Registry of 1009 patients in the International Watch & Wait database (IWWD) for rectal cancer: Results of clinical complete responders

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ABSTRACT

Background
Organ preserving strategies for rectal cancer patients that achieve a complete clinical response (cCR) after neoadjuvant therapy such as watch and wait (W&W) are gaining interest among patients and clinicians. In absence of evidence from randomized controlled trials, the International Watch & Wait Database (IWWD) was initiated in 2014. We aimed to describe the outcome of W&W patients based on pooled individual patient data.

Methods
Participating centres entered data into an online highly secured and encrypted research data server. Data included baseline characteristics, neoadjuvant therapy, imaging protocols, local regrowth, distant metastases rate and survival status. The present analysis concerns all patients with a clinical complete response (cCR) after neoadjuvant treatment who were managed by W&W.

Findings
Between April 2015 and June 2017, 1009 patients were identified in the database from 47 participating institutes (15 countries). 880 patients (87%) with a cCR were included. Median follow-up time was 3·4 years (IQR 1·8 to 5·5). Two-year local regrowth rate was 25·3% (95%CI 22·3-28·6%), 88·3% of all local regrowth was diagnosed in the first two years, and was located in the bowel wall in 96·7%. Five-year overall survival was 84·6% (95%CI 80·8-87·6%), and five-year disease-specific survival was 93·8% (95%CI 90·8-95·8%).

Interpretation
This is 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rectal cancer treated with a W&W approach, consisting of approximately 50% data from previous cohort series and 50% unpublished data.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 two years and in the bowel wall, emphasizing the importance of endoscopic surveillance to ensure the option of deferred curative surgery. Local unsalvageable disease after W&W was rare. It is our hypothesis that the majority of the 6% rectal cancer-specific death was more related to tumour biology rather than to omission of surgery.

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INTRODUCTION

Long-term survival for locally advanced rectal cancer has improved considerably since the introduction of total mesorectal excision and neoadjuvant (chemo-)radiotherapy.[1] However, this treatment remains associated with perioperative mortality of 2% and up to four times higher in the elderly.[2,3] In addition, 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 last years focus has shifted towards a more individualized approach with the aim of improving long-term quality of life and functional outcomes. This has led to a growing interest in organ preserving strategies in a strictly selected population.

Combining neoadjuvant chemo- and radiotherapy has proven to be effective to downstage the primary tumour and it leads in about 20% of the 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 to those without complete response .[5,6]

Since the first introduction of watch and wait (W&W) for rectal cancer patients with a clinical complete response (cCR) after neoadjuvant chemoradiotherapy by Habr-Gama,[7] multiple cohort series are now available in which surgery has been omitted.[8-11] It is known that the diagnosis of a cCR based on the results of conventional imaging modalities does not perfectly correspond to a true CR, as local regrowth rates within 2 years of follow up range from 7 to 33%.[12,13] Despite local tumour regrowth rates, the results so far are promising in terms of survival since the vast majority of local regrowths are amenable to salvage resection. In a recent meta-analysis, no overall survival benefit was suggested for surgical resection versus W&W in patients with a cCR.[12]

Several factors may have contributed for a limited adoption of such 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 individualized oncological risk. Furthermore, international consensus on imaging strategies and timing to identify a cCR, or to detect cancer regrowth timely, is still lacking. Also, neoadjuvant treatment schedules, choice of chemotherapy and radiotherapy dosage are considerably variable across studies, subsequently resulting in a wide range complete clinical response rates (10 to 78%).[9,10] Finally, data on long-term survival outcomes 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. Randomized 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 was initiated by a collaboration of high-profile clinical experts, under the umbrella of EURECCA (European Registration of Cancer Care) and the Champalimaud Foundation Lisbon. The aim of this database is to collect all available data in order 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 of more than 1000 patients from 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 is an international multicentre registry study. In April 2015, the web-based database was opened for patient data registry. Data entry is performed online at participating centres under supervision of the participating investigator, and stored in a highly secured NEN7510 certified and encrypted research data server (ProMISe).[15] The IWWD database 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. All assessments were done according to local W&W protocol of the participating institutions. Data quality checks were performed by the data centre. All participating centres retain full ownership of their data and responsibility for accuracy in the information provided.

Patient selection

All patients with rectal cancer in whom the standard of care, TME surgery, was omitted after neoadjuvant therapy are eligible to be included in the IWWD. For the present analysis, we included patients with a cCR only, as defined according to each institution's criteria. This could be patients who were treated with strict surveillance only, as well as patients without suspicion of residual tumour in whom a standard confirmative local excision was performed. All other reasons for inclusion in the database, as well as patients diagnosed with distant metastasis at baseline but a local complete clinical response were excluded for this analysis.

