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Review

Radiotherapy May Offer a Recurrence and Survival Benefit in Rectal Cancers Treated Surgically with Transanal Endoscopic Microsurgery: A Systematic Review and Meta-analysis

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Abstract. *Background/Aim: Several studies report outcomes of Transanal Endoscopic Microsurgery (TEMS) surgery in combination with radiotherapy, however the combination of those treatments is provided mostly on an adhoc individual basis and the role of radiotherapy remains unclear. The aim of this study was to identify the effect of neo-adjuvant or adjuvant radiotherapy in the oncological outcomes of rectal cancer treated surgically with TEMS. Materials and Methods: We performed a systematic review of the literature on MEDLINE and Pubmed databases. Data were extracted by two independent reviewers and meta-analyzed using an inverse variance heterogeneity model to calculate overall (pooled) effect sizes for survival or recurrence of disease against neo+/-adjuvant treatment. Results: A total of 48 studies were included in the qualitative meta-analysis which included 3,285 patients with rectal cancer. The overall survival odds ratio (OR), was 9.39 (95% CI=6.1-14.4) with a Cochran's Q variable of 151.7 on 47 degrees of freedom (d.f.) (p=0.000). Recurrence-free OR was 8.7 (95%CI=6.58-11.44) with a Cochran's Q variable of Q=145.2 on 44 d.f. (p=0.000). Studies which contained more than 10% of pT3 tumours, and provided neo+/-adjuvant treatment in more than 35% of cases, were associated with survival benefit, as demonstrated by an overall odds of survival of 32.2 (95%CI=16.3-63.5, p=0.001, Q=8.4, p=0.21). Studies that contained more than 10% of pT3 tumours and provided neo+/-adjuvant treatment in more than 20% of the cases had an overall effect size of recurrence-free odds of 20.23 (95%CI=13.84-29.57, p=0.000, Q=2.18, p=0.54). Conclusion: There seems to be a benefit from radiotherapy on overall survival and recurrence-free odds, which is more apparent in cohorts with more than 10% of pT3 tumours. Our results suggest that neo-adjuvant or adjuvant radiotherapy should be considered for inclusion in formal treatment protocols for rectal cancers treated with TEMS as they offer a recurrence and survival benefit.*

The surgical treatment of rectal cancer has been marked since the 1990s when the concept of Total Mesorectal Excision (TME) was introduced by Heald (1) and subsequently accepted by all Colorectal surgeons as the gold standard of surgery (2). The principle of TME is the complete removal of all regional lymph nodes *en-block* with the Mesorectal fascia and the rectum, regardless of whether an open or laparoscopic surgery is performed.

Around the same time as TME another surgical technique for rectal tumours was introduced by Buess (3). That was the Transanal Endoscopic Microsurgery (TEMS), a minimally invasive surgery performed with the aid of an operating endoscope and laparoscopic instruments (4). TEMS was initially introduced for benign rectal tumours offering the advantages of better technical excision and completeness in relation to the older Transanal Resection

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technique (TAR). TEMS required general anesthetic but no abdominal incision and could be performed as day surgery with minimal morbidity and mortality (4). It was the minimally-invasive nature of TEMS which tempted the first pioneers (3, 5) to attempt it as surgical treatment for early cancers, T1N0M0, on selected patients who were too high risk for TME because of comorbidities. On those selected patients TEMS was reported to have good results with survival equal to TME although local recurrence seems to be higher (6). Enthusiasts like the Italian team of Lezoche (7) performed and reported the first randomized trials of TEMS *vs*. TME for tumours of T1-T3 stages with negative nodes and neo-adjuvant radio-chemotherapy (7). The results were so good that a new wave of research has evolved over the last 10 years (4) which has eventually made TEMS, and other forms of endoscopic local excision, a legitimate treatment option for selected early tumours regardless of the patient operative risk. TEMS is recommended as an option now in many official guidelines such as those of NICE in the UK (8).

The issue of recurrence remains the main concern which has not allowed, so far, the wider application of TEMS in many rectal cancer cases. Recurrence is known to relate to several factors, the most important of which is tumour stage. It is widely accepted that TEMS is suitable only for cancers without positive lymph nodes, *i.e*. N0 of the TNM classification. It has also been shown that T3 tumours treated with local excision have an unacceptably high recurrence rate of around 50%. T1N0M0 tumours are currently the main indication with a reported recurrence rate varying from 5 to 12%. T2N0M0 tumours are also confined within the rectal wall and are candidates for TEMS according to the ESMO guidelines. The issue of histology, *i.e*. whether there are adverse histological features, as well as the fitness and perioperative risk of the patient are the other factors taken into account.

Adjuvant or neo-adjuvant radiotherapy with or without the addition of chemotherapy have been reported in this context, with variable results. There are no current guidelines recommending radio-chemotherapy for T1-T2 node-negative rectal tumours. However, it is obvious from the literature, as well as from the authors' own experience that those treatments are often added by multi-disciplinary teams to TEMS surgery when there is concern that surgery alone is not adequate. There is lack of systematic protocols of treatment and this is in contrast with the surgical treatment of rectal cancer with Total Mesorectal Excision where there are detailed protocols of treatment combinations.

The aim of our study was to investigate the effect of radiotherapy, adjuvant or neo-adjuvant, in the treatment of rectal cancers treated with TEMS surgery.

Methods

We searched Pubmed and Medline databases (January 1966-January 2016). We used the following MeSH subheadings "Transanal endoscopic microsurgery" (Medical subject heading [MeSH]), "TEM" (MeSH), and "TEMS" (MeSH) were combined with "rectal neoplasms" (MeSH), "rectal cancer" (MeSH), and "carcinoma of the rectum" (MeSH). In addition, we searched manually through the reference list from the retrieved papers for additional data. We have not included any published conferences extracts or any other non-peer reviewed manuscripts.

Inclusion criteria. We structured our systematic review based on a "Population, Intervention, Comparison, Outcome" strategy. The population included patients who underwent TEMS with both curative or palliative intention for treatment of rectal tumours. That includes both prospective and retrospective observational studies, randomised-controlled trials, case-controlled studies and case-series. More specifically, we included any of the above studies that described at least one of the following primary outcome measures: survival and or overall recurrence of disease (local or distant). Only studies reporting cancers (and not just benign tumours) were included.

We compared our primary outcomes against neoadjuvant +/- adjuvant radiotherapy treatment.

Exclusion criteria. Exclusion criteria included studies not published in English, studies that performed TEMS in less than five rectal cancer cases, studies that had no clear distinction between radical surgery and TEMs (mixed series) and studies that included benign rectal tumours. Reviewers examined all studies and excluded duplicate cohorts (7, 9, 10).

Data extraction. Two independent reviewers selected the studies from the literature search. Data were extracted by both reviewers, and any conflict was resolved by the senior author. A PRISMA flowchart was constructed to map out the selection of studies (Figure 1).

Available Data. Study data were available on median age, sex, pT stage as well as operative time (minutes) and hospital stay (days). We also extracted the number of patients who received either neo-adjuvant or adjuvant chemo+/-radiotherapy, and those who had completion surgery. The outcome variables that we based our analysis were cancer-related deaths, local recurrence and the need for salvage surgery. The effect sizes were therefore expressed in terms of odds of survival or odds of recurrence.

Statistical analysis. The principal analysis consists of meta-analysis and meta-analytic regressions to evaluate the significance of neo+/- adjuvant radiotherapy treatment on the survival and overall recurrence. These meta-analytic algorithms provided valid aggregated (pooled) overall effect sizes for survival or recurrence odds ratios (OR) or log-odds ratio We assessed the significance of any heterogeneity between the effect sizes of the different studies, using Cochran's Q Statistic. The distribution was approximated by a Chi-square distribution with k-1 degrees of freedom (d.f.), where k was the number of studies. In the presence of heterogeneity, we selected a meta-analytic algorithm called "inverse variance heterogeneity" model (IV-Het) (11, 12) which controls for the between-region heterogeneity as the "random-effects algorithm" but,

