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Risks of Organ Preservation in Rectal Cancer: Data From Two International Registries on Rectal Cancer

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ABSTRACT

PURPOSE Organ preservation has become an attractive alternative to surgery (total mesorectal excision [TME]) among patients with rectal cancer after neoadjuvant therapy who achieve a clinical complete response (cCR). Nearly 30% of these patients will develop local regrowth (LR). Although salvage resection is frequently feasible, there may be an increased risk for development of subsequent distant metastases (DM). The aim of this study is to compare the risk of DM between patients with LR after Watch and Wait (WW) and patients with near-complete pathologic response (nPCR) managed by TME at the time of reassessment of response.

METHODS Data from patients enrolled in the International Watch & Wait Database (IWWD) with cCR managed by WW and subsequent LR were compared with patients managed by TME (with ≤10% cancer cells—nPCR) from the Spanish Rectal Cancer Project (VIKINGO project). The primary end point was DM-free survival at 3 years from decision to WW or TME. The secondary end point was possible risk factors associated with DM.

RESULTS Five hundred and eight patients with LR were compared with 893 patients with near-complete response after TME. Overall, DM rate was significantly higher among LRs (22.8% *v* 10.2%; $P \leq .001$). Independent risk factors for DM included LR (*v* TME at reassessment; $P = .001$), ypT3-4 status ($P = .016$), and ypN+ status ($P = .001$) at the time of surgery. 3-year DM-free survival was significantly worse for patients with LR (75% *v* 87%; $P = .001$). When stratified for pathologic stage, patients with LR did significantly worse through all stages ($P \leq .009$).

CONCLUSION Patients with LR appear to have a higher risk for subsequent DM development than patients with nPCR managed by TME at restaging irrespective of final pathology. Leaving the primary undetectable tumor in situ until development of LR may result in worse oncologic outcomes.

ACCOMPANYING CONTENT

Oncology Grand Rounds, p. 1620

Appendix

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INTRODUCTION

Organ preservation has become an attractive alternative to patients with rectal cancer who achieve a clinical complete response (cCR) after neoadjuvant therapy.[1-3] Strict surveillance programs (Watch and Wait [WW]) have been used for patients undergoing neoadjuvant treatment strategies with acceptable outcomes.[3-5] As total neoadjuvant therapy (TNT) regimens are widely implemented and inclusion of patients with early stage, nearly 50%-60% are expected to achieve a cCR.[3,4,6] Therefore, understanding oncologic outcomes and the full landscape of clinical consequences here is very important.

The risk of local regrowth (LRg) after initial cCR is around 25%-30%.[7-9] In the majority of cases, salvage resection of the primary tumor leads to excellent local disease control.[10] However, there seems to be a higher risk for development of subsequent distant metastases (DM).[11]

For these reasons, we have used two large data sets of patients with rectal cancer undergoing neoadjuvant chemoradiotherapy (nCRT)/TNT followed by WW or total

CONTEXT

Key Objective

Are patients managed by watch-and-wait and subsequent local regrowth (LR) at higher risk for distant metastases (DM) when compared with those undergoing immediate radical surgery at the time of reassessment of response?

Knowledge Generated

Patients managed by watch-and-wait and subsequent LR appear to have significantly lower DM-free survival rates when compared with those managed by radical surgery at the time of reassessment of response and near-complete pathologic response. The risk of DM appears to be consistently higher across all final pathologic stages.

Relevance *(E.M. O'Reilly)*

A nonoperative management strategy is gaining increasing traction in rectal cancer and is under investigation in national studies. The authors provide important insights and a cautionary note on the significance of LR and the implications for DM from analyses of two international registries.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD.

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mesorectal excision (TME) to estimate the risk for subsequent DM after a LRg or TME.[2]

The present data attempt to provide evidence for the potential risk of leaving in situ minimal residual disease until detection of LRg to development of subsequent DM despite successful salvage when compared with patients with near-complete pathologic response (nPCR) managed by immediate TME.

METHODS

Hypothesis

Our hypothesis was that patients with LRg undergoing salvage resection have a significantly higher risk for subsequent development of DM at 3 years' follow-up compared with patients with nPCR managed by TME at the time of reassessment after nCRT. Secondary hypothesis was that LRg is an independent risk factor for DM. No other end points were defined or analyzed.

Study Design

This is a retrospective study of two independent prospectively maintained registries.

The International Watch and Wait Database was created in 2014 at the Champalimaud Foundation to allow collection of data from institutions practicing WW.[12] This registry captured both retrospective (patients managed by WW before 2014) and prospective data from patients who achieved a cCR after nCRT and were managed nonoperatively (from 2014 onward).[2]

The Spanish Rectal Cancer Project (VIKINGO) was established in 2006 by the Spanish Society of Surgeons inspired by the Norwegian Rectal Cancer Project and included the creation of a registry following educational workshops focused on radiologic staging, proper TME surgery, and pathologic assessment/reporting.[13,14]

In the International Watch & Wait Database (IWWD) and VIKINGO registries, information from demographics, baseline staging, neoadjuvant therapy, and follow-up is captured and stored anonymously. All participating institutions have to provide individual patient consent and institutional review board (IRB) approval according to specific local authorities for ethics in research.[13]

This study obtained IRB approval at the coordinating center (São Paulo—Angelita & Joaquim Gama Institute/Hospital Alemão Oswaldo Cruz #IRB 5.522.892).

