The risk of distant metastases in patients with clinical complete response managed by watch and wait after neoadjuvant therapy for rectal cancer: the influence of local regrowth in the International Watch and Wait Database

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ORIGINAL CONTRIBUTION

The Risk of Distant Metastases in Patients With Clinical Complete Response Managed by Watch and Wait After Neoadjuvant Therapy for Rectal Cancer: The Influence of Local Regrowth in the International Watch and Wait Database

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BACKGROUND: Nearly 30% of patients with rectal cancer develop local regrowth after initial clinical complete response managed by watch and wait. These patients might be at higher risk for distant metastases.

OBJECTIVE: This study aimed to investigate risk factors for distant metastases using time-dependent analyses.

DESIGN: Data from an international watch and wait database were retrospectively reviewed. Cox regression analysis was used to determine risk factors for worse distant metastases-free survival. Conditional survival modeling was used to investigate the impact of risk factors on the development of distant metastases.

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The International Watch & Wait Database IWWD Consortium is listed in Appendix A at https://links.lww.com/DCR/C61.

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SETTING: Retrospective, multicenter database.

PATIENTS: A total of 793 patients (47 institutions) with rectal cancer and clinical complete response to neoadjuvant treatment from the International Watch & Wait Database were included.

MAIN OUTCOME MEASURES: Distant metastases-free survival.

RESULTS: Of the 793 patients managed with watch and wait (median follow-up 55.2 mo), 85 patients (10.7%) had distant metastases. Fifty-one of 85 patients (60%) had local regrowth at any time. Local regrowth was an independent factor associated with worse distant metastases-free survival in the multivariable model. Using conditional estimates, patients with local regrowth without distant metastases for 5 years (from decision to watch and wait) remained at higher risk for development of distant metastases for 1 subsequent year compared to patients without local regrowth (5-year conditional distant metastases-free survival 94.9% vs 98.4%).

LIMITATIONS: Lack of information on adjuvant chemotherapy, salvage surgery for local regrowth, and heterogeneity of individual surveillance/follow-up strategies used may have affected results.

CONCLUSIONS: In patients with clinical complete response managed by watch and wait, development of local regrowth at any time is a risk factor for distant metastases. The risk of distant metastases remains higher for 5 years after development of local regrowth. See **Video Abstract** at http://links.lww.com/DCR/C53.

EL RIESGO DE METÁSTASIS A DISTANCIA EN PACIENTES CON RESPUESTA CLÍNICA COMPLETA MANEJADA POR WATCH AND WAIT DESPUÉS DE LA TERAPIA NEOADYUVANTE PARA EL CÁNCER DE RECTO: LA INFLUENCIA DEL NUEVO CRECIMIENTO LOCAL EN LA BASE DE DATOS INTERNACIONAL WATCH AND WAIT

ANTECEDENTES: Casi el 30 % de los pacientes con cáncer de recto desarrollan un nuevo crecimiento local después de la respuesta clínica completa inicial manejada por watch and wait. Estos pacientes podrían tener un mayor riesgo de metástasis a distancia.

OBJETIVO: Investigar los factores de riesgo de metástasis a distancia mediante análisis dependientes del tiempo.

DISEÑO: Se revisó retrospectivamente los datos de la base de datos internacional de Watch and Wait. Se utilizó el análisis de regresión de Cox para determinar los factores de riesgo de peor sobrevida libre de metástasis a distancia. Se utilizó un modelo de sobrevida condicional para investigar el impacto de los factores de riesgo en el desarrollo de metástasis a distancia. El tiempo transcurrido hasta el evento se calculó utilizando la fecha de decisión para watch and wait y la fecha del nuevo crecimiento local para el diagnóstico de metástasis a distancia.

ESCENARIO Base de datos multicéntrica retrospectiva.

PACIENTES: Se incluyeron un total de 793 pacientes (47 instituciones) con cáncer de recto y respuesta clínica completa al tratamiento neoadyuvante de la base de datos internacional de Watch and Wait.

PRINCIPALES MEDIDAS DE RESULTADO: Desarrollo de metástasis a distancia.

