ELECTRONIC WEBAPPENDIX

SUPPLEMENTAL MATERIAL

Factors influencing local regrowth after watch-and-wait for clinical complete response following chemoradiotherapy in rectal cancer: an individual participant data meta-analysis (InterCoRe consortium)

Chadi et al.

Search terms (taken directly from Dossa et al.(1))

MEDLINE

1. exp Combined Modality Therapy/ or Chemoradiation.ab,ti. or chemoradiotherapy.ab,ti. or chemotherapy.ab,ti. or radiation therapy.ab,ti. or radiotherapy,ab.ti. or (neoadjuvant adj3 (treatment or therap*)).mp. or (complet* adj3 respon*).ab,ti.
2. Rectal neoplasms/ or ((cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or malignan*) adj4 (rectum or rectal)).ti,ab.
3. Watchful waiting/ or (wait* adj3 (watch* or see)).ab,ti. or ((Avoid* or without) adj5 (operat* or surger* or resect* or excision*)).ab,ti. or ((Nonoperativ* or "non operative" or "non surgical" or nonsurgical or observation* or conserv*) adj4 (strateg* or approach* or treatment* or manage*)).ab,ti.
4. Combine 1, 2 and 3

Embase

1. multimodality cancer therapy/ or Chemoradiation.ab,ti. or chemoradiotherapy.ab,ti. or chemotherapy.ab,ti. or radiation therapy.ab,ti. or radiotherapy,ab.ti. or (neoadjuvant adj3 (treatment or therap*)).mp. or (complet* adj3 respon*).ab,ti.
2. exp rectum tumor/ or ((cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or malignan*) adj4 (rectum or rectal)).ti,ab.
3. Watchful waiting/ or (wait* adj3 (watch* or see)).ab,ti. or ((Avoid* or without) adj5 (operat* or surger* or resect* or excision*)).ab,ti. or ((Nonoperativ* or "non operative" or "non surgical" or nonsurgical or observation* or conserv*) adj4 (strateg* or approach* or treatment* or manage*)).ab,ti.

4. 1 and 2 and 3

From the main searches, we took a cut of the identified studies from 01 Jan 2016 to 05 May 2017, and added these to the studies identified by Dossa et al.(1)

Data harmonisation

One investigator (SC), supported by two co-authors (AH-G, SW), approached chief investigators for identified studies. We sought to collect variables in the following domains: patient characteristics, baseline pre-treatment tumour characteristics, doses and types of chemo-radiotherapy regimens, decision for W&W, and the subsequent oncological events (and their dates) of local regrowth, distant events, last follow-up or death. Data on salvage surgery and post-salvage outcome were additionally sought. For pragmatic reasons, we did not collect data on pre-treatment imaging and W&W surveillance regimens.

Fully anonymised data were shared in encrypted files and transferred under centre-level governance arrangements. Clean-up checks were undertaken (e.g. dates) and study investigators queried as appropriate. The following data fields were harmonised: (i) converted calendar dates to UK format; (ii) performance status converted to ECOG/WHO scores 0 to 5 – thus Karnofsky scoring converted 100 to 90 as ECOG/WHO 0; 80 to 70 as 1; 60 to 50 as 2; 40 to 30 as 3; 20 to 10 as 4; and 0 as 5; (iii) corrections to distance from anal verge (AV) by adding, if reported as anorectal junction distance, 2.0 cm if male, and 1.5 cm if female. Pre-clinical staging (cT and cN) were as per 7th Edition of AJCC,(2) with cN1 and cN2 combined as cN+.

