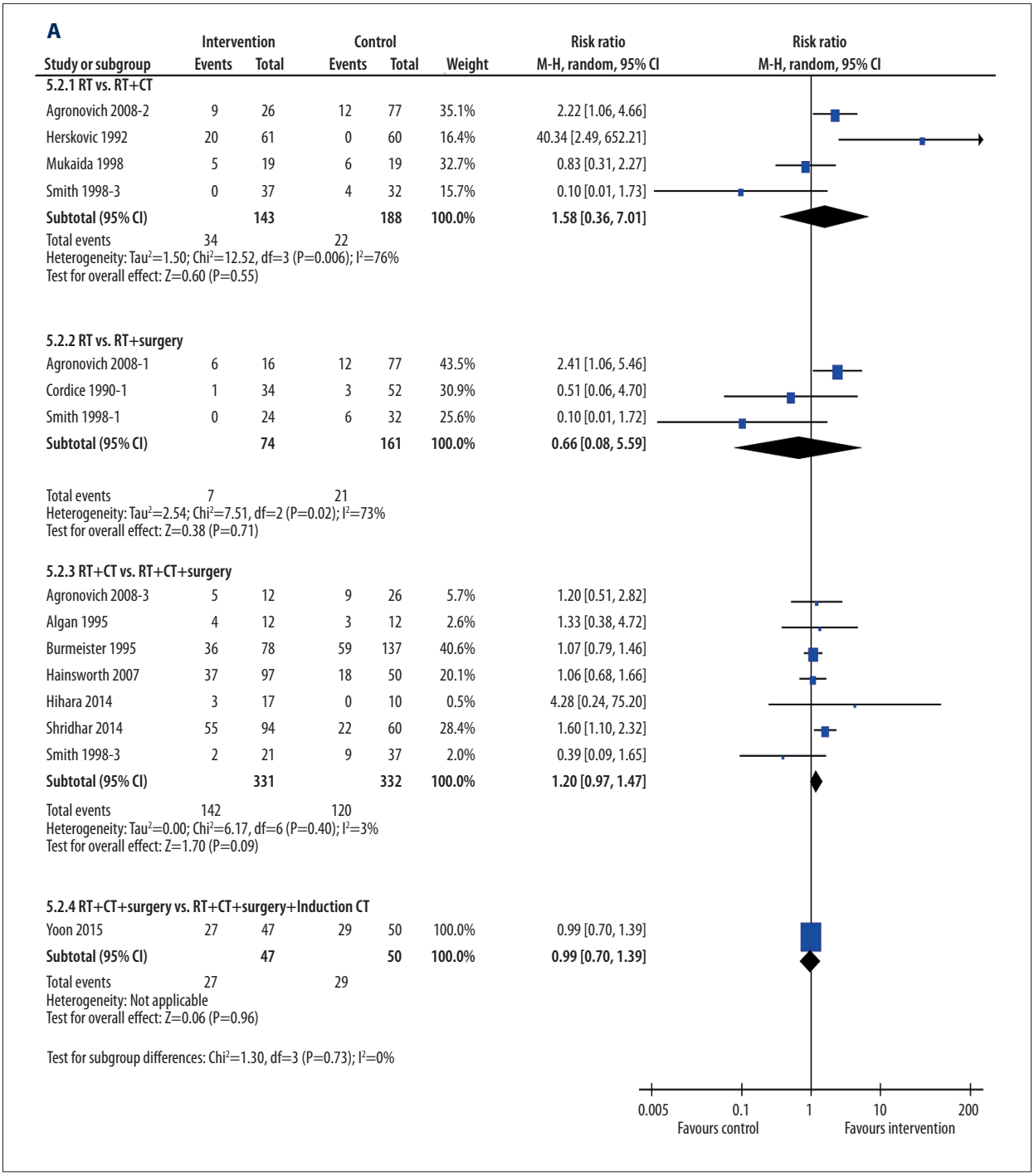

of any stage from I to IV. In order to exclude other variables that could influence the results (e.g., tumor type and treatment regimens), we compared studies using the same treatment regimen and excluded studies on adenocarcinoma. We chose 1-year, 2-year, and 3-year survival as the outcomes most likely to be influenced by tumor stage. At 1 year, the studies including only patients with early-stage cancer did demonstrate greater benefit from adding treatments to radiotherapy than studies in people with later-stage cancer (Figure 11A). Early-stage cancer patients had an improvement in survival rates at 1 year (RR=1.23, 95% CI: 1.06, 1.43, p=0.006) compared with late-stage patients (RR=0.96, 95% CI: 0.82, 1.11, p=0.56). The subgroups were statistically different from one another (p=0.02).

