Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD)

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

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Summary

Background The strategy of watch and wait (W&W) in patients with rectal cancer who achieve a complete clinical response (cCR) after neoadjuvant therapy is new and offers an opportunity for patients to avoid major resection surgery. However, evidence is based on small-to-moderate sized series from specialist centres. The International Watch & Wait Database (IWWD) aims to describe the outcome of the W&W strategy in a large-scale registry of pooled individual patient data. We report the results of a descriptive analysis after inclusion of more than 1000 patients in the registry.

Methods Participating centres entered data in the registry through an online, highly secured, and encrypted research data server. Data included baseline characteristics, neoadjuvant therapy, imaging protocols, incidence of local regrowth and distant metastasis, and survival status. All patients with rectal cancer in whom the standard of care (total mesorectal excision surgery) was omitted after neoadjuvant therapy were eligible to be included in the IWWD. For the present analysis, we only selected patients with no signs of residual tumour at reassessment (a cCR). We analysed the proportion of patients with local regrowth, proportion of patients with distant metastases, 5-year overall survival, and 5-year disease-specific survival.

Findings Between April 14, 2015, and June 30, 2017, we identified 1009 patients who received neoadjuvant treatment and were managed by W&W in the database from 47 participating institutes (15 countries). We included 880 (87%) patients with a cCR. Median follow-up time was 3·3 years (95% CI 3·1–3·6). The 2-year cumulative incidence of local regrowth was 25·2% (95% CI 22·2–28·5%), 88% of all local regrowth was diagnosed in the first 2 years, and 97% of local regrowth was located in the bowel wall. Distant metastasis were diagnosed in 71 (8%) of 880 patients. 5-year overall survival was 85% (95% CI 80·9–87·7%), and 5-year disease-specific survival was 94% (91–96%).

Interpretation This dataset has the largest series of patients with rectal cancer treated with a W&W approach, consisting of approximately 50% data from previous cohort series and 50% unpublished data. Local regrowth occurs mostly in the first 2 years and in the bowel wall, emphasising the importance of endoscopic surveillance to ensure the option of deferred curative surgery. Local unsalvageable disease after W&W was rare.

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Introduction

The standard treatment for locally advanced rectal cancer is neoadjuvant (chemo)radiotherapy followed by major resection surgery, based on the principles of total mesorectal excision (TME).[1] However, this strategy is associated with perioperative mortality of 1–2%, which increases with old age, frailty, and comorbidity.[2,3] Additionally, it can lead to temporary or permanent colostomy and serious long-term morbidity, such as urinary and sexual dysfunction in more than 60% of patients.[4] Over the past two decades, focus has gradually shifted towards a more individualised approach, with the aim of improving long-term quality of life and functional outcomes. This approach has led to a growing interest in organ-preserving strategies in a strictly selected population.

The combination of neoadjuvant chemotherapy and radiotherapy has proven to be effective to downstage the primary tumour and it leads, in about 20% of patients, to complete disappearance of the tumour and tumour-positive lymph nodes—a pathological complete response (pCR), which is associated with favourable long-term outcomes compared with those without complete response.[5,6]

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See Online for appendix

Research in context

Evidence before this study

The watch and wait (W&W) strategy is gaining more attention as a treatment option for patients with rectal cancer with a clinical complete response after neoadjuvant therapy. Up to today, no evidence from randomised trials is available. Although several cohort studies and extensive reviews have been done, concerns remain about the oncological safety in patients who experience tumour regrowth. We did a PubMed search without date or language restrictions with the terms, "rectal neoplasms" as a major mesh term and the terms, "watchful waiting" (or variations, such as "watch-and wait" or "wait-and-see") and "neoadjuvant therapy" for studies in human beings. The search yielded 110 hits, of which several were cohort studies and 33 were review articles published since 2004. The first report was published in 2004 by Habr-Gama and colleagues, and included 71 patients. Several reports from the Habr-Gama research group are now available, in which 5-year overall survival is reported ranging from 85·9% to 100%. The largest cohort study available is from the northwest of England cohort, and includes 129 patients. In this study, the outcomes of W&W patients were compared with patients who had surgery using a propensity matched cohort analysis. 34% of the patients developed local regrowth. Nonetheless, no differences were found in non-regrowth disease-free survival and overall survival (3-year overall survival was 96%). Other cohort studies report similar survival, though they are generally small, mostly retrospective, and the inclusion criteria are variable across studies. A meta-analysis was published by Dossa and colleagues. In this study, a pooled 2-year local regrowth rate of 15·7% was reported, ranging from 5% to 33% in the studies included in the meta-analysis. Although this meta-analysis found no survival benefit for surgical resection in patients with a clinical complete response, this conclusion was based on two studies only, including 48 patients on the W&W strategy.