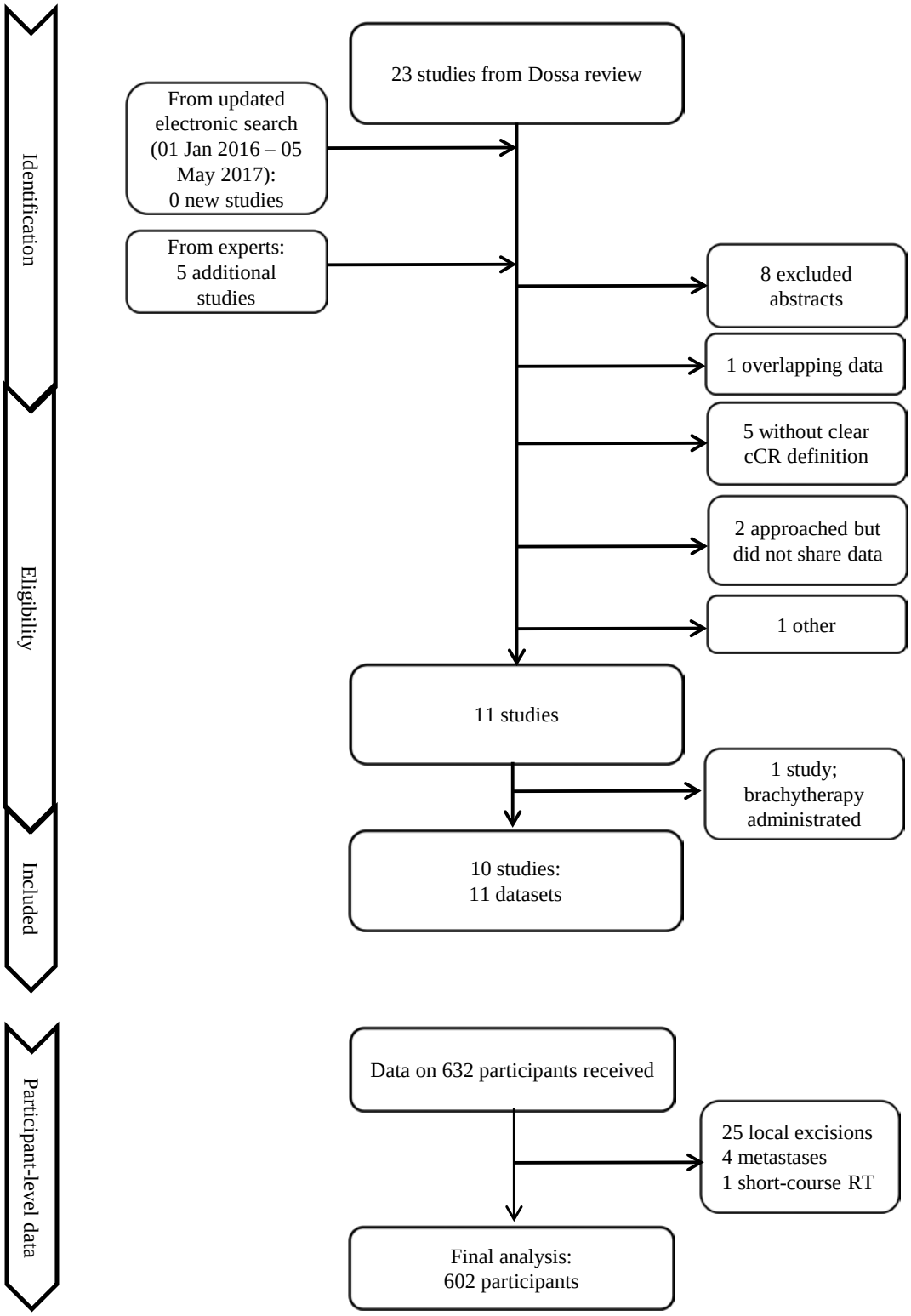


Figure S1 Flow diagram of the search, study identifications, and individual participant level exclusions

Reasons from not including studies

We initially reviewed the 23 articles included in the Dossa et al.(1) systematic review **(Figure S1)**. We immediately excluded eight unpublished studies.(3-10) We identified nine studies, which might have been eligible but were not included for several reasons listed in **Table S1**. We identified five additional published studies from experts, not included in the Dossa review(1) – we obtained data from three(11-13) (which were neither in the Dossa(1) nor Dattani(14) review) but excluded a further two(15, 16) (both in the Dattani(14) review but not the Doss review(1)).

Table S1 Reasons for not including published studies

Authors, year, institute	No. of patients	In Dossa review(1)	In Dattani review(14)	Comments
Perez et al. 2012 Sao Paulo, Brazil(17)	16	Yes	Yes	The lead author on this study has confirmed that the data published in this study stands alone from the papers from Habr-Gama 2013(18) and Habr-Gama 2014,(19) and thus was correctly included the Doss and Dattani review. For the present analysis, these data were included in the Sao Paula shared data files
Not meeting cCR definition				
Nakagawa et al. 2002, Camargo Cancer Hospital, Sao Paulo, Brazil(16)	10	No	Yes	We judged that the cCR not clearly defined. We did not include this study in our selection bias sensitivity analysis, as we deemed the local regrowth rates > 80% as extreme outlier and not applicable to contemporary practice.
Kusters et al. 2016 Oxford, UK(20)	11	Yes	Yes	We judged that the cCR not clearly defined. We included this study in our selection bias sensitivity analysis.
Sanchez-Loria et al. 2016, Surgical Oncology Instituto Alexander Fleming, Buenos Aires, Argentina(21)	62	Yes	Yes	We judged that the cCR not clearly defined. We included this study in our selection bias sensitivity analysis.
Seshadri et al. 2013 Chennai, India(22)	23	Yes	Yes	We judged that the cCR not clearly defined. We included this study in our selection bias sensitivity analysis.
Torres-Mesa et al. 2014, Columbia(23)	19	Yes	No	We judged that the cCR not clearly defined. We included this study in our selection bias sensitivity analysis.
Approached but did not share data				
Li et al. 2015, Chengdu, China(24)	28	Yes	Yes	The present consortium approached these investigators. There was initial interest to share data but this never proceeded. We included this study in our selection bias sensitivity analysis.
Smith JD et al. 2012, Memorial Sloan-Kettering Cancer C	32	No	Yes	The present consortium approached these investigators, but they were unable to share their data.

enter, New York(25) + protocol(26)				We included this study in our selection bias sensitivity analysis.
Others				
Creavin et al. 2017 Dublin, Ireland(15)	10	No	Yes	We did not identify this study by electronic search, but this study was later brought to our attention through expert input. We agreed that this study fulfilled definition criteria equivalent to the Sao Paulo benchmarks. However, there were only 10 patients treated by W&W. As we learnt of this study after our IPD meta-analysis had commenced, for pragmatic reasons, we do not contact these authors requesting data. We included this study in our selection bias sensitivity analysis.