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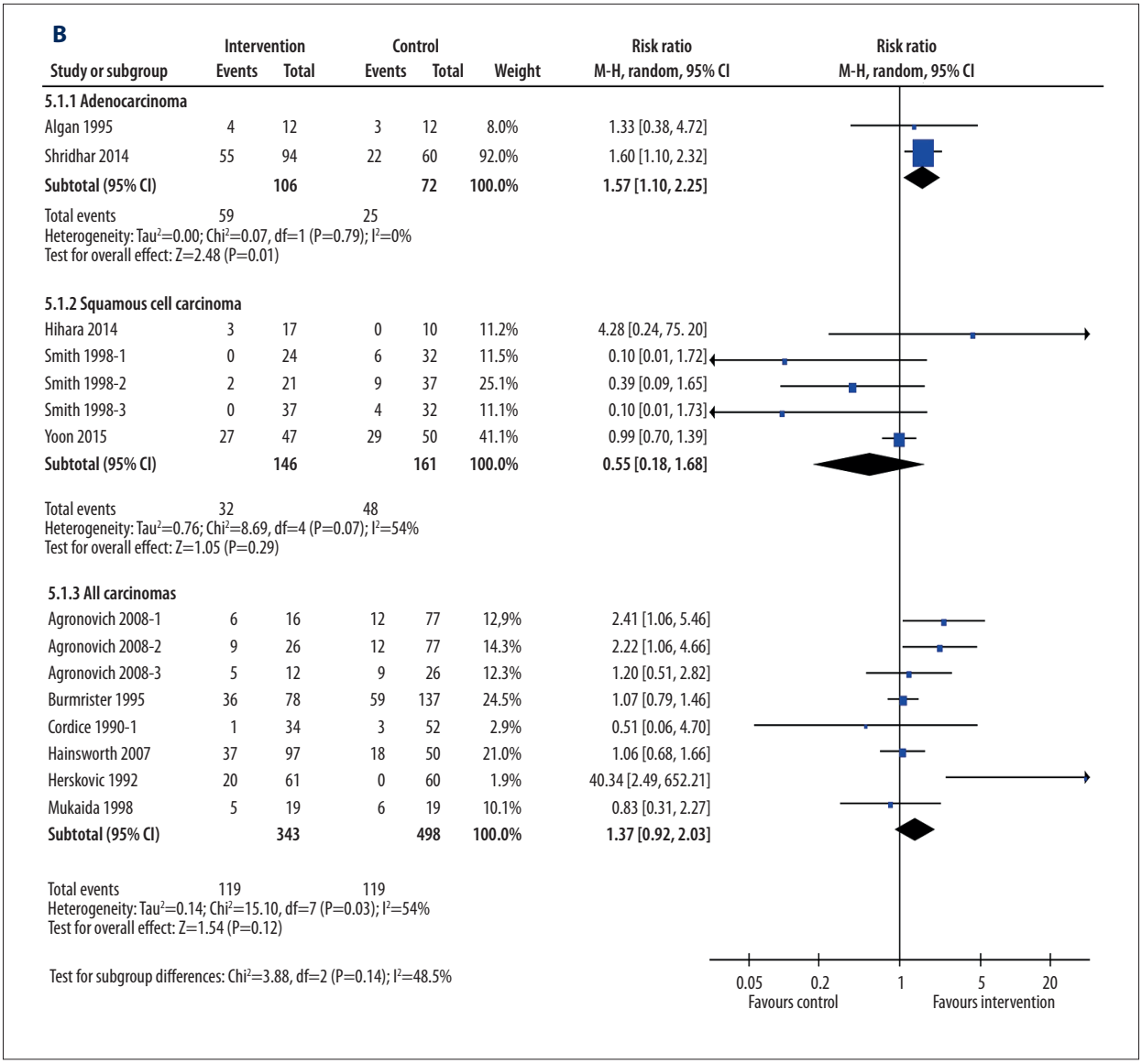

Figure 7. Subgroup meta-analysis of 3-year survival rates after treatment by type of intervention (**A**) or type of cancer (**B**). The interventions included radiotherapy plus chemotherapy, radiotherapy plus surgery, radiotherapy plus chemotherapy plus surgery, and radiotherapy plus chemotherapy plus surgery plus induction chemotherapy. The control groups were radiotherapy alone, radiotherapy plus chemotherapy, or radiotherapy plus chemotherapy plus surgery.

At 2 and 3 years, however, all benefits of adding treatment to radiotherapy in early-stage cancer patients disappeared (Figure 11B, 11C). At 2 years, early-stage cancer patients did not benefit from adding treatments to radiotherapy (RR=1.00, 95% CI: 0.77, 1.28, p=0.98), and neither did late-stage cancer patients (RR=0.98, 95% CI: 0.74, 1.29, p=0.87). There were no subgroup differences (p=0.91). At 3 years, there was no benefit to early-stage cancer patients from adding treatments to radiotherapy (RR=0.78, 95% CI: 0.26, 2.39, p=0.66), nor to late-stage cancer patients (RR=1.18, 95% CI: 0.59, 2.36, p=0.63). There were no subgroup differences (p=053).

Sensitivity analysis – chemotherapy regime

As stated earlier, we had planned a sensitivity analysis by chemotherapy regimen. Unfortunately, the treatment regimens varied widely, and there were insufficient studies to conduct an analysis by chemotherapy type.

Discussion

This meta-analysis investigated the efficacy and safety of using additional treatments with radiotherapy in patients with

