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Article

Cost-Effectiveness and Quality-Adjusted Survival of Watch and Wait After Complete Response to Chemoradiotherapy for Rectal Cancer

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Abstract

Background: Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the standard treatment for locally advanced rectal cancer. There is interest in deescalating local therapy after a clinical complete response to CRT. We hypothesized that a watch-and-wait (WW) strategy offers comparable cancer-specific survival, superior quality-adjusted survival, and reduced cost compared with upfront TME. **Methods:** We developed a decision-analytic model to compare WW, low anterior resection, and abdominoperineal resection for patients achieving a clinical complete response to CRT. Rates of local regrowth, pelvic recurrence, and distant metastasis were derived from series comparing WW with TME after pathologic complete response. Lifetime incremental costs and quality-adjusted life-years (QALY) were calculated between strategies, and sensitivity analyses were performed to study model uncertainty. **Results:** The base case 5-year cancer-specific survival was 93.5% (95% confidence interval [CI] = 91.5% to 94.9%) on a WW program compared with 95.9% (95% CI = 93.6% to 97.4%) after upfront TME. WW was dominant relative to low anterior resection, with cost savings of $28 500 (95% CI = $22 200 to $39 000) and incremental QALY of 0.527 (95% CI = 0.138 to 1.125). WW was also dominant relative to abdominoperineal resection, with a cost savings of $32 100 (95% CI = $21 800 to $49 200) and incremental QALY of 0.601 (95% CI = 0.213 to 1.208). WW remained dominant in sensitivity analysis unless the rate of surgical salvage fell to 73.0%. **Conclusions:** Using current multi-institutional recurrence estimates, we observed comparable cancer-specific survival, superior quality-adjusted survival, and decreased costs with WW compared with upfront TME. Upfront TME was preferred when surgical salvage rates were low.

ARTICLE

Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the standard treatment for locally advanced rectal cancer in the United States (1). Rates of pelvic recurrence (PR) with this approach are approximately 5% (2–4) and are lower (1%) among patients who achieve a pathologic complete response (pCR) (5–7). Despite excellent local control, rates of distant metastasis (DM) can exceed 25% (4,8,9). In response to these disparate local and distant recurrence rates, there has been interest in intensification and adherence to systemic therapy, with concomitant deintensification of local therapies.

Following standard neoadjuvant CRT, approximately 15% of patients achieve a clinical complete response (cCR) by examination, endoscopy, and/or imaging (9,10). For these patients, some centers have offered a watch-and-wait (WW) approach in lieu of TME, with similar rates of DM and cancer-specific survival (6,11–14). This approach may thereby improve short- and long-term quality of life, because TME is associated with perioperative morbidity and mortality; sexual, urinary, and bowel dysfunction; low anterior resection (LAR) syndrome; and/or permanent ostomy (2,15,16). Patients who are offered this approach are closely surveilled for early detection of local regrowth (LR), which occurs in approximately 25% of patients and is surgically salvageable in more than 90% of cases (6,7,11).

With the increasing use of total neoadjuvant therapy, more patients achieve complete responses and may be candidates for WW (17). Given the added morbidity of TME and the encouraging clinical outcomes among patients who achieve cCR, the added benefit and cost-effectiveness of upfront TME are uncertain. We therefore hypothesized that a WW strategy offers comparable cancer-specific survival, superior quality-adjusted survival, and reduced cost relative to upfront TME.

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Methods

Decision Analytic Model

We developed a decision-analytic Markov model to study the cost and quality-adjusted survival of three management strategies using the *R heemod* package (Figure 1A) (18). Adult patients with resectable locally advanced (T3-4N0 or node-positive) rectal adenocarcinoma entered the model after achieving a cCR to standard upfront CRT. Patients proceeded to WW surveillance, upfront LAR with temporary defunctioning ileostomy and standard postoperative surveillance, or upfront abdominoperineal resection (APR) with permanent colostomy and standard postoperative surveillance. Defunctioning ileostomies were reversed 4 months after LAR (19,20). Patients entered the model at age 64 years based on a large registry of 880 patients managed with WW (11).

Perioperative mortality following TME and palliative diverting ostomy were estimated from Nationwide Inpatient Sample data (16). Age-specific background mortality was derived from World Health Organization data (21). Monthly transition probabilities to LR, PR, and DM were derived from three datasets: a multi-institutional international observational registry of patients managed with WW (11), an institutional comparative registry of patients managed with WW or who were found to have achieved a pCR after TME (6), and a separate meta-analysis of 344 patients who were found to have a pCR after CRT and TME (5). Time-dependent estimates of LR, PR, and DM were extracted from these studies using the Engauge Digitizer version 10.9 (Table 1). Extracted data were weighted based on cohort size and fit to flexible, semiparametric, spline-based survival models using the *R flexsurv* package then compared against parametric models with specified survival distributions via the Akaike information criterion (Figure 1; Supplementary Methods; Supplementary Table 1, available online) (33).

All patients who developed LR, PR, or DM were examined in a multidisciplinary setting, biopsied, and restaged (Supplementary Table 2, available online) (1). Following LR in the WW strategy, patients either were salvaged with TME (50% APR, 50% LAR) or were unsalvageable (6,11,34). The probability of successful salvage following LR in the WW cohort was defined by the aforementioned WW series (6,11). Patients who were successfully salvaged with TME continued with standard postoperative surveillance identical to the LAR or APR strategies (Supplementary Table 3, available online). Patients who developed PRs after upfront TME first underwent capecitabine-based, hyperfractionated, preoperative CRT based on consensus recommendations and a phase II trial (Supplementary Tables 4 and 5, available online) (1,23,24,35). Thereafter, 63% of patients underwent attempted radical resection after reirradiation, followed by 4 months of adjuvant capecitabine. Patients with either unsalvageable local recurrence after WW or unsalvageable PR after upfront TME proceeded to palliative diverting ostomy and palliative capecitabine monotherapy (Supplementary Tables 4–7, available online) (1). Survival of such patients was based on two series of isolated LR after TME (23,25). Following