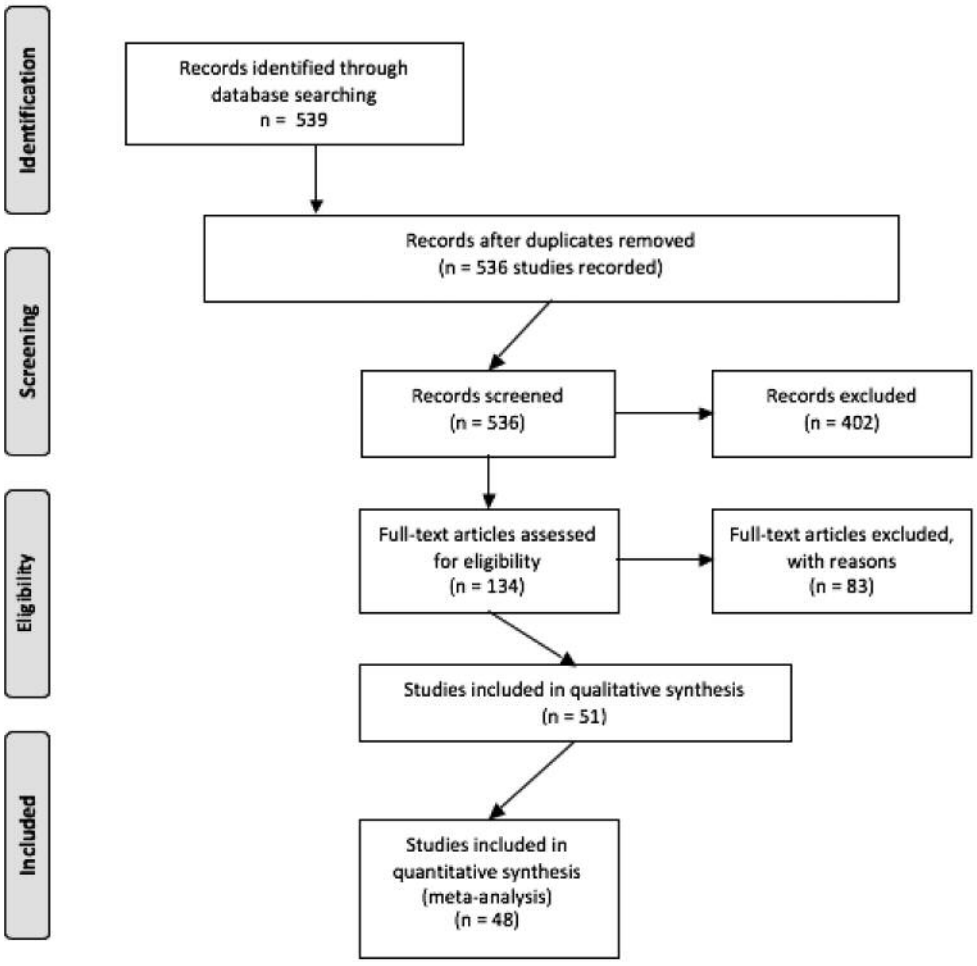

Figure 1. *PRISMA flow chart*.

additionally it gives more weight to those regions with larger sample size and less variability using inverse variance weights.

Results

A total of 51 studies were included in the qualitative synthesis and 48 were meta-analyzed (Table I) following exclusion of duplicate cohorts (4, 7, 9). Those studies reported the results of 3,285 patients treated with TEMS plus or minus Radiotherapy. Overall survival is summarized on the relevant forest plot (Figure 2). Thirty-five out of 48 studies (72.9%) used radiotherapy on a total of 1,069 patients (32.5%). Of those patients 952 (89%) received neo-adjuvant radiotherapy and the remaining 177 (11%) received adjuvant radiotherapy. Only 14 out of 48 studies reported chemotherapy and the total number of patients who received chemotherapy was only 115 out of 3,285 (3.5%). Considering the above numbers, the effect of chemotherapy was not possible to calculate independently and the effects of both adjuvant and neo-adjuvant radiotherapy were pooled together in the analysis.

Outcome: Overall Recurrence of disease

Overall effect size. Recurrence-free odds ratios were between 0 and 0.31. Table II and Figure 3 demonstrate the confidence intervals (CI) for the recurrence-free OR of all the 45 studies included in the final analysis, together with the weights assigned by the meta-analytic method. The overall effect size expressed in log-OR for recurrence-free was 2.16 (95%CI=1.89-2.44; p=0.000) which was statistically significant (Figure 4). This is translated into an OR of recurrence-free of 8.7 (95%CI=6.58-11.44). We detected a highly significant heterogeneity and the Cochran's Q Statistic variable was Q=145.2 on 44 d.f. (p=0.000). The variation in the log-odds-survival was attributed to heterogeneity and the I-sq statistic was 69.8%.

Table I. *Effect sizes, confidence intervals and weights of each study.*

Study		OR	LCI 95%	HCI 95%	Weight (%)
1	Allaix (30)	7.89	4.01	16	5.20
2	Araki (31)	30.00	14.30	3699	0.31
3	Arezzo (32)	28.00	1.67	469	0.30
4	Azimuddin (33)	46.00	2.79	757	0.30
5	Baatrup (34)	6.15	3.85	10	10.91
6	Bačić (35)	6.56	3.31	13	5.08
7	Bretagnol (36)	6	3	14	3.99
8	Caricato (37)	10	1	181	0.28
9	Dafnis (38)	24	1	405	0.30
10	De Graaf (39)	75	15	378	0.91
11	DeMartines (40)	11	2	60	0.82
12	Endreseth (41)	7	2	25	1.31
13	Farmer (42)	13	2	70	0.84
14	Flexer (43)	84	5	1365	0.31
15	Floyd (44)	106	7	1717	0.31
16	Ganai (45)	14	5	41	2.00
17	Guerrieri (4)	38	21	68	6.94
18	Heintz (46)	38	2	629	0.30
19	Jeong (47)	25	5	130	0.88
20	Kanehira (48)	25	11	54	3.86
21	Langer (49)	40	2	661	0.30
22	Lebedyev (50)	48	3	789	0.30
23	Lee-1 (51)	73	14	368	0.91
24	Lee-2 (52)	35	7	179	0.89
25	Lev-Chelouche (53)	58	4	949	0.30
26	Levic (54)	9	4	18	4.71
27	Lezoche (14)	8	4	15	6.32
28	Lloyd (55)	4	2	10	3.24
29	Marks (56)	27	5	140	0.88
30	Maslekar (57)	104	6	1685	0.31
31	Meng (58)	30	2	501	0.30
32	Mentges (59)	196	12	3156	0.31
33	Morino (60)	214	13	3443	0.31
34	Nakagoe (28)	150	9	2420	0.31
35	Neary (61)	38	2	629	0.30
36	Palma1 (62)	46	3	757	0.30
37	Palma2 (63)	8	3	20	2.43
38	Perez (64)	5	2	10	4.32
39	Serra-Aracil (65)	12	5	32	2.55
40	Steele (66)	22	4	115	0.87
41	Stipa (13)	4	3	6	14.20
42	Suzuki (67)	28	2	469	0.30
43	Tsai (68)	15	7	33	3.76
44	Turler (15)	1	1	3	4.61
45	Verseveld (27)	94	6	1525	0.31
46	Whitehouse (69)	84	5	1365	0.31
47	Winde (70)	23	4	120	0.87
48	Zacharakis (71)	56	3	918	0.30

Table II. *Effect sizes, confidence intervals and weights of each study.*

Study		ES	[95% Confidence Interval]		% Weight
1	Allaix 2009 (30)	0.23	0.132	0.405	3.43
2	Araki 2003 (31)	0.02	0.004	0.072	1.98
3	Arezzo 2015 (32)	0.08	0.01	0.588	1.27
4	Azimuddin 2000 (33)	0.10	0.022	0.406	1.91
5	Baatrup 2008 (34)	0.22	0.145	0.34	3.65
6	Bačić 2014 (35)	0.15	0.076	0.308	3.18
7	Bretagnol 2007 (36)	0.18	0.086	0.386	3.08
8	Dafnis 2004 (38)	0.20	0.044	0.913	1.81
9	De Graaf 2002 (39)	0.09	0.037	0.197	2.93
10	DeMartines 2001 (40)	0.09	0.012	0.704	1.25
11	Endreseth 2005 (41)	0.15	0.035	0.682	1.85
12	Flexer 2013 (43)	0.02	0.003	0.177	1.31
13	Floyd 2005 (44)	0.08	0.029	0.226	2.59
14	Ganai 2006 (45)	0.10	0.036	0.279	2.57
15	Guerrieri 2014 (4)	0.04	0.028	0.071	3.57
16	Heintz 1998 (46)	0.46	0.175	1.214	2.68
17	Jeong 2009 (72)	0.04	0.005	0.295	1.3
18	Kanehira 2014 (48)	0.04	0.018	0.092	2.96
19	Langer 2003(49)	0.11	0.026	0.479	1.89
20	Lebedyev 2009 (50)	0.04	0.006	0.322	1.29
21	Lee 2003 (51)	0.09	0.038	0.203	2.93
22	Lee 2007 (52)	0.09	0.028	0.296	2.31
23	Lev-Chelouche 2000 (53)	0.16	0.056	0.46	2.53
24	Levic 2012 (54)	0.50	0.031	8.065	0.79
25	Lezoche 2005 (14)	0.05	0.021	0.129	2.81
26	Lloyd 2002 (55)	0.50	0.031	8.171	0.79
27	Marks 2003 (56)	0.04	0.005	0.273	1.3
28	Maslekar 2007 (57)	0.11	0.042	0.267	2.77
29	Meng 2004 (58)	0.07	0.009	0.543	1.27
30	Mentges 1996 (59)	0.03	0.01	0.1	2.36
31	Morino 2011 (60)	0.24	0.152	0.393	3.57
32	Nakagoe 2002 (28)	0.01	0.002	0.097	1.32
33	Neary 2003 (61)	0.50	0.03	8.297	0.78
34	Palma 2004 (62)	0.05	0.006	0.337	1.29
35	Palma 2009 (63)	0.06	0.015	0.261	1.94
36	Perez 2014 (64)	0.21	0.098	0.451	3.06
37	Serra-Aracil 2008 (65)	0.18	0.086	0.386	3.08
38	Steele 1996 (66)	0.10	0.022	0.406	1.91
39	Stipa 2012 (13)	0.44	0.309	0.627	3.74
40	Suzuki 2005 (67)	0.50	0.03	8.411	0.78
41	Turler 1997 (15)	0.12	0.035	0.381	2.29
42	Verseveld 2015 (27)	0.09	0.033	0.259	2.58
43	Whitehouse 2007 (69)	0.24	0.109	0.508	3.05
44	Winde 1996 (70)	0.04	0.006	0.322	1.29
45	Zacharakis 2005 (71)	0.40	0.176	0.908	2.96
	Pooled effect size	0.115	0.087	0.152	100