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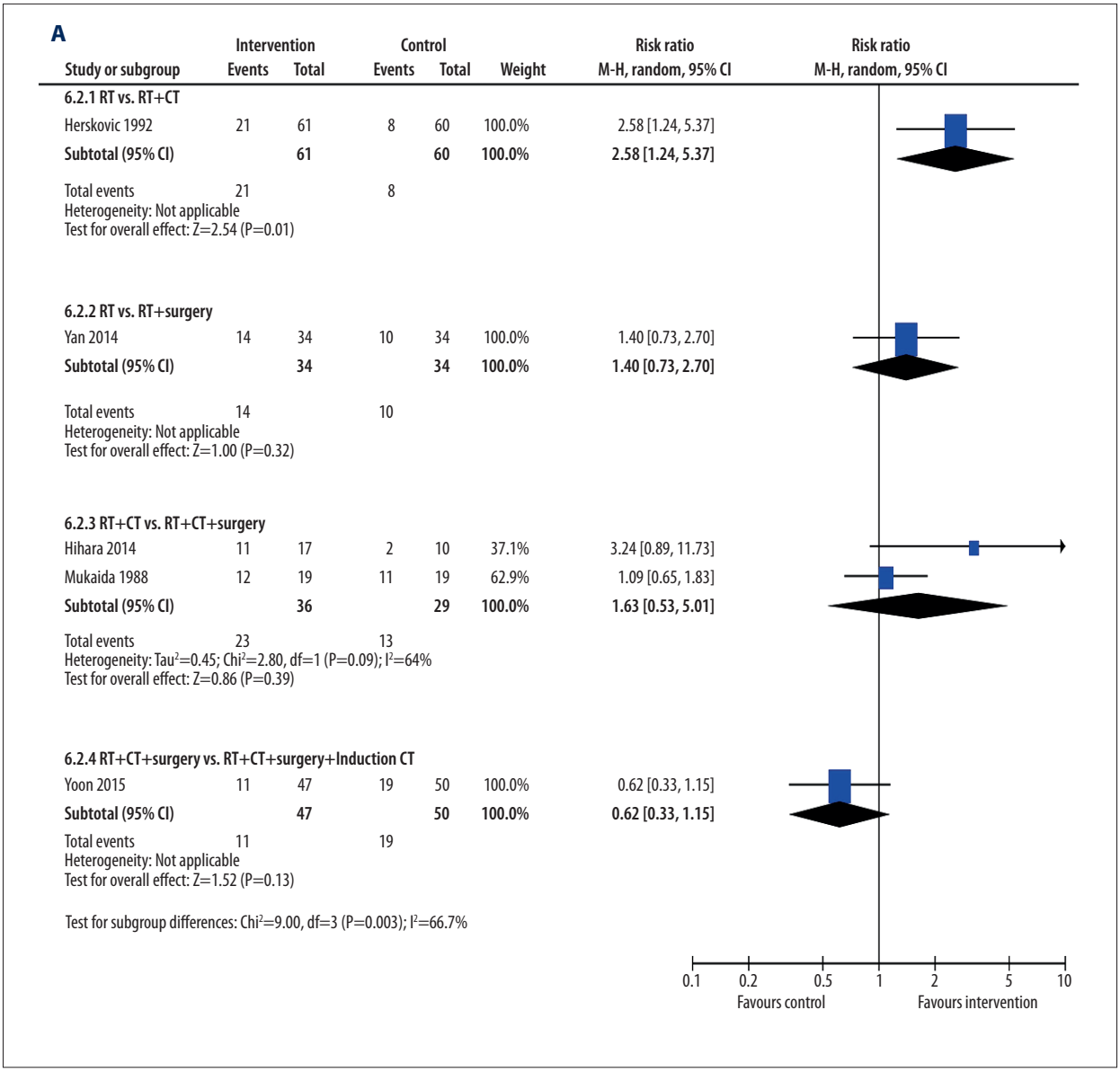

esophageal carcinoma. Treatment strategies included chemotherapy (RT *vs.* RT+CT), surgery (RT *vs.* RT+ surgery, RT+CT *vs.* RT+CT+surgery), and immune therapy (RT *vs.* RT+immune therapy).

Median survival time

Figure 3 displays subgroup meta-analyses of the median survival times by type of treatment (A) and cancer type (B). An interesting observation was the startling lack of efficacy of adding extra treatments to radiotherapy. Neither chemotherapy nor surgery improved median survival times (Figure 3A) above that of radiotherapy alone. The addition of surgery to chemoradiotherapy was significantly better, but this result was driven by the 2 studies in patients with adenocarcinoma. Removal of the 2 adenocarcinoma studies led to a loss of statistical significance for this treatment combination as well.

An imbalance between groups at baseline could explain the lack of efficacy. However, this is unlikely to be the case, as any imbalance, especially towards patients selected for surgery, was more likely to favor additional treatments. That is, patients selected for more aggressive treatment tended to have less advanced cancer, or were physically fitter than those who did not undergo surgery. Thus, it is even more concerning that these groups did not exhibit longer survival times.

A clear finding was that adding treatments to radiotherapy increased the median survival times for patients with adenocarcinomas only. This phenomenon has been observed before in