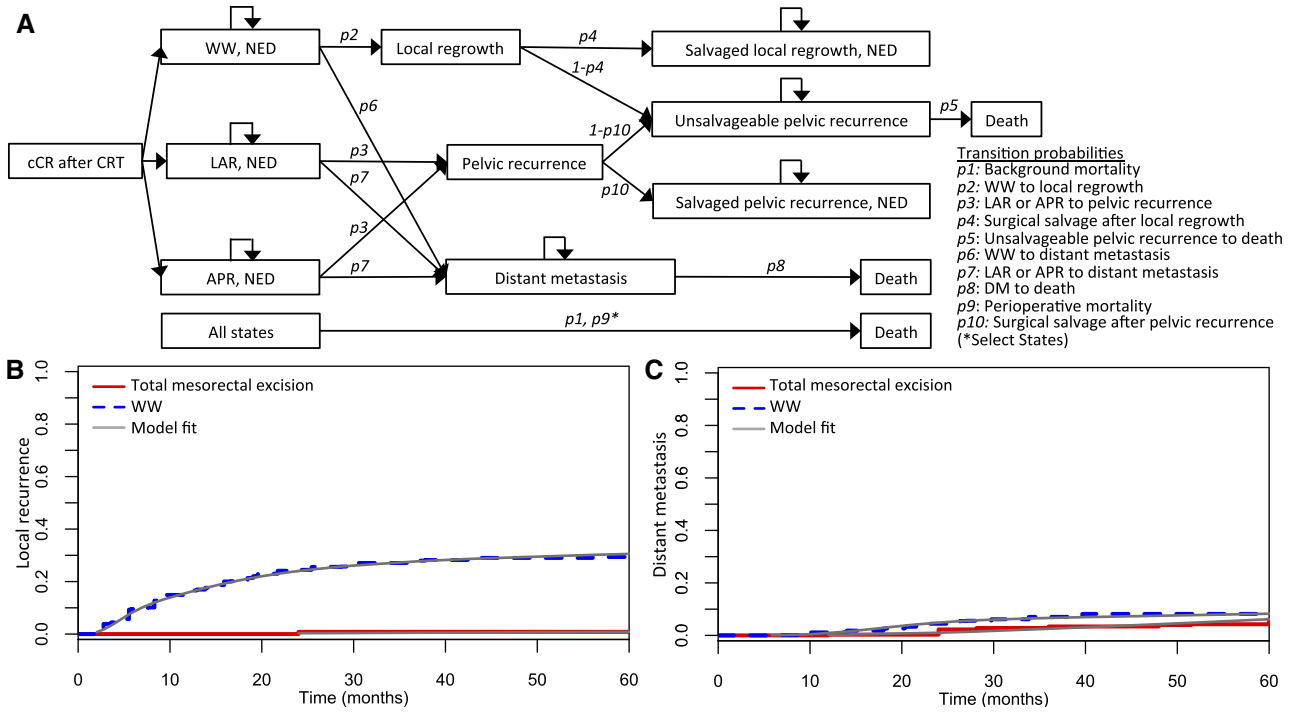

Figure 1. Markov decision-analytic model and cumulative incidences of local recurrence and distant metastasis (DM). **A**) Schematic of Markov decision-analytic model. Patients who achieve a clinical complete response (cCR) to chemoradiotherapy (CRT) proceed to one of three management strategies: watch-and-wait (WW) surveillance, upfront low anterior resection (LAR), or upfront abdominoperineal resection (APR). At model entry, patients had no evidence of disease (NED) but could develop local regrowth, pelvic recurrence, and/or distant metastasis. Local regrowth after WW was either successfully surgically salvaged and entered a state similar to LAR or APR (NED), or were unsalvageable and patients died of their disease. Patients who underwent upfront LAR or APR and developed a pelvic recurrence were either salvaged with multimodality therapy or were unsalvageable and died of their disease. All patients were subject to age-specific background mortality, and patients undergoing LAR or APR or palliative surgery were subject to perioperative mortality. Cumulative incidence of local recurrence (**B**) and distant metastasis (**C**) using extracted and pooled published estimates for total mesorectal excision (**solid lines**) or WW (**dashed lines**). Flexible, semiparametric, spline-based models are fit to these extracted data and superimposed (**solid gray lines**).

Table 1. Summary of model transition probabilities, health state utilities, and costs*