Comparison of recurrence-free OR in those studies which used neo+/-adjuvant treatment in more than 20% of the cases versus those which used in less than 20%. We identified as the possible source of heterogeneity whether the use of neo+/-adjuvant treatment in more or less than 20% of the cases for each study. In those studies where less than 20% of patients received neo+/-adjuvant treatment, the overall recurrence-free odds ratio was 8.0 (95%CI=6.1-10.3, p=0.000) (Figure 5). A significant heterogeneity was detected as the Cochrane Q Statistic was Q=71.9 on 35 d.f.

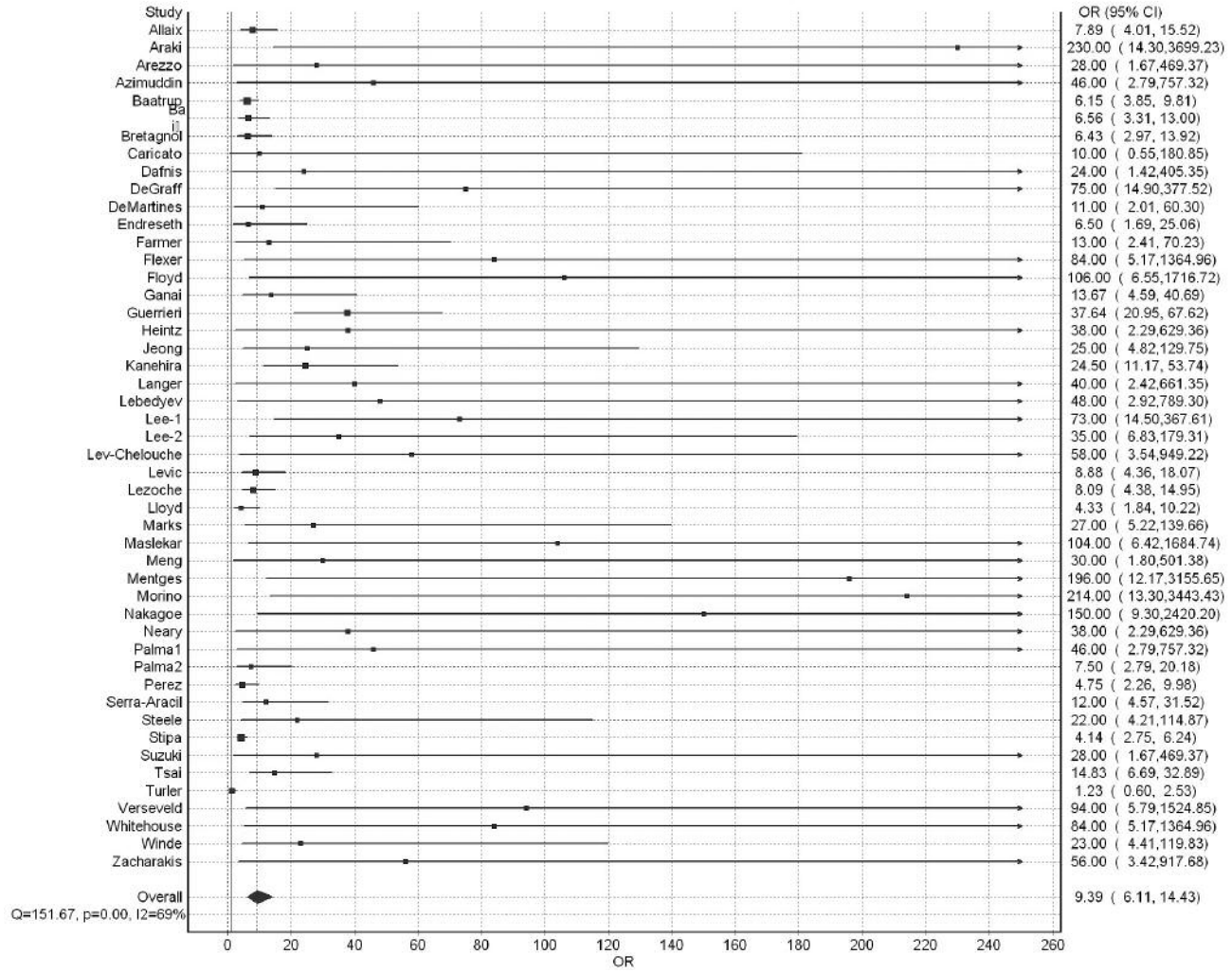

Figure 2. *Survival forest plot*.

(p=0.000) and I-sq=51.3%. On the other hand, those studies where more than 20% of patients received neo+/-adjuvant therapy had an overall recurrence-free OR of 11.3 (95%CI=4.7-26.9; p=0.000), with a highly significant heterogeneity (I-sq=89.1% and p=0.000). This level of heterogeneity was attributed to a single study (Stipa *et al*., 2012 (13)) (Figure 6). By removing this study, (Figure 7) the heterogeneity reduced to a statistically non-significant level (Q=13.9 on 7 d.f., p=0.05, I-sq=49%). Excluding Stipa *et al*. 2012, those studies with over 20% of patients receiving neo+/-adjuvant therapy had an overall recurrence-free OR of 14.0 (95%CI=8.1-24.0; p=0.000).

For studies including less than 20% of patients on neo+/-adjuvant treatment, more benefit is seen with cohorts consisting of less than 10% pT3 tumours with a pooled effect size of OR=10 (95%CI=7.1-14.1; p=0.000) and low heterogeneity (Q=38 on 22 d.f. p=0.02). Nevertheless, in cohorts with more than 10% pT3 tumours, the pooled effect size was OR=5.6 (95%CI=4.1-7.7; p=0.000) with statistically non-significant heterogeneity (Q=20 on 12 d.f. p=0.07).

On multivariate meta-regression, the effect of the percentage of patients who received neo+/-adjuvant treatment on the likelihood of non-recurrence was statistically significant for studies with pT3 tumours in more than 10% of the cohort (OR=1.012; 95%CI=1.001-1.022; p=0.03). In contrast, this effect was not statistically significant for those studies with less than 10% of pT3 cases (OR=0.996; 95%CI=0.98-1.01; p=0.50).