Exact details of the neoadjuvant treatment regimen and scheduling were entirely at the discretion of the participating institution. Unfortunately, accurate data on the use of TNT are not available as this concept was only adopted more recently. However, since the database was created in 2014 and recruited data information retrospectively (long before TNT was even defined) and prospectively, the majority of patients included in the present analysis did not receive TNT regimens.

IWWD Database: LRg

All patients with LRg were extracted from the IWWD exclusively from patients who achieved a cCR and/or underwent nonoperative management (WW).

All patients were expected to exhibit cCR at the time of reassessment of response based on previous attempts to

standardize clinical endoscopic features of a cCR as described elsewhere.[15] In addition, as radiologic imaging for rectal cancer evolved over time, the exact imaging modality used for baseline staging and reassessment of response was entirely at the discretion and availability at each institution. Previous studies from the IWWD have suggested that the outcomes of LRg using more contemporary imaging techniques and interpretation showed no significant differences when compared with the entirety of the database.[7,9] Ultimately, although the suggested definition of cCR was already available and clearly detailed during multiple workshops, final decision to include patients in the WW program and classification as a cCR was at the discretion of each participating institution.[12,15]

Considering the heterogeneity within the registry in terms of defining all strict criteria of a cCR, we also used the criteria used within the database decision to WW. Therefore, all patients reported to have a cCR at any given point after nCRT completion and/or a decision to WW was given with an explicit date were included in the analysis.

Patients under WW were not routinely recommended to receive adjuvant systemic therapy. Follow-up regimens included specific surveillance of the rectum/mesorectum/lateral pelvic nodes and of systemic recurrences. Exact scheduling of surveillance of the rectum and systemic recurrences followed individual institutional recommendations.

LRg was defined as reappearance of primary adenocarcinoma at the original site (rectum), mesorectum, and/or lateral pelvic nodes. Pelvic recurrences were defined as recurrences outside the boundaries of a LRg in the pelvis. Systemic recurrences were defined as any recurrence outside the pelvis confirmed histologically or radiologically.

The exact procedure used for salvage of the LRg was at the discretion of the participating institution. Patients being managed by local excision have also been included in the present analysis since previous data suggested that patients with LRg salvaged by local excision had statistically better survival outcomes when compared with patients salvaged by TME.[16]

The use of adjuvant systemic chemotherapy after salvage was recommended on the basis of final pathologic findings. In general, chemotherapy was offered for patients with pathologically node-positive disease at the time of salvage (ypN+).

VIKINGO Database: nPCR

All patients in the immediate TME group originated from the VIKINGO project, where all patients underwent standardized TME and full pathologic examination.[13]

Exact timing of TME surgery from the date of neoadjuvant therapy completion, use of adjuvant systemic therapy, and follow-up strategy for local disease control and systemic recurrence followed individual institutional protocols.

For the purpose of this study, only patients where pathologic findings included the presence of ≤10% of residual cancer cells were included, irrespective of final ypT and ypN features.

Time-Zero and Synchronous Versus Metachronous Metastases

Considering DM-free survival is the primary end point, two important definitions were made a priori concerning time-zero and timing of diagnosis of metastases:

First, for the time-to-event analysis of DM, two different time-zero definitions were used for patients with LRg. The first, time-zero$_1$, was the date of decision to WW. This allows us to accurately estimate the effect of events occurring between decision to WW and LRg.

Considering the fact that removal of the primary tumor among patients with LRg only occurred at the time of salvage/LRg diagnosis, we also performed a secondary analysis using the date of diagnosis/salvage of LRg as time-zero$_2$. This secondary analysis allowed us to compare both groups from the time that the primary tumor was removed in both groups.

As the variable decision to WW may have included patients who ultimately never developed a cCR and to assure patients included were exclusively those where WW was deemed appropriate (decision to WW and cCR), a subgroup analysis was performed using only patients who have clear definition of cCR before a LRg (avoiding the risk of contaminating the series with nonoperative management for other reasons).

Second, patients with DM being diagnosed up to 3 months from the LRg/TME were considered as synchronous while DM being diagnosed beyond 3 months from the LRg/TME were considered as metachronous. In previous studies using conditional survival estimates, we have demonstrated that the risk of DMs only becomes minimal after patients complete 5 years of follow-up from the diagnosis of a LRg (instead of the baseline cancer).[7] Therefore, there is a possibility that many DMs are derived from the LRg. Furthermore, detection of a LRg may be far more challenging than a DM (often mistaken as an apparent cCR). In this setting, it becomes impossible to rule out the possibility of synchronous DMs being directly associated with the LRg. For these reasons, we have decided to keep synchronous metastases (occurring simultaneously with the detection/salvage of a LRg) for the purpose of the present analysis.

Follow-up was measured using time-zero$_1$ (decision to WW/achievement of a cCR) among patients from IWWD and time of surgery for patients in the VIKINGO project.

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Statistical Analysis

Risk factors for development of DM were identified in the entire cohort through univariate/multivariate analysis. Features associated with the risk of DM in the univariate analysis with a *P* value ≤.1 were included in the multivariate model. Features associated with development of DM with a *P* value ≤.05 were considered statistically significant.

DM-free survival was estimated using Kaplan-Meier curves and compared using log-rank test. *P* values ≤.05 were considered statistically significant.

Reverse Kaplan-Meier curves were used to estimate potential follow-up discrepancies between the two cohorts (IWWD and VIKINGO).

