

ORIGINAL ARTICLE



The ultimate local failure rate after the watch-and-wait strategy for rectal cancer: a systematic review of literature and meta-analysis

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ABSTRACT

Background: We hypothesise that a high rate of tumour regrowth after the watch-and-wait (w&w) strategy may lead, despite salvage surgery, to a significant impairment of ultimate local control compared with immediate surgery.

Materials and methods: To test this hypothesis, we conducted meta-analyses of studies on the w&w strategy (both opportunistic and planned) with an ultimate local failure rate as an endpoint in three patient groups: (1) in all starting radio(chemo)therapy as potential w&w candidates, (2) in a subgroup starting w&w, and (3) in a subgroup with regrowth.

Results: We identified eight studies for evaluation of local failure in group 1 ($N=837$) and 36 studies in group 2 ($N=1914$) and in group 3 ($N=439$). The meta-analysis revealed an ultimate local failure rate of 8.0% (95% CI 4.8%–12.1%) in group 1 and 5.4% (95% CI 3.9%–7.1) in group 2. These rates are similar to those reported in the literature following preoperative chemoradiation and surgery. However, in the most unfavourable group 3 (with regrowth), the rate of ultimate local failure was 24.1% (95% CI 17.9%–30.9%), with the most common causes being patients' refusal of salvage total mesorectal excision (TME) (9.1%), recurrence after salvage TME (7.8%), distant metastases (4.1%), frailty (2.4%), and pelvic tumour unresectability (1.7%).

Conclusion: Nearly 25% of patients with regrowth (unfavourable subgroup) experienced ultimate local failure, primarily due to refusing salvage TME. The risk of ultimate local failure in patients initiating radio(chemo)therapy as potential w&w candidates, or in patients starting w&w, appears comparable to that reported after preoperative chemoradiation and surgery. However, this comparison may be biased, because w&w studies included more early tumours compared with surgical studies.

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KEYWORDS

Rectal cancer; watch-and-wait; local control

Background

Total mesorectal excision (TME) is the cornerstone of rectal cancer management, providing high local control. However, it can lead to adverse effects such as impaired anorectal function or stoma. Therefore, the watch-and-wait (w&w) strategy is increasingly used in patients achieving clinical complete response (cCR) or near-cCR after radio(chemo)therapy. However, the tumour regrowth rate is high, reaching 30% [1,2]. Regrowth is evidence that radio(chemo)resistant subclinical disease persists despite cCR. Thus, there are two groups of patients having cCR: with true complete response (a favourable group with sustained cCR during observation), and with radio(chemo)resistant subclinical disease (an unfavourable group with regrowth during observation). Despite the high rate of tumour regrowth, it is believed that ultimate local control is unaffected, since R0 salvage surgery is performed in most patients [1,3]. However, local failure has not been assessed in the meta-analysis, taking into account all causes of ultimate local failure in addition to the failure of salvage surgery. If all these causes are considered together, it

is possible that the ultimate local failure is higher compared with immediate surgery.

Two w&w strategies exist: opportunistic ('pick the winner') or planned (intentional). In the opportunistic strategy, routine preoperative radio(chemo)therapy is given, and patients achieving cCR are observed without surgery. The planned strategy aims to increase a cCR rate *via* radiotherapy dose escalation or by adding induction or consolidation chemotherapy to the radio(chemo)therapy (i.e., total neoadjuvant therapy [TNT]). This increased rate of cCR may result in more aggressive regrowths in patients undergoing the planned strategy, leading to an increased ultimate local failure rate compared with those undergoing the opportunistic strategy.

For the above reasons, our first hypothesis is that regrowth leads to a meaningful increase of an ultimate local failure rate compared with immediate surgery. Our second hypothesis is that the ultimate local failure rate is higher in the planned strategy compared with the opportunistic strategy. To test these two hypotheses we performed meta-analyses with ultimate local failure rate as an endpoint.

To test the first hypothesis, three meta-analyses were planned: (1) an intention-to-treat meta-analysis, evaluating outcomes in all patients starting radiotherapy as potential candidates for w&w (group 1), (2) a meta-analysis evaluating the ultimate local failure rate in the subgroup of patients with cCR or near-cCR starting opportunistic or planned w&w (group 2), and (3) a meta-analysis evaluating the ultimate local failure rate in the subgroup of patients with regrowth (group 3), along with an estimate of the reasons for this failure. Next, we compared the calculated rates of ultimate local failure with the corresponding values reported in the literature after preoperative radio(chemo) therapy and surgery. To test the second hypothesis, all the above three analyses were performed with stratification based on the type of the w&w strategy.

Material and methods

The definitions we adopted in this review were as follows:

- W&w was defined as a strategy that involves observation without immediate surgery (neither local excision [LE] nor TME) in patients who achieved cCR or near-cCR.
- Regrowth was defined as the (re)appearance of intraluminal tumour or pelvic nodal disease in patients starting w&w.
- Ultimate local control was defined as sustained cCR or regrowth controlled by salvage TME or LE. Patients who had recurrence after salvage LE and subsequently underwent successful re-salvage TME were also considered locally controlled.
- Salvage TME was defined as TME performed for regrowth with or without prior salvage LE.
- In the intention-to-treat analysis, ultimate local failure was defined as pelvic recurrence after salvage TME or uncontrolled local disease caused by various other reasons, such as death during radio(chemo)therapy or patients' refusal of TME.
- The category of planned w&w with radiation dose escalation was assigned when the radiation dose was at least 60 Gy.
- The category of planned w&w using TNT was assigned when induction or consolidation chemotherapy lasted for at least eight weeks.
- In studies where more than one w&w strategy was used, the assigned category depended on the strategy used in the majority of patients.

For comparison, we chose patients who received chemo-radiation before surgery in the recent randomised RAPIDO study by Bahadoer et al. [4] and the PRODIGE23 study by Conroy et al. [5] (standard-of-care arms) as comparators with w&w. Ultimate local failure was defined in the same way as for w&w.

Search strategy, study selection, and data extraction

The systematic review was conducted in accordance with the PRISMA guidelines [6]. The PubMed database was searched

from the first publication on w&w in 2002 until February 2023, using the search terms provided in [Supplementary Appendix 1](#). Citation tracking of included articles was also performed. Only studies in English and Spanish were included. The inclusion criteria were based on the PICO model: Population: patients with adenocarcinoma of the rectum; Intervention: w&w; Control: immediate radical surgery after preoperative radio(chemo)therapy; Outcomes: ultimate local failure rate. Exclusion criteria included (1) studies in which the calculation of the ultimate local failure rate was impossible, such as those without data on recurrence after salvage TME, (2) studies in which w&w was used only in patients unfit for surgery, (3) studies in which planned LE was used for organ preservation in all patients with cCR, and (4) studies in which w&w or LE was used but results were not reported separately.

Articles were screened according to their titles and abstracts. Full texts of all relevant studies were obtained. If there were multiple publications on the same trial, data with the longest follow-up were used. The following data were extracted: patients' and treatment characteristics, length of follow-up, and the number of patients in the following categories: (1) starting radio(chemo)therapy, (2) starting w&w, (3) with regrowth, (4) with ultimate local failure with reasons for this event, and (5) undergoing salvage TME along with the number of those with post-salvage recurrence. The data were extracted by two authors using a pre-designed form, and any disagreements were resolved by consensus. In addition, for the OPERA study [7] and the MORPHEUS study [8], missing relevant data were obtained from the corresponding authors. The modified Newcastle–Ottawa scale [9] was used to evaluate the methodological quality of nonrandomized studies ([Supplementary Table S1](#)).

