Common format for Evidence Table – Treatment Primary studies

Headings	Description
I Study ID	
1. Reference	First author; Journal name; Publication Date;
II Method	
1. Study design	Specify the type of study: RCT, CCT, case control, case series
2. Source of funding/conflicts of interest	Specify the source of funding: public research funds, government, not governmental organization, healthcare industry or other (give name of organization or corporation) presence of declaration of interest.
3. Setting	Numbers of centers, countries involved, healthcare setting, urban/rural/mixed.
4. Sample size	Give the calculated number in each group and the actual number of patients in each group.
5. Duration of the Study	Duration in months or years.
III Patient characteristics	
1. Eligibility criteria	State the most relevant inclusion and exclusion criteria for population (patients and pathology).
2. Patient characteristics	Specify a priori characteristics (age, tumor, stage).
3. Group comparability	p for group comparability.
IV Intervention(s)	
1. Intervention(s)	Precise details of the interventions for each group (including dose, length, regimen and timing if relevant).
2. Comparator(s)	Placebo, other treatment (including dose, length, regimen and timing if relevant).
V Results primary outcome	
1. Effect size primary outcome	Summary of the primary outcome in each and between groups: effect size and its precision (p value, CI) Including efficacy: Absolute risk reduction, relative risk (reduction), odds ratios, confidence intervals.
VI Results secondary and all other outcomes	
1. Effect size secondary outcome(s)	Brief description of secondary outcome(s) and p values.
2. Effect size all other outcomes, endpoints	All other outcomes, endpoints, including adverse effects, toxicity, quality of life
VII Critical appraisal of study quality	
1.Level of evidence	Classification of intervention studies.
2. Dropouts	Number of dropouts/withdrawals in each group
3. Results critical appraisal	Summarize internal validity: sample size, randomization and blinding, use of inappropriate statistical analysis, etc

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KEY QUESTION 1

Assessment table relative importance patient important outcomes

Patient-important outcomes	Mean rating	Relative importance
Local control	8	Critical
Survival	7	Critical
Quality of life	8	Critical

As rated by 7 guideline panel members, 0 of whom were patients

1.1.1.1 Evidence table observational studies grade I

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Luglio 2011	• Observational study • Support: not reported; CoI: not reported • Setting: single centre, Italy • Sample size: N= 18 • Duration: 2000-2005 • Follow-up: 5 years	• Inclusion: T1 rectal cancer patients • Exclusion: not reported • Patient characteristics: 2/18 patients had a T1 tumour that appeared to deeply infiltrate the sub mucosa	Neoadjuvant radiotherapy + local excision	At 5 years follow-up, no local recurrences and 2 systemic recurrences (11%) had occurred	-	• Available in abstract form only • Data for T1 patients only reported here • Retrospective study of a prospectively maintained database • Preoperative staging with endorectal ultrasound • Patients were unfit for surgery, or refused surgery or a stoma • Unclear whether all patients did receive neoadjuvant radiotherapy

Abbreviations: CoI: conflict of interest; RCT: randomised controlled trial

1.1.1.2 Grade table observational studies grade I

Quality assessment							No of patients		Effect (95%CI)			
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Local excision**	**-**	**Relative**	**Absolute**	**Quality**	**Importance**
% recurrence at 5 years												
1	Observational	Serious	No serious	No serious	Serious	No other	18	0	-	11%	Very low	Critical

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	study	limitations [1]	inconsistency	indirectness	imprecision [2]	considerations					⊕OOO	
Overall quality of evidence: very low												

[1] No control group
[2] Small number of events leads to fragility of results

1.1.1.3 Evidence table randomised controlled trials stage II

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality

Lezoche 2012	• RCT
	• Support: not reported ; CoI: none
	• Setting: two centres, Italy
	• Sample size: N= 100
	• Duration: April 1997-April 2004
	• Follow-up: median 9.6 years
		• Inclusion: T2N0M0 rectal cancer; grade G1-G2; <3 cm ; within 6 cm of the anal verge; ASA fitness grade I-II
		• Exclusion: lymphovascular or pernineural invasion; suspicious nodes or inconsistent findings at EUS, CT or MRI tumor staging
		• Patient characteristics:
		  • Age: median 66 years
		  • Male: 64%
			Neoadjuvant chemoradiotherapy + transanal endoscopic microsurgery (n=50)
			vs.
			neoadjuvant chemoradiotherapy + laparoscopic total mesorectal excision (n=50)
			