RESULTS

A total of 2161 patients were included from the IWWD database. After exclusion criteria (1,618 for cCR and 35 for complete pathologic response after surgery for suspected regrowth), 508 patients with a decision to WW and subsequent diagnosis of LRg were included in the analysis. Of this, 401 patients clearly had the description of cCR before the diagnosis of LRg in the IWWD.

With a total of 20,395 patients from the VIKINGO database, after exclusion criteria (8,866 did not receive nCRT; 10,395 with incomplete/complete pathologic response; 22 stage IV patients; 110 with partial mesorectal resection, seven for palliative surgery and 102 lost to follow-up), the analysis included 893 patients with TME for nPCR (Appendix Fig A1, online only).

The median follow-up for patients with LRg (IWWD) was 35 months compared with 23 months for patients with nPCR (*P* = <.001). In the group of patients from the IWWD who underwent salvage resection for LRg, the median follow-up was 37 months (*P* = .045).

Comparison between baseline features of both cohorts is available in Table 1. Briefly, patients with LRg were slightly younger (63 *v* 65 years; *P* = .001), had more proximal tumors (3.5 *v* 3.0 cm from the anal verge), and harbored more baseline cN+ disease (37% *v* 15%; *P* < .0001).

LRg was more likely to harbor more advanced ypT stage (ypT3-4—44% *v* 37%; *P* < .0001; Table 1).

DM were more frequently observed in patients with LRg (23% *v* 10%; *P* < .001). In addition, time to development of DM was also longer for LRg (22 *v* 17 months; *P* = .02) using time-zero$_1$ (decision to WW).

Risk Factors

After univariate and multivariate analyses (Table 2), advanced ypT stage (ypT3-4; hazard ratio [HR], 4.2 [95% CI, 1.3 to 13.5]; *P* = .01) and ypN+ (HR, 2.4 [95% CI, 1.7 to 3.3]; *P* < .001) were independently associated with the development of DM, while immediate TME and nPCR (*v* surgery after LRg) were associated with a decreased risk of DM (HR, 0.6 [95% CI, 0 to 0.8]; *P* = .01).

DM-Free Survival

DM-free survival was estimated using two different time-zero points.

Initially, patients were compared using time-zero$_1$ as decision to WW (for LRg) and TME (for nPCR). Patients with LRg had significantly worse distant metastases-free survival (DMFS) at 3 years when compared with immediate TME patients (75% *v* 87%; *P* < .001 [Fig 1A]), similar to when we analyzed only patients who achieved cCR before LRg (76% *v* 87%; *P* = .001 [Appendix Fig A2A]).

When time-zero$_2$ was used (salvage of LRg and TME—to control for exact time of removal of the primary), DMFS was also inferior for patients with LRg when compared with TME for nPCR. Of note, patients in the LRg group in this scenario (time-zero$_2$) already started with Kaplan-Meier curves under 100%. This is because many of these patients at the time of salvage (time-zero$_2$) already presented with synchronous DM and therefore <100% were metastases-free (Fig 1B), similar to when we analyzed only patients who achieved cCR before LRg (74% *v* 87%; *P* < .0001 [Appendix Fig A2B]).

DM-Free Survival and Associated Risk Factors

After identification of risk factors independently associated with the development of DM, we stratified subgroups of patients with LRg and immediate TME using ypT status and ypN status.

Among ypT1-2, DMFS at 3 years was worse for LRg when compared with immediate TME (82.8% *v* 91.0%; *P* = .001). Similar differences were observed for ypT3-4 (62.9% *v* 79.1%; *P* < .001; Fig 2).

Among ypN0, DMFS at 3 years was worse for LRg when compared with immediate TME (77.7% *v* 90.4%; *P* < .001). Similar differences were observed for ypN+ (49.4% *v* 75.0%; *P* < .001; Fig 3).

After classifying patients according to final UICC stages I to III, and comparing patients stage by stage, 3-year DMFS was significantly worse for LRg when compared with immediate

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TABLE 1. Clinical and Radiologic Features According to Treatment Group

Variable	Surgery (n = 893)	Regrowth (n = 508)	*P*
Years of inclusion	2006-2011	1992-2021	
Age, years	65.7 ± 10.7	63.2 ± 11.9	**<.0001**
Sex, No. (%)			.94
Male	609 (68.1)	349 (68.3)	
Female	285 (31.9)	162 (31.7)	
Distance anal verge, cm	3.0 ± 4.3	3.5 ± 3.4	**.02**
cT, No. (%)			.99
2	189 (21.6)	99 (21.6)	
3-4	687 (78.4)	360 (78.4)	
cN, No. (%)			**<.0001**
–	736 (84.6)	291 (62.8)	
+	134 (15.4)	172 (37.2)	
ypT, No. (%)			**<.0001**
0	9 (1.0)	15 (4.2)	
1-2	549 (62.0)	185 (51.4)	
3-4	327 (37.0)	160 (44.4)	
ypN, No. (%)			.98
–	686 (76.7)	230 (76.7)	
+	208 (23.3)	70 (23.3)	
Neoadjuvant treatment, No. (%)			**<.0001**
Long-course chemoradiation	829 (93.5)	506 (99.6)	
Short-course radiotherapy	38 (4.3)	2 (0.4)	
Radiotherapy alone	20 (2.2)	0 (0)	
Organ preservation, No. (%)	0	60 (15.3)	**<.001**
Systemic recurrence, No. (%)	91 (10.2)	116 (22.8)	**<.0001**
Time to systemic recurrence, months	16.7 ± 14.5	21.8 ± 17.0	**.02**

NOTE. Statistically significant values ($P < .05$) are shown in bold.