Statistical methods

The pooled weighted rates with 95% confidence intervals (CIs) were estimated using a random-effects meta-analytic approach allowing for between-study heterogeneity using MetaXL (www.epigear.com), an add-in for meta-analysis in Microsoft Excel. Between-study heterogeneity was tested using Cochran's Q (2) with a significance level of $p < .10$ and quantified using I² statistics. To evaluate potential publication and related biases, a Doi plot and its associated Luis Furuya-Kanamori index [10] were used. Sensitivity analysis was conducted by withdrawing one study at a time from the meta-analysis to evaluate its effect on the pooled rate. The meta-analysis was performed according to the MOOSE guidelines [11] ([Supplementary Table S2](#)).

Results

The ultimate local failure in all patients starting radio(chemo)therapy as potential candidates for w&w (group 1)

The systematic search ([Supplementary Figure S1](#)) identified eight trials ($N = 837$) that presented outcomes in all patients starting radio(chemo)therapy as potential candidates for

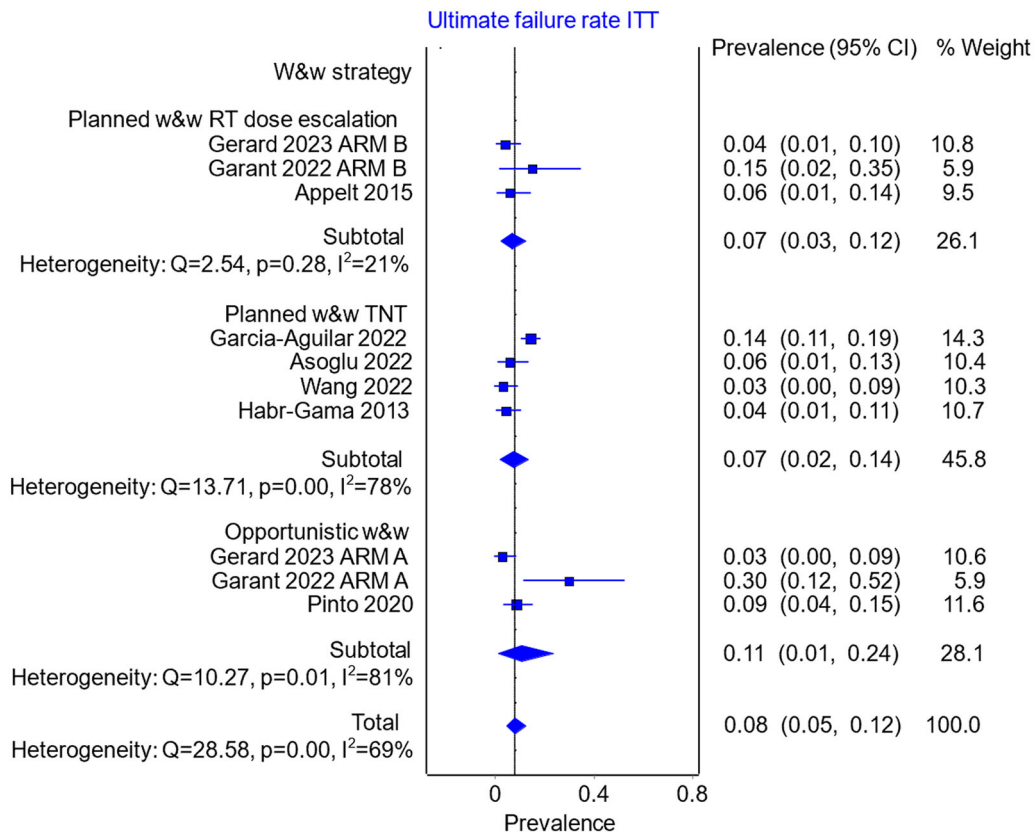


Figure 1. The pooled weighted rate of the ultimate local failure in the intention-to-treat analysis of all the patients starting radio(chemo)therapy (potential candidates for w&w).

w&w, allowing for intention-to-treat analysis (Table 1) [2,7,8,12–17]. Seven studies were prospective, and one was retrospective. Three studies employed the planned strategy with radiation dose escalation, four used the planned strategy with TNT, and one used the opportunistic strategy. The meta-analysis of these studies showed that the pooled weighted rate of ultimate local failure was 8.0% (95% CI 4.8%–12.1%; heterogeneity, $p=.001$) (Figure 1). There were no major differences in the ultimate local failure rate between the w&w strategies. In the planned strategy using radiation dose escalation ($N=143$), the ultimate local failure rate was 6.9% (95% CI 2.6%–12.3%); in the planned strategy using TNT ($N=512$), it was 7.3% (95% CI 2.3%–13.6%); and in the opportunistic strategy ($N=182$), it was 10.8% (95% CI 1.2%–23.5%).

The ultimate locoregional failure in patients starting w&w (group 2)

Thirty-six relevant references ($N=1914$) were identified for the evaluation of outcomes in patients starting w&w (Table 2) [2,7,8,12–45]. Ten studies were prospective, and 26 were retrospective. In three studies, the planned strategy with radiation dose escalation was employed, in nine studies, the planned strategy with TNT, and in the remaining 24 trials, the opportunistic strategy. The rate of ultimate local failure among patients starting w&w was 5.4% (95% CI 3.9%–7.1%; heterogeneity, $p=.001$). There were no major differences in the ultimate local failure rate between the w&w

strategies (Figure 2). In the planned strategy using radiation dose escalation ($N=121$), the ultimate local failure rate was 4.4% (95% CI 0.0%–11.5%); in the planned strategy using TNT ($N=650$), it was 4.3% (95% CI 1.8%–7.3%); and in the opportunistic strategy ($N=1143$), it was 6.2% (95% CI 4.1%–8.5%).

The ultimate locoregional failure in patients with regrowth (group 3), and the reasons for this failure

The rate of ultimate local failure among the subgroup with regrowth (36 references, $N=439$) was 24.1% (95% CI 17.9%–30.9%; heterogeneity, $p<.001$). There were no major differences in the ultimate local failure rate between the w&w strategies (Figure 3). In the planned strategy using radiation dose escalation ($N=22$), the ultimate local failure rate was 23.3% (95% CI 0.0%–60.4%); in the planned strategy using TNT ($N=161$), it was 18.9% (95% CI 11.1%–27.8%); and in the opportunistic strategy ($N=256$), it was 28.7% (95% CI 19.2%–38.9%).