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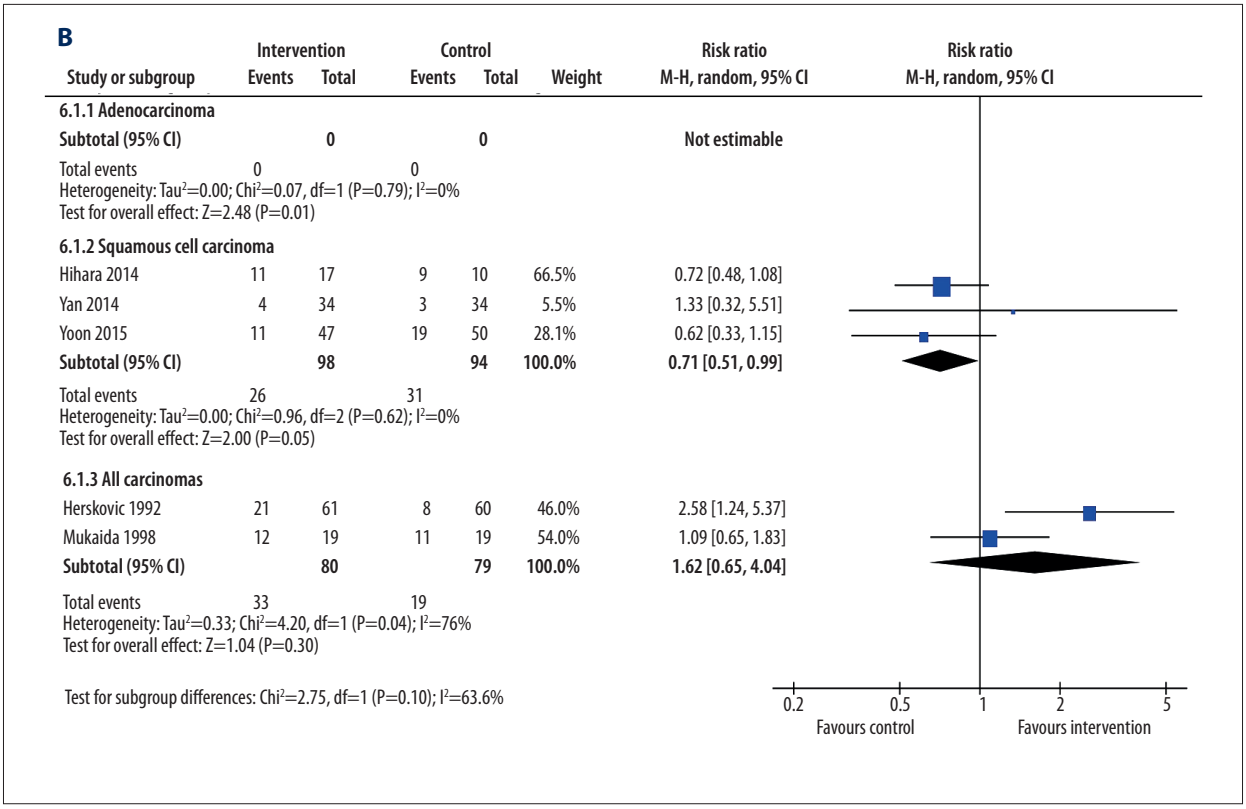

Figure 8. Subgroup meta-analysis of response rates after treatment by type of intervention (**A**) or type of cancer (**B**). The interventions included radiotherapy plus chemotherapy, radiotherapy plus immunotherapy, radiotherapy plus chemotherapy plus surgery, and radiotherapy plus chemotherapy plus surgery plus induction chemotherapy. The control groups were radiotherapy alone, radiotherapy plus chemotherapy, or radiotherapy plus chemotherapy plus surgery.

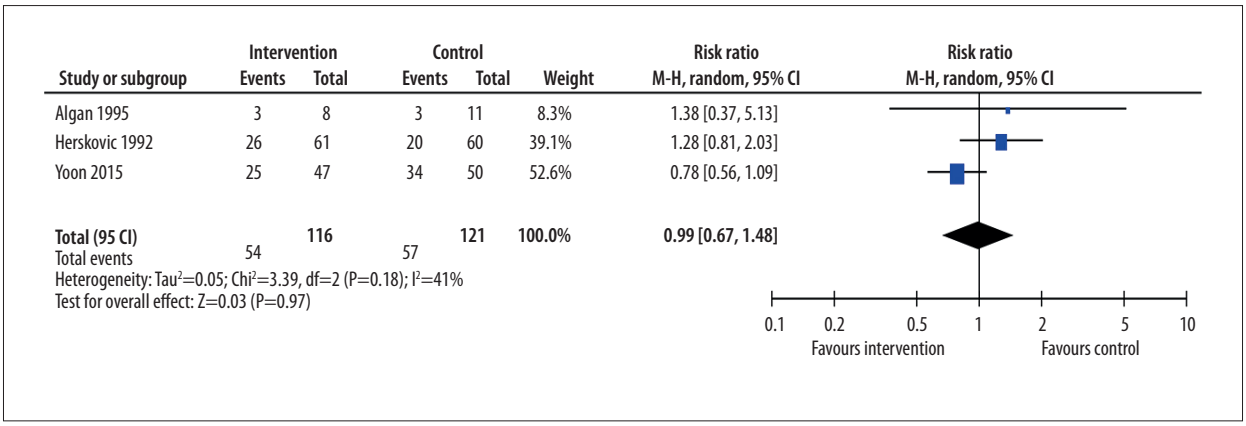

Figure 9. Meta-analysis of incidence of dysphagia. The interventions included radiotherapy plus chemotherapy (Herskovich 1992), radiotherapy plus chemotherapy plus surgery (Algan 1995), and radiotherapy plus chemotherapy plus surgery plus induction chemotherapy (Yoon 2015). The control groups were radiotherapy alone (Herskovich 1992), radiotherapy plus chemotherapy (Algan 1995), or radiotherapy plus chemotherapy plus surgery (Yoon 2015).

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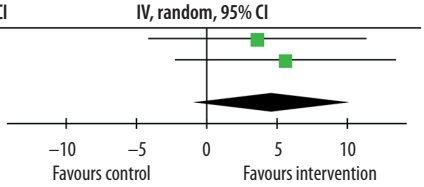
A

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Herskovic 1992	12.5	27.6	61	8.9	13.8	60	57.4%	3.60 [−4.16, 11.36]
Smith 1998	14.8	27.6	59	9.2	13.8	60	49.3%	5.60 [−2.26, 13.46]
Total (95 CI)			**120**			**120**	**100.0%**	**4.59 [−0.93, 10.11]**

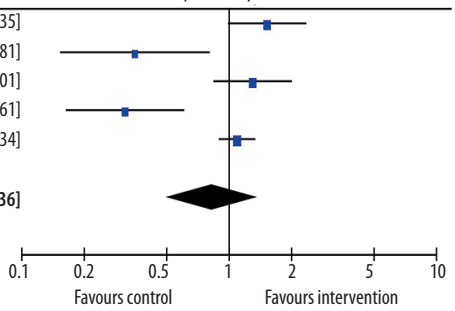
Heterogeneity: Tau²=0.00; Chi²=0.13, df=1 (P=0.72); I²=0%
Test for overall effect: Z=1.63 (P=0.10)