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TME—UICC stage I (ypT1-2N0): 83.5% *v* 93.5%; $P < .001$; UICC stage II (ypT3-4N0): 72.3% *v* 83.1% $P = .009$; and UICC stage III (ypT0-4N+): 49.4% *v* 75.0% $P < .001$ (Figs 4A-4C).

DISCUSSION

This study suggests that patients with initial cCR/decision to WW followed by LRg are at higher risk for development of DM when compared with patients with incomplete pathologic response (≤10% residual cancer cells) to nCRT. In this large series of patients with LRg or immediate TME with nPCR, LRg remained as an independent risk factor for DM. Even when stratified for other independent risk factors (ypT and ypN status), LRg appear to be associated with worse oncologic outcomes.

Previous studies already attempted to compare patients with LRg with incomplete responders managed by TME with no significant differences.[17] Such comparison is probably unfair since groups are not balanced for response to nCRT. Although LRg had excellent initial response, patients undergoing immediate TME at restaging probably did not. Ultimately, LRg are tumors that probably harbored microscopic residual disease at the time of reassessment (likely ≤10% residual cancer cells) but with apparent cCR. As a comparator, we used data from the well-organized VIKINGO project providing standardized and uniform data on patients with rectal cancer.[13]

Exact reasons for the present findings are still unclear. First, patients with incomplete response after delivery of nCRT may result in a selection of the super resistant cellular clones.[18] Second, leaving these resistant clones in situ for long periods of time may be critical to the development of DM.[19] Finally, surveillance strategies may also contribute to a delay in the detection of LRg.

Interestingly, the use of different time-zero scenarios here resulted in small statistical differences. Although using date of decision to WW as time-zero for IWWD patients provides a balanced comparison from the initiation of treatment and allows the estimate of events occurring between decision to WW and development of LRg, it does not focus on the fact that the primary tumor remains in situ in one group and is surgically removed in the other group. In addition, the

TABLE 2. Clinical and Radiologic Features According to the Development of Distant Metastases

Variable	Patients Without Distant Metastases (n = 1,194)	Patients With Distant Metastases (n = 207)	Univariable Analysis, *P*	Multivariable Analysis, *P*
Age, years, mean (SD)	64.9 (11.2)	64.2 (11.3)	.37	
Sex, No. (%)			.27	
Male	807 (67.6)	148 (71.5)		
Female	387 (32.4)	59 (28.5)		
Initial staging, No. (%)				
cT				
1-2	247 (21.6)	41 (21.5)	.95	
3-4	894 (78.4)	150 (78.5)		
cN				
–	245 (21.6)	60 (31.1)	**.004**	.1
+	892 (78.4)	133 (68.9)		
Surgical procedure, No. (%)			.72	
Local excision	52 (4.7)	7 (4.1)		
TME	1,059 (95.3)	165 (95.9)		
Final pathologic staging, No. (%)				
ypT				
0	21 (2.0)	3 (1.8)		
1-2	672 (62.4)	60 (36.4)		
3-4	384 (35.6)	102 (61.8)	**<.0001**	**.016**
ypN				
–	822 (79.5)	92 (58.2)		
+	212 (20.5)	66 (41.8)	**<.0001**	**<.0001**
Management group, No. (%)				
Immediate TME	802 (67.2)	91 (44.0)		
Local regrowth	392 (32.8)	116 (56.0)	**<.0001**	**.001**

NOTE. Statistically significant values ($P < .05$) are shown in bold.
Abbreviations: SD, standard deviation; TME, total mesorectal excision.

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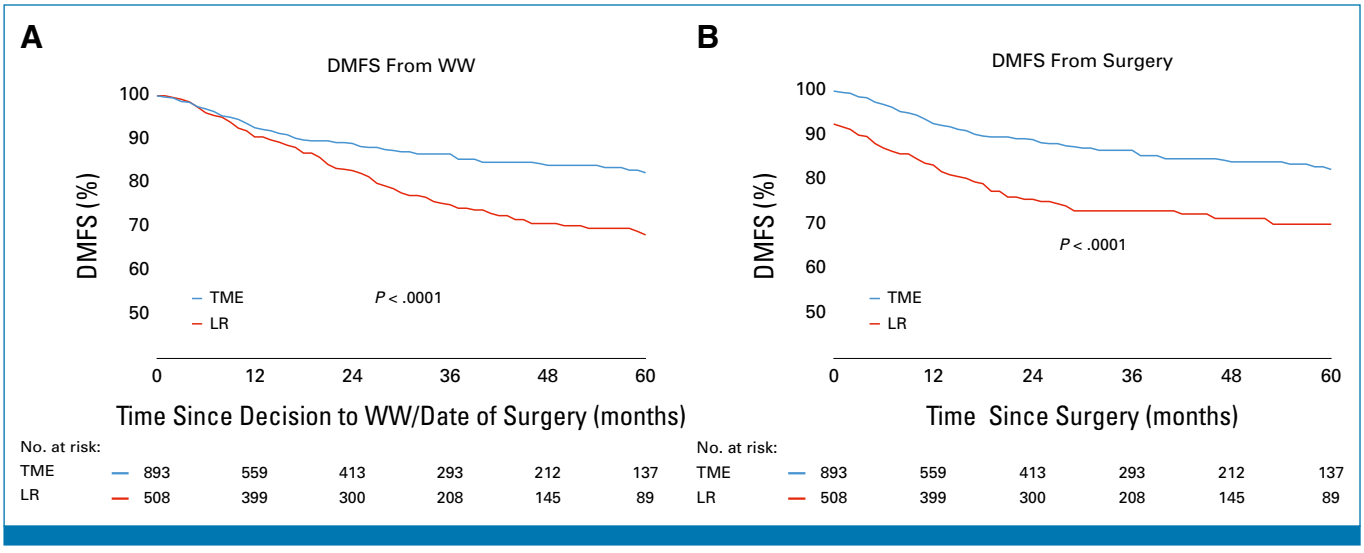