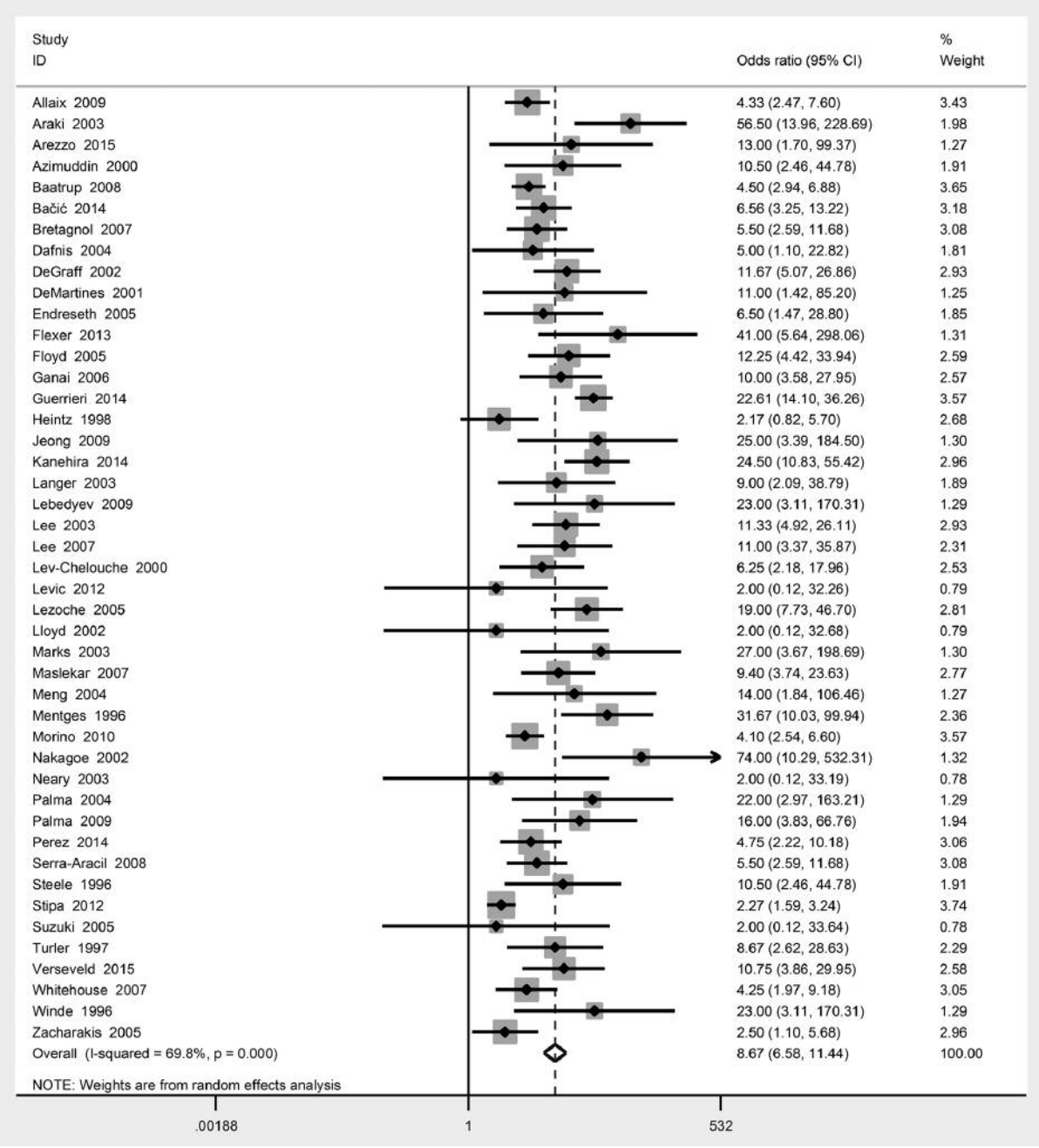

Figure 3. *Odds Ratios for recurrence-free along with confidence intervals and weights.*

Comparison of recurrence-free odds in those studies which used neo+/-adjuvant treatment in more than 20% of the cases and the cohorts consisted of less than 10% pT3 tumours versus those which consisted with more than 10% of pT3 tumours. Studies with more than 10% pT3 and more than 20% patients received neo+/-adjuvant therapy: The overall effect size was significant (OR=12.3; 95%CI=3.4-44.5, p=0.000) although the highly significant heterogeneity that was detected required further inspection and stratification of the studies by effect size (Cochran Q=70 on 4 d.f. p=0.000 and I-sq=94%) (Figure 8). The source of this heterogeneity was due to a single study, Stipa *et al*. 2012. Excluding this study (Figure 9), we found a completely homogeneous effect of neo+/-adjuvant treatment on recurrence-free survival with an OR of 20.2 (95%CI=13.8-29.6, p=0.000). The heterogeneity was non-significant (Q=2.18 on 3 d.f., p=0.54 and 0% of the variation attributable to heterogeneity).

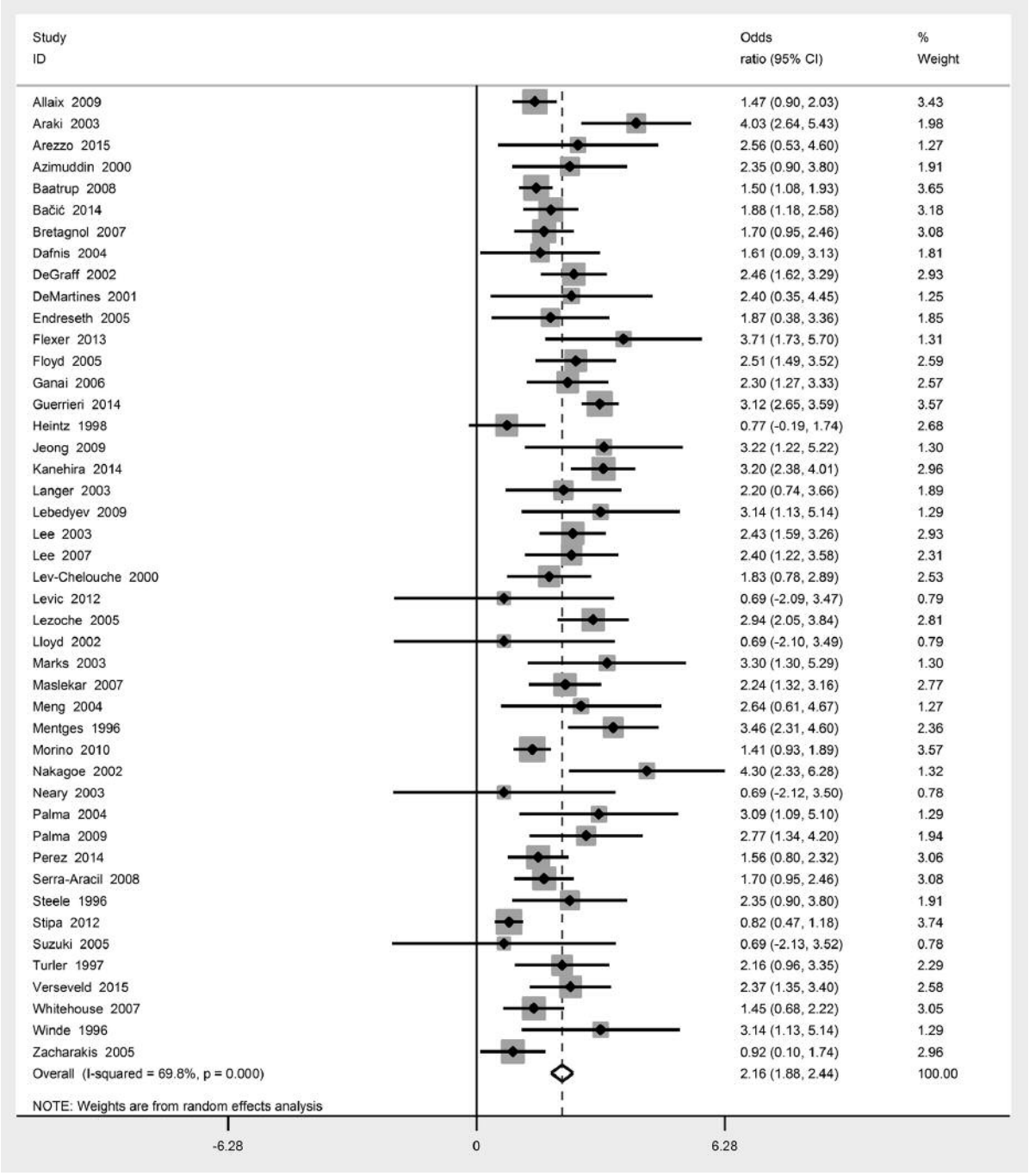

Figure 4. *Log-OR for recurrence-free*.

Studies with less than 10% pT3 AND more than 20% patients received neo+/-adjuvant therapy: The overall (pooled) effect size was statistically significant (OR=7.6; 95%CI-=3.8-44.8, p=0.000). No heterogeneity was present and the Cochran Q statistic was 3.4 (p=0.33) with I-sq=12% (Figure 10).

Outcome: Cancer-Related Survival

Overall effect sizes. Table I and Figure 2 show the confidence intervals for the overall (pooled) effect size for the 48 studies included in the final qualitative analysis, together with the assigned weights. The overall log-odds