B

Study or subgroup	Control Events	Total	Intervention Events	Total	Weight	Risk ratio M-H, random, 95% CI
Herskovic 1992	31	61	20	60	21.4%	1.52 [0.99, 2.35]
Smith 1998-1	5	24	19	32	15.0%	0.35 [0.15, 0.81]
Smith 1998-2	14	21	19	37	21.4%	1.30 [0.84, 2.01]
Smith 1998-3	8	37	22	32	17.8%	0.31 [0.16, 0.61]
Yoon 2015	39	47	38	50	24.4%	1.09 [0.89, 1.34]
Total (95 CI)		**190**		**211**	**100.0%**	**0.82 [0.50, 1.36]**
Total events	97		118			

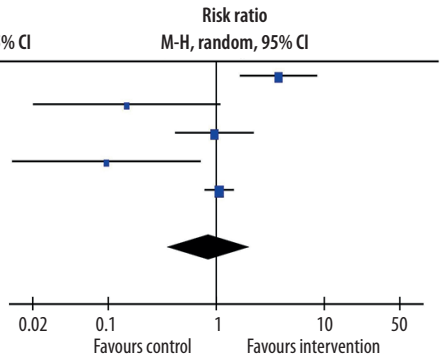
Heterogeneity: Tau²=0.26; Chi²=25.71, df=4 (P<0.0001); I²=84%
Test for overall effect: Z=0.76 (P=0.45)



C

Study or subgroup	Intervention Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95% CI
Herskovic 1992	23	61	6	60	23.8%	3.77 [1.65, 8.60]
Smith 1998-1	1	24	9	32	11.8%	0.15 [0.02, 1.09]
Smith 1998-2	6	21	11	37	23.7%	0.96 [0.42, 2.22]
Smith 1998-3	1	37	9	32	11.7%	0.10 [0.01, 0.72]
Yoon 2015	30	47	30	50	29.0%	1.06 [0.78, 1.45]
Total (95 CI)		**190**		**211**	**100.0%**	**0.84 [0.35, 2.02]**
Total events	61		65			

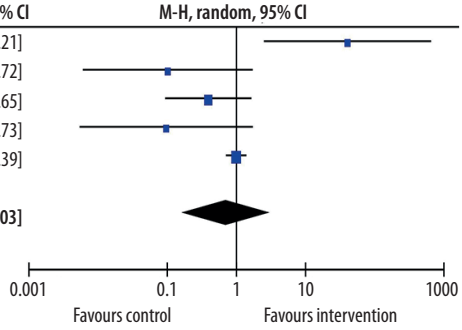
Heterogeneity: Tau²= 0.67; Chi²= 18.40, df= 4 (P= 0.001); I²= 78%
Test for overall effect: Z= 0.39 (P= 0.70)



D

Study or subgroup	Intervention Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95% CI
Herskovic 1992	20	61	0	60	14.9%	40.34 [2.49, 652.21]
Smith 1998-1	0	24	6	32	14.6%	0.10 [0.01, 1.72]
Smith 1998-2	2	21	9	37	24.6%	0.39 [0.09, 1.65]
Smith 1998-3	0	37	4	32	14.3%	0.10 [0.01, 1.73]
Yoon 2015	27	47	29	50	31.7%	0.99 [0.70, 1.39]
Total (95 CI)		**190**		**211**	**100.0%**	**0.70 [0.16, 3.03]**
Total events	49		48			

Heterogeneity: Tau²=1.72; Chi²=14.67, df=4 (P=0.005); I²=73%
Test for overall effect: Z=0.47 (P=0.64)