Table S2 Assessment tools and criteria to define clinical complete response in studies in the InterCoRe consortium

No.	Centres	Authors (ref)	DRE	Endo Ass	Tumour MR	Comments*
1	Buenos Aires, Arg	Vaccaro 2016(27)	✓	✓	✓	1. DRE/ endoluminal assessment "As per Habr-Gama"(28) 2. MRI: presence of residual low-signal-intensity area
2	Exeter, UK	Dalton 2011(12)	✓	✓	✓	1. EUA and biopsy of scar tissue • Residual mucosal ulcer is considered tumour even if biopsy is benign 2. MRI assessment • No evidence of residual tumour PET after that for any residual disease before cCR is considered
3	Maastricht, NL	Martens 2016(29)	✓	✓	✓	1. DRE • No palpable tumour when initially palpable before NACRT 2. Endoscopic assessment • No residual tumour • Small residual erythematous ulcer or scar • Negative biopsies from the scar, ulcer, or former tumour location 3. MRI assessment • Substantial downsizing with no residual tumour or fibrosis only (low signal on high b-value DWI) • No suspicious lymph node • Residual wall thickening due to oedema
4	NYU, US	Bitterman (11)	✓	✓	✓	1. DRE/ Endoscopic assessment • absence of residual tumour, ulceration, or rectal wall irregularity 2. MRI/PET-CT assessment • presence of residual low-signal intensity and absence of restriction to diffusion on MRI, or • absence of residual FDG avidity in the rectal wall on PET/CT.
5	OnCoRe, UK	Renehan 2016(30)	✓	✓		1. DRE/endoscopic assessment • Absence of residual ulceration, stenosis, or mass • Whitening of the mucosa or telangiectasia 2. Radiological assessment • Normal radiological imaging (nearly all MR imaging) of the mesorectum and pelvis
6	Rio de Janeiro, Brazil	Araujo 2015(31)	✓	✓	✓	Overall assessment • "based on digital examination, endoscopy and magnetic resonance (MRI)" Endoscopic assessment • "classified as residual tumour/ulceration versus a flat scar."
7	Sao Paulo I, Brazil	Habr-Gama 2010(28)	✓	✓		Clinical and endoscopic assessment • Absence of residual ulceration, mass, or mucosal irregularity • Whitening of the mucosa and the presence of neovasculature
8	Sao Paulo II, Brazil	Habr-Gama 2013(18)	✓	✓	✓	1. Clinical and endoscopic assessment • Absence of residual ulceration, mass, or mucosal irregularity • Whitening of the mucosa and the presence of neovasculature 2. Radiological assessment • MRI: presence of residual low-signal-intensity area

						• Diffusion-weighted MRI: absence of restriction to diffusion • PET/CT: absence of residual FDG uptake within the rectal wall or nodal metastases in patients with baseline cN+
9	Taipei, Taiwan, China	Lai 2016(32)	✓	✓		1. DRE/ endoluminal As per Habr-Gama 2. TRUS assessment • No evidence of hypoechoic or inhomogeneous lesion with irregular borders • Absence of thickening or destruction of the bowel wall
10	University Penn, US	Smith_R 2015(33)	✓	✓		"based upon digital rectal exam, rigid proctoscopy, ERUS, axial imaging, and in some instances endoscopic biopsy"
11	Vejle, DK	Appelt 2015(34)	✓	✓		1. Endoscopic assessment • Small, white scar in the rectal wall • Superficial erosion or ulceration without palpable tumour • If persistent ulcer or erosion – additional biopsies at the edge to ensure no evidence of disease 2. MRI assessment • Assess regional lymph nodes (suspected node was considered malignant if diameter > 5 mm)

DRE: digital rectal examination. Endo. Ass: Endoscopic or endoluminal assessment. NACRT: neoadjuvant chemo-radiotherapy. RUS: transrectal ultrasound

*Comments to study nos. 2, 3, 5, 8, 9 and 11 taken directly from Table 2 in the systematic review reported by Kong et al.(35)

Table S3 Numbers of patients per centre in original reports and numbers in this analysis

No.	Centres	Authors (ref)	cCR/ denominator rectal cancers (%)	No. W&W in original paper	No. excluded	Eligible no. for this analysis previously reported	No. in this analysis	No. previously unreported
1	Buenos Aires, Arg	Vaccaro 2016(27)	30/ 204 (14.7%)	23		23	23	0
2	Exeter, UK	Dalton 2011(12)	12/57 (24%)	12	1 not included in transferred data	11	11	0
3	Maastricht, NL	Martens 2016(29)	Not reported	100	15 LE 1 short course RT	84	84	0
4	NYU, US	Bitterman(11)	36/ 138 (26.3%)	6	x1 metastatic	5	8	3
5	OnCoRe, UK	Renehan 2016(30)	31/ 259 (11.9%)	129	x2 metastatic	127	162	35
6	Rio de Janeiro, Brazil	Araujo 2015(31)	Not reported	42		42	42	0
7	Sao Paulo I, Brazil	Habr-Gama 2014(19)	90/131 (49%)	90	10 LE	80	131	51
8	Sao Paulo II, Brazil	Habr-Gama 2013(18)	47/70 (68%)	47		47	66	19
9	Taipei, Taiwan, China	Lai 2016(32)	Not reported	18		18	18	0
10	University Penn, US	Smith_R 2015(33)	Not reported	18	x1 metastatic	17	17	0
11	Vejle, DK	Appelt 2015(34)	40/55 (72.7%)	40		40	40	0
		Totals				**494**	**602**	**108**