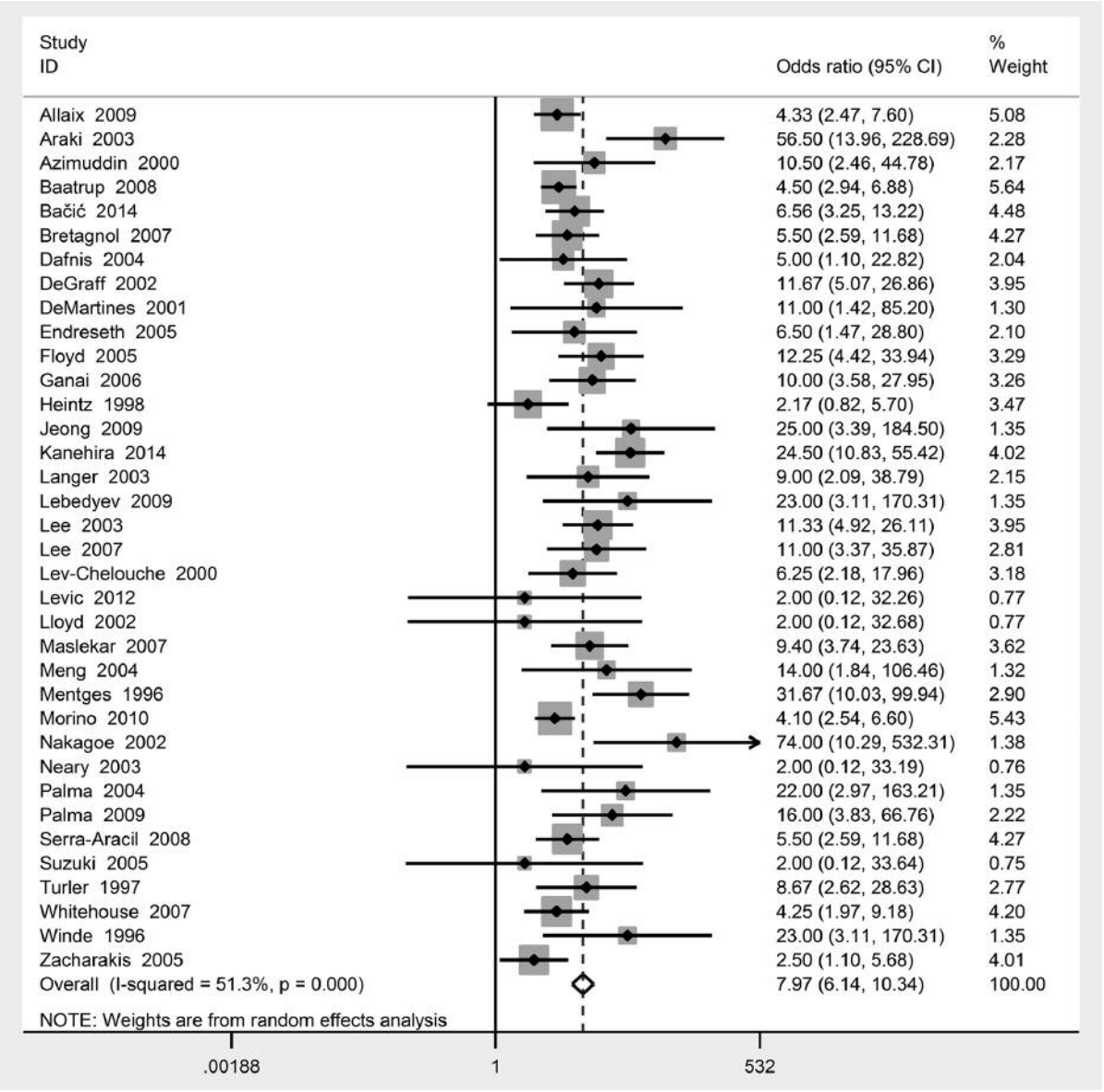

Figure 5. *Recurrence-free OR for studies where less than 20% of patients that received neo+/-adjuvant treatment.*

ratio for survival was 2.21 (95%CI=2.1-2.4, p=0.000). This translates into an odds ratio (OR) for survival of 9.39 (95%CI=6.1-14.4). Cochran's Q heterogeneity statistics variable was Q=151.7 on 47 degrees of freedom (d.f.) (p=0.000, I-sq=69%,) which was translated to a highly significant heterogeneity. We identified two possible sources of heterogeneity. Firstly, whether the study used neo+/-adjuvant treatment in more or less than 35% of patients and secondly, whether the cohort of the study included more or less than 10% of pT3 stage specimens. A significant interaction between these two factors was also confirmed.

Comparison of survival OR in those studies which used neo+/-adjuvant treatment in more than 35% of the cases versus those which used in less than 35%. We identified 34 studies which used neo+/-adjuvant treatment in less than 35% patients (Figure 11a). The overall (pooled) OR for survival on this group was 12.7 (95%CI=9.6-16.6; p=0.000) and the Cochran's Q heterogeneity statistic was Q=102.1 on 33 d.f. (p=0.000). In contrary, 13 studies reported that more than 35% of their cases received neo+/-adjuvant treatment (Figure 11b). On that group, survival OR was 8.1 (95%CI=6.7-9.8; p=0.000) and Cochran's Q Statistic

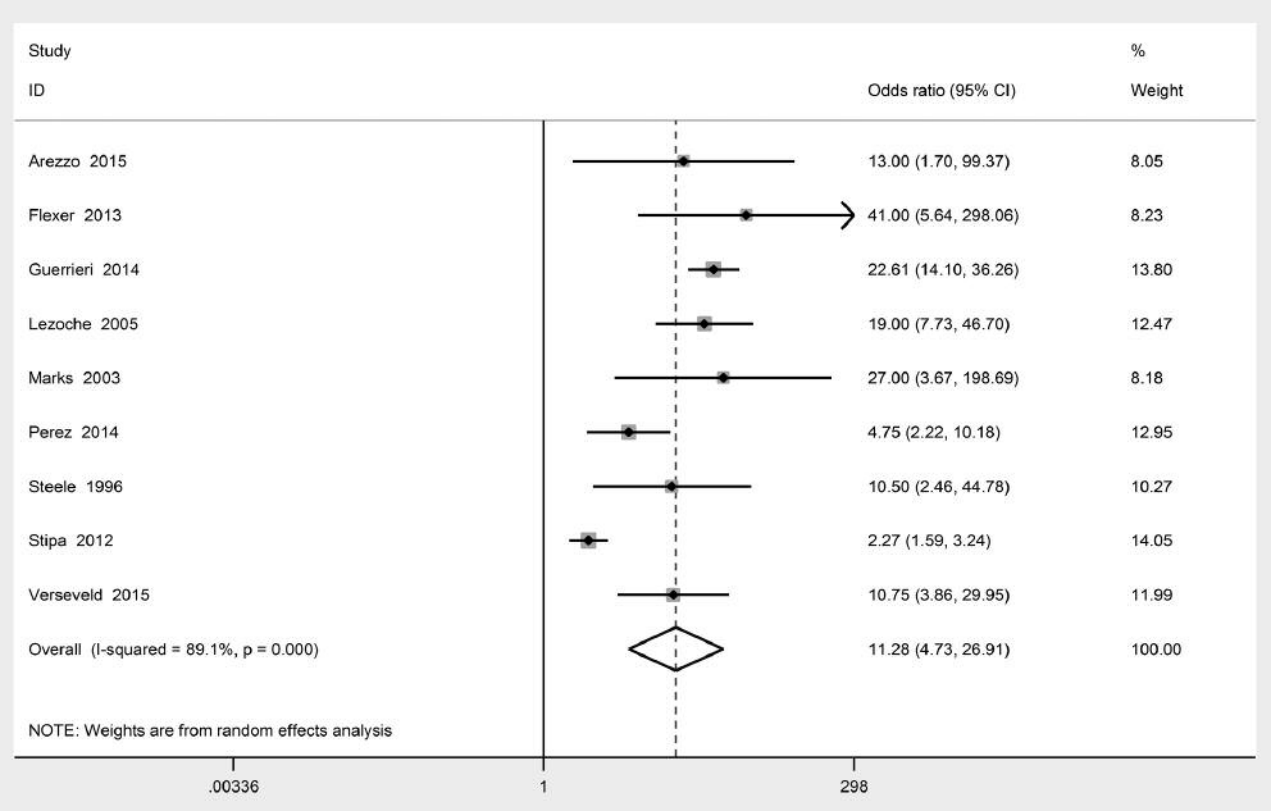

Figure 6. *Recurrence-free OR for studies where more than 20% of patients that received neo+/-adjuvant treatment (including Stipa et al., 2012 (13)).*

variable was Q=44.3 on 12 d.f. (p=0.000). This indicates that there is slightly better survival OR ratio for studies where 35% or more of the patients received neo+/-adjuvant treatment. The forest plots of these two groups are summarized in Figures 3a and 3b.

On univariate meta-regression neither the high percent of neo-adjuvant Rx (Odds=1.11; 95% CI=0.50-2.5; p=0.78) nor the high percent of patients with T3-stage (Odds=0.71; 95%CI= 0.34-1.5; p=0.34) significantly affect the odds of survival (Table III). Beyond the effects of the neo+/-adjuvant treatment and the percentage of pT3 stage cases, the OR of survival are 11.7-fold for those studies which offer neo+/-adjuvant treatment in more than 35% of the cases (95%CI=3.1-44; p=0.001).

Comparison of survival in those studies the cohorts of which had more than 10% pT3 and used neo+/-adjuvant treatment in more than 35% of the cases versus those which used in less than 35%. In contrary to the univariate meta-regression, multivariate meta-regression analysis concluded to a statistically significant survival benefit from neo+/-adjuvant treatment in the presence of pT3 tumours (p=0.001). More specifically, from the studies with cohorts that included more than 10% of pT3 specimens, those which offered neo+/-adjuvant treatment in more than 35% of the cases demonstrated higher OR of survival. To illustrate this significant interaction between pT3 stage and neo+/-adjuvant treatment, we stratified the studies into three groups according to the percentage of pT3-tumours. 17 studies with no pT3 specimens at all (Group 1), 12 studies with 1% to 10% pT3 specimens (Group 2) and the 19 studies with more than 10% pT3 specimens (Group-3). On meta-regression analysis, the overall OR for survival was statistically non-significant for Group-1 and Group-2 (p=0.11) but highly significant for Group-3 where the OR for survival was OR=3.9 (95%CI=1.3-12.0; p=0.02).