Added value of this study

This is the first large registry-based study on international W&W strategies for patients with rectal cancer, consisting of pooled individual patient data of approximately 50% patients from previously published series and 50% unpublished data. Despite the heterogeneity, this study provides a reliable reflection of the real-world risks and benefits of W&W. Local regrowth was most frequently diagnosed in the first 2 years of follow-up and was located in the bowel wall in most patients. Nodal local tumour regrowth was very uncommon. This indicates that strict endoscopic surveillance in W&W protocols is essential and enables early detection followed by curative treatment. In this series, survival was excellent and the risk of local unsalvageable disease was small.

Implications of all the available evidence

This study provides a valuable insight into W&W strategies worldwide. However, further expansion of the network and prospective data collection are essential to learn more on long-term outcomes of W&W, including functional outcomes. The IWWD Consortium will focus on the development of uniform protocols for selection and follow-up of patients on the W&W strategy. All interested clinicians who perform organ-preserving strategies on patients with rectal cancer are welcome to join our network.

Since the first introduction of the watch and wait (W&W) strategy for patients with rectal cancer with a clinical complete response (cCR) after neoadjuvant chemoradiotherapy by Habr-Gama and colleagues,[7] multiple cohort series[8–11] are now available in which surgery has been omitted. The diagnosis of a cCR based on the results of conventional imaging modalities does not perfectly correspond to a true complete response because local regrowth rates within 2 years of follow-up range from 7% to 33%.[8,12,13] Despite the incidence of local tumour regrowth, the results so far are promising in terms of survival since most local regrowths are amenable to salvage resection.[12]

Several factors might have contributed to a limited adoption of such a strategy so far and its absence in most surgical oncology guidelines. Most available cohort series are small and have heterogeneous study populations and, therefore, are not adequate to define the individualised oncological risk. Furthermore, international consensus has not been reached on imaging strategies and timing to identify a cCR, or follow-up protocols for timely detection of tumour regrowth. Also, neoadjuvant treatment schedules and choice of chemotherapy and radiotherapy dosage are considerably variable across studies, subsequently resulting in a wide range of cCR rates (10–78%).[9,10] Finally, data on long-term survival, such as functional and quality-of-life results, are still scarce.

In this setting, more evidence supporting organ-preserving strategies is needed to implement W&W as a safe treatment option for selected cases. Randomised controlled trials for this indication are challenging for both practical and ethical reasons: patients are likely to prefer avoiding surgery, especially when they are facing permanent colostomy. The International Watch & Wait Database (IWWD) was established in February, 2014.[14] This database was initiated by a collaboration of high-profile clinical experts, under the umbrella of the European Registration of Cancer Care and the Champalimaud Foundation Lisbon. The aim of this database is to collect all available data to expand knowledge on the benefits, risks, and oncological safety of organ-preserving strategies in rectal cancer. For the present study, the primary aim was to describe the pooled information after collection of patient data from more than 1000 patients in our network, which consists of data

from previously published cohort series and about 50% of unpublished data from smaller W&W centres. Furthermore, we aimed to explore the local regrowth rate and survival in this population.

Methods

Study design

This was an international multicentre registry study. On April 14, 2015, the web-based database was opened for patient-data registry. Clinical experts on W&W strategies were invited to participate. Additionally, clinicians could join the network via our website or contact addresses. Participating centres agreed to enter information on all patients in their institute who had organ-preservation treatment after neoadjuvant therapy for rectal cancer, whether or not patients had been part of previously published studies. Data were entered online at the centre under supervision of the participating investigator and stored in a highly secured NEN7510 certified and encrypted research data server (ProMISe). The IWWD contains information on patient and tumour characteristics at the time of diagnosis, the reason for organ-preserving treatment, type of neoadjuvant therapy, results of imaging modalities at diagnosis, reassessment after neoadjuvant therapy and follow-up, details of the treatment for disease recurrence, and survival status. The indication for neoadjuvant therapy, the decision for W&W, and all restaging and follow-up assessments were done according to local protocol of the participating institutions. We encouraged completeness of the data by using mandatory fields. The central data centre performed additional data quality checks in case of missing data irregularities, or lag in follow-up time. All participating centres retain full ownership of their data and responsibility for accuracy in the information provided.