FIG 1. (A) DMFS for patients with LR and TME at the time of reassessment of response (TME) using time-zero$_1$—decision to WW (in the LR group) and date of surgery in the TME group—showing statistically significant differences between groups. (B) Estimates for DMFS using time-zero$_2$—the date of removal of primary tumor in both groups (salvage of LR and TME at reassessment)—also resulted in significant differences between groups. Of note, using time-zero$_2$, LR estimates does not start at 100% to account for synchronous (distant metastases and LRs) observed in a proportion of patients already at time zero. DMFS, distant metastases-free survival; LR, local regrowth; TME, total mesorectal excision; WW, Watch and Wait.

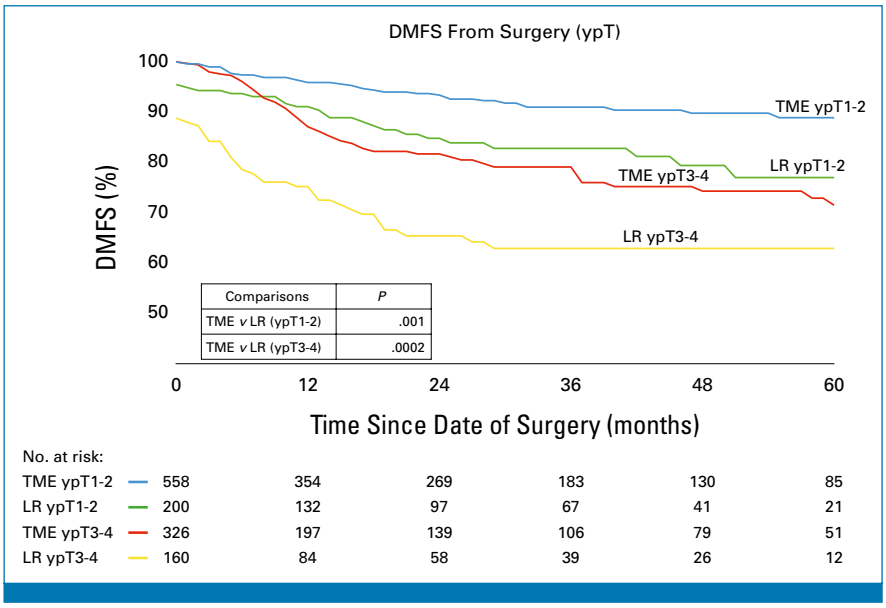

FIG 2. Distant metastases-free survival estimates for patients with LR and TME at reassessment stratified by final ypT status. Patients with LR show significantly worse survival estimates for subgroups ypT1-2 and ypT3-4. DMFS, distant metastases-free survival; LR, local regrowth; TME, total mesorectal excision.

decision to WW is another source of significant heterogeneity across different participating institutions in IWWD.

Although the differences are statistically significant between groups, one has to consider that we are dealing with a very select group of patients (considerably small) with rectal cancer who achieve a cCR and subsequent local regrowth. Therefore, absolute numbers of patients impacted by these findings are rather limited, requiring large data sets to demonstrate them.[20]

Still, this study has several important limitations. First, although registries may be successful in gathering significant numbers of patients, it becomes impossible to rule out significant heterogeneity in exact criteria for the definition of cCR, exact criteria for decision to WW, and surveillance