The overall pooled OR of survival for all these 19 studies was 8.1 (95%CI=4.1-15.8) with a Cochran's Q heterogeneity variable of Q=94 (18 d.f.). Of those 19 studies, 8 (42.1%) studies used neo+/-adjuvant treatment in over 35% of the cases, where the overall pooled OR of survival was 20.4 (95%CI=8.2-50.7), and the Cochran's Q value was Q=21.4 (10 d.f.). The only source of heterogeneity was found by Lezoche *et al*. (14). After removing this study, the remaining cohorts gave a homogeneous profile with odds of survival of 32.2 (95%CI=16.3-63.5) and Cochran's Q Statistic of Q=8.4 p=0.21. In the rest 11 studies neo+/-

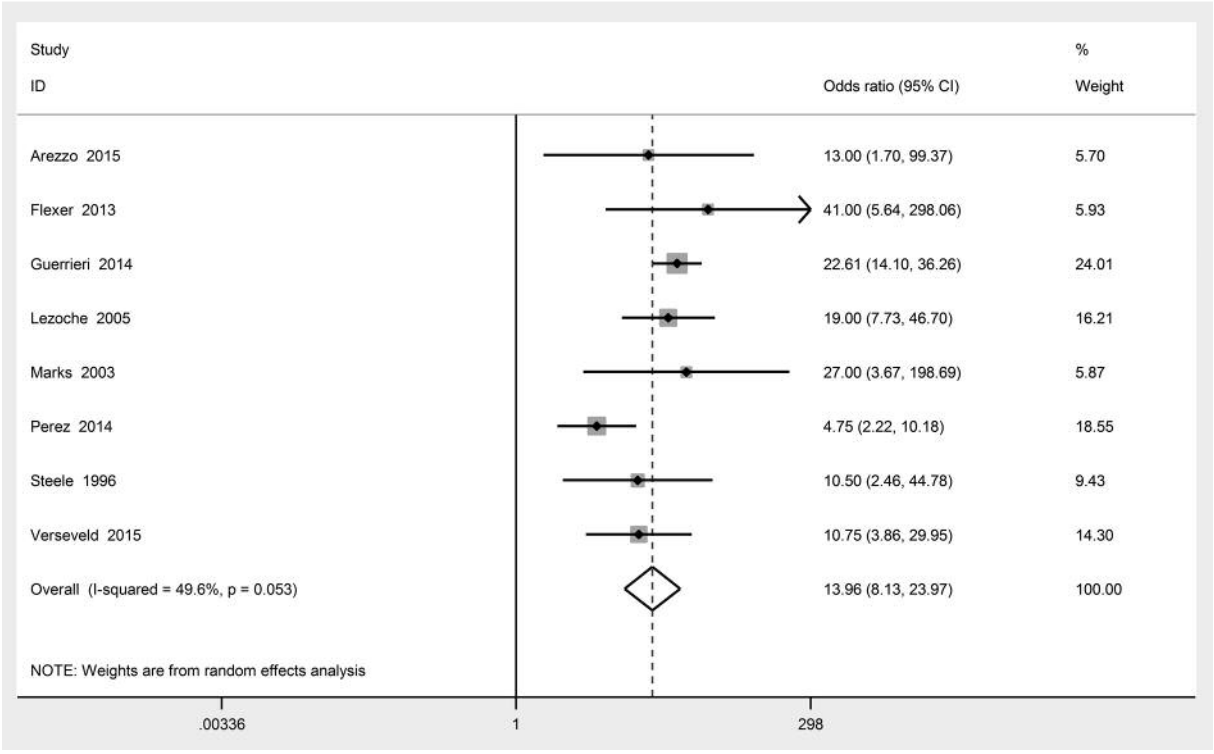

Figure 7. *Recurrence-free OR for studies where more than 20% of patients that received neo+/- adjuvant treatment (excluding Stipa et al. 2012 (13)).*

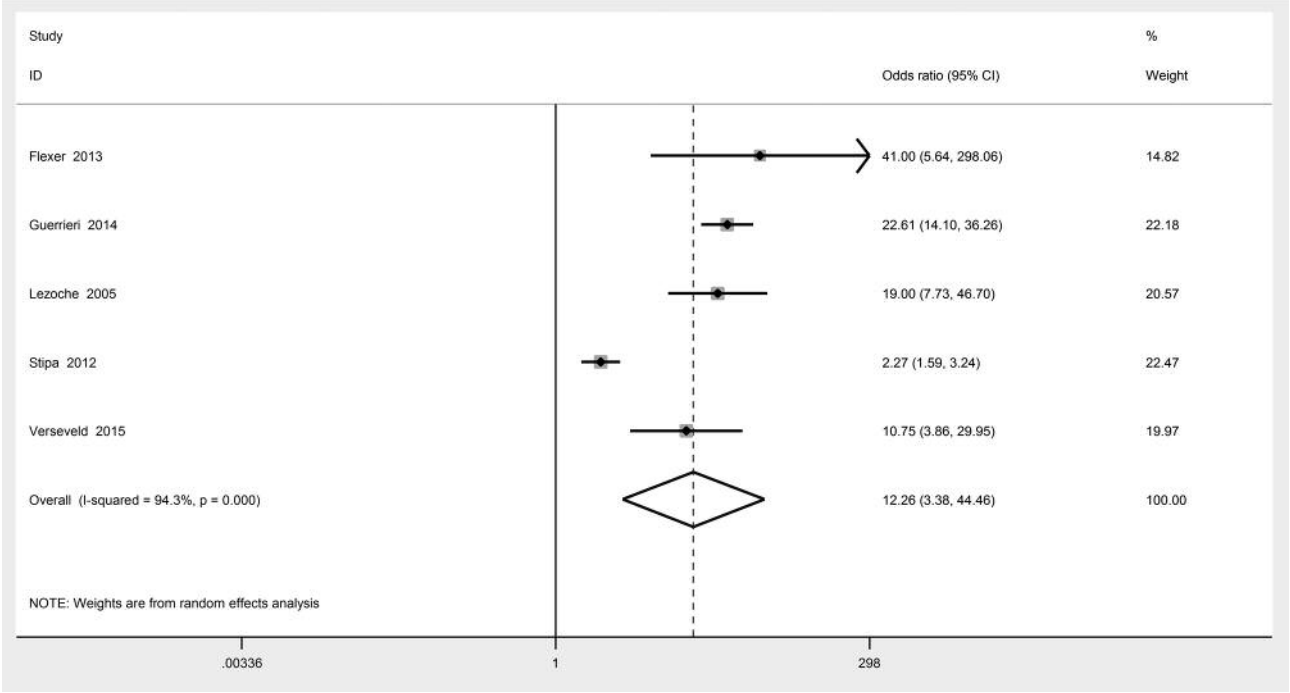

Figure 8. *Overall effect size of recurrence-free OR for studies with more than 10% pT3 and more than 20% patients received neo+/-adjuvant therapy (including Stipa et al. 2012 (13)).*

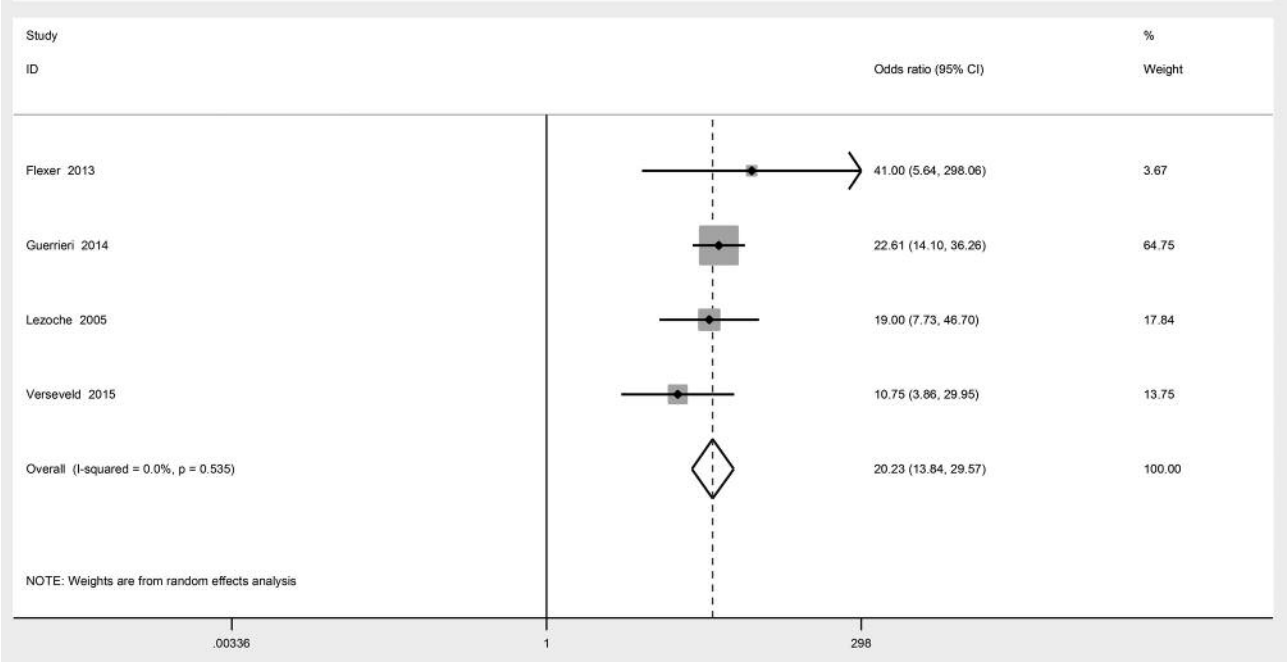

Figure 9. *Overall effect size of recurrence-free OR for studies with more than 10% pT3 and more than 20% patients received neo+/-adjuvant therapy (excluding Stipa et al. 2012 (13)).*