Outcomes

The primary aim was to describe the available information on internationally applied W&W strategies within our network. For baseline clinical tumour stage, data of all performed radiologic imaging modalities at baseline were combined. If MRI was performed, this was considered the leading imaging modality. The incidence of local tumour regrowth and distant metastasis during follow-up was assessed. Since the 2014 Champalimaud consensus meeting, 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.[16] Therefore, this is indicated as local regrowth-rate in the present study. Furthermore, overall survival (OS) and disease-specific survival (DSS) were assessed. For analysis of DSS, deaths due to the primary malignancy (local disease and/or distant metastasis of rectal cancer) or related to treatment were considered an event.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 23.0 and Stata/SE version 12.0. Descriptive features were calculated for the whole registry, no comparisons were made. Median follow-up was calculated according to the reverse Kaplan-Meier method. The time to diagnosis of local regrowth was calculated from the date of decision for W&W. For survival analysis Kaplan-Meier survival methods were used. Date of diagnosis was considered the baseline time point for survival analysis and the actuarial rate of distant metastasis. If the date of diagnosis was unknown, this was estimated using the dates of endoscopy and imaging at baseline.

Ethical approval

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

Role of the funding source

The funders had no role in the study design, data analysis or writing the report. The members of the executive board of the IWWD consortium shared the responsibility for the final decision to submit the report for publication.

RESULTS

Patient characteristics

On June 30th, 2017, 1009 patients were included in the database from 47 participating institutes and 15 countries (appendix B). Of these, 880 patients had a cCR as defined by the criteria of participating institutes, and were included for the present analysis. Other reasons for inclusion in the database but exclusion for 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 are listed in table 1. There was great variability between baseline characteristics from included centres. When looking at the three largest centres of our network, some differences were noted (appendix C).

Diagnostic procedures

Imaging modalities used at baseline and reassessment for local staging are listed in table 2. Baseline imaging protocols were varying. Almost all patients underwent endoscopy at baseline (96·4%), and in the three-quarters of patients MRI imaging was performed (77·0%).

For identification of a cCR after neoadjuvant therapy, endoscopy was performed in 88·5% of cases. In 44·9% of all patients that underwent endoscopy for reassesment after neoadjuvant therapy, biopsies were taken. Restaging MRI was performed in 70·5% of all patients. Less frequently performed were CT pelvis and endorectal ultrasound (29·7% and 7·6% respectively). In most patients (70·6%) two or more imaging modalities were combined for local restaging. Both endoscopy and MRI were done in 64·0% of all patients. A combination of DRE, endoscopy and MRI was performed in 45·2% of patients. In 44 patients local excision was performed in the initial treatment window without clinical evidence of local regrowth – of these, 88·6% had no residual adenocarcinoma.

Neoadjuvant therapy

Chemoradiotherapy was most commonly used (804/880 patients, 91·4%), with schedules of 45 Gy (24·6%), 50-50·4 Gy (50·4%), 54 Gy (14·5%) or 60 Gy (5·7%). In the majority of patients capecitabine (61·5%) or 5-FU (29·2%) was used. The compliance of chemoradiotherapy was high: 98·8% of all patients completed all radiotherapy, and 95·1% of 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

Local regrowth occurred in 213 out of 880 patients, with a 2-year actuarial rate of 25·3% (95%CI 22·3-28·6%). In 63·8% (n=136) local regrowth was diagnosed in the first year after the decision for a W&W regimen, and in 88·3% (n=158) within two years (figure 2). Local regrowths were located in the bowel wall in 96·7%. In 11 patients local regrowth was located in the regional lymph nodes, in four of whom simultaneously with tumour regrowth in the bowel wall. Only seven patients were diagnosed with tumour regrowth in the regional lymph nodes only (3·3%).

For 148 out of 213 patients with local regrowth, details of surgical treatment for regrowth were available. Of these, 46 patients were treated with local excision (31·1%), of which 13 underwent additional surgical resection subsequently. In total 115 patients underwent TME resection for local regrowth (77·7%), of which 99·1% with curative intention. In 87·8% of all surgical resections for local regrowth, the resection margins were tumour negative (R0 resection), in 6·1% tumour margins were positive (R+), and in the remaining cases the margin involvment was unknown (6·1%).

Distant metastasis

Distant metastasis were diagnosed in 71 patients during follow-up, with a 3-year actuarial rate of 7·6% (95%CI 5·8-10.0). Only 9·9% (n=7) of all distant metastasis were diagnosed in the first year after diagnosis, 47·9% (n=34) were diagnosed within 2 years, and 67·6% (n=48) within 3 years.