LE: local excision. RT: radiotherapy

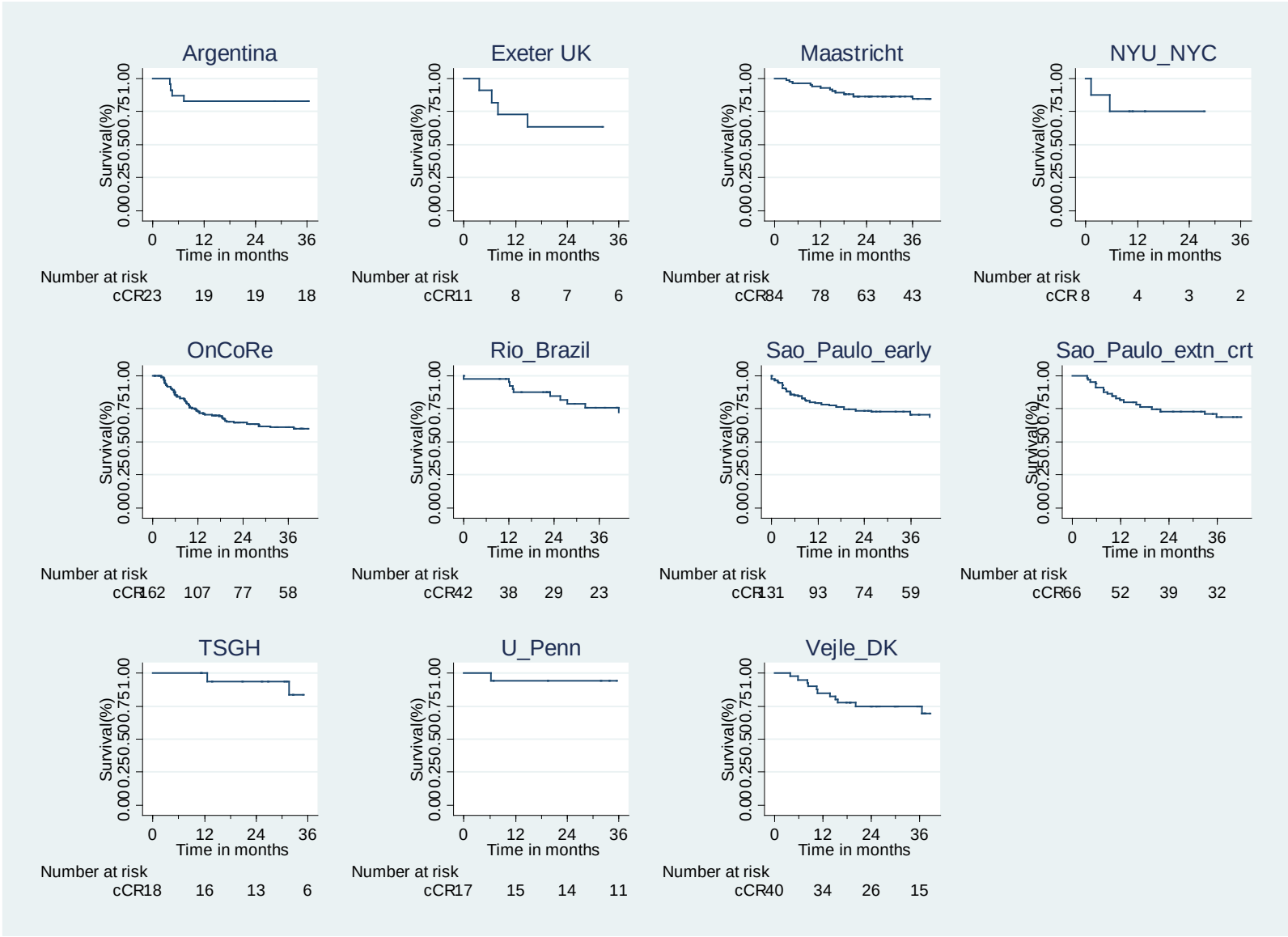
Study quality assessment

We use the Institute of Health Economics Quality Appraisal Checklist to assess single arm studies. Ten of the 11 studies were judged to be at low-risk of bias; one study was judged to be moderate-risk of bias (Figure S2).

Figure S2 'Traffic light' study quality assessment

Criteria	Buenos Aires, Arg	Exeter, UK	Maastricht, NL	NYU, US	OnCore, UK	Rio de Janeiro, Brazil	Sao Paulo I, Brazil	Sao Paulo II, Brazil	Taipei, Taiwan, China	Uni Penn, US	Vejle, DK
Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?											
Are the characteristics of the participants included in the study described?											
Were the cases collected in more than one centre?											
Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate?											
Were participants recruited consecutively?											
Did participants enter the study at a similar point in the disease?											
Was the intervention clearly described in the study?											
Were additional interventions (co-interventions) clearly reported in the study?											
Are the outcome measures clearly defined in the introduction or methods section?											
Were relevant outcomes appropriately measured with objective and/or subjective methods?											
Were outcomes measured before and after intervention?											

