

SUPPLEMENTAL MATERIAL

Economic evidence for a watch-and-wait strategy in patients with clinical complete response following neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and a subject-specific critical appraisal

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Appendix 1 Clinical terms search strategy

Search terms for key words for creating search strategy

Rectal cancer	Surgery	Watch-and-wait strategy	Clinical Complete Response
-Locally advanced rectal cancer -Rectal cancer -Rectal neoplasms -Bowel cancer -Colorectal cancer -Colorectal neoplasms -Rectum neoplasms -Rectum tumour	-Radical surgery -Tailored excision -Low anterior resection -Abdominoperineal resection	-Watchful waiting -Watch and wait -Watch-and-wait -Watch & wait -Follow up -Organ-sparing -Organ preservation -Active surveillance -Surveillance -Endoscopic surveillance -Active monitoring	-Clinical complete response -Complete clinical response

Appendix 2 Medline search strategy

Ovid MEDLINE(R)

- 1 economics/
- 2 exp "costs and cost analysis"/
- 3 Economics, Dental/
- 4 exp economics, hospital/
- 5 Economics, Medical/
- 6 Economics, Nursing/
- 7 Economics, Pharmaceutical/
- 8 (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic\$).ti,ab.
- 9 (expenditure\$ not energy).ti,ab.
- 10 value for money.ti,ab.
- 11 budget\$.ti,ab.
- 12 or/1-11
- 13 ((energy or oxygen) adj cost).ti,ab.
- 14 (metabolic adj cost).ti,ab.
- 15 ((energy or oxygen) adj expenditure).ti,ab.
- 16 13 or 14 or 15
- 17 12 not 16
- 18 Locally advanced rectal cancer.mp.
- 19 rectal cancer.mp.
- 20 Rectal Neoplasms/
- 21 bowel cancer.mp.
- 22 Colorectal Neoplasms/
- 23 ((cancer* or neoplas* or tumor* or carcinoma* or adenocarcinoma* or malignan*) adj4 (rectum or rectal)).ti,ab.
- 24 or/18-23
- 25 radical surgery.mp.
- 26 tailored excision.mp.

- 27 low anterior resection.mp.
- 28 abdominoperineal resection.mp.
- 29 or/25-28
- 30 complete clinical response.mp.
- 31 clinical complete response.mp.
- 32 30 or 31
- 33 organ-sparing.mp.
- 34 organ preservation.mp.
- 35 Organ Preservation/
- 36 organ preserving.mp.
- 37 active surveillance.mp.
- 38 surveillance.mp.
- 39 endoscopic surveillance.mp.
- 40 active monitoring.mp.
- 41 watchful waiting.mp.
- 42 exp Watchful Waiting/
- 43 (Watch and wait).mp.
- 44 watch-and-wait.mp.
- 45 watch & wait.mp.
- 46 follow up.mp.
- 47 ((wait* adj3 (watch* or see)) or ((avoid* or without) adj5 (operat* or surger* or resect* or excision*)) or ((nonoperativ* or "non operative" or "non surgical" or nonsurgical or observation* or conserv*) adj4 (strateg* or approach* or treatment* or manage*))) .ti,ab.
- 48 or/33-47
- 49 17 and 24 and 29 and 32 and 48

Appendix 3 Embase search strategy

- 1 Health Economics/
- 2 exp Economic Evaluation/
- 3 exp Health Care Cost/
- 4 exp Pharmacoeconomics/
- 5 1 or 2 or 3 or 4
- 6 (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab.
- 7 (expenditure\$ not energy).ti,ab.
- 8 (value adj2 money).ti,ab.
- 9 budget\$.ti,ab.
- 10 6 or 7 or 8 or 9
- 11 5 or 10
- 12 (metabolic adj cost).ti,ab.
- 13 ((energy or oxygen) adj cost).ti,ab.
- 14 ((energy or oxygen) adj expenditure).ti,ab.
- 15 12 or 13 or 14
- 16 11 not 15
- 17 rectum cancer/ or Locally advanced rectal cancer.mp.
- 18 rectal cancer.mp.
- 19 rectal neoplasms.mp. or rectum tumor/
- 20 bowel cancer.mp.
- 21 colorectal neoplasm.mp. or colorectal tumor/
- 22 ((cancer* or neoplas* or tumo?r* or carcinoma* or adenocarcinoma* or malignan*) adj4 (rectum or rectal)).ti,ab.
- 23 or/17-22
- 24 radical surgery.mp. or cancer surgery/
- 25 excision/ or tailored excision.mp.
- 26 rectum anterior resection/ or low anterior resection.mp.
- 27 abdominoperineal resection.mp. or rectum abdominoperineal resection/

28 or/24-27

29 clinical complete response.mp.