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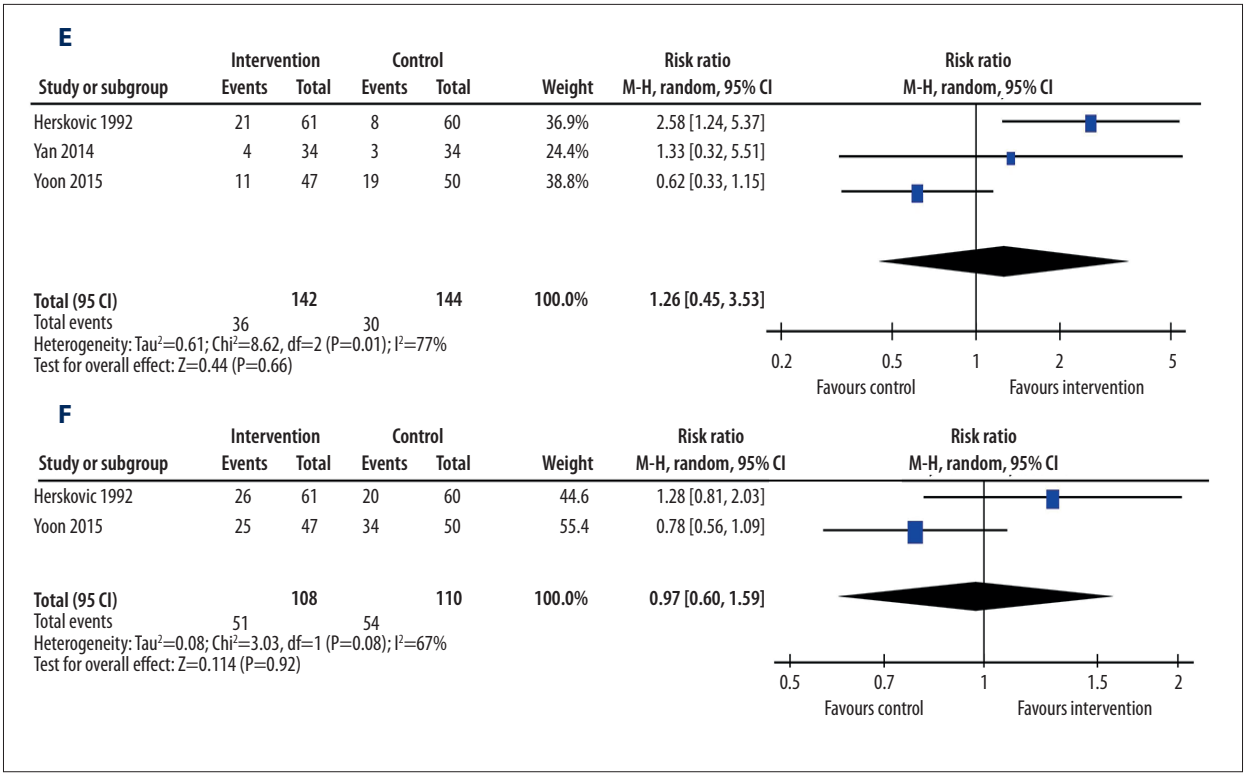
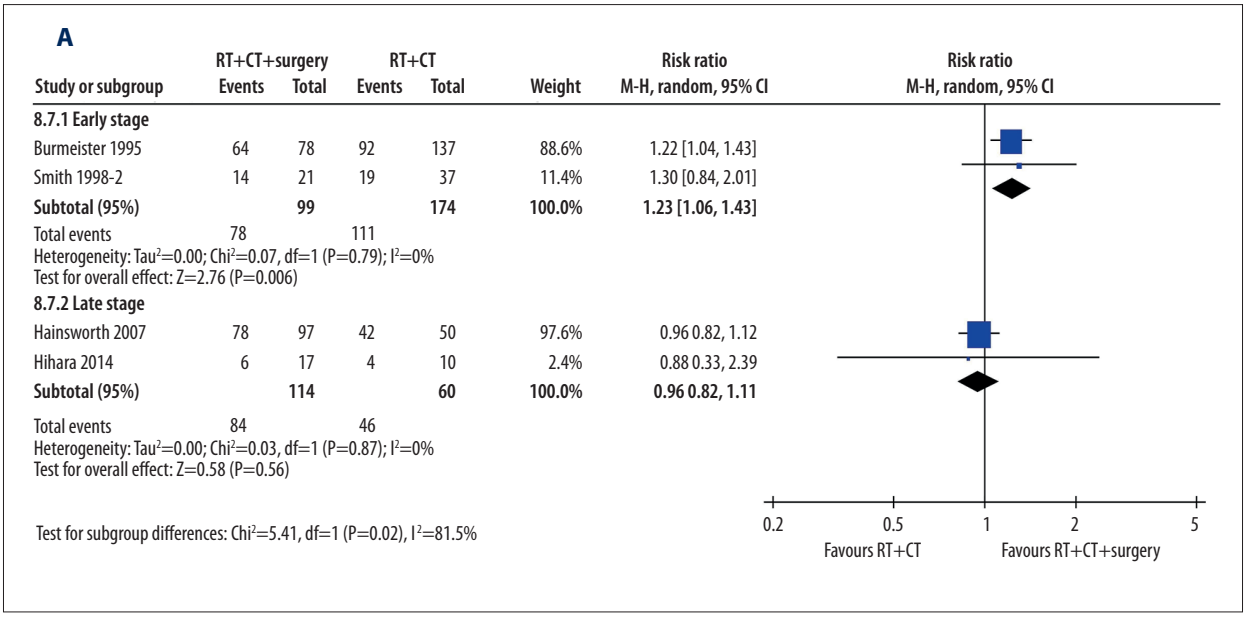


Figure 10. Meta-analysis of randomized controlled trials. (**A**) Median survival time; (**B**) 1-year survival time; (**C**) 2-year survival time; (**D**) 3-year survival time; (**E**) response rate; (**F**) incidence of dysphagia. The interventions included radiotherapy plus chemotherapy (Herskovich 1992, Smith 1998-3), radiotherapy plus immunotherapy (Yan 2014), radiotherapy plus surgery (Smith 1998-1), radiotherapy plus chemotherapy plus surgery (Smith 1998-2), and radiotherapy plus chemotherapy plus surgery plus induction chemotherapy (Yoon 2015). The control groups were radiotherapy alone (Herskovich 1992, Smith 1998-1, Smith 1998-3 Yan 2014), radiotherapy plus chemotherapy (Smith 1998-2), or radiotherapy plus chemotherapy plus surgery (Yoon 2015).