Among patients who experienced regrowth, the most common causes of ultimate local failure were patients' refusal of salvage TME (9.1%, 95% CI 5.3%–13.7%), recurrence after salvage TME (7.8%, 95% CI 5.2%–11.0%), distant metastases (4.1%, 95% CI 2.4%–6.1%), frailty (2.4%, 95% CI 1.2%–4.0%), unresectable pelvic tumours (1.7%, 95% CI 0.7%–3.2%), and other reasons (2.3%, 95% CI 1.1%–3.9%) (Supplementary Figures S5–S10). There were no significant differences between the w&w strategies for each of the

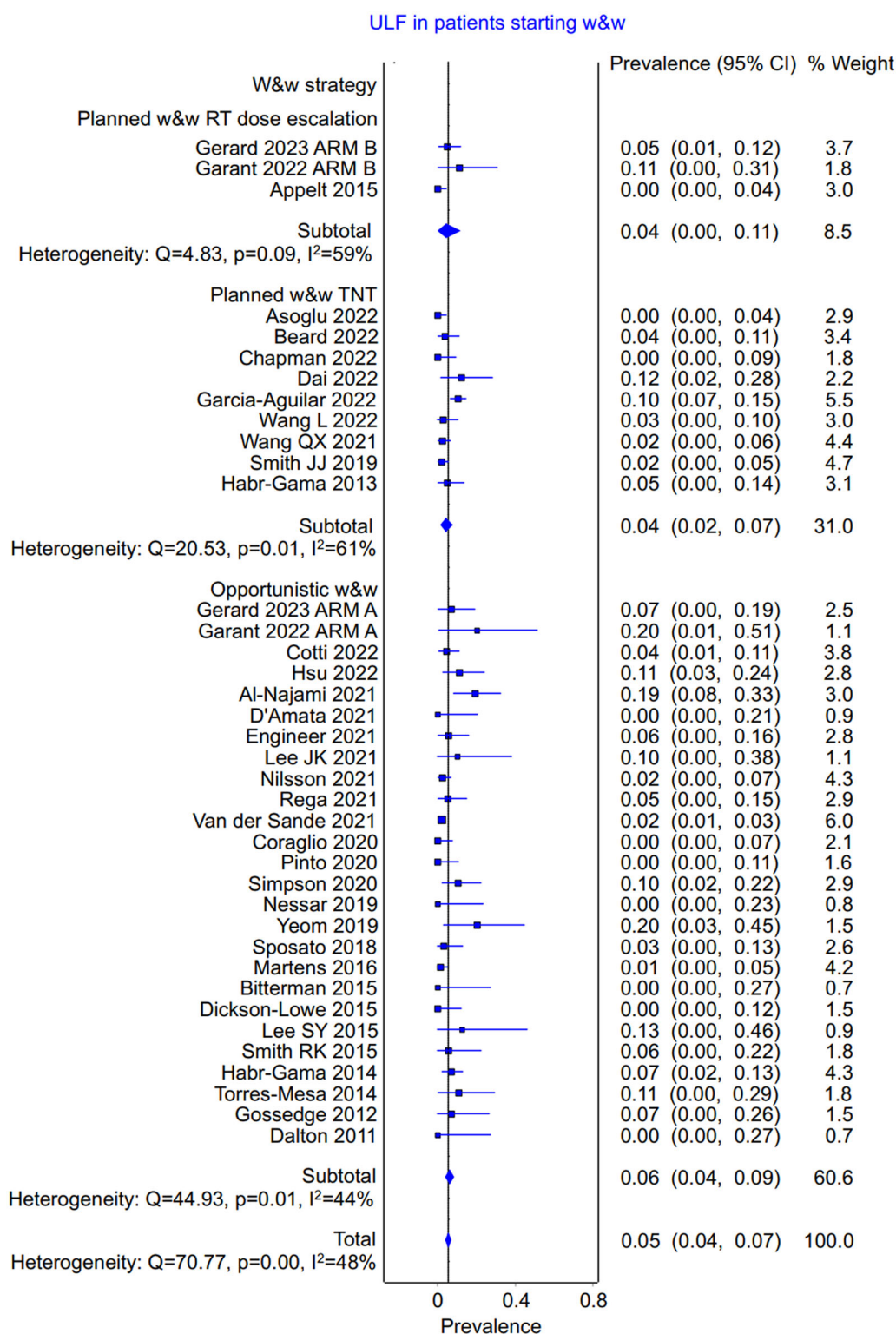


Figure 2. The pooled weighted rate of ultimate local failure among patients starting w&w.

above-mentioned causes of ultimate local failure (Supplementary Figures S5–S10).

There might be two reasons for the patients' refusal of salvage TME: (1) patients participating in w&w already refuse TME at diagnosis or (2) patients decide to refuse TME later at the time of regrowth. To explore this further, we conducted an additional post-hoc meta-analysis, which found a lower rate of patients refusing surgery among those with persistent

tumours at response evaluation, at 1.9% (95% CI 0.6%–3.9%, Supplementary Figure S11), compared with 9.1% (95% CI 5.3%–13.7%) among those with regrowth.

Sensitivity analysis and publication bias assessment

Sensitivity analyses showed no significant impact on the outcomes when individual studies were removed

Table 1. Ultimate local failure among all the patients starting radio(chemo)therapy as potential candidates for w&w.

	Patients' and treatment characteristics	Median follow-up (months)	Rate of patients starting w&w N starting w&w/N starting radio(chemo)therapy	Regrowth rate N with regrowth/N starting w&w	Ultimate local failure rate N with local failure/N starting radio(chemo)therapy
OPRA, Garcia-Aguilar [2]	Stage II-III. Randomised study on planned w&w using TNT and comparing 4 months of induction vs consolidation FOLFOX or CAPOX combined with chemoradiation (50–56 Gy with FU continuous infusion or with cap.) W&w in cCR and all near-cCR. Low or mid tumours, cT2-T3ab ≤5 cm in length and <50% circumferential involvement, cN0-N1 < 8 mm. Randomised study comparing after chemoradiation (45 Gy with cap.) an EBRT boost of 9 Gy in 5 fractions, arm A (opportunistic strategy) vs RT dose escalation with a CXB boost of 90 Gy in 3 fractions, arm B (planned strategy). W&w in cCR and all near-cCR. 113 patients started w&w: 93 who achieved cCR/near-cCR and 20 after local excision.	36	225/312 (72%)	75/225 (33%)	45/312 (14%) ^b
OPERA, Gerard [7]	Low or mid tumours, cT2-T3ab ≤5 cm in length and <50% circumferential involvement, cN0. Randomised study comparing after chemoradiation (45 Gy with cap.) an EBRT boost of 9 Gy in 5 fractions, arm A (opportunistic strategy) vs a BRT boost of 30 Gy in 3 fractions, arm B (planned strategy). W&w only in cCR. ^a	38	Arm A 30/69 (43%) Arm B 63/72 (88%)	Arm A 10/30 (33%) Arm B 9/63 (14%)	Arm A 2/69 (3%) Arm B 3/72 (4%) ^c
MORPHEUS, Garant [8]	Low or mid tumours, cT2-T3ab ≤5 cm in length and <50% circumferential involvement, cN0. Randomised study comparing after chemoradiation (45 Gy with cap.) an EBRT boost of 9 Gy in 5 fractions, arm A (opportunistic strategy) vs a BRT boost of 30 Gy in 3 fractions, arm B (planned strategy). W&w only in cCR. ^a	39	Arm A 10/20 (50%) Arm B 18/20 (90%)	Arm A 4/10 (40%) Arm B 4/18 (22%)	Arm A 6/20 (30%) Arm B 3/20 (15%) ^d
Habr-Gama [12]	Low and mid tumours, cT2-4 N1-2. Prospective study on planned w&w using TNT consisting of chemoradiation (54 Gy + 3 cycles of bolus FU and LV) and 2 months of consolidation bolus FU and LV. W&w group included cCR and near-cCR showing ypT0 after local excision.	23	43/70 (61%)	12/43 (28%)	3/70 (4%) ^e
Appelt [13]	Low tumours, cT2-3 N0. Prospective study on planned w&w using RT dose escalation (60 Gy + BRT 5 Gy one fraction + tegafur-uracil). W&w only in cCR. ^a	24	40/51 (78%)	9/40 (23%)	3/51 (6%) ^f
Wang [14]	Low tumours, cT2-T3ab, MRF (–), EMVI (–), lateral nodes (–). Prospective study on planned w&w using TNT chemoradiation (50.6 Gy + cap.) + 3 months of consolidation CAPOX. W&w in cCR and all near-cCR.	40	40/64 (63%)	7/40 (18%)	2/64 (3%) ^g
Asoglu [15,16]	Stage II-III. Retrospective study on planned w&w using TNT consisting of chemoradiation (50.4 Gy + cap.) + 3 months of consolidation FOLFOX or 6 months of consolidation CAPOX. W&w only in cCR. ^a	63	39/66 (59%)	10/39 (26%)	4/66 (6%) ^h
PINTO [17]	Low tumours, stage I–III. Prospective study on opportunistic w&w after chemoradiation (50.4 Gy + cap.). W&w only in cCR. ^a	12	16/93 (17%)	4/16 (25%)	8/93 (9%) ⁱ