Figure S3 Local growth rates (shown as local regrowth-free survivals) with time for all 11 datasets



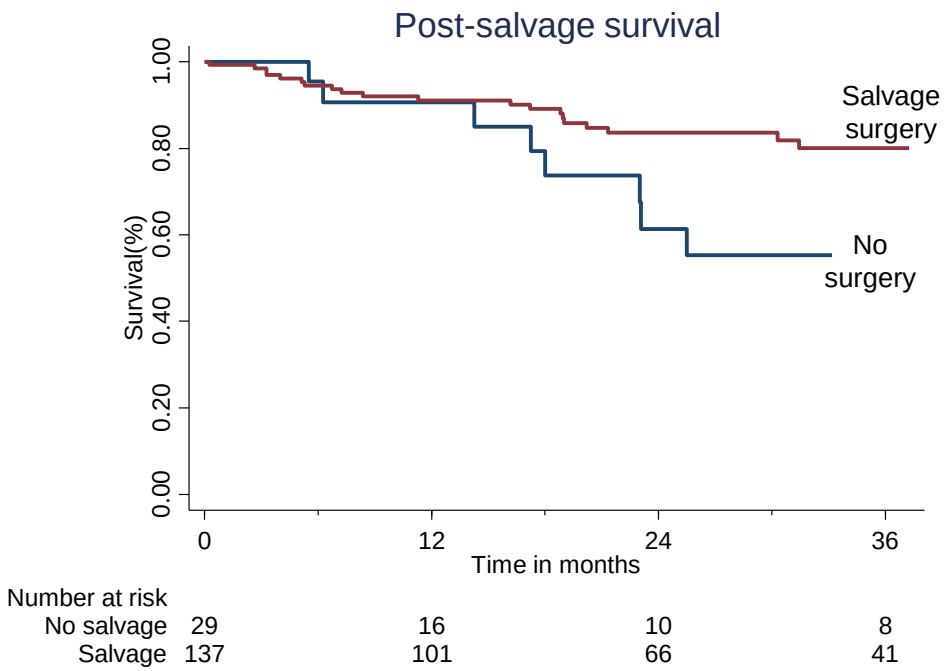


Figure S4 Post-salvage survival. Comparison of 137 patients with local regrowth treated by surgery versus those not managed by surgery.

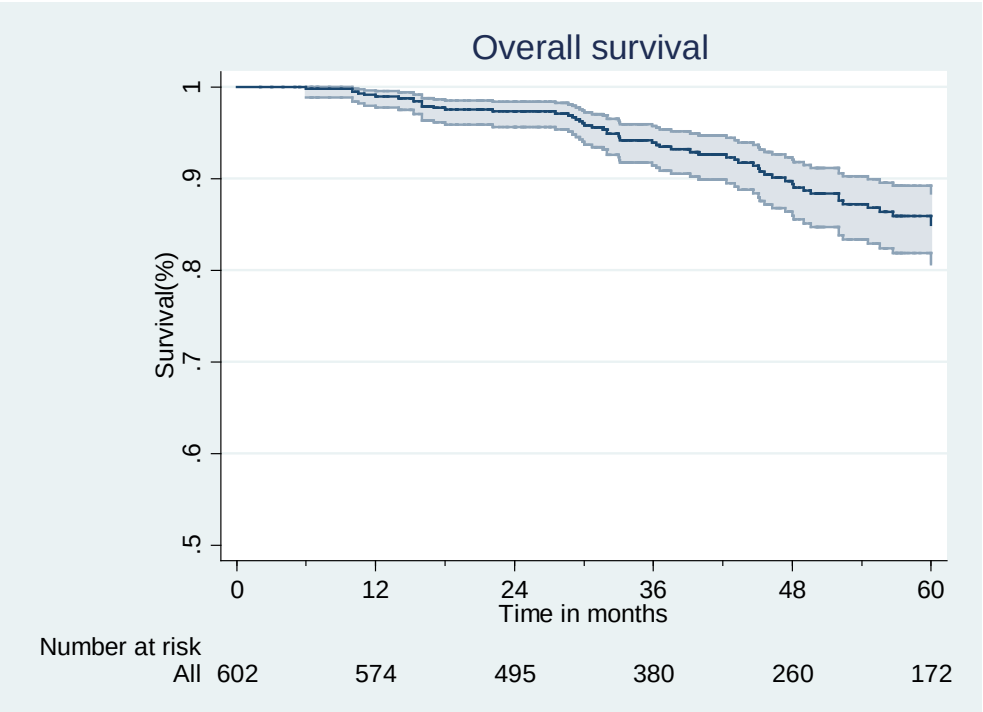


Figure S5 Overall survival in patients managed by W&W. Start time is date of first treatment with chemo-radiotherapy. The shaded area is 95% confidence interval. Note: abridged y-axis.