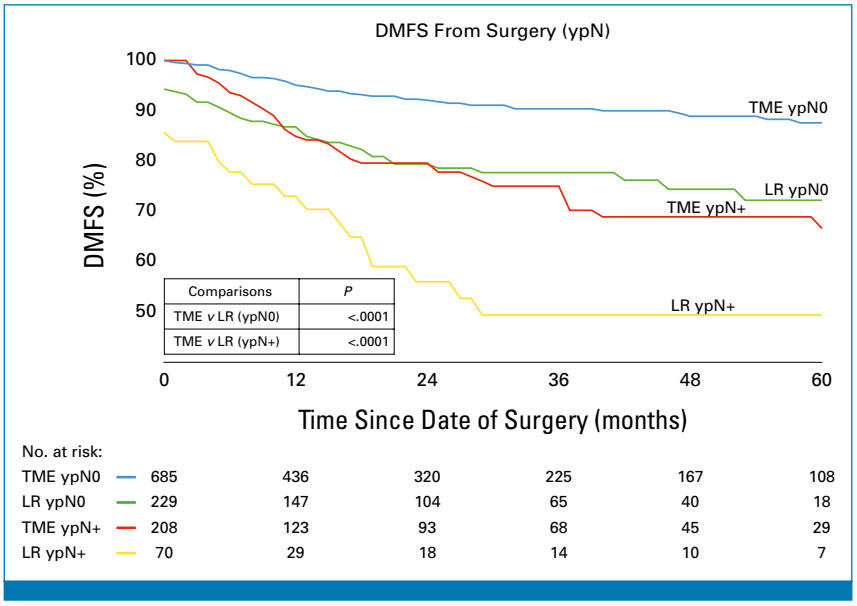

FIG 3. Distant metastases-free survival estimates for patients with LR and TME at reassessment stratified by final ypN status. Patients with LR show significantly worse survival estimates for subgroups ypN0 and ypN+. DMFS, distant metastases-free survival; LR, local regrowth; TME, total mesorectal excision.

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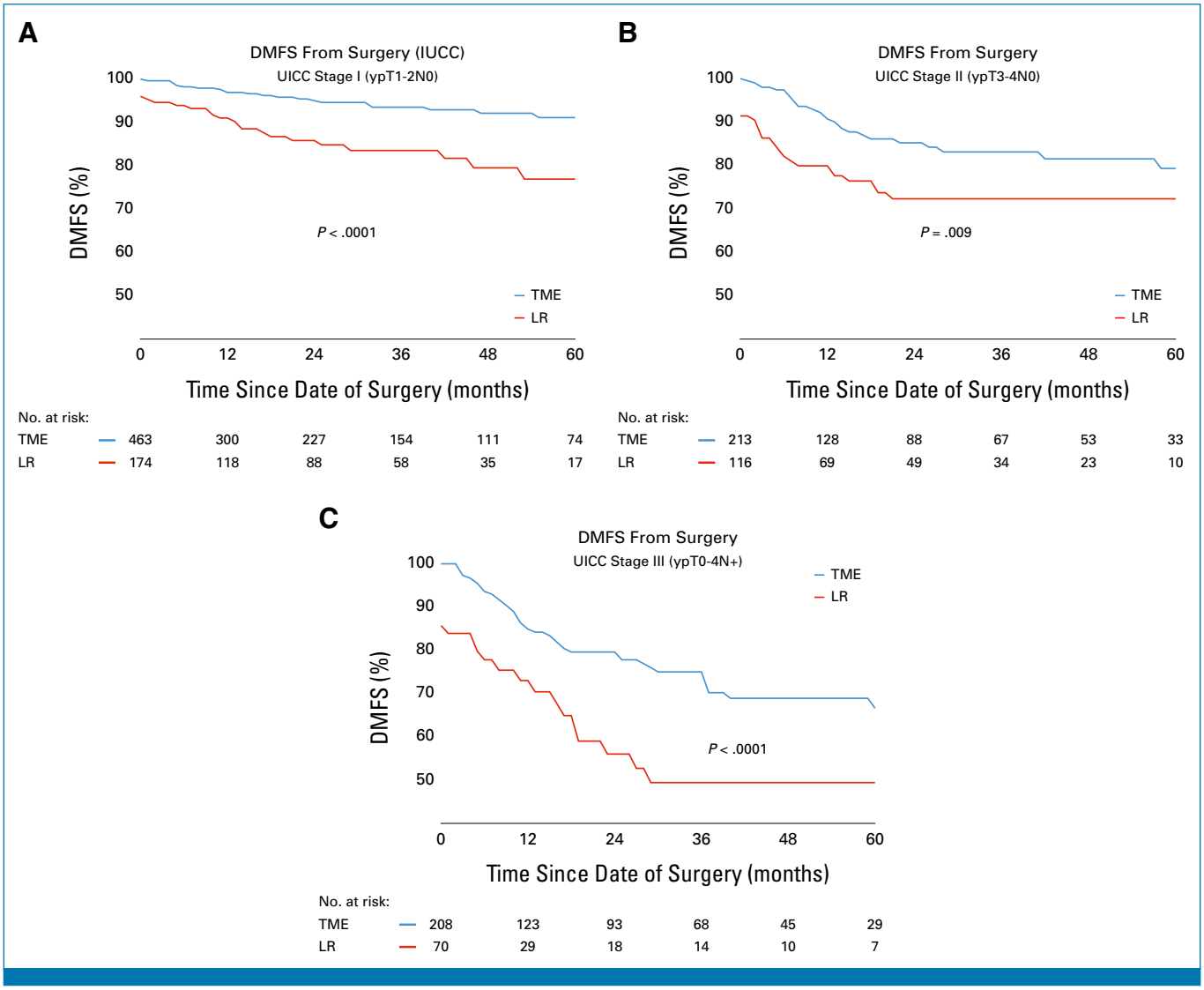

FIG 4. (A-C) Distant metastases-free survival estimates for patients with LR and TME at reassessment stratified by final pathologic UICC stage. Patients with LR show significantly worse survival estimates for subgroups (A) ypT1-2N0, (B) ypT3-4N0, and (C) ypT0-4N+. DMFS, distant metastases-free survival; LR, local regrowth; TME, total mesorectal excision; UICC, Union for International Cancer Control.