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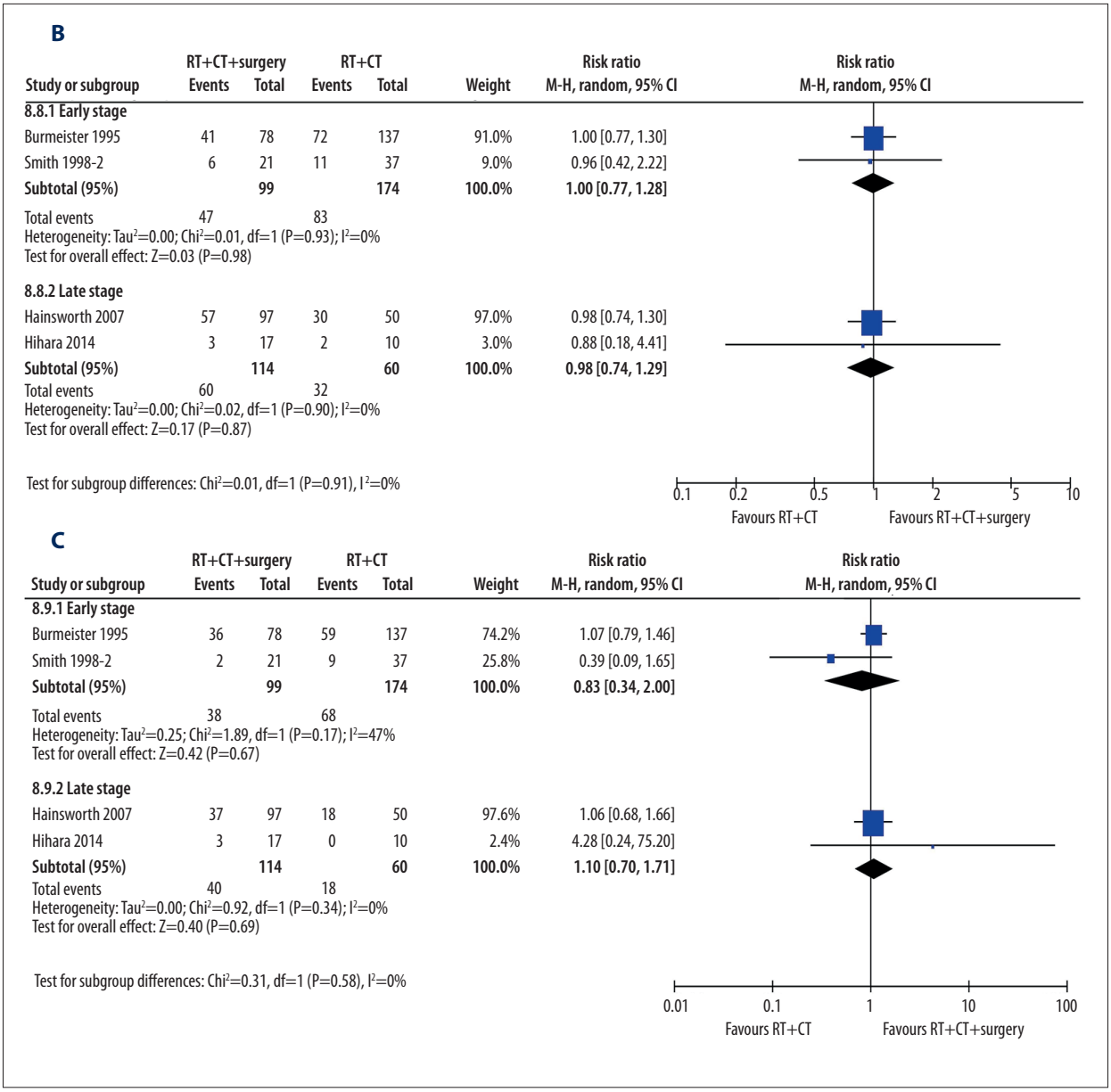

Figure 11. Sensitivity analysis of early versus late-stage tumors. (**A**) 1-year survival; (**B**) 2-year survival; (**C**) 3-year survival. A single treatment type (radiotherapy plus chemotherapy versus radiotherapy plus chemotherapy plus surgery) was chosen, and studies in adenocarcinoma were removed to reduce between-study variability. Two studies in patients with early- to mid-stage cancer (Burmeister 1995, Smith 1998) were compared with 2 studies in patients with mid- to late-stage cancer (Hainsworth 2007, Hihara 2014).

esophageal cancer [28,29] as well as for other cancers such as pulmonary cancers [30–32], but contrasts with survival in cervical cancer [33].

Disease-free survival

Unfortunately, only 3 studies reported on this important outcome. All 3 studies compared chemo-radiotherapy alone with chemo-radiotherapy plus surgery. Two of the 3 studies were in patients with adenocarcinoma [26,27] and the third was in patients with any carcinoma [21]. Similarly to median survival times, disease-free survival was only significantly better in patients with adenocarcinoma. This suggests that in these patients, undertaking surgery will improve outcomes, but that in patients with squamous cell carcinoma, surgery will not improve survival. A similar lack of efficacy was seen in cervical squamous cell carcinomas [34], where disease-free survival times were not significantly extended by the addition of

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Table 2. Adverse effects of additional treatment versus control treatment regimens.

Side effect	Adeno-carcinoma	Squamous cell carcinoma	Any carcinoma	Additional treatment (%)	Control treatment (%)	Difference (Int – Cont) (%)	Risk ratio	95% CIs	P-value
Anorexia/weight loss	+*	+	–	2	2	0	1.06	0.07, 16.53	0.96
AST/ALT elevation	+*	+	–	2	0	2	3.19	0.13, 76.36	0.47
Dermatological	–	+	–	5	2	3	2.95	0.32, 27.58	0.34
Gastrointestinal tract	+*	+	+	18	17	1	1.01	0.61, 1.68	0.96
Hematological	+*	+	+	36	14	22	2.59	1.63, 4.11	**<0.0001**
Hyperglycemia	+*	+	–	0	2	–2	0.35	0.01, 8.48	0.52
Infection	+*	+	–	2	0	2	3.19	0.13, 76.36	0.47
Insomnia	–	+	–	12	15	–3	0.80	0.23, 2.73	0.72
Nausea/vomiting	+*	+	–	0	4	–4	0.21	0.01, 4.31	0.31
Nervous system	–	–	+	1	0	1	3.06	0.13, 74.18	0.49
Over-excitation	–	+	–	35	15	20	2.40	0.95, 6.07	0.06
Respiratory tract	–	–	+	3	0	3	4.92	0.24, 100.37	0.30
Shivering & fever	–	+	–	9	3	6	3.00	0.33, 27.42	0.33
Tracheitis	–	+	–	32	26	6	1.22	0.58, 2.57	0.60
Upper aerodigestive tract	–	–	+	33	18	15	1.79	0.94, 3.40	0.08