30 complete clinical response.mp.

31 29 or 30

32 organ-sparing.mp.

33 organ preservation.mp. or organ preservation/

34 organ preserving.mp.

35 active surveillance/

36 surveillance.mp. or monitoring/

37 active monitoring.mp.

38 exp watchful waiting/

39 (watch and wait).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

40 watch-and-wait.mp.

41 watch & wait.mp.

42 follow up/

43 ((wait* adj3 (watch* or see)) or ((avoid* or without) adj5 (operat* or surger* or resect* or excision*)) or ((nonoperativ* or "non operative" or "non surgical" or nonsurgical or observation* or conserv*) adj4 (strateg* or approach* or treatment* or manage*))).ti,ab

44 or/32-43

45 16 and 23 and 28 and 31 and 44

Appendix 4 Data extraction table for included studies in the review

First author (country) date	Study population	Interventions included	Comparator	Model type	Data sources	Resource use and costs	Consequences	Type of economic evaluation and analysis	Result	Sensitivity Analysis
Cui (USA) 2021	Patients with cCR after neoadjuvant chemoradiation for locally advanced (stage II or III) rectal cancer (cohort size =10,000) extra info: NCCN guideline used for LAR and APR For WW: Memorial Sloan-Kettering nonoperative management surveillance programs	WW (no definition or description)	Radical surgery: APR or LAR	Model type: Two state transition Markov models (APR; LAR) with six health states Software : Treeage Time Horizon: 5-year Cycle length:1-month	Published studies but not clear if systematic review was completed Disease progression and cancer death - peer reviewed sources Probability of death from natural causes- Social Security life tables	Resource use: operation; chemotherapy, ostomy care, and post-treatment cancer surveillance . Currency: Dollars Price year: 2019 Source of unit costs: Current Procedural Terminology (CPT) billing codes and the 2019 Physician's Fee Schedule Previously published source	Effectiveness: 5-year overall survival, 5-year cancer specific survival, Health benefits: QALY	Cost-effectiveness Incremental Cost-Effectiveness Ratio compared with WW	WW dominant vs LAR (- \$23,984 + 0.17 QALYs) Vs APR (- \$16,760 .63 + 0.23 QALYs)	One- way sensitivity analysis: all probabilities, utilities and costs Scenario analysis: adjuvant chemotherapy to start at 4, 8, and 12 weeks post-intervention PSA (100 iterations) One-way sensitivity analysis result: APR and LAR vs WW was sensitive to 2-year local regrowth rates

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				Discount rate: 3% Perspective: Payer						following WW, 5-year distant recurrence rates following WW, and WW utility. APR versus WW was sensitive to APR utility. LAR versus WW was sensitive to LAR utility following ostomy reversal Scenario analysis result: WW remained dominant vs APR and LAR

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										PSA result: WW vs LAR and APR was dominant or was cost effective between WTP thresholds from \$0 to \$200,000/QALY in 100% of the iterations tested.
Rodriguez-Pascual (Spain) 2022	Locally advanced rectal (Stage II and III) patients with cCR (cohort size not reported)	WW (no definition or description)	Standard resection (SR) and Robotic Rectal Resection (RRR)	Model type: state transition Markov model with six health states Software: Microsoft	Published studies but not clear if systematic review was completed QALYs data of SR and RRR estimated from own	Resource use: Operative costs, hospitalization cost and programmed and emergency surgical visits readmission costs up to 180 days from surgery Currency: Euros	Effectiveness: Clinical outcomes not reported Health benefits: QALY	Cost-utility analysis Incremental Cost-Effectiveness Ratio compared with WW	WW dominant over SR (-€75,486.75, +2.04 QALYs) and RRR (-€75,486.75, +0.41 QALYs)	PSA (5000 iterations) PSA result: WW saves costs 99.98% of the iterations; WW more effective than SR (86.9%) and RRR (55.38%) of the iterations