Table III. *Results of the univariate meta-regressions for the overall log-odds of survival.*

	Log odds survival	95%CI		*p*-Value
Age	–0.01	–0.08	0.07	0.85
Male patients	–0.36	–0.86	0.14	0.15
Distance from anal verge (cm)	0.04	–0.18	0.27	0.69
Tumor size	0.00	–0.02	0.01	0.60
Hospital stay (days)	–0.05	–0.26	0.15	0.61
Follow up (months)	–0.01	–0.03	0.01	0.33
pT1 cases	0.003	–0.01	0.02	0.62
pT2 cases	–0.01	–0.03	0.01	0.25
pT3 cases	–0.03	–0.07	0.01	0.18
pt4 cases	–0.10	–0.35	0.15	0.43
Percentage pT3-stage above 10%	–0.34	–1.1	0.38	0.34
Neo+/-adjuvant chemo radiotherapy	–0.001	–0.01	0.01	0.84
Percentage of neo+/-adjuvant chemo radiotherapy >35%	0.11	–0.68	0.90	0.78
Completion Surgery	–0.0044	0.10	1.86	0.07

adjuvant treatment was used in less than 35% of the cases. The overall pooled odds of survival for those 11 studies was 5.4 (95%CI=2.9-10.1) with a Cochran's heterogeneity statistic of Q=34.7 (10 d.f.). Turler *et al*. (15) study was identified as the only source of heterogeneity and, after removing it, the rest gave a homogeneous profile with odds of survival of 6.4 (95%CI=4.1-10.1) and a Cochran's Q Statistic of Q=16.5 p=0.06. For comparison, both forest plots (including the heterogeneous ones) are presented in Figure 12a and b.

Discussion

The introduction of local excision (either transanal (TAR), TEMS or TAMIS) for selected rectal cancers offered an alternative to patients who were either high risk for complications or refused to accept the option of a temporary or permanent stoma or the risk of sexual dysfunction. The limiting factor has been the higher risk of recurrence when surgery is the only modality (16). At the same time

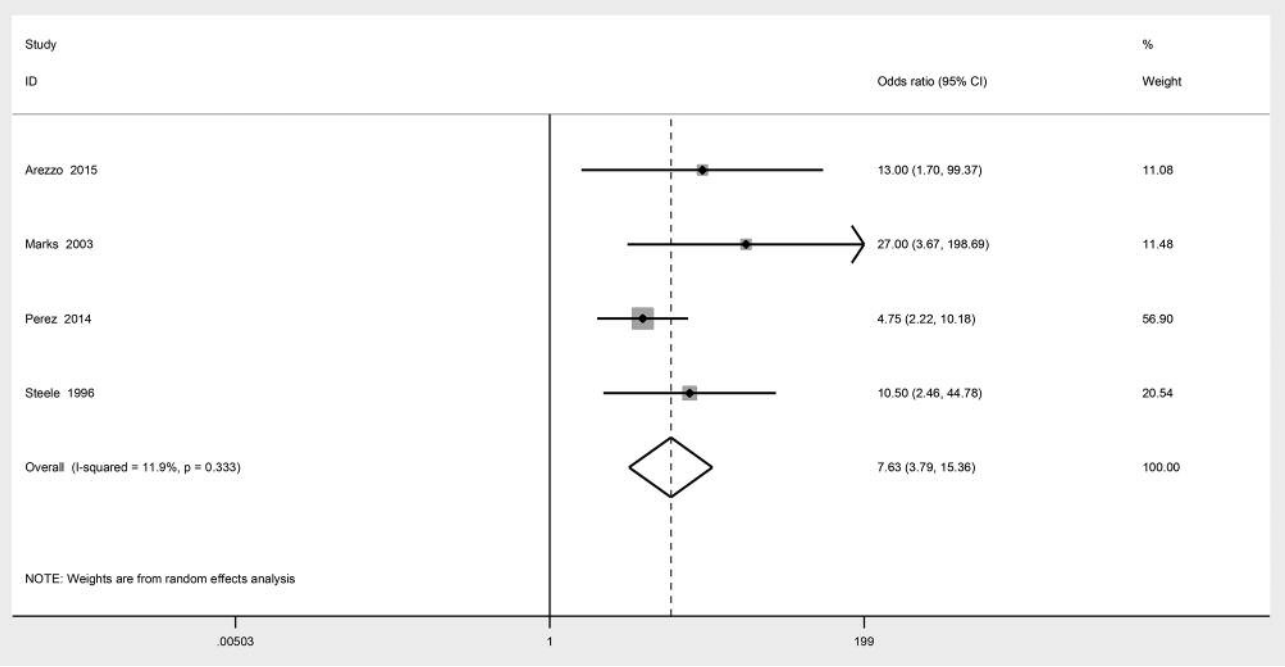

Figure 10. *Overall effect size of recurrence-free OR for studies with less than 10% pT3 and more than 20% patients received neo+/-adjuvant therapy.*

radiotherapy and chemotherapy are not indicated in the so far guidelines for early tumours T1 and T2, which are by default the primary target group for TEMS excision (17). Needless to say, the toxicity of radiotherapy and chemotherapy need to be taken into account and also communicated to the patient prior to any treatment decision, and that toxicity needs to be weighed against the risks of radical TME surgery (18). Last but not least, there has to be evidence of benefit of adjuvant/neo-adjuvant radiotherapy and/or chemotherapy. So far there is evidence for benefit of neoadjuvant radio-chemotherapy only for T3 tumours which had radical TME surgery and the benefit is primarily on local recurrence, and possibly on survival (19-21).

At present even though local excision, in the form of TAR, TEMS or TAMIS, is advised as one of the options to consider in the guidelines of ESMO, there is no guidance for adjuvant treatment in that setting (22). Our study aimed to investigate whether it is possible to isolate the effect of adjuvant radiotherapy in the context of TEMS for rectal cancer.

Several meta-analyses have been performed so far on the oncological outcomes of TEMS but none has reported on adjuvant radiotherapy. Wu *et al*. looked into T1 tumours and reported TEMS to have a similar 5 year survival between TEMS and TME with a lower mortality and complications rate for TEMS , which however carried a higher recurrence risk (12% for TEMS *vs*. 0.5% for TME) (23).

Sgourakis *et al*. (24) looked into both T1 and T2 tumours and concluded that TEMS had a higher local recurrence than TME but there was no difference in survival.

Kidane *et al*. (25) found that local resection of several techniques had higher local recurrence and lower overall survival but they attributed the findings to bias of the studies towards more adverse lower rectal tumours in the local resection group.

Lu *et al*. (6) also found that for T1 tumours there were no differences in survival and disease-free survival between TEMS and TME although there was a higher recurrence rate for TEMS.

Sajid *et al*. (26) examined T1 and T2 tumours and found similar survival and distal recurrence between TEMS and TME but TEMS had a higher local recurrence.

All the above referenced meta-analyses have similar results with regards to the oncological outcomes of TEMS for T1 or T1+T2 tumours. However, none of these report on the potential role of adjuvant radiotherapy, presumably because of inadequate existing data.

The possibility of radiotherapy as adjuvant treatment after TEMS is important because in cases of unfavourable histology (higher than expected stage, adverse histological factors) then the only other option is "completion surgery", *i.e*. the performance within a short time of radical TME as means of preventing local recurrence (5, 27, 28). If it was shown that in those cases chemo-radiotherapy could be used instead, this would be an additional beneficial option for those patients.