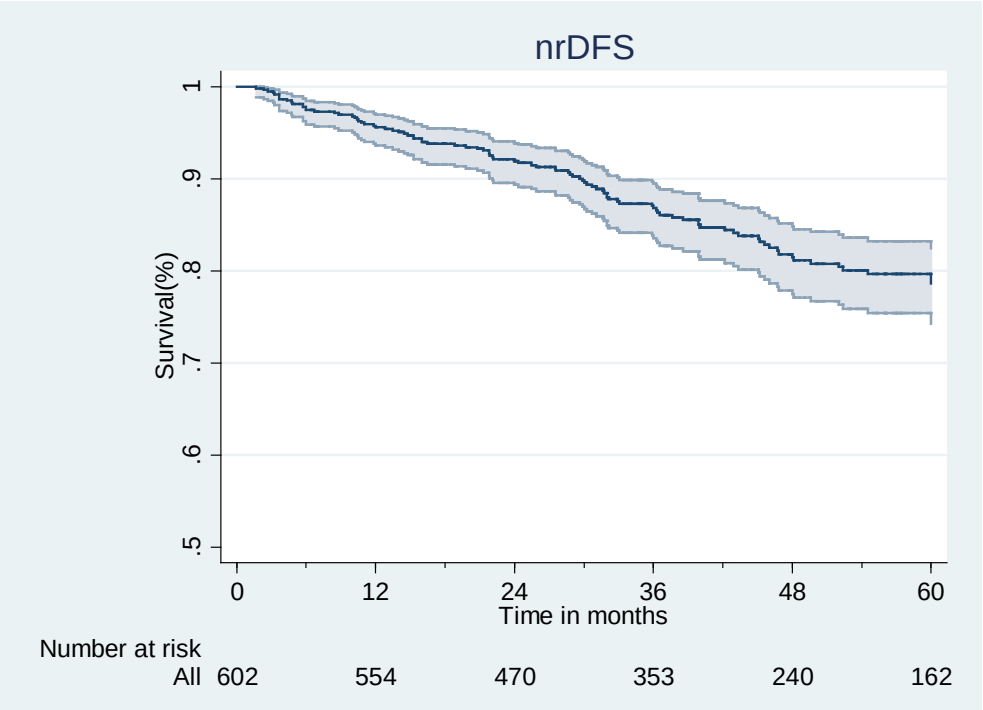


Figure S6 non-regrowth Disease-free survival in patients managed by W&W. Start time is date of first treatment with chemo-radiotherapy. The shaded area is 95% confidence interval. Note: abridged y-axis.

Table S4 Sites of distant metastases of 602 patient managed by W&W in the InterCoRe consortium

	N	3-year rates (RE 95% CIs)
No. of patients with distant metastases	60 (10)	9.1% (5.3-12.6)
Anatomic site of distant metastasis		
Lung	31 (52)*	
Liver	23 (38)*	
Nodes	4†	
Bone	2	
Brain	2	
Peritoneum	3	
Proportion of distant metastases with local regrowth	31 (52)*	
Distant metastasis diagnosed before local regrowth	4	
Distant metastasis diagnosed synchronous with local regrowth‡	12 (40)¶	
Distant metastasis diagnosed after local regrowth	14 (47)¶	

Percentages only cited if value greater than five. RE: random-effects estimates.
*As a proportion of distant metastases.
† One patient documented with an inguinal lymph node involvement.
‡ Defined as diagnosis of distant metastasis less than 3 months either before or after local regrowth diagnosis.
¶ As a proportion of patients with distant metastases and local regrowth, at any time. Dates missing on one patient.