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				t Excel 365 Time Horizon: Lifetime Cycle length: 1-month Discount rate: 3% Perspective: Payer	previous report For SR rectal cancer database	Price year: 2019 Source of unit costs: Direct cost, published studies				Significant uncertainty due to the high utility value assigned to cCR after chemoradiotherapy in the RRR alternative
Miller (USA) 2020	Adult (64 years old) patients with resectable locally advanced (T3-4N0 or node-positive) rectal adenocarcinoma entered the model after	WW (defined by NCCN guidelines with additional or more frequent examinations , carcinoembr	LAR and APR	Model type: state transition Markov model with seven	Published studies Meta-analysis Multi-institutional internal	Resource use: Micro-costing done hospital admission, surgical, postoperative care, potdischarge	Effectiveness: 5-year cancer specific survival, overall survival	Cost-effectiveness analysis Incremental Cost-Effectiveness Ratio (ICER)	WW dominant vs LAR (-\$-28 500, + 0.527 QALYs) Vs APR	Deterministic sensitivity analyses (one-way and two-way): all model parameters PSA (100,000 iterations)

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	achieving a cCR (cohort size = 880)	cytotoxic chemotherapy, surveillance proctoscopy and pelvic MRI)		health states Software : R heemod package Time Horizon: Lifetime Cycle length: one-month Discount rate: 3% Perspective: Payer	registry of patients Institutional comparative registry of patients (WW) World Health Organization data (age-specific background mortality) Nationwide Inpatient Sample data (perioperative)	home care, ileostomy, colostomy, radical resection, palliative colostomy, stoma care, surveillance, clinical evaluation and restaging, local regrowth, distant recurrence, reirradiation, chemotherapy, reirradiation with concurrent capecitabine, monotherapy capecitabine, adjuvant capecitabine, palliative capecitabine,	Health benefits: QALY		(- \$32,100 , + 0.601 QALYs)	Deterministic sensitivity analysis results: sensitive when 5-year DM was 12% in WW when local regrowth was 50% Sensitive to salvage rates after local resection when set at 70% Cost savings driven by postdischarge home care, surveillance, stoma care

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					tive mortality) Dutch randomised trial (utility)	palliative mFOLFOX6 Currency: Dollars Price year (currency): 2019 Source of unit costs: Medicare inpatient and home health-care prospective payment systems, 2019 Medicare Fee Schedule, Published studies				PSA results: LAR was cost-effective in 0.005 to 0.079% of iterations; APR was cost-effective in 0 to 0.014% of iterations
Rao (UK) 2017	Patient with cCR defined by criteria from published guideline.	WW (two options base case: <i>Colorectal Cancer: Diagnosis and</i>	Radical surgery (APR)	Model type: decision tree linked with stated	Published studies but not clear if systematic review	Resource use: Radical surgery; Outpatient visit; CT scans; rigid sigmoidoscopy; flexible sigmoidoscopy;	Effectiveness: Clinical outcomes not reported	Cost-effectiveness, Incremental Cost-Effectiveness	For all three cohorts WW dominant over surgery	One-way sensitivity analysis of all parameters PSA (1000 iterations):