Model parameter	Strategy A: WW	Strategy B: low anterior resection	Strategy C: APR	Range studied	Distribution	Reference
Modeled transition probabilities						
cCR (NED) to local regrowth (WW) or PR (LAR or APR): 2 y†	24.0%	0.0%	0.0%	WW: 8.0–28.0%	Beta	Li 2016 (5), Smith 2019 (6), van der Valk 2018 (11) (base case); Maas 2011 (12), Renehan 2016 (13) (range)
cCR (NED) to local regrowth (WW) or PR (LAR or APR): 5 y†	30.5%	1.0%	1.0%	WW: 10.0–35.0%	Beta	Li 2016 (5), Smith 2019 (6), van der Valk 2018 (11) (base case); Maas 2011 (12), Renehan 2016 (13) (range)
cCR (NED) to DM: 2 y†	3.4%	2.0%	2.0%	WW: 2.0–5.9%	Beta	Li 2016 (5), Smith 2019 (6), van der Valk 2018 (11) (base case); Smith 2019 (6), Habr—Gama 2014 (22) (range)
cCR (NED) to DM: 5 y†	8.2%	6.2%	6.2%	WW: 6.2–10.0%	Beta	Li 2016 (5), Smith 2019 (6), van der Valk 2018 (11) (base case); Smith 2019 (6), Habr—Gama 2014 (22) (range)
Local regrowth to NED via TME salvage: WW‡	94.5%	—	—	70–100%	Beta	Smith 2019 (6), van der Valk 2018 (11) (base case); Smith 62019), Renehan 2016 (13) (range)
Local regrowth to unsalvageable PR: WW‡	5.5%	—	—	0–30%	Beta	Smith 2019 (6), van der Valk 2018 (11) (base case); Smith 2019 (6), Renehan 2016 (13) (range)
PR after LAR or APR to attempted radical resection§	—	63%	63%	20–80%	Beta	Valentini 2006 (23) (base case); Guren 2014 (24) (range)
PR after LAR or APR to unsalvageable PR§	—	37%	37%	20–80%	Beta	Valentini 2006 (23) (base case); Guren 2014 (24) (range)
Attempted radical resection after PR to death: 2 y†	—	25%	25%	0–35%	Beta	Valentini 2006 (23) (base case); Guren 2014 (24) (range)
Unsalvageable PR to death: 2 y†	39%	39%	39%	30–55%	Beta	Valentini 2006 (23), Ikoma 2017 (25) (base case); Guren 2014 (24) (range)
Perioperative mortality	0.6%†	0.6%	0.6%	0.1–1.0%	Beta	Moghadamyeghaneh 2015 (16) (base case); Mohiuddin 2002 (26) (range)
Age-specific background mortality‖	Age dependent, >0.1% per y	Age dependent, >0.1% per y	Age dependent, >0.1% per y	Age 40–75 y at model entry	Beta	The Global Health Observatory 2017 (21)
DM to death: 1 y†	27%	27%	27%	15–50%	Beta	Goldberg 2004 (27)
Health state utilities						
Disutility of LAR or APR relative to WW	—	−0.079	−0.079	−0.099, −0.059	Beta	Hupkens 2017 (28), Crott 2010 (29)
cCR after CRT and APR: 0–4 mo	—	—	0.740	0.720–0.760	Beta	Van Den Brink 2004 (30)
cCR after CRT and APR: 5–9 mo	—	—	0.790	0.770–0.810	Beta	Van Den Brink 2004 (30)
cCR after CRT and APR: >9 mo	—	—	0.850	0.830–0.870	Beta	Van Den Brink 2004 (30)
cCR after CRT and LAR: 0–4 mo¶	—	0.710	—	0.690–0.730	Beta	Van Den Brink 2004 (30)
cCR after CRT and LAR: 5–9 mo	—	0.850	—	0.830–0.870	Beta	Van Den Brink 2004 (30)
cCR after CRT and LAR: >9 mo	—	0.860	—	0.840–0.880	Beta	Van Den Brink 2004 (30)
cCR after CRT alone: 0–4 mo#	0.804	—	—	0.784–0.824	Beta	Van Den Brink 2004 (30)
cCR after CRT alone: 5–9 mo#	0.899	—	—	0.879–0.919	Beta	Van Den Brink 2004 (30)
cCR after CRT alone: >9 mo#	0.934	—	—	0.914–0.954	Beta	Van Den Brink 2004 (30)
PR	0.670	0.670	0.670	0.650–0.690	Beta	Van Den Brink 2004 (30)

(continued)

Table 1. (continued)

Model parameter	Strategy A: WW	Strategy B: low anterior resection	Strategy C: APR	Range studied	Distribution	Reference
Distant recurrence	0.700	0.700	0.700	0.680–0.720	Beta	Van Den Brink 2004 (30)
Death	0	0	0			
Summary of costs						
Hospital, surgical, and postoperative costs						
Admission (×2), LAR, diverting ileostomy, and ileostomy reversal	—	$43 100	—	80–150%	Gamma	Supplementary Table 7 (available online)
Admission (×1), APR, permanent colostomy	—	—	$23 000	80–150%	Gamma	Supplementary Table 7 (available online)
Admission (×1) and radical resection for PR	—	$22 800	$22 800	80–150%	Gamma	Supplementary Table 7 (available online)
Admission (×1) and palliative colostomy for PR	$22 200	$22 200	$22 200	80–150%	Gamma	Supplementary Table 7 (available online)
Postdischarge home health care, per episode	$2700	$2700	$2700	80–150%	Gamma	Supplementary Table 7 (available online) (31)
Stoma care, per y	$1900	$1900	$1900	80–150%	Gamma	Supplementary Table 7 (available online) (32)
Surveillance costs after CRT ± LAR or APR, y 1–5	$11 200	$5700	$5700	80–150%	Gamma	Supplementary Table 3 (available online)
Clinical evaluation and restaging for recurrent disease						
Local regrowth or PR	$2100	$2100	$2100	80–150%	Gamma	Supplementary Table 2 (available online)
Distant recurrence	$1200	$1200	$1200	80–150%	Gamma	Supplementary Table 2 (available online)
Reirradiation for PR, single course	—	$19 800	$19 800	80–150%	Gamma	Supplementary Table 4 (available online)
Chemotherapy for recurrent or metastatic disease						
Reirradiation: concurrent capecitabine monotherapy, single course	—	$1100	$1100	80–150%	Gamma	Supplementary Table 5 (available online)
Adjuvant capecitabine after reirradiation, 4 mo	—	$3100	$3100	80–150%	Gamma	Supplementary Table 5 (available online)
Palliative capecitabine for unsalvageable PR, per cycle	$510	$510	$510	80–150%	Gamma	Supplementary Table 5 (available online)
Palliative mFOLFOX6 for DM, per cycle	$850	$850	$850	80–150%	Gamma	Supplementary Table 5 (available online)

*All costs are presented in 2019 US dollars. APR = abdominoperineal resection; cCR = complete clinical response; CRT = chemoradiotherapy; DM = distant metastasis; LAR = low anterior resection; mFOLFOX = modified 5-fluorouracil, leucovorin, and oxaliplatin; NED = no evidence of disease; PR = pelvic recurrence; TME = total mesorectal excision; WW = watch and wait.

†Time dependent.

‡A total 94.5% of local regrowths are salvageable with TME, and return to NED, and the remaining 5.5% are ultimately unsalvageable PRs.[6, 11]

§In a phase II trial, 37% of patients were failure free at 5 years after preoperative hyperfractionated CRT, radical resection, and adjuvant chemotherapy for PR after TME. A total of 63% of patients underwent attempted radical resection after reirradiation.

||Varies with patient age as model time increases.

¶Health utility for patients undergoing a temporary defunctioning stoma that was ultimately reversed was 0.710 for months 0–4 after LAR.[30] After reversal (months 5+), health utility was identical between patients who had a reversed stoma and those with no history of any stoma.

#Average of LAR and APR minus disutility of LAR or APR (0.079).