Distant metastasis were most frequently located in lungs (62·0%), followed by liver (40·8%). Thirteen patients (18·3%) were diagnosed with lung and liver metastasis simultaneously. Other locations of distant metastasis were distant lymph nodes (11·3%) and peritoneum (5·6%).
In patients with local regrowth, the incidence of distant metastasis was 17·8% (38/213), whereas in patients with a sustained complete response this was 4·9% (33/634). Of the patients with both distant metastasis and local regrowth, the distant metastases were diagnosed prior to the local regrowth in 2 patients (5·3%), simultaneously in 12 patients (within 3 months, 31·6%), and more than 3 months after the local regrowth in 19 patients (50·0%). For five patients (13·2%) the time between local regrowth and distant metastasis was unknown.

Survival
Five-year DSS was 93·8% (95%CI 90·8 - 95·8) and 5-year OS was 84·6% (95%CI 80·8 - 87·6) (figure 3). For patients with a sustained cCR, the 5-year DSS was 97·3% (95%CI 94·5-98·7) and 5-year OS was 87·9% (95%CI 83·8-91·0). For patients that were diagnosed with local regrowth, the 5-year DSS was 84·0% (95%CI 75·0-89·9) and 5-year OS 75·4% (95%CI 66·2-82·4).
In 33 patients (3·75%) the cause of death was related to rectal cancer. Ten patients died of metastatic disease in the presence of a sustained local cCR. Fourteen 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 undergone 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 rectal cancer patients with a W&W strategy after neoadjuvant therapy. The main aim of this study was to provide an insight in the strategies and real world oncological outcome of W&W series worldwide. The registry has collected data of more than 1000 patients, approximately 50% from published cohort studies, and 50% of unpublished data.[7,8,10,11,17-19]

In the registry, 25·3% of patients in a W&W approach developed a local regrowth in the first two years of follow-up. This local regrowth rate is considerably higher than the pooled 2-year local regrowth rate of 15·7% reported in the meta-analyis of Dossa et al. This is probably explained by the strict inclusion criteria in the studies of the meta-analysis, whereas the registry is more based on an ' all-comers' strategy without narrow selection criteria. Most likely this better reflects the outcome of a W&W strategy on a more population-based level. The regrowths were nearly always located in the bowel wall (97%), highlighting the importance of endoscopic assessments in the follow-up protocols for W&W strategies.

The survival outcome in this W&W population is excellent: a 5-year OS of 84·6% and a 5-year DSS of 93·8%. Despite the heterogeneity in the registry, these 5-year outcome figures are remarkable good compared to survival rates of rectal cancer patients who undergo surgery.[20] The main concern about implementation of W&W strategies remains whether survival and the chance of curative treatment are compromised by not performing immediate surgery in patients with a clinical complete response, but rather to delay surgery and restrict it to only those patients who experience a regrowth. It is clear that patients with a sustained complete response are better off with a W&W policy, as immediate TME surgery could not have improved their 100% local control rate, and could only have contributed operative mortality and short and long term morbidity. The oncological prognosis should be broadly similar to pCR patients after TME surgery. The 87·9% 5-year OS in patients with a sustained clinical complete response in the present study is comparable to the 5-year OS of 87·6% in pCR patients in the pooled analysis of Maas et al.[6] Patients with a regrowth are at least theoretically at risk to develop uncurable local disease, and to develop metastases arising from the regrowth.

In this study, five out of 880 patients died of local tumour recurrence (0·6%). In two of these patients salvage treatment was technically not possible, one patients declined treatment, and in two patients the reason was not documented. If we presume the worst case scenario, that all four patients in which the sites of rectal cancer were unknown also died of local uncontrollable disease, the risk of locally unsalvagable disease would be between 0·2% to 1·3%. This is within the same range of the 0.2% reported in the recent meta-analysis of Dossa and collegues.[12] Due to the inclusion of unpublished series and patients in our registry, this figure is most likely a reliable reflection of the true population risk. It can be used in a trade-off discussion with a patient with a clinical complete response to decide between a W&W policy and TME surgery. The benefits of a radical resection should be balanced against the operative risk, short and long term morbidity and risk for definitive colostomy.

It is more difficult to estimate the excess risk of metastatic disease in patients with a regrowth, if there is any. Patients with a regrowth most likely would have shown residual tumour and would not have been labeled pCR if they would have had TME surgery after the chemoradiation. It is well documented that incomplete responders have an inherently higher risk for metastases and a lower OS than complete responders, suggesting a more unfavorable biological profile. In the pooled analysis of Maas et al. 22·7% of non-pCR patients developed metastasis and 5-year OS was 76·5%.[6] In our data, distant metastasis were diagnosed in 17·8% of patients that were diagnosed with local regrowth, and their 5-year OS was 75·4%. Although the two populations are somewhat different, the figures are in the same range. It is our hypothesis that the majority of the 6% deaths due to rectal cancer in the present series are due to metastatic disease that was already present at the time of diagnosis and treatment, and therefore related to the biology of the tumor rather then to the omission of TME surgery.