			Neoadjuvant therapy: total dose of 50.4 Gy in 28 fractions over 5 weeks + continuous infusion of 5-fluorouracil 200 mg/m2/day during radiotherapy
				Local recurrence: 8 vs. 6%
				
				Distant metastases: 4 vs. 4%
				
				Probability of developing recurrence or metastasis at end of follow-up: 12% (95%CI: 6-25%) vs.10% (4-22%) (p=0.69)
				
				Cancer-related survival rate at the end of follow-up: 89% (95%CI: 70-96%) vs. 94% (82-98%) (p=0.69)
				
				Overall survival rate at the end of follow-up: 72% (95%CI: 51-86%) vs. 80% (95%CI: 62-90%) (p=0.61)
				
				Temporary stoma: 0 vs. 11 (p<0.001)
				
				Permanent stoma: 0 vs. 12 (p<0.001)
					30-day mortality rate: 0 vs. 0
					
					Operative programme change/conversion to open surgery: 0 vs. 6 (p=0.01)
					
					Minor postoperative complications: 6 vs. 7 (p=0.77)
					
					Major postoperative complications: 1 vs. 3 (p=0.25)
					
					In a Cox regression analysis type of procedure (RR: 14.24, 95%CI: 1.36-149.16; p=0.03) and blood loss (RR: 1.01, 95%CI: 1.00 to 1.01; p<0.001) were the only variables with a significant effect on the development of recurrence or metastases. The authors conclude that: ´the significantly higher risk could be explained by the earlier occurrence of events´ in the local excision group. 5/6 events occurred in the first year in the local excision group vs. 0/5 events in the radical resection group
					
					When the RR of death was evaluated, no variable significantly affected the probability of failure
						• Computer-generated randomisation sequence
						• Allocation concealment by sealed opaque envelopes
						• Blinding of patients not possible
						• Blinded outcome assessment: not reported
						• ITT analysis, no loss to follow-up
						• Patients characteristics similar across groups
						• Staging included: endorectal ultrasonography ; rigid sigmoidoscopy and tumour biopsies; total colonoscopy; whole-body CT; and pelvic MRI

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Abbreviations: ASA: American Society of Anesthesiologists; CoI: conflict of interest; RCT: randomised controlled trial

1.1.1.4 Grade table stage 2

Quality assessment							No of patients		Effect (95%CI)			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Transanal endoscopic microsurgery**	**Laparoscopic resection**	**Relative**	**Absolute**	**Quality**	**Importance**
Probability of local recurrence or metastasis at 10 years												
1	RCT	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [2]	No other considerations	50	50	-	12% (95%CI: 6-25%) vs. 10% (4-22%) (p=0.69)	Low ⊕⊕OO	Critical
10-year cancer-related survival												
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision [2]	No other considerations	50	50	-	89% (95%CI: 70-96%) vs. 94% (82-98%) (p=0.69)	Moderate ⊕⊕⊕O	Critical
10-year overall survival												
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision [2]	No other considerations	50	50	-	72% (95%CI: 51-86%) vs. 80% (95%CI: 62-90%) (p=0.61)	Moderate ⊕⊕⊕O	Critical
Permanent stoma												
1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision [2]	No other considerations	50	50	-	0 vs. 12 (p<0.01)	Moderate ⊕⊕⊕O	Critical
Overall quality of evidence: moderate												

[1] Blinding of patients not possible; no blinding of outcome assessors, or unlikely
[2] Few events lead to fragility of results

1.1.1.5 Evidence table observational studies stage III

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Callender 2010	• Comparative cohort study • Support: not reported; CoI: not reported	• Inclusion: T3N0-1M0 rectal cancer • Exclusion: not reported	Neoadjuvant CRT + full-thickness local excision (Kraske n=6; transanal	10-year actuarial local recurrence rate: 10.6 vs. 7.6% (p=0.52)	Adverse effects were only reported for the	• Retrospective study • Local excision patients were older, had smaller