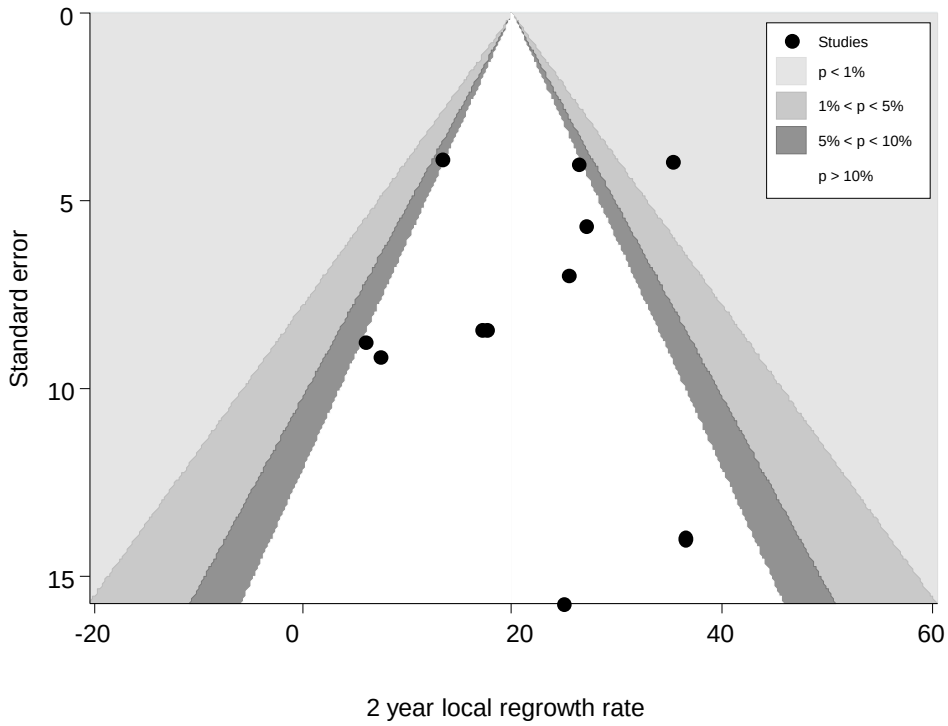


Figure S7 Contour enhanced funnel plot of the 11 datasets included in the IPD meta-analysis. As we were dealing with proportions rather than effect sizes, we normalised our data so that the '0 effect' was approximately equal to the summary estimate rate for 2-year local regrowth, which was 21.4. Thus, we normalised by subtracting 20 from our summary rate and its lower and upper confidence intervals.

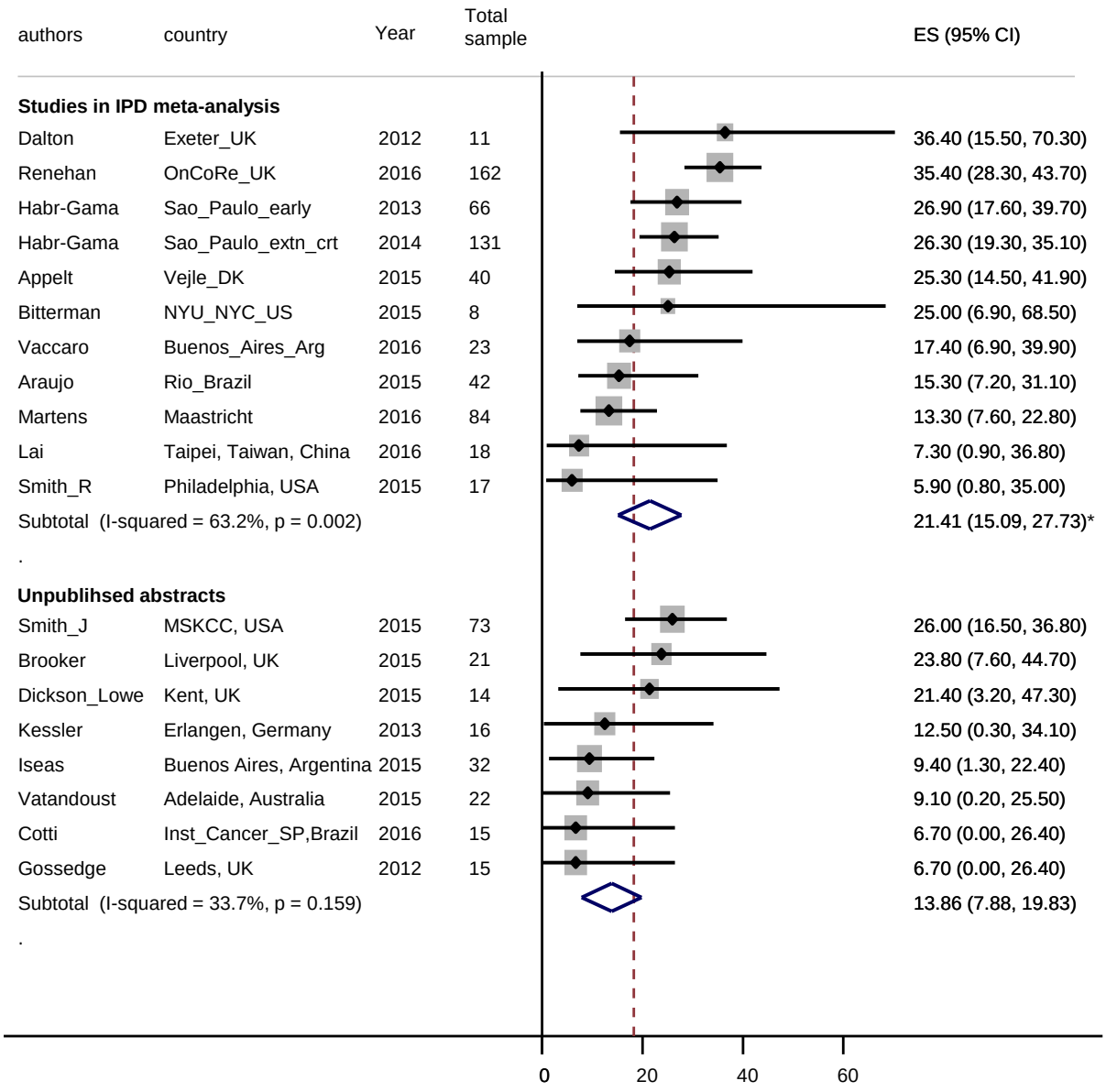


Figure S8 Evaluation of data availability bias. Forest plots for estimates of 2-year local regrowth after W&W among studies included in IPD (11 datasets) versus estimates among unpublished abstract (from Dossa et al. review) but not included in present IPD meta-analysis.

* Slight differences with Figure 1 summary estimates, where the reml option was used.

In meta-regression models, we tested for differences between summary estimates according to whether there was individual level data or not, p = 0.111.