DM, patients were managed with mFOLFOX6 every 2 weeks until death, with transition estimates to death based on a randomized trial (Supplementary Tables 5–6, available online) (27). Patients were followed until death from rectal cancer or background mortality on a lifetime horizon with a monthly cycle length.

Surveillance Programs

Two surveillance programs were considered. The first was defined by NCCN guidelines for patients who proceeded with standard upfront TME and was also used for patients who were salvaged after LR in the WW strategy (Supplementary Table 3, available online) (1). Patients in the WW strategy also completed this surveillance program but were followed with additional or more frequent examinations, carcinoembryonic antigen, surveillance proctoscopy, and pelvic MRI, as defined by a Dutch WW protocol (Supplementary Table 3, available online) (12). Patients remained under surveillance until experiencing LR, DM, or death. Patients who were salvaged after LR returned to standard postoperative surveillance.

Health States and Utilities

Health states included no evidence of disease (NED) after CRT alone (months 0–4, 5–9, and >9), NED after APR (months 0–4, 5–9, and >9), NED after LAR (months 0–4, 5–9, and >9), LR, DM, and death (Table 1). All health states except for the disutility of LAR or APR relative to WW were derived from a Dutch randomized trial (15,30). Specifically, utilities in the CRT+TME trial arm were used to define the time-dependent utility after LAR (temporary diverting stoma [months 0–4], then no stoma [months 5+]) or APR (permanent stoma). Utilities of LR and DM were also derived from this dataset. To ascertain the disutility of LAR or APR relative to WW after CRT, we mapped EORTC QLQ-C30 responses from a matched cohort study of patients managed with either WW after cCR or TME without long-term recurrence (28,29). To calculate utilities in the WW cohort, the disutility of TME (0.079) was subtracted from the average of LAR and APR utilities at each time point in the Dutch cohort.

Costs and Discounting

We performed microcosting for all services except for the bundled hospital costs of LAR or APR, defunctioning stoma reversal after LAR, palliative diverting ostomy, radical resection for PRs, and annual stoma care (Supplementary Table 7, available online). For each procedure, hospital costs were calculated using national payment amounts for relevant diagnosis-related group codes, weighted by the national distribution of discharges for each individual severity-adjusted diagnosis-related group. Each surgical episode of care included procedural costs, hospital costs, and home health wound or ostomy care. Data were obtained the Medicare inpatient and home health-care prospective payment systems (31,36). The cost of stoma care was obtained from a randomized trial of skin barriers (32). Beyond home health care and stoma care, other postdischarge costs related to readmission after TME were not explicitly included because of relatively low readmission rates (37). All other microcosting was performed using 2019 Medicare fee schedules (38–40). Costs were analyzed from the payer's perspective and presented in 2019 US dollars rounded to the nearest 100. All costs were inflated to the year 2019 using the Consumer Price Index, and all costs and utilities were discounted at a rate of 3% annually (41).

Statistical Analysis

Total costs and quality-adjusted life-years (QALY) were recorded for each of the three treatment strategies over a lifetime horizon. Incremental costs, incremental QALY, and incremental cost-effectiveness ratios were calculated between each of the strategies. We considered a range of willingness to pay (WTP) thresholds ($50 000, $63 000 [United States per-capita GDP], $100 000, $126 000, and $150 000) in accordance with World Health Organization recommendations (42).

To assess the robustness of the model, we performed one-way deterministic and probabilistic sensitivity analyses by varying all model parameters. Transition probabilities and health utilities were varied according to published confidence intervals and modeled using beta distributions (43). Costs were varied from 80% to 150% around the base case assumption and modeled with gamma distributions. Probabilistic sensitivity analysis was performed with 100 000 iterations to study the impact of uncertainty in costs and utilities on cost-effectiveness. We incorporated correlation in health utility uncertainty distributions based on commonsense preferences for those states using a preference order matrix (Supplementary Methods, available online) (44). This study was conducted in accordance with CHEERS reporting standards (45).

Results

Base Case Result

In the base case assumption, 5-year modeled cancer-specific survival was 93.5% (95% CI = 91.5% to 94.9%) among patients managed with WW compared with 95.9% (95% CI = 93.6% to 97.4%) among patients managed with upfront LAR or APR (Supplementary Table 1; Supplementary Figure 1, available online). Over a lifetime horizon, 9.9% of patients managed with WW died of their disease, compared with 7.5% with upfront LAR or APR, because of the modeled attributable increase in DM and unsalvageable PR. Nevertheless, the WW strategy was dominant relative to LAR, with an incremental cost of −$28 500 (Supplementary Figure 2A, available online) and incremental QALY of 0.527 (Supplementary Figure 2B, available online). Relative to APR, the WW strategy was also dominant, with an incremental cost of −$32 100 and incremental QALY of 0.601 (Table 2).

Deterministic Sensitivity Analysis

Rates of LR and DM were primary determinants of cancer-specific survival and QALY (Table 3; Figure 2). WW remained dominant even at the upper bound of 5-year LR (35.0%), albeit with a smaller incremental effectiveness (0.470 vs LAR, 0.545 vs APR). Similarly, at the upper bound of 5-year DM (10.0%), lifetime incremental QALY continued to favor WW over LAR (0.374) and APR (0.448). Upfront LAR was only preferred when both the rate of 5-year DM in the WW strategy was increased above published estimates to 12.0% and the rate of LR was at least 50.0% (Supplementary Figure 3A; Supplementary Table 8, available online).