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	• Setting: single centre, United States
	• Sample size: N= 47 vs. 473
	• Duration: January 1990-July 2008
	• Follow-up: 63 vs. 59 months
		• Patient characteristics:
		  • Age: 62.5 ± 14.2 vs. 57.8 ± 12.5 years (p=0.02)
		  • Tumor size (SD): 3.9 (± 1.4) vs. 5.2 (± 1.9) cm (p<0.001)
		  • Distance from anal verge (SD): 3.7 (± 1.6) vs. 5.5 (± 3.0) cm (p=0.001)
		  • Gross residual disease : 15 vs. 58% (p<0.0001)
		  • N1 disease: 27.7 vs. 53.7%
			n=41)
			vs.
			neoadjuvant CRT + TME
			
			Radiation doses of 45, 50.4, or 52.5 Gy with concurrent 5-fluorouracil-based chemotherapy
				10-year disease recurrence: 21.3 vs. 24.9%
				
				10-year disease-free survival rate: actual data reported in a figure (p=0.59)
				
				10-year disease-specific survival: actual data reported in a figure (p=0.64)
				
				10 year overall survival: actual data reported in a figure (p=0.81)
					local excision group, not for the TME group	tumours, fewer gross residual disease and fewer N1 disease. No control for these factors in the analyses
						• Patients were staged by means of clinical examination, digital rectal examination, chest X-ray, CT of the abdomen and pelvis, and endoscopy. Endoscopic ultrasound was routinely performed
						• Patients underwent local excision because of co-morbidity (n=12); refusal of TME (n=15); complete clinical response with a strong preference for local excision (n=15); other/undocumented reasons (n=5)

Guerrieri 2008	• Observational study
	• Support: not reported; CoI: not reported
	• Setting: single centre, Italy
	• Sample size: N= 61
	• Duration: May 1992-December 2005
	• Follow-up: range: 12-178 months (including T2 patients)
		• Inclusion: T3N0M0
		• Exclusion: not reported
		• Patient characteristics: not reported separately for T3 patients
			Neoadjuvant radiotherapy + TEM
			
			Neoadjuvant radiotherapy: 180 cGy in 28 fractions for a total dose of 5,040 cGy over 5 weeks
			
			From January 1997, 70-year-old patients with good performance status underwent preoperative RCT with a continuous infusion of 5-fluorouracil 200 mg/m2/day.
				Probability of local recurrence (95%CI):
				  • 12 months: 0
				  • 36 months: 0.05 (0.02-0.16)
				  • End of follow-up: 0.05 (0.02-0.16)
				
				Probability of metastasis (95%CI):
				  • 12 months: 0
				  • 36 months: 0.02 (0.0–0.12)
				  • End of follow-up: 0.04 (0.01–0.15)
				
				Probability of disease-free survival (95%CI):
				  • 12 months: 1
				  • 36 months: 0.87 (0.64–0.96)
				  • End of follow-up: 0.77 (0.53–0.90)
					-	• Data on clinical T3 patients reported here
						• No control group
						• Unclear what the follow-up for T3 patients was
						• Patients were staged preoperatively by colonoscopy, rigid rectoscopy, transanal endosonography, CT or MRI, bone scintigraphy and chest-X-rays
						• Patients underwent local excision because they were high risk (ASA 3-4) patients or had refused conventional resection

Kennelly 2012	• Observational study • Support: not reported; CoI:	• Inclusion: T3N0-1M0 rectal cancer patients	Neoadjuvant chemoradiotherapy +	No local recurrence or metastasis detected at longest follow-up	-	• No control group • Prospective study

Validated

	none
	• Setting: single centre, Ireland
	• Sample size: N= 10
	• Duration: July 2006-July 2009
	• Follow-up: median 24 months (range: 9-42 months)
		• Exclusion: fit for and agreed to surgery; patients who had little or no clinical response to neo-adjuvant treatment
		• Patient characteristics:
		  • Age: mean 71.4 years
		  • Male: 60%
			full-thickness local excision
			