Participants

All patients with rectal cancer in whom the standard of care (TME surgery) was omitted after neoadjuvant therapy were eligible to be included in the IWWD. We asked participating investigators to include all patients who did not have surgery after reassessment. For the present analysis, we only included patients with a cCR, defined as no signs of residual tumour at reassessment after neoadjuvant therapy. We also included patients who had a local excision to confirm the clinical diagnosis of a cCR. Reassessment consisted of digital rectal examination (DRE), endoscopy, and various imaging modalities according to each institution's policy. We excluded from our analysis patients who were included in the IWWD for other reasons and patients who were diagnosed with distant metastasis at baseline.

This was an observational registry study. Data were entered into the online data server in a coded format. Ethical approval was handled according to local authorities per participating institute.

Outcomes

At the start of the initiative, the IWWD executive board decided to do a descriptive analysis after inclusion of 1000 patients in the database. The primary outcome measure was the cumulative incidence of local regrowth. Since the 2014 Champalimaud consensus meeting (Lisbon, Portugal, Feb 14, 2014), it is agreed that local tumour regrowth after an initial cCR should be distinguished from local recurrence after TME surgery, which is known for its poor prognosis, whereas local regrowth after a cCR is usually readily salvageable.[15] Therefore, we classified any local regrowth of rectal cancer at the local tumour location or regional lymph nodes detected with DRE, endoscopy, or imaging as local regrowth in the present study. We defined the absence of signs of tumour regrowth up to the date of the last assessment as a sustained cCR. Secondary endpoints were the incidence of distant metastasis, overall survival, and disease-specific survival.

Statistical analysis

We did statistical analyses using IBM SPSS Statistics version 23.0 and Stata/SE version 12.0.

We calculated descriptives for the whole registry without comparisons. For baseline clinical tumour stage, we combined data of all performed radiological imaging modalities at baseline. If MRI was done, we considered it the leading imaging modality. We calculated median follow-up according to the reverse Kaplan-Meier method. We used Kaplan-Meier survival methods for survival analyses. We calculated the time to diagnosis of local regrowth from the date of decision for W&W. We considered the date of diagnosis as the baseline timepoint for survival analysis and the incidence of distant metastasis. If the date of diagnosis was unknown, we estimated it using the dates of endoscopy and imaging at baseline. If the date of diagnosis of distant metastasis was unknown, we estimated it on the basis of the date of clinical assessments. For analysis of disease-specific survival, we considered deaths due to the primary malignancy (local disease or distant metastasis of rectal cancer) or related to treatment as an event.

Role of the funding source

The funders had no role in the study design, data collection and analysis, or writing the report. The members of the academic committee had access to all the data and shared the responsibility for the final decision to submit the report for publication.

Results

Between April 14, 2015, and June 30, 2017, 1009 patients were included in the database from 47 participating institutes and 15 countries (appendix). Of these, 880 patients had a cCR as defined by the criteria of participating institutes and were included for the present analysis, with a median follow-up time of 3·3 years (3·1–3·6; table 1).

Other reasons for inclusion in the database but exclusion from this analysis were clinical near complete response or patient-related factors such as refusal of surgery by patient or inoperability due to comorbidity (figure 1). Patient and tumour characteristics at baseline varied between centres (table 1). These baseline differences were also present across the three largest participating institutes—partly due to inclusion of patients, for example, by Instituto Angelita e Joaquim, Brazil, Gama as early as 1991, when MRI was not yet routinely done and thus T stage was not available in the database.

Imaging modalities used at baseline and reassessment for local staging are listed in table 2. Almost all patients had endoscopy at baseline. An MRI was done in three-quarters of all patients and, in 631 (90%) of 703 patients who were selected for W&W after 2010.

For identification of a cCR after neoadjuvant therapy, endoscopy was done in 779 (90%) of 880 cases. Biopsy samples were taken in 325 (42%) of the 779 patients who had endoscopy for reassessment. Restaging MRI was done in 620 (71%) of all 880 patients. Most patients who did not have a reassessment MRI were included before 2010. An MRI was done in 536 (83%) of the 703 patients selected for W&W after 2010. In most patients (621 [71%] of 880), two or more imaging modalities were combined for local restaging. Both endoscopy and MRI were done in 563 (64%) of 880 patients. A combination of DRE, endoscopy, and MRI was done in 398 (45%) of