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strategies during WW. However, it provides real-world data and reflects actual clinical practice with this novel treatment strategy (WW). This is particularly important for patients where a decision to WW was made. Another limitation is related with the dynamic evolution of pathologic responses, where some patients with nPCR could have transitioned to complete pathologic response if surgery had been delayed by a few weeks (approximately 8 weeks as recommended within the VIKINGO workshops). In addition, the comparison of LRg to nPCR is not necessarily fair and well balanced. Ultimately, LRg may represent a distinct group of patients to nPCR and biologically worse for reasons other than the actual percentage of residual cancer cells in the resected specimen. The lack of information regarding the distribution of metastatic site among patients in IWWD is also a significant limitation as there is a possibility that LRg and TME at reassessment could be associated with different patterns of dissemination and site of metastatic disease. In addition, although there is a substantial number of patients in either group, there is a considerable amount of follow-up losses within both groups as indicated by the reverse Kaplan-Meier curve (Appendix Fig A3). Still, these differences may reflect an unintentional bias associated with the fact that patients undergoing a novel strategy are more likely to be closely monitored and for longer periods of time when compared with regular/standard TME surgery.

Also, the majority of patients in this study were managed before widespread implementation of TNT regimens. More contemporary data consistently using induction/consolidation chemotherapy during TNT regimens may ultimately affect DMFS among these patients. Surprisingly, however, in recent data published by a secondary analysis of the OPRA trial, where 100% of patients were treated with TNT, the risk of DM among

LRg was similar to the rates reported here (nearly 30%). Although the comparison with all patients managed by TME was not statistically different, patients with near-complete response in OPRA managed by TME at the time of reassessment also had a lower DM rate (15%).[21] Altogether, these data are consistent with our findings despite the fact that TNT was not used for the majority of patients in our series.

In conclusion, LRg after initial cCR managed by WW after nCRT appears to be at higher risk for subsequent development of DM than patients with nPCR managed by TME at restaging. In addition, LRg appears to develop DM at longer intervals from initial treatment. Worse DM-free survival is expected for LRg regardless (even when stratified) of other independent risk factors such as ypT and ypN stage at the time of resection. Although long-term data from regimens incorporating TNT regimen are awaited, this information may be crucial for patient counseling and decision making. Allowing physicians to better inform patients about the risks, benefits, and possible scenarios related to their treatment alternatives when organ preservation is an option. Future studies should consider the risk of subsequent DM development among LRg in the design of trials incorporating organ preservation with WW.

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Lists of the VIKINGO and IWWD consortium members can be found in Appendix 1 and Appendix 2.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risks of Organ Preservation in Rectal Cancer: Data From Two International Registries on Rectal Cancer

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APPENDIX 1. VIKINGO CONSORTIUM

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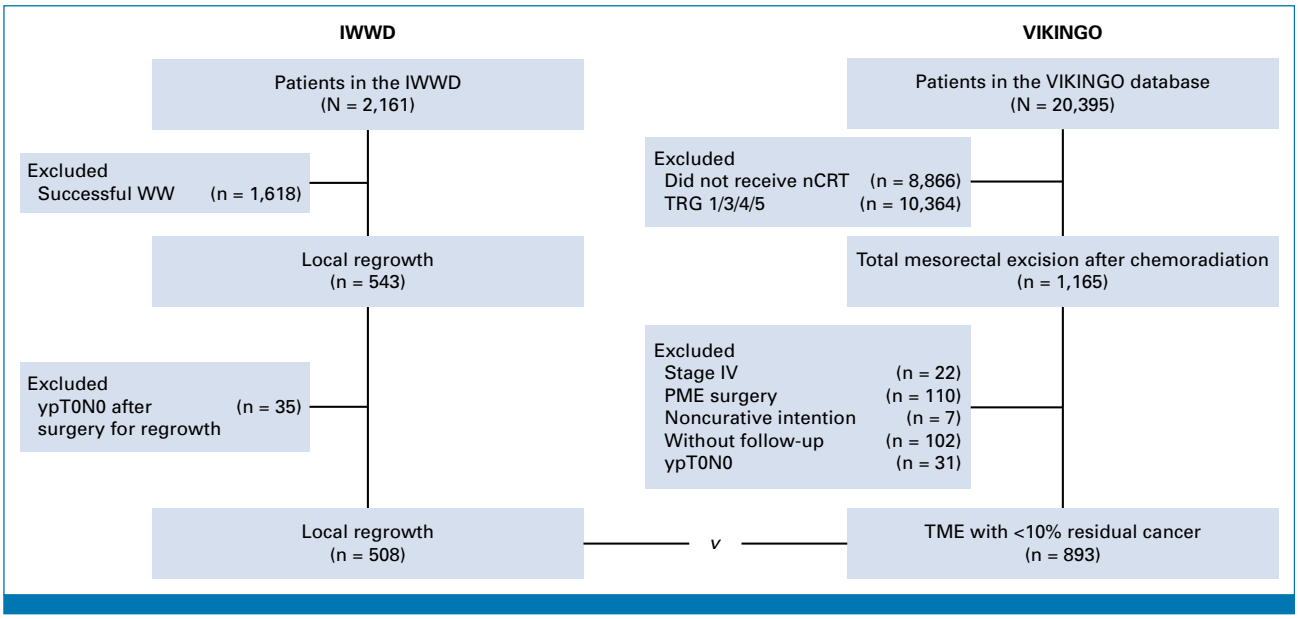

FIG A1. Flow diagram demonstrating the study population in each database (IWWD and VIKINGO) and patients excluded from the analyses. IWWD, International Watch & Wait Database; nCRT, neoadjuvant chemoradiotherapy; PME, partial mesorectal excision; TME, total mesorectal excision; TRG, tumor regression grade; VIKINGO, the Spanish Rectal Cancer Project; WW, Watch and Wait.