			50 Gy for 5 weeks and 5-fluorouracil infusion week 1 and 5: 1 g/kg
						• No loss to follow-up
						• Staging was done by CEA; CT of thorax, abdomen and pelvis; and MRI of pelvis
						• Patients were unfit for or refused resection
						• Patients with little or no clinical response to neo-adjuvant treatment were excluded

Meadows 2006	• Observational study • Support: not reported; CoI: not reported • Setting: single centre, United States • Sample size: N= 16 • Duration: July 1988-April 2004 • Follow-up: median 27 months (range: 2-123 months, including T1-2 patients)	• Inclusion: T3 patients • Exclusion: not reported • Patient characteristics: not reported separately for T3 patients	Neoadjuvant (C)RT + full-thickness local excision Minimum tumor dose of 4500 cGy to the rectum and low pelvis, and 22 patients (out of 32 T1-3 patients) received a 3-field boost to 5040 cGy Concomitant chemotherapy was routinely added to the preoperative RT regimen since 1991; 25 patients out of all 32 T1-3 patients received chemotherapy and 7 patients received RT alone	Local-regional recurrence-free survival: 71%	-	• No control group • Data on clinical T3 patients reported here • 28/32 T1-3 patients were staged preoperatively by endoscopic ultrasound
Mohiuddin 1994	• Observational study • Support: not reported; CoI: not reported • Setting: single centre, United States • Sample size: N= 30 • Duration: not reported • Follow-up: median 40 months including ≤T2 patients (range: 12-96 months)	• Inclusion: ≥T3 adenocarcinoma of the distal rectum located 0-6 cm from the anal ring • Exclusion: not reported • Patient characteristics: not reported separately for ≥T3 patients	Neoadjuvant RT + full-thickness local excision RT was a total dose of 40-45 Gy at 1.8-2.5 Gy/fraction with a boost in selected patients with tumor fixation (T3/T4) to a total of 55 Gy	Local recurrence: 3/30 (10%) 5-year actuarial survival rates: - 15 medically unfit patients: 74% - 15 patients assessed as ≤T2 and <3 cm post radiation: 88%	-	• No control group • Data on clinical ≥T3 patients reported here • No loss to follow-up • Patients were staged with clinical examination, chest X-ray, barium enema, CT of the abdomen and pelvis, endoscopy, and more recently by MRI • 15 patients were medically unfit for radical surgery; 15 patients had T3 tumours that were

Validated

						assessed as ≤T2 post radiation, and were <3 cm
Nair 2008	• Observational study • Support: not reported; CoI: not reported • Setting: single centre, United States • Sample size: N= 22 • Duration: July 1994-August 2006 • Follow-up: median 64 months (range: 6-153, including T2 patients)	• Inclusion: T3N0 patients who underwent local excision for rectal carcinoma after neoadjuvant CRT • Exclusion: not reported • Patient characteristics: not reported separately for T3 patients	Neoadjuvant CRT + full-thickness local excision 4,500 cGy in 25 fractions to the pelvis + 540 cGy boost focused at the primary tumor site, concomitantly with 5-fluoruracil as a continuous infusion at a dose of 300 mg/m^2 /day, 5 days/week on days of radiation	1/22 (5%) patients had a local recurrence 2/22 (10%) patients had a distal recurrence 2/22 (10%) patients died of disease	-	• No control group • Data on clinical T3N0 patients reported here • Retrospective study • Patients were staged preoperatively by endoscopic ultrasound and CT of the abdomen and pelvis • Patients underwent local excision because they refused radical surgery or were unfit for it

Schell 2002	• Observational study
	• Support: not reported; CoI: none
	• Setting: United States
	• Sample size: N= 11
	• Duration: 1992-2000
	• Follow-up: median 47.9 months (range: 18-105)
		• Inclusion: T3N0-1 rectal cancer patients with significant downstaging after neoadjuvant therapy
		• Exclusion: not reported
		• Patient characteristics:
		  • Age: mean 53 years
		  • Male: 82%
		  • 3 N1 patients on MRI
			Neoadjuvant chemoradiotherapy + full-thickness local excision
			