	Total number of patients (N=880)	Instituto Angelita e Joaquim Gama, São Paolo, Brazil (n=192)	Antoni van Leeuwenhoek and Maastricht University Medical Center, Netherlands (n=239)	OncoRe research database, UK (n=149)	Other participating institutes (n=300)
Country					
Argentina	46 (5%)	..	..	..	46 (15%)
Belgium	27 (3%)	..	..	..	27 (9%)
Brazil	201 (23%)	192 (100%)	..	..	9 (3%)
Germany	25 (3%)	..	..	..	25 (8%)
Denmark	40 (5%)	..	..	..	40 (13%)
France	42 (5%)	..	..	..	42 (14%)
UK	150 (17%)	..	..	149 (100%)	1 (0%)
Ireland	35 (4%)	..	..	..	35 (12%)
Netherlands	252 (29%)	..	239 (100%)	..	13 (4%)
Poland	15 (2%)	..	..	..	15 (5%)
Portugal	21 (2%)	..	..	..	21 (7%)
Russia	5 (1%)	..	..	..	5 (2%)
Sweden	15 (2%)	..	..	..	15 (5%)
Turkey	6 (1%)	..	..	..	6 (2%)
Age, mean (SD)	63·6 (11·7)	59·7 (12·6)	63·5 (9·92)	65·9 (9·4)	65·0 (13·0)
BMI, mean (SD)	26·7 (4·9)	26·1 (3·9)	26·3 (5·4)	27·5 (6·2)	26·4 (4·3)
Sex					
Male	603 (69%)	126 (66%)	161 (67%)	110 (74%)	206 (69%)
Female	277 (32%)	66 (34%)	78 (33%)	39 (26%)	94 (31%)
Comorbidity					
Yes	252 (29%)	58 (30%)	74 (31%)	0 (0%)	120 (40%)
No	337 (38%)	131 (68%)	103 (43%)	17 (11%)	86 (29%)
Unknown	291 (33%)	3 (2%)	62 (26%)	132 (89%)	94 (31%)
Year of decision for W&W					
Before 2010	177 (20%)	113 (59%)	10 (4%)	11 (7%)	43 (14%)
2010–14	450 (51%)	73 (38%)	95 (40%)	131 (88%)	151 (50%)
2015–17	253 (29%)	6 (3%)	134 (56%)	7 (5%)	106 (35%)
Median follow-up time, years (95% CI)	3·3 (3·1–3·6)	7·1 (6·3–8·0)	2·1 (1·9–2·3)	3·7 (3·4–4·1)	2·8 (2·4–3·3)
Clinical T stage baseline*					
cT1	14 (2%)	5 (3%)	1 (0%)	0 (0%)	8 (3%)
cT2	226 (26%)	21 (11%)	50 (21%)	36 (24%)	119 (40%)
cT3	451 (51%)	26 (14%)	170 (71%)	104 (70%)	151 (50%)
cT4	30 (3%)	0 (0%)	15 (6%)	7 (5%)	8 (3%)
Unknown	159 (18%)	140 (73%)	3 (1%)	2 (1%)	14 (5%)

(Table 1 continues on next page)

	Total number of patients (N=880)	Instituto Angelita e Joaquim Gama, São Paolo, Brazil (n=192)	Antoni van Leeuwenhoek and Maastricht University Medical Center, Netherlands (n= 239)	OncoRe research database,UK (n=149)	Other participating institutes (n=300)
(Continued from previous page)					
Clinical N stage baseline					
cN0	309 (35%)	59 (31%)	62 (26%)	47 (32%)	141 (47%)
cN1	271 (31%)	22 (12%)	79 (33%)	63 (42%)	107 (36%)
cN2	167 (19%)	2 (1%)	96 (40%)	37 (25%)	32 (11%)
Unknown	133 (15%)	109 (57%)	2 (1%)	2 (1%)	20 (7%)
Local regrowth					
Yes	213 (24%)	70 (37%)	35 (15%)	59 (40%)	49 (16%)
No	667 (76%)	122(64%)	204 (85%)	90 (60%)	251 (84%)
Distant metastasis					
Yes	71 (8%)	27 (14%)	9 (4%)	14 (9%)	21 (7%)
No	809 (92%)	165 (86%)	230 (96%)	135 (91%)	279 (93%)
Last study status					
In follow-up	660 (75%)	98 (51%)	202 (85%)	127 (85%)	233 (78%)
Follow-up completed	57 (7%)	28 (15%)	17 (7%)	0 (0%)	12 (4%)
Lost to follow-up	64 (7%)	28 (15%)	14 (6%)	1 (1%)	21 (7%)
Deceased	99 (11%)	38 (20%)	6 (3%)	21 (14%)	34 (11%)

Data are n (%), unless otherwise specified. BMI=body-mass index. *Clinical T stage based on radiological imaging is displayed if patients were assessed with endoscopy or endorectal ultrasound; the baseline T stage was not documented in the database.