The treatment modalities in this table included RT+CT *vs.* RT (any carcinoma) (Herskovich 1992), RT plus immunotherapy *vs.* RT (squamous cell carcinoma (Yan 2014), and RT+CT+Surgery+Induction CT *vs.* RT+CT+Surgery (98% squamous cell carcinoma, 2% adenocarcinoma) (Yoon 2015). * Only 2% of cases in this study were adenocarcinoma (Yoon 2015).

chemotherapy to radiotherapy. Given that surgery necessarily involves risk, it may be that the risks outweigh the benefits for squamous cell carcinoma patients.

Survival rates

Comparison of 1-year, 2-year, and 3-year survival rates underlies the superior prognosis of patients with adenocarcinomas. When looking at treatment types, initial inspection suggests that adding surgery to chemo-radiotherapy benefited patients at 1-year post-treatment. However, removal of the 2 studies in patients with adenocarcinoma shifted the treatment effect from significant (p=0.02) to non-significant (p=0.13). Thus, oncologists should take care to explain to their patients with non-adenocarcinoma the risks versus benefits of potential treatment options.

Although at 1 year there was little difference between the different cancer types, patients with adenocarcinoma benefited increasingly from additional treatments as time went on. In contrast, other carcinoma types failed to show any benefit from adding treatments. Study reports evaluating therapeutic strategies in different cancers, such as lung cancer [31,32], rectal cancer [35,36], and cervical cancer [34] similarly failed to find any benefit in terms of survival rates from adding multiple therapies to radiotherapy.

Response rates

As we have seen with all other outcomes, adding additional treatments to radiotherapy saw no improvement in response rates. Only 5 studies [16,18,19,22] reported on this outcome, and each study defined "response" in a different way; however, overall, no significant difference was seen in any study except Herskovic (1992) [16]. A close examination of this study reveals that 20% of the combined therapy group had adenocarcinoma as opposed to 10% of the radiation therapy group. This additional set of patients with adenocarcinoma may account for the observed increase in effectiveness of combined therapy seen in the study [16].

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Dysphagia

Dysphagia is a very common and highly debilitating symptom in esophageal cancer. Indeed, dysphagia, and later treatment for it, can result in malnutrition [37]. Therefore, treatments that reduce dysphagia, even if they do not increase survival times, could be regarded as important for quality of life [38]. It was surprising, then, that only 3 of the included 18 study arms reported on dysphagia incidence between treatment types. One study added surgery to chemo-radiotherapy [27], another study added chemotherapy to radiotherapy [16], and the third study added induction chemotherapy to chemo-radiotherapy [19]. Regardless of the treatment type, no decrease in the incidence of dysphagia was seen in any study. This was a surprising finding, until one looks at the effectiveness of radiotherapy alone for dysphagia. A recent clinical trial determined that radiotherapy alone is as effective as radiotherapy with chemotherapy in reducing dysphagia [39]. Thus, adding chemotherapy, surgery, or induction chemotherapy to radiation would perhaps do more harm than good, compared with the effect of radiation alone.

Adverse effects

With additional cancer treatments comes the risk of increased adverse effects [40–43]. Unfortunately, few studies directly compared adverse effects between different treatment types. As a result, most adverse effects in our meta-analysis are based on between 68 and 120 patients. Only 2 adverse effects (gastrointestinal and hematological) were sufficiently powered (286 patients) to capture incidence of adverse effects with reasonable confidence intervals. Of these, no significant difference was seen for gastrointestinal adverse effects. In contrast, hematological adverse effects were significantly increased. This is not surprising, given that the 2 studies that showed a significant increase both involved either adding or increasing chemotherapy [16,19]. A recent meta-analysis on doublet versus triplet chemotherapy concluded that triplet therapy was more effective, but came at the expense of significant hematological damage [44]. Overall, 12 of the 15 reported that adverse effects were worse when treatments were added to the control therapy. Traditionally, little difference occurs in approaches to therapy based on type of cancer (adenocarcinoma *vs.* squamous cell carcinoma) [45]. Given this, much thought should be given to the use of chemotherapy in patients with squamous cell carcinoma, and how much patients will benefit compared with the harm done to their health and quality of life.

Limitations

Only 4 of the studies in the meta-analysis were RCTs, and none of these was blinded. However, a sensitivity analysis of RCTs did not reveal any differences between the RCTs alone compared with all studies together.

Conclusions

This meta-analysis has demonstrated the importance of cancer type on response to multiple esophageal cancer treatment. We found that in almost all cases of squamous cell carcinoma, additional treatments did not increase patient survival, but did increase the incidence of adverse effects. In stark contrast to this finding, patients with adenocarcinoma clearly responded to adding treatments such as chemotherapy and surgery to radiotherapy. Given the fact that, at present, little difference occurs in the treatment of the 2 forms of cancer, we believe that this review is of vital importance. Patients with squamous cell carcinoma may experience a significantly better quality of life by forgoing futile interventions. We believe that this evidence is of great value to oncologists discussing treatment options with their patients.

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