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	(A cCR was judged to have occurred in the absence of residual ulceration, stenosis, or mass within the rectum during digital rectal examination and proctoscopy ≥ 8 weeks after chemoradiotherapy) Three patient cohorts: 60-year-old male cohort with no comorbidities (fm60); 80-year-old male cohorts with no	Management . and scenario analysis: National Comprehensive Cancer Network Guidelines		Transition Markov model with five health states Software : Treeage Time Horizon: Lifetime Cycle length: Yearly Discount rate: 3.5% Perspective: Payer (NHS)	was completed Perioperative mortality from Hospital Episode Statistics Utility values from Dutch Total Mesorectal Excision study	colonoscopy; Multidisciplinary team discussion; exam under anaesthesia, MRI of pelvis; salvage surgery; palliative chemoradiotherapy; palliative surgery; liver resection. Currency: Dollars (later converted to Pounds using exchange rate (\$1.41 = £1)) Price year (currency): Not reported Source of unit costs: NHS	Health benefits: QALY	ess Ratio (ICER)	fm60 cohort = - \$11,332.35 (- £8094.54), + 0.63 QALYs fm80 cohort= - \$8783.93 (- £6274.24), + 0.56 QALYs cm80 cohort = - \$10,206.01 (- £7290.0	using two thresholds and assuming uncorrelated and correlated cost parameters Scenario analysis: (i) analysis performed according to National Comprehensive Cancer Network Guidelines (ii) double healthcare costs (iii) only nonsurgical costs doubled

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	comorbidities (fm80); 80-year-old male cohorts with significant comorbidities (cm80) ^a (cohort size = 1000)					Reference Cost (2014-2015)			1), +0.72 QALYs	One-way sensitivity analysis result: sensitive to relative recurrence rates, impact of RS on HRQoL, perioperative mortality when HRQoL benefit of WW was reduced PSA results: assuming a threshold of \$50,000 per QALY and uncorrelated cost parameters in fm60 cohort WW was cost-effective in 69.6% of

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										iterations; in fm80 WW was cost-effective in 83.5% of iterations; in cm80 cohort WW was cost-effective in 89.2% of iterations Assuming a threshold of \$28,000 per QALY and uncorrelated cost parameters in fm60 cohort WW was cost-effective in 74.0% of iterations; in fm80 WW was cost-effective in 85.0% of iterations; in

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										cm80 cohort WW was cost-effective in 90.1% of iterations assuming a threshold of \$50,000 per QALY and correlated cost parameters in fm60 cohort WW was cost-effective in 71.6% of iterations; in fm80 WW was cost-effective in 83.7% of iterations; in cm80 cohort WW was cost-effective in 90.8% of iterations

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										Assuming a threshold of \$28,000 per QALY and correlated cost parameters in fm60 cohort WW was cost-effective in 75.1.0% of iterations; in fm80 WW was cost-effective in 85.4% of iterations; in cm80 cohort WW was cost-effective in 91.3% of iterations Scenario analysis results: (i) WW less costly in all three cohorts

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										(range: - \$9833.57 (£7023.98) to - \$11,929.62 (£8521.16) with 70.2% to 89.7% probability of being cost-effective at a threshold of \$50,000 per QALY (ii) WW less costly in all three cohorts (range: - \$18,711.61 (£13,365.44) to - \$11,929.62 (£8521.16) with 74.8% to 91.0% probability of being cost-effective at a threshold of

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										\$50,000 per QALY (iii) WW less costly in all three cohorts (range: - \$10,822.69 (£7730.49) to - \$15,845.08 (£11,317.91) with 70.4% to 84.3% probability of being cost-effective at a threshold of \$50,000 per QALY

Prospective study

First author (country, date)	Study population	Intervention	Comparator	Study design	Type of cost included	Valuation of cost	Outcome reported	Type of economic evaluation and analysis	Result	Sensitivity Analysis
Ferri V et al. Spain 2023	cCR defined 40 patients who underwent watch-and-wait compared with 40 patients treated by surgery and who have pathological complete response.	Watch-and-wait	Resection surgery (TME)	Cohort study Perspective: Not reported (only reported direct hospital cost) Time horizon: Not reported Discount rate: Not reported	Direct: Direct hospital cost. For surgical group: all cost of care during hospital stay. For watch and wait, only follow-up cost. The detail cost is not presented	Currency: Euros Price year (currency): Not reported Sources of unit costs: Institute of Validation of Efficacy Clinic (IVEC) of the HM Hospitals group. Patient's unique medical	Effectiveness: Oncological outcomes: Overall survival, metastasis-free survival, recurrence-free survival, local regrowth Valuation of benefit: Quality Adjusted Life Years (QALYs)	Cost-utility analysis	(-4,439, +0.260)	Not reported

						record number				
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