Table 1: **Baseline characteristics of clinical complete responders in the total registry and difference between the three largest centres**

880 patients. In 44 (5%) of 880 patients a diagnostic local excision was done to confirm a cCR—of these, 39 (89%) had no residual adenocarcinoma.

Chemoradiotherapy was most commonly used (804 [91%] of 880 patients), most frequently with schedules of 45 gray (Gy; n=173), 50 Gy (n=354), 54 Gy (n=102), or 60 Gy (n=40). In most patients, capecitabine (396 of 804) or 5-fluorouracil (188 of 804) was used. The compliance of chemoradiotherapy was high: 791 (98%) of all 804 patients completed all radiotherapy, and 756 (94%) of 804 patients completed the chemotherapy component. The different combinations of neoadjuvant therapy are displayed in table 3. In seven patients, the details of neoadjuvant therapy were unknown.

Local regrowth occurred in 213 of 880 patients, with a 2-year rate of 25·2% (95% CI 22·2–28·5%). Local regrowth was diagnosed in the first year after the decision for a new W&W regimen in 136 (64%) of the 213 patients with local regrowth. Local regrowth was diagnosed within 2 years in 188 (88%) of 213 patients (figure 2). Local regrowths were located in the bowel wall in 97% (206 of 213) of patients. In 11 patients, local regrowth was located in the regional lymph nodes; four of whom had simultaneous tumour regrowth in the bowel wall. Only seven (3%) patients were diagnosed with tumour regrowth in the regional lymph nodes only.

For 148 (69%) of 213 patients with local regrowth, details of surgical treatment for regrowth were available. For the remaining 65 patients, the treatment details were not documented in the registry mainly because many patients were referred back to their primary hospital for salvage therapy and, therefore, the participating centres did not have access to this information. 46 (31%) of these 148 patients were treated with local excision, of whom 13 had subsequent TME surgery. In total, 115 (78%) of 148 patients had TME resection for local regrowth, 114 (99%) of 115 with curative intention. In 101 (88%) of all 115 surgical resections for local regrowth, the resection margins were tumour negative (R0 resection), in 6% (seven of 115) tumour margins were positive (R+), and in the remaining cases the margin involvment was unknown (seven [6%] of 115).

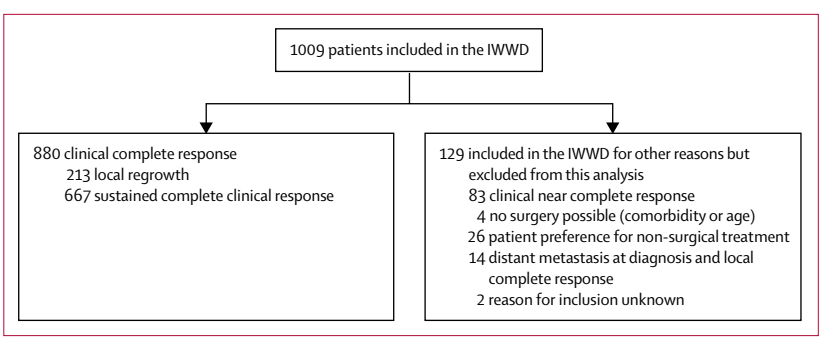

Figure 1: **Patients included in the IWWD and in this study**
IWWD=International Watch & Wait Database.

Distant metastases were diagnosed in 71 (8%) of 880 patients during follow-up, with a 3-year rate of 8·1% (95% CI 6·2–10·5; figure 2B). Only eight (11%) of all 71 distant metastases were diagnosed in the first year after diagnosis, 38 (54%) of 71 patients were diagnosed within 2 years, and 53 (75%) of

	Baseline (n=880)	Reassessment
Endoscopy	848 (96%)	779 (89%)
MRI pelvis	678 (77%)	620 (71%)
CT pelvis	378 (43%)	261 (30%)
Endorectal ultrasound	146 (17%)	67 (8%)
PET scane	116 (13%)	39 (4%)
CEA	540 (61%)	196 (22%)
Local excision	..	45 (5%)
ypT0	..	40 (4%)
ypT+	..	5 (1%)

Data are n (%). CEA=carcinoembryonic antigen.