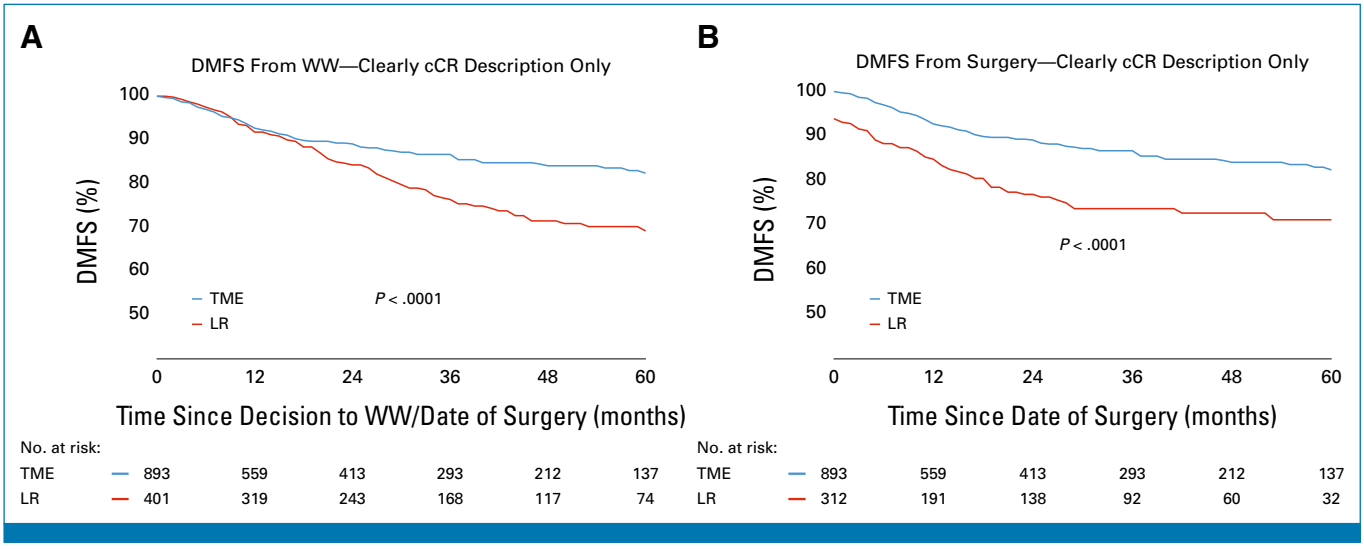

FIG A2. (A, B) DMFS analysis considering only patients who clearly have the clinical complete response description available in the IWWD. (A) DMFS for patients with LR and TME at the time of reassessment of response (TME) using time-zero$_1$—decision to WW (in LR group) and date of surgery in TME group—showing statistically significant differences between groups. (B) Estimates for DMFS using time-zero$_2$—the date of removal of primary tumor in both groups (salvage of LR and TME at reassessment)—also resulted is significant differences between groups. Of note, using time-zero$_2$, LR estimates does not start at 100% to account for synchronous (distant metastases and LRs) observed in a proportion of patients already at time zero. DMFS, distant metastases-free survival; LR, local regrowth; TME, total mesorectal excision; WW, Watch and Wait.

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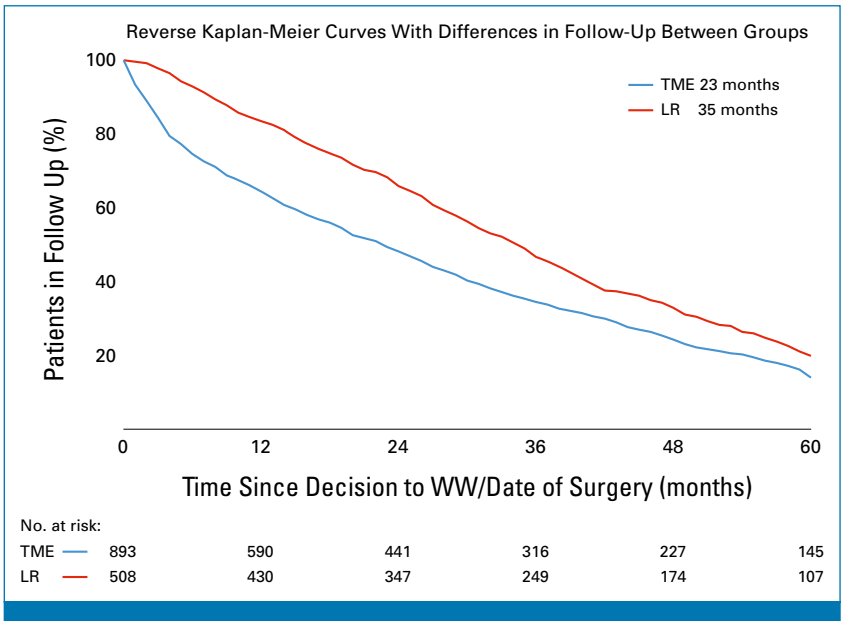

FIG A3. Reverse Kaplan-Meier curves for both cohorts (LR and TME at reassessment). LR, local regrowth; TME, total mesorectal excision.

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