This study has several limitations. First of all, this is a database-based registry study. As expected, we found considerable variances between participating centers in baseline characteristics, neoadjuvant therapy and imaging strategies. Although all participants have performed data entry with the same instructions and agreements, and multiple quality checks were performed to detect entry errors, it is possible that items are interpreted and filled in differently. We did not have access to the original patient reports, causing missing data on some details of imaging and treatment strategies. For example, details on the treatment for local regrowth was avaliable in only 69% of cases. This might be caused by the fact that W&W patients are often referred from W&W expert centers to their primary hospital for salvage therapy. However, the survival status was available. Because part of the data was prospectively collected at the participating institutes, but entered at a later date in the IWWD, it is possible that not all patients that initially were selected for W&W strategies are included in the database, potentially leading to selection bias.

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 show the importance of frequent endoscopic surveillance in W&W patients in the first two years of follow-up, the location and incidence of distant metastasis and the small risk of incurable disease. However, many uncertainties and clinical challenges remain. Importantly, long-term quality of life outcomes, and effects of (chemo)radiotherapy on bowel function in W&W patients are still unknown. As the percentage of cancer survivors is growing rapidly due to population screening and improved therapeutic strategies, the importance of quality of life outcomes and patient preferences grows concomittantly.

It is our aim to expand the expert network on organ preservation in rectal cancer within the IWWD to provide evidence for the development of uniform neoadjuvant treatment, imaging and follow-up protocols, specifically including quality of life and functional outcomes. An international consensus meeting on W&W strategies is scheduled for the end of 2018. Moreover, by prospective collection of population-based data, we aim to improve the estimation of individualized risks, and to aid shared-decision making between doctors and patients. The IWWD consortium welcomes all interested clinicians that perform organ preserving stategies in rectal cancer patients to join our network.

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Legend figures and tables

Table 1: Patient characteristics at baseline
Data are displayed as n(%), unless indicated otherwise.
BMI=body mass index

		N=880 (%)
Age	Mean (SD)	63.6 (11·7)
BMI	Mean (SD)	26.7 (4·9)
Sex	Male	603 (68·5)
	Female	277 (31·5)
Comorbidity	yes	252 (28·6)
	no	337 (38·3)
	unknown	273 (33·1)
Country	Argentina	46 (5·2)
	Belgium	27 (3·1)
	Brazil	201 (22·8)
	Germany	25 (2·8)
	Denmark	40 (4·5)
	France	42 (4.8)
	Great Britain	150 (17·0)
	Ireland	35 (4·0)
	the Netherlands	252 (28·6)
	Poland	15 (1·7)
	Portugal	21 (2·4)
	Russia	5 (0·6)
	Sweden	15 (1·7)
	Turkey	6 (0·7)
Year of decision for W&W	Before 2010	177 (20·2)
	2010-2014	450 (51·1)
	2015 - present	253 (28·8)
clinical T stage baseline	cT1	14(1·6)
	cT2	226 (25·7)
	cT3	451 (51·3)
	cT4	30 (3·4)
	unknown	159 (18·1)
clinical N stage baseline	cN0	309 (35·1)
	cN1	271 (30·8)
	cN2	167 (19·0)
	unknown	133 (15·1)
Last study status	In follow-up	660 (75·0)
	Follow-up completed	57 (6·5)
	Lost to follow-up	64 (7·3)
	Deceased	99 (11·3)

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

Data are displayed as n(%).

	Baseline: n (%)	Reassessment: n (%)
Endoscopy	848 (96·4)	779 (88·5)
MRI pelvis	678 (77·0)	620 (70·5)
CT pelvis	378 (43·0)	261 (29·7)
Endorectal ultrasound	146 (16·6)	67 (7·6)
PET scan	116 (13·2)	39 (4·4)
CEA	540 (61·4)	196 (22·3)
Local excision		45 (5·0)
ypT0	-	40
ypT+		5

Table 3: Different types and combinations of induction therapy

Data are displayed as frequencies (n).
CRT= Chemo-radiotherapy, BRT= Brachy radiotherapy, EBT= External-beam radiotherapy, CT= Chemotherapy.

Single therapy	**n**
Chemo-radiotherapy (CRT)	*738*
Brachy radiotherapy (BRT)	*5*
External beam radiotherapy (EBT)	*35*
Chemotherapy(CT)	*3*
Total	**781**
Different combinations	
CRT + BRT	*57*
CRT+ CT	*7*
BRT+ EBT	*19*
EBT+ CT	*7*
CRT+ BRT+ EBT	*2*
Total	**92**
Missing	**7**
Total	**880**