Table 2: **Diagnostic procedures at baseline and at reassessment after induction therapy**

	Patients
Single therapy	
Chemoradiotherapy	738
Brachyradiotherapy	5
External beam radiotherapy	35
Chemotherapy	3
Total for single therapy	781
Different combinations	
Chemoradiotherapy and brachyradiotherapy	57
Chemoradiotherapy and chemotherapy	7
Brachyradiotherapy and external beam radiotherapy	19
External beam radiotherapy and chemotherapy	7
Chemoradiotherapy, brachyradiotherapy, and external beam radiotherapy	2
Total for different combination	92
Missing	7
Total	880

Data are n.

Table 3: **Different types and combinations of induction therapy**

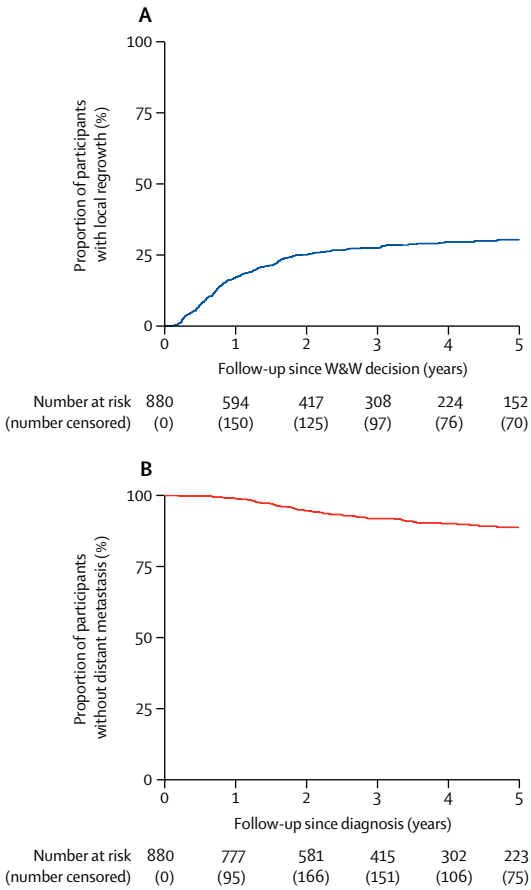

Figure 2: **Local tumour regrowth (A) and distant metastasis-free period (B)**
W&W=watch and wait.

71 patients within 3 years. Distant metastases were most frequently located in lungs (44 [62%] of 71), followed by liver (29 [41%] of 71). 13 (18%) patients were diagnosed with lung and liver metastases simultaneously. Other locations of distant metastasis were distant lymph nodes (eight [11%] of 71) and peritoneum (four [6%] of 71). In patients with local regrowth, the proportion of patients with distant metastasis was 18% (38 of 213), whereas the proportion of patients with a sustained complete response was 5% (33 of 634). Of the patients with both distant metastasis and local regrowth, the distant metastases were diagnosed before the local regrowth in two (5%) patients, simultaneously in 12 (32%) patients within 3 months, and in 24 (63%) patients more than 3 months after the local regrowth.

5-year disease-specific survival was 93·8% (95% CI 90·9–95·9) and 5-year overall survival was 84·7% (80·9–87·7; figure 3). For patients with a sustained cCR, the 5-year disease-specific survival was 97·3% (95% CI 94·5–98·7) and 5-year overall survival was 87·9% (83·8–91·0). For patients who were diagnosed with local regrowth, the 5-year disease-specific survival was 84·0% (95% CI 75·0–89·9) and 5-year overall survival 75·4% (66·2–82·4).

In 33 (4%) of 880 patients the cause of death was related to rectal cancer. Ten patients died of metastatic disease in the presence of a sustained local cCR. 14 patients who died of rectal cancer were diagnosed with both distant metastasis and local regrowth, and five patients only had local residual disease at the time of death. Of these five patients, two had had surgical resection for regrowth with curative intention, one had refused surgery, and in two patients the details were unknown. In the four remaining patients, the sites of rectal cancer at death were unknown.

Discussion

This is the largest series of pooled individual data of patients with rectal cancer and a cCR after neoadjuvant therapy, treated with W&W. The main aim of this study

was to provide insight in the W&W strategies worldwide and oncological outcome of W&W patients. The registry has collected data of more than 1000 patients, approximately 50% from published cohort studies and 50% of unpublished data.[7,8,10,11,13,16,17]

In the registry, 25% of patients with a cCR after neoadjuvant therapy and treated with a W&W approach developed a local regrowth in the first 2 years of follow-up, with regrowths nearly always located in the bowel wall (97%). The local regrowth rate is considerably higher than the pooled 2-year local regrowth rate of 16% reported by Dossa and colleagues.[12] This difference is probably related to the strict inclusion criteria in the studies of the meta-analysis, whereas the registry is more based on a so-called all-comers strategy, without narrow selection criteria. Most likely this result reflects the outcome of a W&W strategy on a more population-based level.