A range of published surgical salvage rates after LR was studied (70.0–100.0%) (6,7,11,13,14,34,46). At the lower bound of these

Table 2. Base case results*

Strategy A: WW					Strategy B: LAR				Strategy C: APR			
WW		Relative to LAR			LAR	Relative to APR			APR	Relative to APR		
Costs	QALY	Incremental cost	Incremental QALY	ICER	Costs	Incremental cost	Incremental QALY	ICER	Costs	Incremental cost	Incremental QALY	ICER
$31 800	12.652	−$28 500	0.527	Dominant	$60 200	−$32 100	0.601	Dominant	$63 800	−$3600	0.075	Dominant
					12.125				12.050			

*All costs are presented in 2019 US dollars. APR = abdominoperineal resection; ICER = incremental cost-effectiveness ratio; LAR = low anterior resection; QALY = quality-adjusted life-years; WW = watch and wait.

salvage rates (70.0%), LAR and APR both offered slightly superior lifetime QALY to WW (LAR = −0.088, APR = −0.014) because an unsalvageable PR was assumed to confer a poor prognosis (23–25). The surgical salvage rate at which LAR and APR offered superior lifetime QALY over WW were 73.0% and 70.0%, respectively (Supplementary Figure 3, C and D, available online). There was little change (≤0.1) in incremental QALY when varying perioperative mortality and survival with distant metastatic or unsalvageable locally recurrent disease, with WW remaining dominant across the range of published estimates.

When varying all health utilities by twice the published SD in a cohort of patients with rectal cancer (29,43), WW remained dominant relative to both LAR and APR (Table 3; Figure 2). When the long-term utility after LAR and APR was increased to the upper limit, incremental QALY of WW decreased to 0.298 and 0.370, respectively. When the disutility of LAR and APR relative to WW was respectively decreased to 0.035 and 0.019 (from 0.079), upfront TME offered superior lifetime incremental QALY.

Increasing WW surveillance costs from 80% to 150% of the base case reduced incremental cost savings by approximately $6000 (Table 3; Figure 2). Similarly, increasing postoperative surveillance costs from 80% to 150% of the base case increased incremental cost savings in the WW strategy by $3500. Increasing the cost of LAR or APR from 80% to 150% of the base case considerably increased WW incremental cost savings from $15 800 to $41 700 relative to LAR, and from $25 800 to $39 700 relative to APR. Beyond the cost of TME itself, the primary determinants of total cost were LR after WW, postdischarge home health care, surveillance after WW or TME, and stoma care (particularly for younger patients). Incremental cost savings of WW relative to APR were notably sensitive to the cost of annual stoma care ($27 400–$43 900 from 80% to 150% of the base case). The cost of a palliative diverting ostomy, salvage therapies for PRs, and palliative chemotherapy for DM or unsalvageable PR had little impact on cost savings.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analyses were in close agreement with the base case analysis. Compared with LAR, the WW strategy demonstrated a median incremental cost of −$29 000 (95% CI = −$22 200 to −$39 000) and incremental QALY of 0.536 (95% CI = 0.138 to 1.125). LAR was less costly than WW in 0.0% of simulations and offered superior incremental QALY in only 0.5% of simulations (Figure 3). Among the WTP thresholds, upfront LAR was cost-effective in 0.005–0.079% of simulations (Supplementary Table 9, available online).

Compared with APR, the median WW strategy demonstrated an incremental cost of −$33 100 (95% CI = −$21 800 to −$49 200) and incremental QALY of 0.646 (95% CI = 0.213 to 1.208). APR was less costly than WW in 0.0% of simulations and offered superior incremental QALY in only 0.2% of simulations. Among the WTP thresholds, upfront APR was cost-effective in 0.000–0.014% of simulations (Supplementary Table 9, available online).

Compared with APR, the median LAR strategy demonstrated an incremental cost of −$3900 (95% CI = −$17 400 to +$7000) and incremental QALY of 0.070 (95% CI = −0.055 to 0.219). APR was less costly than WW in 26.7% of simulations and offered superior incremental QALY in 12.9% of simulations (Figure 3).

Table 3. Results of one-way deterministic and probabilistic sensitivity analyses*