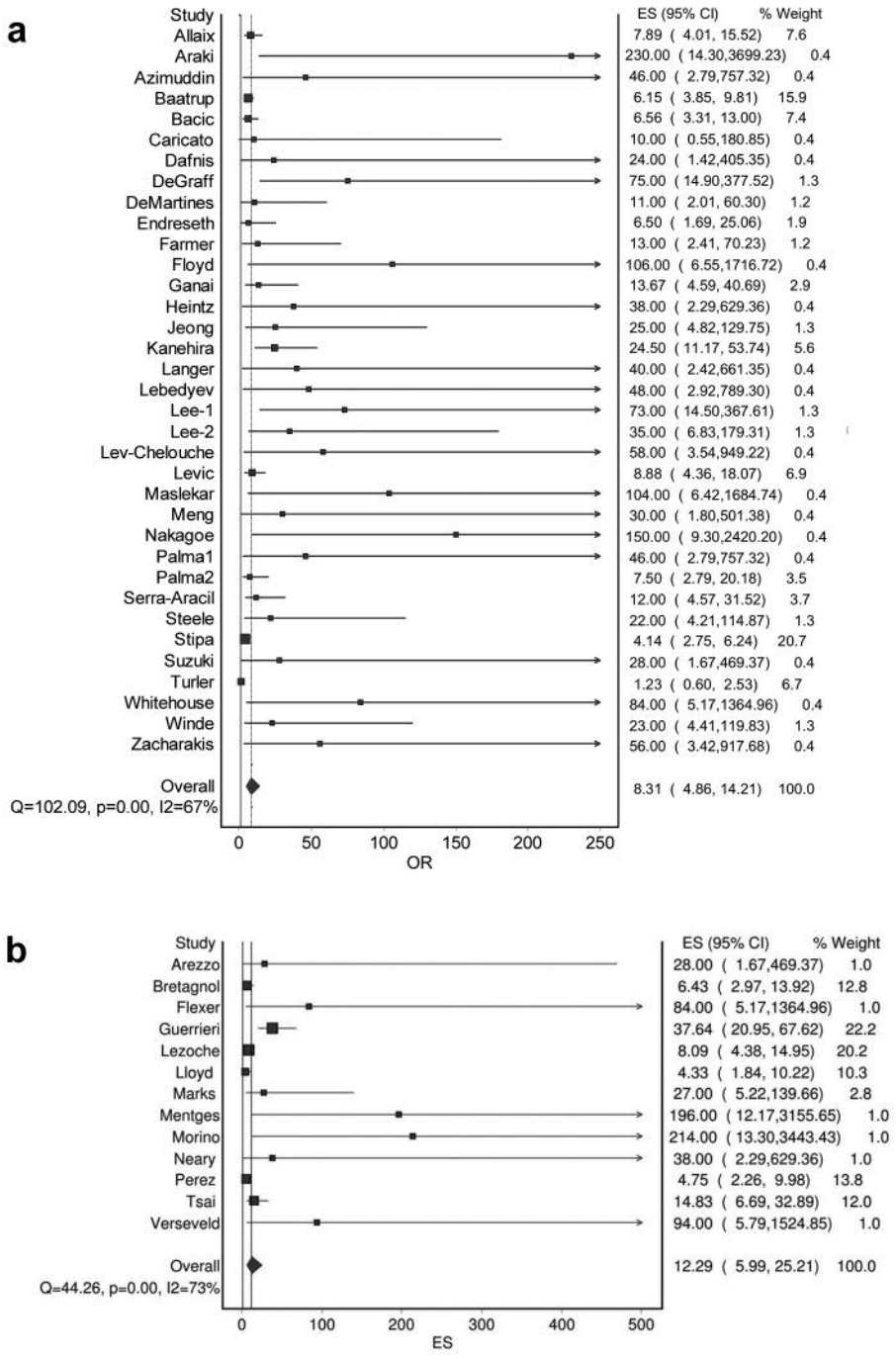

Figure 11. *Forest plot for survival OR in studies with neo+/-adjuvant treatment a) in less than 35% of the cohorts, b) in 35% or more of the cohort cases.*

Our systematic review aimed to investigate the effect of radiotherapy as adjuvant treatment to TEMS surgery and we believe has produced some interesting findings.

Our review was limited by the quality of the existing studies, few of which were randomised and there was a great degree of heterogeneity which we eliminated as much as possible with valid statistical methods.

On first analysis, there was no overall effect of radiotherapy on survival, however this changed when we analyzed studies according to the extent of adjuvant treatment.

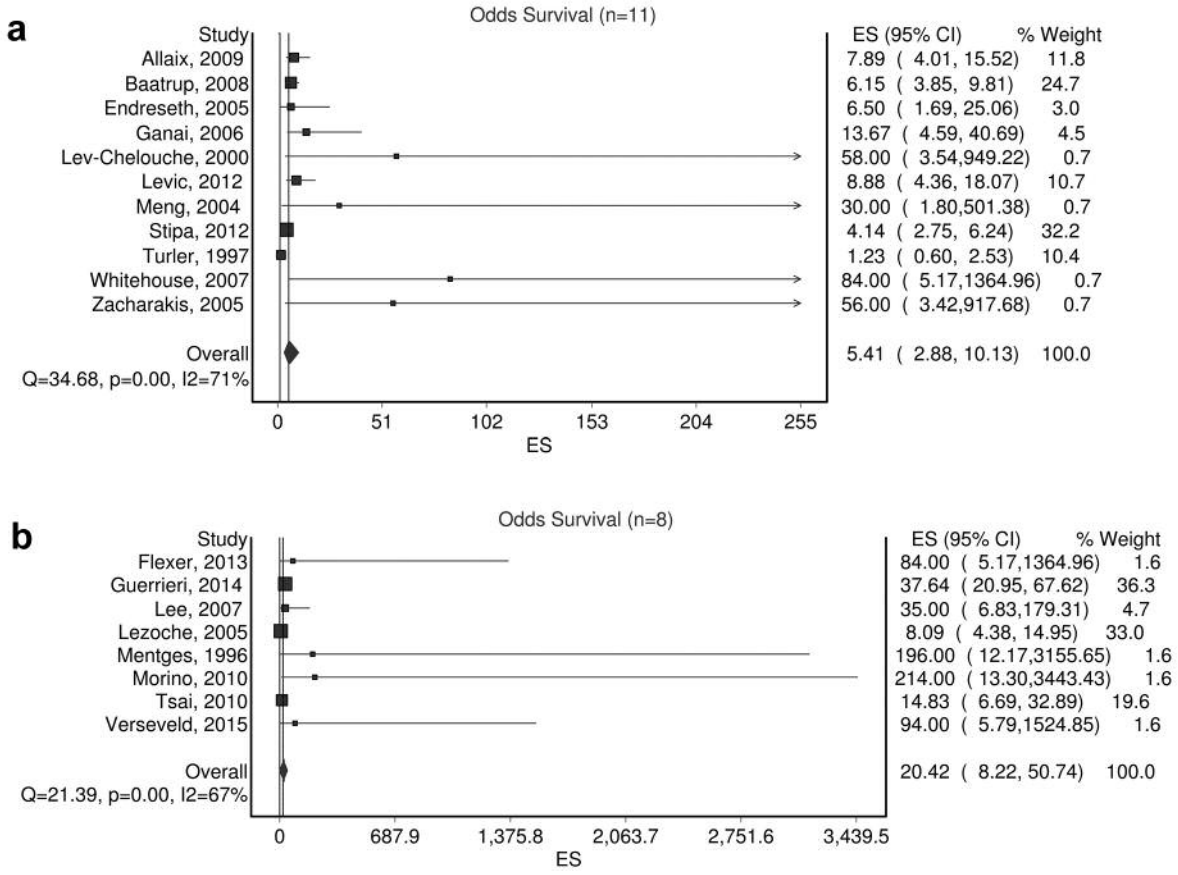

Figure 12. *Forest plot for survival in studies having over 10% of pT3 stage tumours and a) 35% or less neo+/-adjuvant treatment or b) more than 35% in neoadjuvant Rx.*

There was a positive effect of radiotherapy regardless of stage if it was used in more than 35% of the patients. Interestingly this result persisted even when there was a higher percentage of T3 tumours in the study. T3 is a stage not normally indicated for TEMS and we can only hypothesize that those tumours were either discovered with a higher than expected histology post-resection or were treated that way because of fitness issues of the patients. It is interesting that survival is positively affected by radiotherapy uniformly, to our knowledge this is the first time that radiotherapy is shown to have a survival benefit on rectal cancer in this context. Of course, we appreciate that the methodology of a meta-analysis with inclusion of many non-randomized studies may carry a degree of bias and needs further testing with prospective randomised trials designed to address the specific issue.

A similar effect of radiotherapy was found on cancer recurrence. The consistency of the effect on both recurrence and survival decreases the possibility of a chance finding.

Are our findings capable of producing recommendations for change of strategy in treatment of rectal cancers by TEMS and radio-chemotherapy? No, not at this stage of research. There remains a plethora of unanswered questions with regards to tumor size, differentiation, and other adverse histological factors. There are also new directions of research into the effect of molecular factors in recurrence: we recently presented our finding that wild-type KRAS may be a favourable factor for decreased risk of local recurrence after TEMS surgery for rectal cancer (29). However, the effect is strong enough to motivate us to propose randomised controlled trials for further exploration.

Conflicts of Interest

None declared.

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