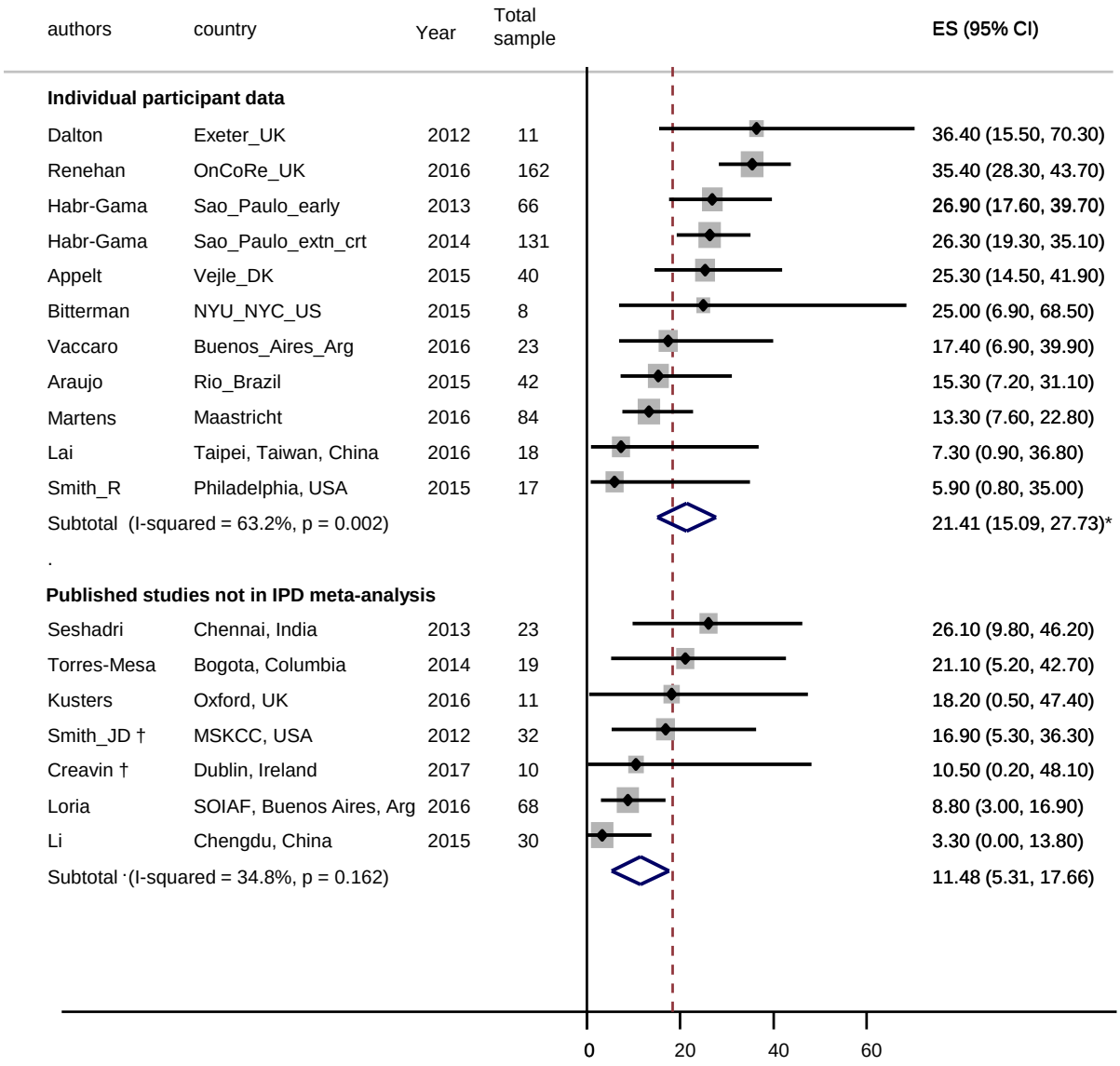


Figure S9 Evaluation of reviewer selection bias. Forest plots for estimates of 2-year local regrowth after W&W among studies included in IPD (11 datasets) versus estimates among published studies but not included in present IPD meta-analysis.

* Slight differences with Figure 1 summary estimates, where the reml option was used.

† Local regrowth rates taken from Dattani et al. meta-analysis. 3-year cumulative rate taken as equivalent to 2-year local regrowth.

In meta-regression models, we tested for differences between summary estimates according to whether there was individual level data or not, p = 0.089.

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InterCoRe Data Sharing Statement

Will individual participant data be available (including data dictionaries)?	Planned for OnCoRe – from March 2019
What data in particular will be shared?	Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices).
What other documents will be available?	Study protocol & statistical analysis plan. Available on PROSPERO
When will data be available (start and end dates)?	Beginning 6 months and ending 5 years following article publication
With whom?	Investigators who provide a methodologically sound proposal and whose proposed use of the data has been approved by a representative from each of the sites from the InterCoRe consortium
For what types of analyses?	To achieve aims in the approved proposal
By what mechanism will data be made available?	Proposals may be submitted up to 5 years following article publication. Proposals should be directed to lee.malcomson@nhs.net ; to gain access, data requestors will need to sign a data access agreement. Information regarding submitting proposals and accessing data may be found at www.complete-response.com/intercore