Parameter			WW, relative to LAR						WW, relative to APR					
			Incremental cost		Incremental effect		Incremental ICER		Incremental cost		Incremental effect		Incremental ICER	
	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Base case result			−$28 500		0.527		Dominant	Dominant	−$32 100		0.601		Dominant	Dominant
Age-specific background mortality†,‡	40 y	75 y	−$26 500	−$30 400	0.755	0.301	Dominant	Dominant	−$43 700	−$20 700	0.863	0.341	Dominant	Dominant
Modeled transition probabilities														
cCR (NED) to local regrowth: WW, 5 y‡	10%	35%	−$37 500	−$26 700	0.823	0.470	Dominant	Dominant	−$41 100	−$30 400	0.897	0.545	Dominant	Dominant
cCR (NED) to DM: WW, 5 y‡	6.2%	10%	−$29 800	−$27 400	0.780	0.374	Dominant	Dominant	−$33 400	−$31 000	0.854	0.448	Dominant	Dominant
Local regrowth to NED via TME: surgical salvage rate for WW	70%	100%	−$27 300	−$28 700	−0.088	0.640	$310 200	Dominant	−$31 000	−$32 300	−0.014	0.714	$2 214 300	Dominant
Attempted radical resection rate for PR after LAR or APR	20%	80%	−$28 300	−$28 500	0.520	0.529	Dominant	Dominant	−$31 800	−$32 200	0.595	0.604	Dominant	Dominant
Attempted radical resection for PR to death: 2 y‡	15%	40%	−$28 500	−$28 500	0.509	0.534	Dominant	Dominant	−$32 100	−$32 100	0.583	0.608	Dominant	Dominant
Unsalvageable PR to death: 2 y‡	30%	55%	−$28 600	−$28 800	0.518	0.509	Dominant	Dominant	−$32 200	−$32 400	0.592	0.583	Dominant	Dominant
DM to death:1 y‡	15%	50%	−$27 300	−$29 300	0.561	0.504	Dominant	Dominant	−$31 100	−$32 700	0.635	0.579	Dominant	Dominant
Perioperative mortality	0.1%	1.0%	−$28 800	−$28 200	0.420	0.612	Dominant	Dominant	−$32 300	−$31 900	0.556	0.637	Dominant	Dominant
Health utilities														
cCR after CRT and APR: 0–4 mo	0.720	0.760	−$28 500	−$28 500	0.527¶	0.527	Dominant	Dominant	−$32 100	−$32 100	0.608	0.594	Dominant	Dominant
cCR after CRT and APR: 5–9 mo	0.770	0.810	−$28 500	−$28 500	0.527	0.527	Dominant	Dominant	−$32 100	−$32 100	0.609	0.593	Dominant	Dominant
cCR after CRT and APR: >9 mo	0.830	0.870	−$28 500	−$28 500	0.491	0.563	Dominant	Dominant	−$32 100	−$32 100	0.832	0.370	Dominant	Dominant
cCR after CRT and LAR: 0–4 mo	0.690	0.730	−$28 500	−$28 500	0.514	0.500	Dominant	Dominant	−$32 100	−$32 100	0.601¶	0.601	Dominant	Dominant
cCR after CRT and LAR: 5–9 mo	0.830	0.870	−$28 500	−$28 500	0.535	0.519	Dominant	Dominant	−$32 100	−$32 100	0.601	0.601	Dominant	Dominant
cCR after CRT and LAR: >9 mo	0.840	0.880	−$28 500	−$28 500	0.755	0.298	Dominant	Dominant	−$32 100	−$32 100	0.565	0.637	Dominant	Dominant
cCR after CRT alone: 0–4 mo§	0.784	0.824	−$28 500	−$28 500	0.520	0.533	Dominant	Dominant	−$32 100	−$32 100	0.595	0.608	Dominant	Dominant
cCR after CRT alone: 5–9 mo§	0.879	0.919	−$28 500	−$28 500	0.519	0.534	Dominant	Dominant	−$32 100	−$32 100	0.594	0.609	Dominant	Dominant
cCR after CRT alone: >9 mo§	0.914	0.954	−$28 500	−$28 500	0.340	0.713	Dominant	Dominant	−$32 100	−$32 100	0.414	0.788	Dominant	Dominant
PR	0.650	0.690	−$28 500	−$28 500	0.525	0.528	Dominant	Dominant	−$32 100	−$32 100	0.600	0.602	Dominant	Dominant
Distant recurrence	0.680	0.720	−$28 500	−$28 500	0.525	0.528	Dominant	Dominant	−$32 100	−$32 100	0.600	0.603	Dominant	Dominant
Costs‖														
Hospital, surgical, and postoperative costs														
Admission (×2), LAR, diverting ileostomy, and ileostomy reversal	$34 500	$64 700	−$15 800	−$41 700	0.527	0.527	Dominant	Dominant	−$34 100	−$30 000	0.601	0.601	Dominant	Dominant
Admission (×1), APR, permanent colostomy	$18 400	$34 500	−$29 500	−$27 300	0.527	0.527	Dominant	Dominant	−$25 800	−$39 700	0.601	0.601	Dominant	Dominant
Admission (×1) and radical resection for PR	$18 200	$34 200	−$28 400	−$28 500	0.527	0.527	Dominant	Dominant	−$32 000	−$32 100	0.601	0.601	Dominant	Dominant
Admission (×1) and palliative colostomy for PR	$17 800	$33 300	−$28 500	−$28 300	0.527	0.527	Dominant	Dominant	−$32 200	−$31 900	0.601	0.601	Dominant	Dominant
Postdischarge home health care, per episode	$2200	$4100	−$27 600	−$30 600	0.527	0.527	Dominant	Dominant	−$31 800	−$32 900	0.601	0.601	Dominant	Dominant
Stoma care, per year	$1500	$2900	−$29 100	−$26 800	0.527	0.527	Dominant	Dominant	−$27 400	−$43 900	0.601	0.601	Dominant	Dominant
Surveillance costs after CRT for WW, y 1–5	$9000	$16 800	−$30 200	−$24 000	0.527	0.527	Dominant	Dominant	−$33 900	−$27 600	0.601	0.601	Dominant	Dominant
Surveillance costs after CRT + LAR or APR, y 1–5	$4600	$8600	−$27 500	−$30 900	0.527	0.527	Dominant	Dominant	−$31 100	−$34 500	0.601	0.601	Dominant	Dominant
Restaging for local regrowth or PR	$1700	$3200	−$28 600	−$28 200	0.527	0.527	Dominant	Dominant	−$32 200	−$31 800	0.601	0.601	Dominant	Dominant
Restaging for distant recurrence	$1000	$1800	−$28 600	−$28 200	0.527	0.527	Dominant	Dominant	−$32 200	−$31 800	0.601	0.601	Dominant	Dominant
Reirradiation for PR, single course	$15 800	$29 700	−$28 400	−$28 500	0.527	0.527	Dominant	Dominant	−$32 000	−$32 200	0.601	0.601	Dominant	Dominant
Postoperative chemotherapy after radical resection	$2500	$4700	−$28 500	−$28 500	0.527	0.527	Dominant	Dominant	−$32 100	−$32 100	0.601	0.601	Dominant	Dominant
Annual cost of managing unsalvageable PR	$9700	$18 200	−$28 600	−$28 200	0.527	0.527	Dominant	Dominant	−$32 200	−$31 800	0.601	0.601	Dominant	Dominant
Annual cost of managing DM	$19 600	$36 700	−$28 800	−$27 600	0.527	0.527	Dominant	Dominant	−$32 400	−$31 200	0.601	0.601	Dominant	Dominant
Probabilistic sensitivity analysis			−$29 000 (95% CI = −$22 200 to −$39 000)		0.536 (95% CI = 0.138 to 1.125)		Dominant	Dominant	−$33 100 (95% CI = −$21 800 to −$49 200)		0.646 (95% CI = 0.213 to 1.208)		Dominant	Dominant

*All costs are presented in 2019 US dollars. APR = abdominoperineal resection; cCR = complete clinical response; CI = confidence interval; CRT = chemoradiotherapy; DM = distant metastasis; ICER = incremental cost-effectiveness ratio; LAR = low anterior resection; NED = no evidence of disease; PR = pelvic recurrence; WW = watch and wait.

†Varies with patient age as model time increases. Range is equivalent to varying patient age from 40 to 75 years at model entry.

‡Time dependent.

§Equivalent to varying disutility of LAR or APR relative to WW over this period.

‖Total 80–150% of base case cost.

¶Included for patients who develop local regrowth and undergo salvage LAR or APR.