RESULTADOS: De los 793 pacientes tratados con watch and wait (mediana de seguimiento de 55,2 meses), 85 (10,7%) tenían metástasis a distancia. 51 de 85 (60%) tuvieron recrecimiento local en algún momento. El recrecimiento local fue un factor independiente asociado a una peor supervivencia libre de metástasis a distancia en el modelo multivariable. Además, al usar estimaciones condicionales, los pacientes con recrecimiento local sin metástasis a distancia durante 5 años (desde la decisión de watch and wait) permanecieron en mayor riesgo de desarrollar metástasis a distancia durante un año subsiguiente en comparación con los pacientes sin recrecimiento local (sobrevida libre de metástasis a distancia a 5 años: recrecimiento local 94,9% frente a no recrecimiento local 98,4%).

LIMITACIONES: La falta de información relacionada con el uso de quimioterapia adyuvante, las características específicas de la cirugía de rescate para el nuevo crecimient o local y la heterogeneidad de las estrategias individuales de vigilancia/seguimiento utilizadas pueden haber afectado los resultados observados.

CONCLUSIONES: En pacientes con respuesta clínica completa manejados por Watch and Wait, el desarrollo de recrecimiento local en cualquier momento es un factor de riesgo para metástasis a distancia. El riesgo de metástasis a distancia sigue siendo mayor durante 5 años después del desarrollo de un nuevo crecimiento local. Consulte **Video Resumen** en http://links.lww.com/DCR/C53. *(Traducción—Dr. Felipe Bellolio)*

KEY WORDS: Complete clinical response; Distant; Local regrowth; Neoadjuvant treatment; Rectal cancer; Watch and wait.

Watch and wait for patients with rectal cancer with clinical complete response (cCR) after neoadjuvant treatment is a novel management strategy with the potential to avoid immediate surgery, postsurgical functional consequences, and stoma formation.[1,2] Initial concerns were related to the risk of leaving microscopic disease within the rectum leading to local regrowth.[3] Nearly

30% of patients develop local regrowth by 3 years, the majority of which can be successfully controlled through deferred surgery, with high rates of R0 resection and apparent no negative impact on local disease control.[3–8]

In this setting, concerns over the watch and wait have shifted toward the risk of developing distant metastasis. Although patients with cCR sustained over time have a low risk of developing distant metastases, patients who develop local regrowth appear to represent a distinct subgroup of patients in whom the risk of distant metastases is higher.[9–11]

In the present study, using the largest international multicenter watch and wait database available, we investigated risk factors for distant metastases using time-dependent analyses (to reduce immortal time bias). Using conditional survival estimates, we analyzed whether the impact of these risk factors changed over time.

MATERIALS AND METHODS

Study Design

This is a retrospective analysis of patients with cCR after neoadjuvant treatment managed by watch and wait from the International Watch & Wait Database (IWWD).

IWWD is an international multicenter registry for patient-data entry established in April 2015. In this database, institutions were allowed to include all of their patients managed by watch and wait since the beginning of their institutional experience with such treatment strategy. Therefore, the IWWD included prospective and retrospectively collected data. As previously reported, requirements for participant consent, and ethical and institutional review board approval were handled according to the local authorities of participating centers or institutions.[12] The present study has been submitted to the Ethics committee and received full institutional review board approval (São Paulo). Information regarding baseline clinical stage, neoadjuvant therapy, final dose of radiation, follow-up, dates and type of treatment after local regrowth and/or distant disease recurrence, and survival status were extracted.[7]

Only patients who achieved a cCR and underwent initial nonoperative management were included. Definitions of cCR used in the original reports for watch and wait were already available at the time of establishment of the IWWD.[1,13] Findings consistent with a cCR included the presence of white scars or telangiectasias and the absence of any irregularity, mass, ulceration, or stenosis during clinical assessment.[13] In addition, only patients with radiological imaging consistent with complete tumor regression (including the absence of metastatic mesorectal and lateral pelvic lymph nodes) were considered to have a cCR.[14,15] However, definitive diagnosis of cCR and decision to watch and wait was entirely at the discretion of each participating center.

Procedures

The baseline clinical stage, including cT and cN classification, was defined by each center. The indication and type of neoadjuvant therapy and the exact surveillance strategy (related to the primary tumor) including imaging modality used for baseline/assessment of response were entirely at the discretion of each participant center. Details of neoadjuvant treatment and follow-up strategies are available elsewhere.[7]

In addition to surveillance of the rectum and mesorectum/lateral compartment, patients were followed for the risk of distant metastases. Follow-up for distant metastases was in agreement with each institutional protocol including periodical imaging of the liver and lungs associated with CEA determination. Exact imaging modalities and time intervals for follow-up were entirely at the discretion of the participating center.