The registry represents a period of two and a half decades in which W&W evolved from the first W&W patient to an adopted treatment strategy in dedicated centres. Our data show that imaging strategies, selection of patients, and follow-up protocols have evolved accordingly. The current standard of care for rectal cancer includes high-resolution MRI for both primary staging and restaging after neoadjuvant therapy, and MRI is now also considered essential in the selection and follow-up of W&W patients.[18,19] All centres agree that the identification of a cCR is best done with a combination of DRE, endoscopy, and high-resolution imaging. A typical cCR is seen as a flat white scar on endoscopy, with only signs of fibrosis on DRE and MRI.[20,21] The value of biopsy samples and additional imaging, such as PET-scanning, is still unclear and not recommended.[22–24] Surveillance in W&W regimens should focus on early detection and treatment of regrowth. Although a uniform protocol has not yet been established, all experts agree that it should include intensive surveillance with DRE, flexible endoscopy, and MRI in the first 2 years, and decreasing intensity in subsequent years (appendix).

Survival in this registry is excellent: a 5-year overall survival of 84·7% and a 5-year disease-specific survival of 93·8%. Ideally, outcomes of W&W patients and outcomes of patients with a cCR who had radical surgery should be compared. However, such a comparative population is not available. The main concern about implementation of W&W strategies remains whether survival and the chance of curative treatment are compromised in patients who experience a regrowth. Patients with a sustained cCR clearly have no oncological disadvantage from a W&W policy because surgery could not have improved their 100% local control rate and could only have contributed operative mortality and morbidity. The overall survival of patients with a sustained cCR should be in the same range as patients with pCR after TME surgery. The 5-year overall survival of 87·9% in sustained clinical responders in the present study is

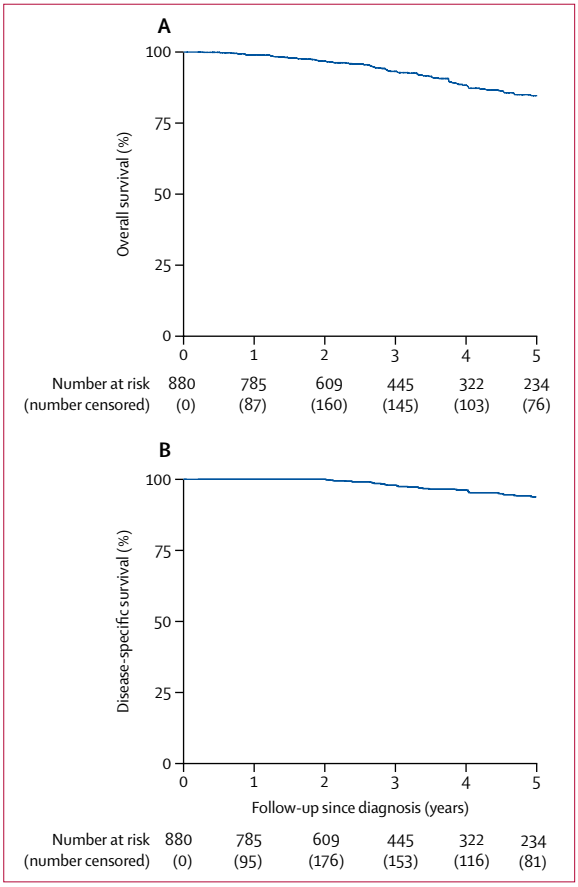

Figure 3: 5-year overall survival (A) and disease-specific survival (B)

similar to the 5-year overall survival of 87·6% in patients with pCR in the pooled analysis of Maas and colleagues.[5] Patients with a regrowth should be considered different from those with pCR because patients with residual tumour have inherently lower survival than patients with no residual tumour because of the inherent increased risk of distant metastasis. In our data, 5-year overall survival was 75·4% for patients with local regrowth, and distant metastasis occurred in 17·8% of these patients. In the study of Maas and colleagues,[5] 5-year overall survival for non-pCR patients was 76·5%, and 22·7% of these patients developed metastasis. Although the two populations are somewhat different, these numbers are within the same range. We hypothesise that the risk of metastases and rectal-cancer specific death in these patients is more related to the biology of the tumour rather than to the omission of immediate surgery.