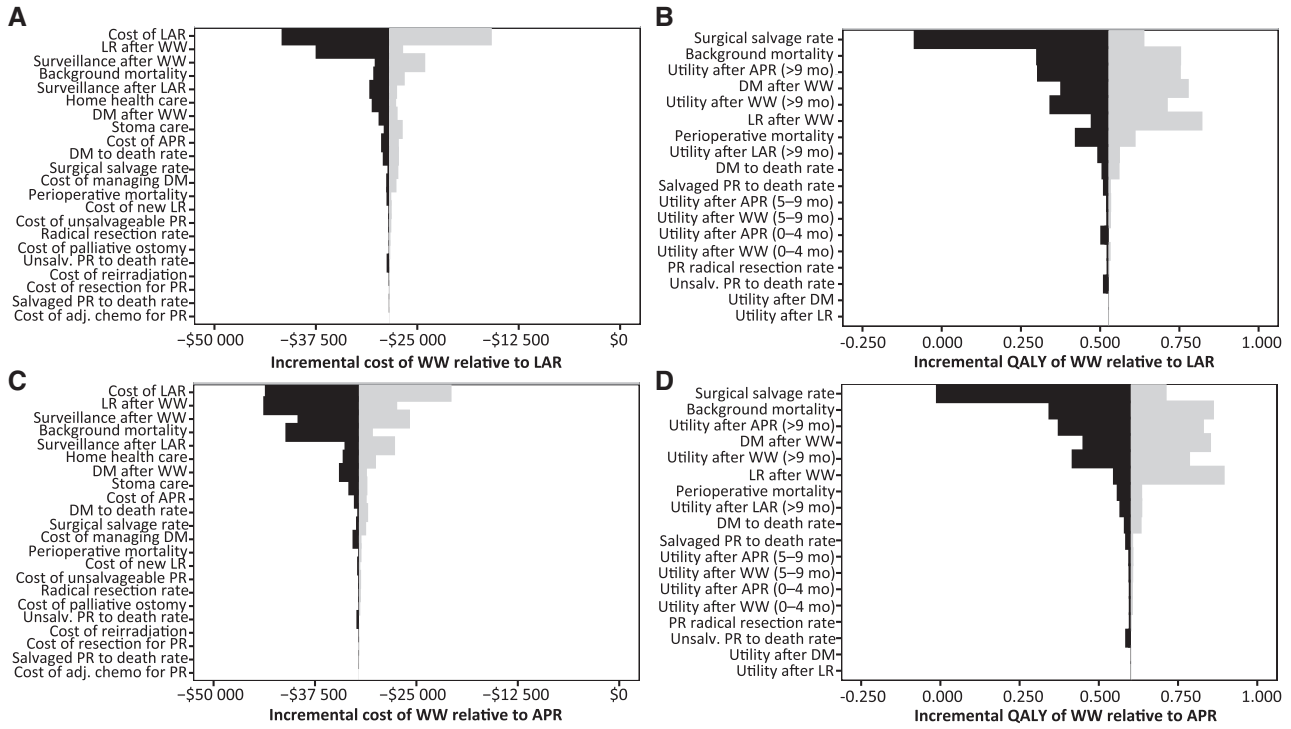

Figure 2. Tornado plots of one-way deterministic sensitivity analyses of watch and wait (WW) relative to low anterior resection (LAR) and abdominoperineal resection (APR). Incremental costs [WW vs LAR (**A**) and WW vs APR (**C**)] and incremental quality-adjusted life-years [QALY; WW vs LAR (**B**) and WW vs APR (**D**)] are plotted against model parameters. Adj. = adjuvant; DM = distant metastasis; LR = local regrowth; PR = pelvic recurrence; Unsalv. = unsalvageable.