Intention-to-treat analysis.

N: number of patients; w&w: watch-and-wait; FU: fluorouracil; FOLFOX: fluorouracil + leucovorin + oxaliplatin; CAPOX: capecitabine + oxaliplatin; cap.: capecitabine; LV: leucovorin; EBRT: external beam radiotherapy; CXB: contact X-ray brachytherapy; BRT: brachytherapy using Iridium; TME: total mesorectal excision; TNT: total neoadjuvant therapy; MRF(–): mesorectal fascia unphretened; EMVI(–): extramural vascular invasion absent.

^a“w&w only in cCR” confers that an analysis was performed in the subgroup of patients starting w&w formed after excluding those with near-cCR who did not achieved cCR and eventually required salvage surgery because of persistent or progressive near-cCR diagnosed during further observation.^bRecurrence after TME for persistent tumour (n = 10), recurrence after salvage TME (n = 15), refused TME for persistent tumour (n = 4), refused salvage TME (n = 6) and did not have salvage surgery because of distant metastases (n = 4).^cArm A: refused salvage TME (n = 2), Arm B: no salvage surgery because of distant metastases (n = 1), refused salvage TME (n = 2).^dArm A: died during chemoradiation (n = 1), unresectable persistent tumour (n = 1), refused salvage TME (n = 1), and recurrence after salvage TME (n = 2), Arm B: died from non-cancer reason before TME for persistent tumour (n = 1), refused salvage TME (n = 1) and recurrence after salvage TME (n = 1).^eRecurrence after salvage TME (n = 1), no salvage TME because of frailty (n = 1), death during neoadjuvant CRT (n = 1).^fRefused TME for persistent tumour (n = 3).^gRefused TME for persistent tumour (n = 1), refused salvage TME (n = 1).^hNo salvage TME because of distant metastases (n = 2), no TME for persistent tumour because of liver toxicity during TNT (n = 1), recurrence after TME for persistent tumour (n = 1).ⁱRecurrences after TME for persistent tumour (n = 3), died before TME for persistent tumour (n = 1), patients who died or were severely disabled before re-evaluation (n = 4).

Table 2. Ultimate local failure among the patients starting w&w strategy.

STUDY	Treatment characteristics	Median follow-up (months)	Rate of patients starting w&w N starting radio(chemo)therapy	Regrowth rate N with regrowth/N starting w&w	Ultimate local failure rate N with local failure/N starting w&w	Local failure rate after salvage TME/N with local failure/N undergoing salvage TME	Rate of patients with local failure because of unresectable pelvic regrowth/N with regrowth	Rate of patients without salvage TME because of DM N without salvage TME because of DM/N with regrowth	Rate of pts refusing salvage TME N refusing salvage TME surgery/N with regrowth
OPRA, García-Aguilar [2]	Stage II-III. Randomised study on planned w&w using TNT and comparing 4 months of induction vs consolidation FOLFOX or CAPOX combined with chemoradiation (50–56 Gy with FU continuous infusion or with cap.) W&w in cCR and all near-cCR.	36	225/512 (72%)	75/225 (33%)	23/225 (10%) ^b	15/62 (24%)	0/75	2/75 (3%)	6/75 (8%)
OPERA Gerard [7]	Low or mid tumours, cT2-T3ab ≤5 cm in length and <50% circumferential involvement cN0-N1 < 8mm. Randomised study comparing after chemoradiation (45 Gy with cap.) an EBRT boost of 9 Gy in 5 fractions, arm A (opportunistic strategy) vs RT dose escalation with a CXB boost of 90 Gy in 3 fractions, arm B (planned strategy). w&w in cCR and all near-cCR. 113 patients started w&w: 93 who achieved cCR/near-cCR and 20 after local excision.	38	Arm A 30/69 (43%) Arm B 63/72 (88%)	Arm A 10/30 (33%) Arm B 9/63 (14%)	Arm A 2/30 (7%) Arm B 3/63 (5%) ^c	Arm A 0/7 Arm B 0/6	Arm A 0/10 Arm B 0/9	Arm A 0/10 Arm B 1/9 (11%)	Arm A 2/10 (20%) Arm B 2/9 (22%)
MORPHEUS Garant [8]	Low or mid tumours, cT2-T3ab ≤5 cm in length and <50% circumferential involvement cN0. Randomised study comparing after chemoradiation (45 Gy with cap.) an EBRT boost of 9 Gy in 5 fractions, arm A (opportunistic strategy) vs a BRT boost of 30 Gy in 3 fractions, Arm B (planned strategy). W&w only in cCR. ^a	39	Arm A 10/20 (50%) Arm B 18/20 (90%)	Arm A 4/10 (40%) Arm B 4/18 (22%)	Arm A 2/10 (20%) Arm B 2/18 (11%) ^d	Arm A 2/3 (67%) Arm B 1/2 (50%)	Arm A 0/4 Arm B 0/4	Arm A 0/4 Arm B 0/4	Arm A 0/4 Arm B 1/4 (25%)
Habr-Gama [12]	Low and mid tumours, cT2-4 N1-2. Prospective study on planned I w&w using TNT consisting of chemoradiation (54 Gy + 3 cycles of bolus FU and LV) and 2 months of consolidation bolus FU and LV. w&w included cCR and near-cCR showing ypT0 after local excision.	23	43/70 (61%)	12/43 (28%)	2/43 (5%) ^e	1/6 (17%)	0/12	0/12	0/12
Appelt [13]	Low tumours, cT2-3 N0. Prospective study on planned w&w using RT dose escalation (60 Gy + BRT 5 Gy one fraction + tegafur-uracil). W&w only in cCR. ^a	24	40/51 (78%)	9/40 (23%)	0/40	0/9	0/9	0/9	0/9
Wang [14]	Low tumours, T2-T3ab, MRF (–), EMVI (–), lateral nodes (–). Prospective study on planned w&w using TNT consisting of chemoradiation (50.6 Gy + cap.) + 3 months of consolidation CAPOX. W&w in cCR and all near-cCR.	40	40/64 (63%)	7/40 (18%)	1/40 (3%) ^f	0/4	0/7	0/7	1/7 (14%)
Asoglu [15,16]	Stage II–III. Retrospective study on planned w&w using TNT consisting of chemoradiation (50.4 Gy + cap.) + 3 months of consolidation FOLFOX or 6 months of consolidation CAPOX. W&w only in cCR. ^a	63	39/66 (59%)	10/39 (26%)	0/39	0/7	0/10	0/10	0/10
PINTO [17]	Low tumours, stage I–III. Prospective study on opportunistic w&w after	17	16/93 (17%)	4/16 (25%)	0/16	0/4	0/4	0/4	0/4

(continued)

Table 2. Continued.