Five of the 33 patients that died because of rectal cancer were diagnosed with local disease only. When we take into account the missing information on disease salvage and the missing sites of rectal cancer in four patients, the risk of locally unsalvageable disease is estimated to be 1% at the most. This estimate is congruent with the 0·2% reported in the meta-analysis of Dossa and

colleagues.[12] With the inclusion of 50% unpublished patients in the registry, this figure is likely to be a reliable reflection of the true population risk. Although detailed information on treatment for local regrowth is scarce, in some patients salvage surgery was not done because of various reasons, such as patient refusal, high operative risk, and synchronous metastatic disease. The standard salvage therapy is TME surgery. Local excision can be considered an alternative strategy in specific cases of minimal tumour regrowth or frail patients, but inferior oncological outcomes have been reported with tumours greater than ypT1.[25]

This study has several limitations. First of all, this is a database-based registry study. As expected, we found considerable variability between participating centres in baseline characteristics, neoadjuvant therapy, and imaging strategies. Some strategies, such as the use of MRI, changed over time. Furthermore, the criteria for a cCR might have been variable across centres. This variability might have influenced the proportion of cCR and the number of regrowths. Although all participants have entered data with the same instructions, and multiple quality checks were done to detect entry errors, items could have been interpreted and filled in differently. Some details of imaging and treatment strategies were missing because the original patient reports could not be accessed centrally. Furthermore, part of the data was prospectively collected at the participating institutes and entered at a later date in the IWWD. All patients who initially were selected for W&W strategies might not have been included in the database, potentially leading to selection bias. We did not have access to the complete population of patients with rectal cancer treated with chemoradiotherapy at each institute, precluding a good estimate of the proportion of patients with a cCR and the proportion followed up in a W&W regimen. A last and highly important issue with regard to applicability of the results in other settings is that patients in the present study were generally treated in high-volume centres with experience and dedicated facilities for W&W.

Despite these limitations, we feel that the results of this study are valuable and increase the knowledge on the risks and benefits of W&W for individual patients. The data collected so far provide information on the location and incidence of local regrowth and distant metastasis, and the small risk of incurable disease in strictly selected and monitored patients with a cCR after neoadjuvant therapy. The study shows the importance of frequent surveillance in W&W patients in the first 2 years of follow-up. The main question, however, is whether W&W is ready for clinical practice. Although demand is high from patients and our data suggest the W&W approach is a good alternative to TME resection in patients with a cCR, there are several caveats. W&W regimens should preferably be done in centres that have sufficient volume and a dedicated programme for W&W, with state-of-the-art flexible endoscopy and MRI to enable accurate selection and intensive surveillance. Patients should be involved in the shared-decision process, considering all the benefits, risks, and uncertainties of both standard TME resection and the W&W approach. The results of this study can be used in a trade-off discussion with a patient when reassessment after neoadjuvant therapy shows a cCR. However, this study does not address the issue of whether or not neoadjuvant therapy with the goal of organ preservation is justified in patients with small distal tumours who can be treated with TME surgery without neoadjuvant therapy. Although early tumours have a higher chance for a cCR than more advanced tumours, the non-responders might be more disadvantaged when they still require major surgery.[17]

Many other clinical challenges and questions remain. What is the optimal selection and follow-up protocol? What is the best approach for a near-complete clinical response? Who are the best candidates to pursue organ preservation? Importantly, long-term quality-of-life outcomes and effects of (chemo)radiotherapy on bowel function in W&W patients are still unknown.

This study shows that in strictly selected patients with a clinical complete response, W&W can be a good alternative to major surgery with very little oncological risk. At least at present, selection and surveillance of these patients should be done in dedicated centres. Through the ongoing collaborative effort, the IWWD consortium will address a number of remaining questions regarding W&W in the future, to the benefit of patients with rectal cancer.

Contributors

MJMV, DEH, GLB, NLF, ROP, AH-G, and CJHV designed the study. MJMV, DEH, and GLB wrote the first draft of the manuscript. MJMV, DEH, EB, EM-KK, GLB, AH-G, AGR, NLF, ROP, and CJHV interpreted, critically evaluated, and improved the study design and manuscript, and share the responsibility for the final manuscript and the decision to submit. The IWWD Consortium members were responsible for data collection and evaluation, and approval of the manuscript.

Declaration of interests

We declare no competing interests.

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