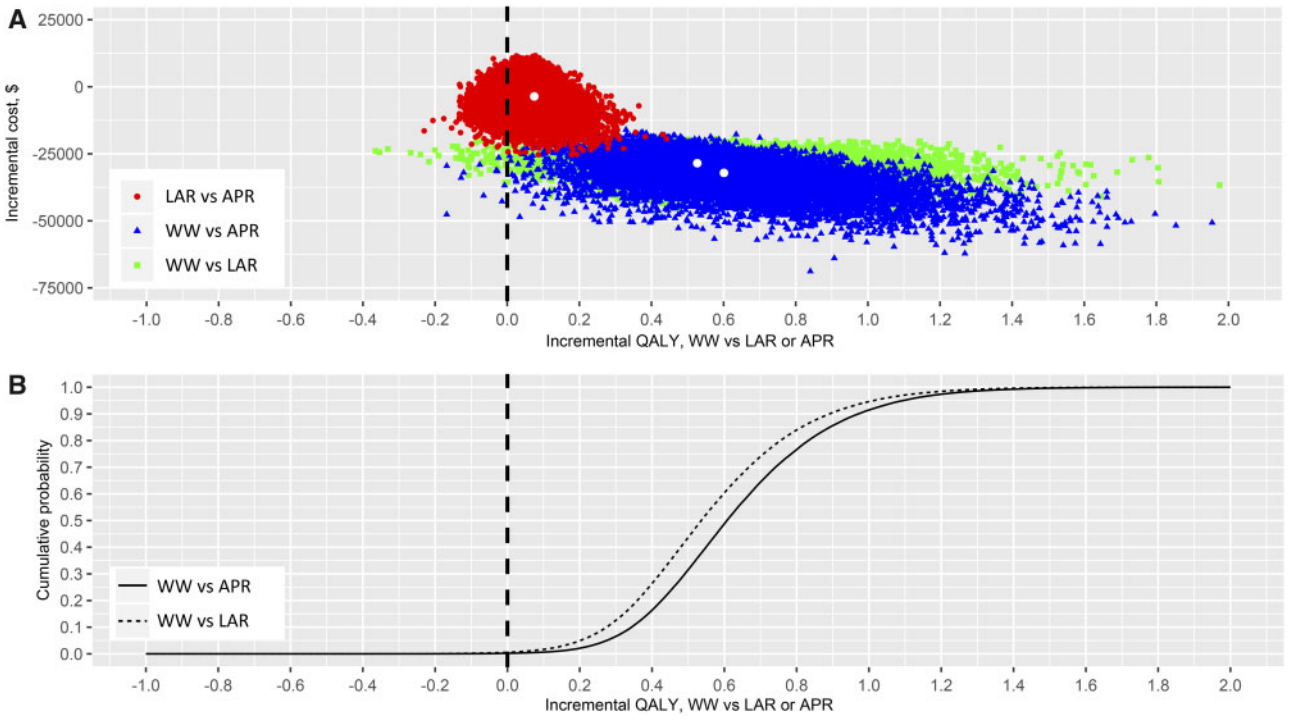

Figure 3. Probabilistic sensitivity analysis. **A**) Scatter plot of simulations from probabilistic sensitivity analyses. Incremental costs are plotted against incremental quality-adjusted life-years (QALY) for WW relative to low anterior resection (LAR, **squares**), watch and wait (WW) relative to abdominoperineal resection (APR, **triangles**), and LAR relative to APR (**circles**). **White circles** represent results of base case analyses. **B**) Cumulative probability of simulations from probabilistic sensitivity analyses at a given incremental QALY threshold. A total 99.5% of simulations of WW relative to LAR (**dotted line**) and 99.8% of simulations of WW relative to APR (**solid line**) demonstrated incremental QALY in favor of WW.

Discussion

Although 20–30% of patients develop LR after CRT on a WW program, it is uncertain whether upfront TME after a cCR to CRT improves cancer-specific survival, because the vast majority of local regrowths are surgically salvageable (5–7,11). In this decision-analytic model, we observed superior quality-adjusted survival, comparable cancer-specific survival, and reduced cost on a WW program relative to both upfront LAR and APR.

Following the publication of multiple single-institutional WW series, van der Valk and colleagues reported a multi-institutional international registry of 880 patients who achieved a cCR to CRT and were then surveilled (11). After a median follow-up of 3.3 years, the 5-year cumulative incidences of LR and DM were 30.5% and 8.6%, and 5-year cancer-specific survival was 94%. Among patients who developed LR and for whom surgical salvage data were available, 95% were salvaged with TME or local excision. Although this series was limited by missing data and duration of follow-up, rates of LR, DM, and surgical salvage were comparable with single-institutional series with longer follow-up and with a separate meta-analysis (6,7,13,14,22,34,47).

However, the risk of LR and its potential impact on DM and survival have raised concern. A recent institutional series reported lower survival among patients managed with WW compared with patients who underwent TME after a pCR (6). Given imperfect concordance between cCR and pCR, these results may be biased in favor of TME. Moreover, patients in the WW cohort were older, raising concerns for imbalanced other-cause mortality. Although the authors emphasized lower overall survival in the WW cohort, 5-year cancer-specific survival was nevertheless 90%, indicative of other-cause mortality. The authors appropriately discussed that upfront TME may not have averted DM, which may instead be dictated by disease biology rather than LR.

In our analysis, we observed similar cancer-specific survival and improved quality-adjusted survival in a simulated WW cohort. We assumed a 2% absolute increase in the risk of DM relative to upfront TME, though a recent meta-analysis demonstrated similar rates of DM between WW after cCR and TME after pCR (5). These results were particularly sensitive to the rate of surgical salvage after LR, which in the literature varies from approximately 70% to 100% (6,13,14,22,34). We assumed that all patients who were not surgically salvaged died of their disease, although long-term survival has been observed in some patients treated with re-irradiation (26).

Although the benefit in quality-adjusted survival attributed to WW over upfront TME is presumably related to LAR syndrome or permanent ostomy after APR, perioperative morbidity and mortality are also considerations for omitting TME. We assumed a perioperative in-hospital mortality rate of only 0.6% (16). However, 90-day mortality after proctectomy in the United Kingdom is only as low as 1.2% in young (≤60 years) healthy patients but is considerably higher (2–15%) among patients older than 60 years or those with comorbid disease (48). Moreover, clinically significant in-hospital morbidity after TME approaches 40% (16).

Currently, a minority of patients treated with CRT develop cCR. With increasing use of total neoadjuvant therapy, more patients may be eligible for WW and successful rectal preservation (17). In our study, the quality-of-life benefit of WW was derived from a retrospective matched cohort study (28). Patients managed with WW reported superior quality of life across a range of domains, corroborated by quality-of-life and objective manometry data comparing CRT with or without transanal excision and a recent institutional protocol of WW (49,50).

Strengths of our study include comprehensive time-dependent modeling of health states with use of randomized or multi-institutional observational data for transition estimates and health utilities. Detailed micro-costing was performed, and probabilistic analyses were in close agreement with base case analyses.

Several limitations must be considered. Decision-analytic models are inherent simplifications of disease processes and are limited by the quality of data used to generate transition estimates, utilities, and costs. Although multi-institutional data were used to generate transition estimates, these observational data may be biased, subject to heterogeneity, or may lack generalizability to all patients and practices. Although estimates of PR after TME with pCR are consistently 0–2% in the literature, rates of DM after WW or upfront TME are more variable across studies included in these meta-analyses (5–7). Moreover, although nearly all patients treated on these studies received preoperative long-course, fluorouracil-based CRT, 23% of patients included in Smith et al. received total neoadjuvant therapy, limiting comparisons across studies. Furthermore, there are very limited data supporting radiotherapy alone or short-course radiotherapy on a WW program, which represents an important contradistinction to current clinical practice in which preoperative short-course radiotherapy is a standard treatment. Finally, it is important to consider that there is heterogeneity across studies in patient selection, surveillance programs, and assessment and timing of clinical response to CRT for patients managed with WW. Although the vast majority of WW studies indicate very low rates of unsalvageable local recurrences, a standardized WW program is lacking, and our results should be considered in this context. Until randomized data with adequate follow-up are available, this study remains hypothesis generating.

Using current multi-institutional observational estimates of disease recurrence after cCR to CRT on a WW program, we observed similar cancer-specific survival, superior long-term quality-adjusted survival, and decreased costs relative to upfront TME. These findings were consistent across a range of published estimates, However, upfront TME was preferred when the rate of surgical salvage for LR was low, highlighting the need for standardized surveillance protocols. Ultimately, randomized data are required to confirm these findings.

Notes

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