STUDY	Treatment characteristics	Median follow-up (months)	Rate of patients starting w&w N starting radio(chemo)therapy	Regrowth rate N with regrowth/N starting w&w	Ultimate local failure rate N with local failure/N starting w&w	Local failure rate after salvage TME/N with local failure after salvage TME/N undergoing salvage TME	Rate of patients with local failure because of unresectable pelvic regrowth N with unresectable pelvic regrowth/N with regrowth	Rate of patients without salvage TME because of DM N without salvage TME because of DM/N with regrowth	Rate of pts refusing salvage TME N refusing salvage TME surgery/N with regrowth
Van der Sande [18]	chemoradiation (50.4 Gy + cap.). W&w only in cCR. ^a cT2-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation or 5 × 5 Gy. W&w in cCR and all near-cCR.	28	385/n. d.	89/385 (23%)	7/385 (2%) ^g	2/65 (3%)	0/89	1/89 (1%)	1/89 (1%)
Habr-Gama [19]	cT2-4 N0-2. Prospective study on opportunistic w&w after chemoradiation (50.4–54 Gy with FU-based chemotherapy) W&w only in cCR. ^a	60	90/183 (49%)	28/90 (31%)	6/90 (7%) ^h	4/18 (22%)	0/28	1/28 (6%)	0/28
Martens [20]	cT1-4 N0-2. Prospective study on opportunistic w&w after chemoradiation (50.4 Gy with cap.) or 5 × 5 Gy. W&w only in cCR. ^a	41	85/n. d.	12/85 (14%)	1/85 (1%) ⁱ	0/11	0/12	1/12	0/12
Bitterman [21]	cT1-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (50.4 Gy with cap. or continuous FU). W&w only in cCR. ^a	22	6/138 (4%)	0/6	0/6	0/0	0/0	0/0	0/0
Dalton [22]	cT2-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (45 Gy with cap.). W&w only in cCR. ^a	mean 26	6/49 (12%)	0/6	0/6	0/0	0/0	0/0	0/0
Torres-Mesa [23]	cT2-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (40–55 Gy with FU). W&w only in cCR. ^a	21	19/480 (4%)	8/19 (42%)	2/19 (10%) ^j	0/6	2/8 (25%)	0/8	0/8
Gossedge [24]	cT2-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (50 Gy with cap.). W&w only in cCR. ^a	48	15/28 (54%)	1/15 (7%)	1/15 (7%) ^k	0/0	0/1	1/1 (100%)	0/1
Dickson-Lowe [25]	Stage not given. Retrospective study on opportunistic w&w after chemoradiation. W&w only in cCR. ^a	Ng	14/n. d.	7/14 (50%)	0/14	0/3	0/7	0/7	0/7
Coraglio [26]	cT1-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (45–50.4 Gy with cap.). 3 months of induction XELOX was given for high risk tumours. W&w only in cCR. ^a	47	23/256 (9%)	2/23 (9%)	0/23	0/2	0/2	0/2	0/2
Lee [27]	Low or mid tumours. cT2-3 N0-2. Retrospective study on opportunistic w&w after chemoradiation with cap. or FU. W&w only in cCR. ^a	64.7	14/n. d.	3/14 (21%)	1/14 (7%) ^l	0/2	0/3	0/3	1/3 (33%)
Yeom [28]	cT1-4 or N+. Retrospective study on opportunistic w&w after chemoradiation (50.4 Gy with FU). W&w only in cCR. ^a	20	169/1140 (15%)	4/15 (27%)	3/15 (20%) ^m	0/1	0/4	1/4 (25%)	1/4 (25%)
Al-Najami [29]	cT1-4 or N0-2. Retrospective study on opportunistic w&w after chemoradiation (52 Gy with cap. or FU continuous infusion). W&w only in cCR. ^a Some patients were included because of frailty.	45	42/231 (18%)	11/42 (26%)	8/42 (19%) ⁿ	0/2	0/11	0/11	6/11 (55%)
Wang [30]	Stage II-III. Retrospective study on opportunistic w&w after chemoradiation (50 Gy with cap. or FU ± oxaliplatin [28%]). 72% of the patients received consolidation or induction chemotherapy. W&w only in cCR. ^a	38	94/n. d.	14/94 (15%)	2/94 (2%) ^o	0/12	0/14	2/14 (14%)	0/14

(continued)

Table 2. Continued.