			4,500 cGy and either standard or continuous 5-FU/leucovorin chemotherapy
				Local recurrence: 0
				
				Metastasis: 1 (9%)
				
				Deaths: 0
					1 patient (9%) experienced sphincter laxity, with intermittent soiling, which was successfully repaired
					
					1 patient (9%) developed postoperative urgency that resolved spontaneously
						• No control group
						• Patients who down staged to clinical T stage 0 or 1 were offered transanal excision of their residual rectal cancer or rectal scar, if not more than 2cm in diameter

Tennyson 2012	• Observational study • Support: not reported; CoI: not reported • Setting: single centre, United States • Sample size: N= 11 • Duration: 1998-2008 • Follow-up: median 5.9 years, range: 0.3-11.1 (including patients with other stages)	• Inclusion: T3N0-1M0 rectal cancer patients • Exclusion: not reported • Patient characteristics: not reported separately for T3 patients	Neoadjuvant (chemo)radiotherapy + local excision 4500 cGy with a 3-field boost to 5040 cGy Concomitant chemotherapy was given to 26 of 32 preoperative patients (including all stage patients)	3 (27%) local recurrences occurred 20% local recurrence at 5 years	-	• No control group • Retrospective study • Only data for neoadjuvantly treated T3 patients reported here • Staging included CT scans of the abdomen and pelvis, chest CT or X-ray, complete blood count, liver function tests, EUS, and carcinoembryonic antigen levels • Patients were unfit for, or refused surgery
Yeo 2010	• Observational study • Support: National Cancer	• Inclusion: T3N0-1M0 • Exclusion: not reported	Neoadjuvant chemoradiotherapy + full-thickness local	1 local recurrence occurred (9%) 1 metastasis occurred (9%), this	No grade 3 or worse gastrointestinal	• No control group • Retrospective study

Validated

	Center Grant; CoI: none • Setting: Korea • Sample size: N= 11 • Duration: January 2003-February 2008 • Follow-up: median 59 months (range: 24-85)	• Patient characteristics: • Age: median 61 years • Median tumour size: 3 cm • 5 patients were N1	excision 50.4 Gy in 28 fractions with concurrent chemotherapy	patient died The 5-year local recurrence-free, disease-free and overall survival rates were 90.9%, 81.8% and 88.9%, respectively	toxicity was detected	• 10 patients received postoperative chemotherapy • Patients refused surgery

Abbreviations: ASA: American Society of Anesthesiology; CoI: conflict of interest; CRT: chemoradiotherapy; SD: standard deviation; TEM: transanal endoscopic microsurgery; TME: total mesorectal excision

1.1.1.6 Grade table stage III

Quality assessment							No of patients		Effect (95%CI)			
No. of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Neo-adjuvant CRT + local excision**	**Neo-adjuvant CRT + TME**	**Relative**	**Absolute**	**Quality**	**Importance**
10-year local recurrence												
1	Comparative cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	47	473	-	10.6% vs. 7.6% (p=0.52)	Very low ⊕OOO	Critical
10 year disease-specific survival												
1	Comparative cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	47	473	-	Data reported in a figure (p=0.64)	Very low ⊕OOO	Critical
10 year overall survival												
1	Comparative cohort study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	47	473	-	Data reported in a figure (p=0.81)	Very low ⊕OOO	Critical
% local recurrence at 4-178 months												
7	Observational studies	Serious limitations [2]	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	156	0	-	0-27%	Very low ⊕OOO	Critical
Overall survival at ± 5 years												
4	Observational studies	Serious limitations [2]	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	74	0	-	74-100%	Very low ⊕OOO	Critical
Disease-free survival at ± 5 years												
4	Observational studies	Serious limitations [2]	No serious inconsistency	No serious indirectness	Serious imprecision [1]	No other considerations	99	0	-	71-91%	Very low ⊕OOO	Critical
Overall quality of evidence: very low												

Abbreviations: CRT: chemoradiotherapy; TME: total mesorectal excision
[1] Small number of events (in some series/groups) leads to fragility of results
[2] No control group. Retrospective studies

Validated