STUDY	Treatment characteristics	Median follow-up (months)	Rate of patients starting w&w N starting radio(chemo)therapy	Regrowth rate N with regrowth/N starting w&w	Ultimate local failure rate N with local failure/N starting w&w	Local failure rate after salvage TME/N with local failure after salvage TME/N undergoing salvage TME	Rate of patients with local failure because of unresectable pelvic regrowth/N with unresectable pelvic regrowth	Rate of patients without salvage TME because of DM N without salvage TME because of DM/N with regrowth	Rate of pts refusing salvage TME N refusing salvage TME surgery/N with regrowth
Nilsson [31]	cT1-4 or N0-2. Prospective study on opportunistic w&w after 5 × 5 Gy, 5 × 5 Gy with 3 months of consolidation CAPOX or chemoradiation. W&w only in cCR. ^a	33	87/n. d.	17/87 (20%)	2/87 (2%) ^p	1/16 (6%)	0/17	1/17 (6%)	0/17
Cotti [32]	cT3-4 or N+ or low cT2N0. Retrospective study on opportunistic w&w after chemoradiation (50.4 Gy with FU continuous infusion). w&w only in cCR. ^a	63	67/792 (8%)	20/67 (30%)	3/67 (4%) ^q	3/20 (15%)	0/20	0/20	0/20
Lee [33]	cT3-4 or N+ or low cT2N0. Retrospective study on opportunistic w&w after chemoradiation (50.4 Gy with FU-based chemotherapy ± oxaliplatin). W&w only in cCR. ^a	41	8/319 (3%)	2/8 (25%)	1/8 ^r	0/1	1/2 (50%)	0/2	0/2
Hsu [34]	Low or mid tumours cT1-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (50.4 Gy with FU ± oxaliplatin) or 5 × 5 Gy. W&w only in cCR.	78	36/680 (5%)	7/36 (19%)	4/36 (11%) ^s	1/4 (25%)	1/7 (14%)	0/7 (6%)	1/7 (14%)
Nessar [35]	cT2-4 N+. Retrospective study on opportunistic w&w after chemoradiation (50.4 Gy with bolus FU). W&w only in cCR. ^a	56	7/61 (11%)	0/7	0/7	0/0	0/0	0/0	0/0
Sposato [36]	Stage II-III. Retrospective study on opportunistic w&w after chemoradiation (50.4 Gy with cap. or infusional FU). W&w only in cCR. ^a	38	32/185 (17%)	7/32 (22%)	1/32 (3%) ^t	1/6 (17%)	0/7	0/7	0/7
d'Amata [37]	cT1-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (55 Gy with cap.). W&w only in cCR. ^a	24	8/n. d.	1/8 (13%)	0/8	0/1	0/1	0/1	0/1
Beard [38]	cT1-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (50.4 Gy with cap. or infusional FU). 15% of the patients received induction or consolidation FOLFOX or CAPOX.	35	53/465 (11%)	6/53 (11%)	2/53 (4%) ^u	0/4	0/6	0/6	2/6 (33%)
Dai [39]	cT1-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (50 Gy with cap.). 93% of the patients received induction CAPOX.	34	25/100 (25%)	12/25 (48%)	3/25 (12%) ^v	0/6	0/12	2/12 (17%)	1/12 (8%)
Engineer [40]	cT2-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (50-54 Gy with cap.). W&w in cCR and all near-cCR.	35	36/n. d.	6/36 (17%)	2/36 (6%) ^w	0/4	0/6	0/6	2/6 (33%)
Simpson [41]	cT2-4 N0-2. Retrospective study on opportunistic w&w after chemoradiation (45 Gy with cap. or infusional FU). W&w only in cCR. ^a	44	39/155 (25%)	6/39 (15%)	4/39 (10%) ^x	0/1	0/6	0/6	3/6 (50%)
Rege [42]	cT2-4 N0-N+. Retrospective study on opportunistic w&w after chemoradiation (50 Gy with cap.) or 5 × 5 Gy. W-w only in cCR. ^a	28	39/670 (6%)	6/39 (15%)	2/39 (5%) ^y	0/4	0/6	0/6	2/6 (33%)

(continued)

Table 2. Continued.

STUDY	Treatment characteristics	Median follow-up (months)	Rate of patients starting w&w N starting radio(chemo)therapy	Regrowth rate N with regrowth/N starting w&w	Ultimate local failure rate N with local failure/N starting w&w	Local failure rate after salvage TME/N with local failure after salvage TME/N undergoing salvage TME	Rate of patients with local failure because of unresectable pelvic regrowth N with unresectable pelvic regrowth/N with regrowth	Rate of patients without salvage TME because of DM N without salvage TME because of DM/N with regrowth	Rate of pts refusing salvage TME N refusing salvage TME surgery/N with regrowth
Chapman [43]	Stage II-III. Retrospective study on opportunistic w&w after TNT (4 months of induction CAPOX or FOLFOX, 50.4 Gy with cap. or infusional FU). W-w only in cCR. ^a	23	18/102 (18%)	3/18 (17%)	0/18	0/2	0/3	0/3	0/3
Smith [44]	cT2-4 NO-1 Retrospective study on opportunistic w&w after 4 months of induction or consolidation FOLFOX with chemoradiation (45-54 Gy with cap. or infusional FU). W-w only in cCR. ^a	33	113/1070 (11%)	22/113 (19%)	2/113 (2%) ^z	2/20 (10%)	0/22	0/22	0/22
Smith RK [45]	cT1-4 NO-2 Retrospective study on opportunistic w&w after chemoradiation with cap. or FU. w-w only in cCR. ^a	68	18/n. d.	1/18	1/18 (6%) ^A	1/1	0/1	0/1	0/1

N: number of patients; w&w: watch-and-wait; FU: fluorouracil; FOLFOX: fluorouracil + leucovorin + oxaliplatin; cap.: capecitabine; CAPOX: capecitabine + oxaliplatin; cap.: capecitabine; LV: leucovorin; EBRT: external beam radiotherapy; CXB: contact X-ray brachytherapy; BRT: brachytherapy using Iridium; TME: total mesorectal excision; TNT: total neoadjuvant therapy; DM: distant metastases; n. d.: no data.

^aw&w only in cCR^a confers that an analysis was performed in the subgroup of patients starting w&w formed after excluding those with near-cCR who did not achieved cCR and eventually required salvage surgery because of persistent or progressive near-cCR diagnosed during further observation.

^bRecurrence after salvage TME ($n = 15$), refused salvage TME ($n = 6$), no salvage TME because of distant metastases ($n = 2$).

^cArm A: refused salvage TME ($n = 2$), Arm B: refused salvage TME ($n = 2$), no salvage TME because of distant metastases ($n = 1$).

^dArm A: recurrence after salvage TME ($n = 2$), Arm B: recurrence after salvage TME ($n = 1$), refused salvage TME ($n = 1$).

^eRecurrence after salvage TME ($n = 1$), no salvage TME because of frailty ($n = 1$).

^fRefused salvage TME ($n = 1$).

^gRecurrence after salvage TME ($n = 2$), recurrence after salvage brachytherapy ($n = 2$), refused salvage TME ($n = 1$), no salvage TME because of distant metastases ($n = 1$), no salvage TME because of frailty ($n = 1$).

^hRecurrence after salvage TME ($n = 4$), no salvage TME because of distant metastases ($n = 1$), no salvage TME because of frailty ($n = 1$).

ⁱNo salvage TME because of distant metastases ($n = 1$).

^jNo salvage TME because of unresectable pelvic disease ($n = 2$).

^kNo salvage TME because of distant metastases ($n = 1$).

^lRefused salvage TME ($n = 1$).

^mRefused salvage TME ($n = 1$), no salvage TME because of distant metastases ($n = 1$), regrowth treated with chemotherapy only - no reason given for the absence of TME ($n = 1$).

ⁿRefused salvage TME ($n = 6$), no TME because of frailty ($n = 2$).

^oNo salvage TME because of distant metastases ($n = 2$).

^pNo salvage TME because of distant metastases ($n = 1$), recurrence after salvage TME ($n = 1$).

^qRecurrence after salvage TME ($n = 3$).

^rNo salvage TME because of 'inoperable stage', details not given ($n = 1$).

^sRecurrence after salvage TME ($n = 1$), pelvic recurrence after salvage TME ($n = 1$), refused salvage TME ($n = 1$), lost from follow-up with regrowth without salvage TME ($n = 1$).

^tRecurrence after salvage TME ($n = 1$).

^uRefused salvage TME ($n = 2$).

^vNo salvage TME because of distant metastases ($n = 2$), refused salvage TME ($n = 1$).

^wRefused salvage TME ($n = 2$).

^xRefused salvage TME ($n = 3$), salvage TME not performed because of frailty ($n = 1$). All these 4 patients had salvage CXB.

^yRefused salvage TME ($n = 2$).

^zRecurrence after salvage TME ($n = 2$).

^ARecurrence after salvage TME ($n = 1$).

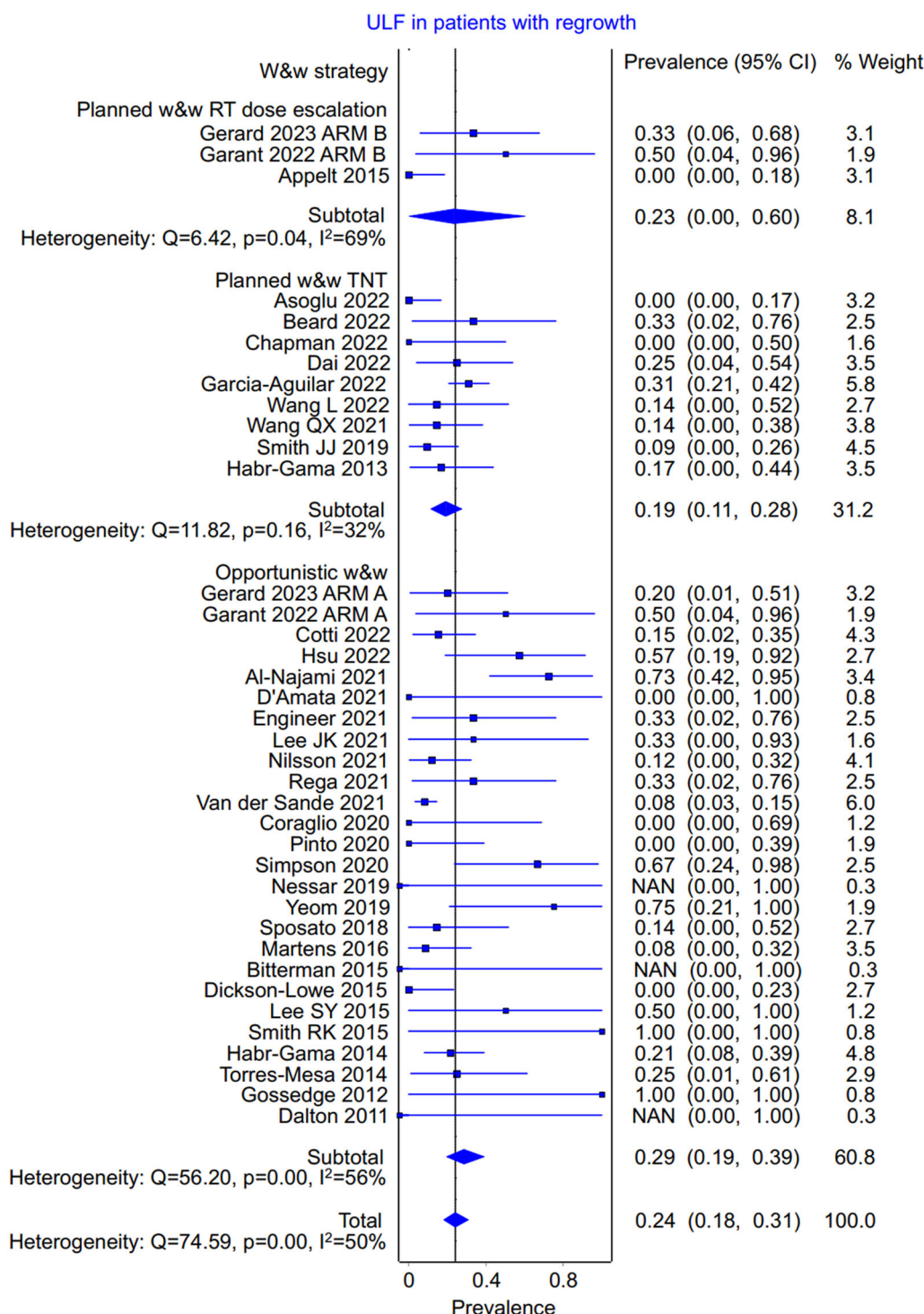


Figure 3. The pooled weighted rate of ultimate local failure among patients with regrowth.

(Supplementary Tables S3–S5). Publication and related bias assessments suggest that the pooled effect may have been overestimated in patients starting w&w and those with regrowth (Supplementary Figures S2–S4).

Discussion

The results of our systematic review and meta-analysis showed an unexpectedly high rate of ultimate local failure in patients with regrowth, affecting nearly a quarter of them,

predominantly attributable to their refusal of salvage TME. This finding contradicts the belief that regrowth poses no meaningful oncological risk [1,3].

The ultimate local failure in all patients starting radio(chemo)therapy as potential candidates for w&w (group 1)

The incidence of ultimate local failure in the intention-to-treat analysis of all patients who underwent radio(chemo)therapy

Table 3. Measures potentially leading to a reduction of regrowth risk in the watch-and-wait (w&w) strategy.

1. Avoiding the use of the w&w strategy in patients with very advanced cancer where sustained complete clinical response (cCR) is unlikely, such as in patients with circular tumours or with a tumour length greater than 7 cm [49]. Moreover, in such advanced tumours, residual fibrosis and bowel narrowing make early detection of regrowth challenging.
2. Avoiding the w&w strategy in patients with major tumour response, i.e., those with a small gross tumour that persists at evaluation. The implementation of w&w in such cases results in a high rate of regrowth [49,50].
3. Limiting the use of w&w in fit patients with cancer located beyond the reach of digital rectal examination. In such cases, digital rectal examination cannot be used as an accurate diagnostic tool for tumour response evaluation and for the early detection of regrowth. Furthermore, the benefits of w&w, such as avoiding a permanent stoma, are less likely to be achieved in these patients compared with those with low-lying tumours.
4. Applying brachytherapy boost. This technique has been shown to result in a reduction of the regrowth rate to about 15% [7,8,51].
5. Using consolidation instead of induction chemotherapy when adopting TNT. The OPRA trial demonstrated a lower regrowth rate after consolidation chemotherapy compared with induction chemotherapy [2]. This could be attributed to the higher risk of repopulation of surviving clonogens with induction chemotherapy. The risk of such repopulation is lower when radiotherapy is administered first, as the number of clonogens is more effectively reduced at the onset of treatment.
6. Evaluating tumour response at the midpoint of consolidation chemotherapy. A reduction of tumour volume by more than 80% after chemoradiation predicts ypT0 [52]. Therefore, for patients with a smaller response at the midpoint of consolidation chemotherapy, immediate surgery might be considered.

as potential candidates for w&w was 8.0% (95% CI 4.8%–12.1%) (Table 1, Figure 1). This rate is comparable to the corresponding rates of 8.7% (95% CI 6.1%–11.3%, 39 of 449) observed in surgically treated patients after chemoradiation in the RAPIDO trial [4,46] and 12.1% (95% CI 7.9%–16.3%, 28 of 230) in the PRODIGE23 trial [5]. However, this comparison is biased with respect to the tumour size and stage, because the tumours in these trials were more advanced. For example, most studies included in our meta-analysis did not enrol patients with cT4 tumours (Table 1), whereas in the RAPIDO and PRODIGE23 trials they constituted 31% and 16% of the patients, respectively. Consequently, our analysis may substantially underestimate the additional risk of ultimate locoregional failure in patients who underwent radio(chemo)therapy as potential candidates for w&w compared with those undergoing immediate surgery.

The ultimate locoregional failure in patients starting w&w (group 2)

The incidence of ultimate locoregional failure was 5.4% (95% CI 3.9%–7.1%) in patients starting w&w (Table 2, Figure 2). This rate was comparable to the locoregional failure rate of 5.6% (95% CI 3.4%–7.8%, 24 of 426) observed in patients who underwent R0 or R1 resection after chemoradiation in the RAPIDO trial [4,46] and 6.1% (95% CI 2.9%–9.3%, 13 of 212) in the PRODIGE23 trial [5]. Of note, patients achieving cCR represent a selected subgroup with favourable cancer biology. For example, in the OnCoRe study by Renehan et al. [47], the overall survival at 3 years was 96% in patients undergoing w&w compared with 87% in patients undergoing immediate surgery for persistent tumour, $p = .024$. Thus, in our analysis the selection bias is present. The additional risk of ultimate locoregional failure in patients starting w&w compared with those undergoing immediate surgery may therefore be underestimated.

The ultimate locoregional failure in patients with regrowth (group 3)

Our meta-analysis found a locoregional recurrence rate of 7.8% (95% CI 5.2%–11.0%) after salvage TME (Supplementary Figure S6). This rate is similar to the rates of locoregional

recurrence in patients who underwent R0 or R1 resection after chemoradiation in the RAPIDO trial (5.6%, 95% CI 3.4%–7.8%) [4,46] and the PRODIGE23 trial (6.1%, 95% CI 2.9%–9.3%) [5]. Therefore, our meta-analysis suggests that patients undergoing salvage TME for regrowth do not have a meaningfully higher risk of ultimate locoregional failure compared with those undergoing immediate TME.

However, when all causes of ultimate local failure were considered (such as recurrence after salvage TME, patients' refusal of salvage TME, distant metastases, frailty, or unresectable pelvic tumour), the rate of ultimate locoregional failure in the patients with regrowth was 24.1% (95% CI 17.9%–30.9%). This appears to be in contradiction with the results showing 5.4% of ultimate locoregional failure among patients starting w&w. However, this contradiction can be explained by the different denominators used in the calculations—the former only included cases with regrowth, while the latter consists of two quite different subgroups: (1) the larger subgroup with sustained cCR having excellent prognosis (winners), and the smaller subgroup with regrowth having much worse prognosis (losers). This issue is further illustrated by a pooled analysis of the surgical series showing a 5-year risk of local recurrence of 2.8% in the pathological complete response (pCR) group and 9.7% in the no pCR group, $p < .0001$ [48].

Due to such a high rate of ultimate local failure in patients with regrowth, we suggest measures to reduce the risk of regrowth (see Table 3). These measures also aim to decrease the risk of distant metastases, which may result from seeding from an uncontrolled primary tumour [53,54].

Notably, the most common reason for ultimate local failure was patients' refusal of salvage TME, reported in 9.1% (95% CI 5.3%–13.7%) of those with regrowth (Supplementary Figure S5), whereas the rate of patients refusing surgery among those with persistent tumours at response evaluation was only 1.9% (95% CI 0.6%–3.9%) (Supplementary Figure S11). Similarly, the intention-to-treat analysis showed 1.1% (95% CI 0.9%–3.0%, 5 of 449) of patients refusing surgery in the standard-of-care arm of the RAPIDO trial [4]. This suggests that the desire for organ preservation, initially arising from achieving cCR, may have been deeply rooted in these patients' consciousness, making it difficult to accept salvage TME, especially abdominoperineal resection. Thus, the high rate of patients refusing a salvage TME may be regarded as

a drawback of the w&w strategy. This information can be communicated to patients as a warning. Frailty was the reason for ultimate local failure only in 2.4% of patients with regrowth. Nevertheless, it cannot be excluded that some patients who refused salvage TME were driven by a subjective sense of frailty. On the other hand, in the OPERA trial 21% (4 of 19, Table 2) of patients with regrowth did not agree for salvage TME, despite only fully operable patients being eligible for entry into this study.

Does planned strategy jeopardise ultimate locoregional control compared with the opportunistic strategy?

We did not observe major differences in the ultimate failure rates between the opportunistic strategy and the planned strategy (using either radiation dose escalation or TNT) (Figures 1–3). Thus, our hypothesis that ultimate local failure is higher in the planned strategy compared with the opportunistic strategy is not supported. It is worth noting that a higher number of patients achieving cCR in the planned strategy, together with a similar ultimate local failure rate, results in a clinically significant increase in the number of patients with long-term organ preservation compared with the opportunistic strategy [1,2,7,8].

Limitations

The calculated rates of ultimate local failure are uncertain for various reasons. First, they could be underestimated because the follow-up periods were shorter than 3 years in 38% (3 of 8) of the studies included in our intention-to-treat analysis (Table 1) and in 44% (16 of 36) of the studies included in our analysis of patients starting w&w (Table 2). In addition, these follow-up periods were measured from radiotherapy, which means that they would be approximately one year shorter if measured from salvage TME. Second, the ultimate local failure rates could be overestimated because some patients with recurrence after salvage TME could be cured after re-salvage surgery; such attempts or outcomes were usually not reported. However, achieving a cure from recurrence following TME is rare; a median overall survival of only about 1.5 years from the onset of local recurrence has been reported [46]. Finally, the ultimate local failure rates could also be overestimated because some patients who initially refused salvage TME might have changed their minds later.

The aforementioned sources of bias, variability in patient population and treatment modalities (reflected by statistically significant tests for heterogeneity), as well as low quality of evidence (most included studies were small retrospective or cohort studies), and a possible systematic bias from the use of language restrictions, make our estimations and conclusions uncertain. Thus, the evidence from our meta-analysis is weak and does not allow for ruling out a small additional risk of an increased ultimate locoregional failure rate associated with w&w.

A call for standardisation of reporting outcomes

While performing our meta-analysis, we noticed that the reporting of results varied among publications, making it difficult to compare outcomes. Therefore, we suggest standardising the reporting of outcomes. First, it would be helpful in assessing treatment efficacy to report outcomes not only in patients who started w&w but also in all patients who started radio(chemo)therapy as potential candidates for w&w. Second, outcomes after w&w are reported in two ways: (1) in the total group of patients who initiate w&w with either cCR or near-CR [2,7,14,18,40]. In this approach, patients with near-CR who do not eventually achieve cCR and subsequently require salvage surgery are categorised as having ‘regrowth’ (although they actually present with the persistent disease rather than tumour reappearance), and (2) only in patients with cCR and those with near-CR who eventually achieve cCR [19–27,30–37,41–45]. This approach excludes patients with near-cCR who do not eventually reach cCR and require salvage surgery due to persistent or progressive near-CR from the analyses. This leads to presenting artificially lower regrowth risk in the second way compared with the first. We believe that reporting outcomes in all patients starting w&w (way 1) is desirable, because it includes all patients at risk of deferred surgery.

Conclusion

Nearly a quarter of patients with regrowth (an unfavourable subgroup) experience ultimate local failure, primarily due to their refusal of salvage TME. The risk of ultimate local failure in patients starting radio(chemo)therapy as potential candidates for w&w, or those starting w&w, seems to be comparable to that reported after preoperative chemoradiation and surgery. This comparison may be biased because w&w studies included more early tumours compared with surgical studies.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its [supplementary materials](#).

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