The database does not provide accurate information regarding the use and type of adjuvant chemotherapy. Therefore, although the use of adjuvant chemotherapy for patients who achieved a cCR was at the discretion of the participating center, this information was not available.

Outcomes

The main outcome measure was time to the diagnosis of distant metastases aiming to identify risk factors and their impact over the years.

Local regrowth was defined as any reappearance of tumor at the original location or regional lymph nodes detected with clinical assessment, endoscopy, or imaging as described previously. The specific outcomes and risk factors associated with the development of local regrowth after the achievement of a cCR have been reported previously.[12]

Distant metastases were defined as the presence of radiological evidence or histological confirmation of metastatic disease (outside of the pelvis).

Time to event (diagnosis of distant metastases) was calculated using 2 different scenarios. Time zero was the date of the decision for watch and wait (scenario 1) or the date of the diagnosis of local regrowth (scenario 2). Therefore, distant metastases-free survival curves were determined using the date of diagnosis of distant metastases as an event considering these 2 "time zero" scenarios. Patients were censored for loss to follow-up or death (by any cause).

Patients with a diagnosis of distant metastases concomitant within 1 month after or before (at any time) the detection of local regrowth were considered to be synchronous.

The primary end point was prespecified as the identification of independent factors associated with worse distant metastases-free survival. Secondary end points included the identification of time intervals in which

significant risk factors for worse distant metastases-free survival become nonsignificant.

Statistical Analysis

Risk factors for distant metastases-free survival were identified using univariable and multivariable conditional Cox regression analyses considering different time points (0, 1, 2, 3, 4, 5, and 6 y after decision for watch and wait). Crude and adjusted HRs estimate with corresponding 95% CIs were also presented. Proportional hazards assumption of Cox regression model was verified using Schoenfeld residuals. Risk factors that attained p values of ≤0.25 in the univariable analysis were candidates to the multivariable model, and accordingly, age, sex, clinical baseline tumor stage, clinical baseline nodal status, final total dose of radiotherapy received (using the 50.4 Gy cutoff—upper limit of recommended standard dose in most guidelines), and development of local regrowth at any time were evaluated.

Conditional distant metastases-free survival analysis was used to investigate the evolution of the identified risk factors for distant metastases over time. Conditional survival (CS) was calculated as $CS(y|x)$, the probability of surviving further y years, given that the person has already survived for x years, and is obtained from Kaplan-Meier survival estimates, as previously described by Zabor et al.[16] For example, in the context of this study, CS (3/2) indicates the conditional probability of being distant metastases-free 3 + 2 = 5 years, given that the patient is still distant metastases-free at 2 years. In this univariable study, different time points were considered (0, 1, 3, 5, and 6 y after decision for watch and wait [scenario 1] and after date of diagnosis of local regrowth [for those with local regrowth—scenario 2]. To estimate differences between CS curves, the standardized differences method was used as described by Cucchetti et al,[17] referring to effect size. A $|d| < 0.3$ suggests small differences, $0.3 < |d| < 0.5$ moderate differences, and $|d| > 0.5$, large differences, where $|d|$ refers to effect size.

All statistical analyses were performed using Addinsoft (2020) XLSTAT statistical and data analysis solution (Long Island, NY). An arbitrary p value of <0.05 was considered statistically significant.

RESULTS

A total of 793 patients with rectal cancer and cCR to neoadjuvant treatment from November 25, 1991, to December 31, 2015, entered in the IWWD (provided by 47 centers) were included in the analysis. The median follow-up was 55.2 (IQR, 36.0–75.6) months (data lock May 2020). Clinical and radiological features of these patients according to the development of distant metastases are available in Table 1.

Overall, 85 patients (10.7%) developed distant metastases. Of these, 61 patients (71.8%) developed distant metastases in the first 3 years after watch and wait decision (when distant metastases would typically develop), but 24 patients (28.2%) developed later. However, among patients who achieved a cCR followed by local regrowth, 51 patients (24.1%) developed distant metastases at a median time of 22.5 (IQR, 9.8–41.8) months from the date of decision to watch and wait. There were only 3 patients in whom distant metastases were detected before (>30 d) the diagnosis of local regrowth, whereas an additional 11 patients were detected within 1 month after diagnosis of local regrowth. These 14 patients were considered synchronous metastatic/locally recurrent for the purpose of the present analysis.

Risk Factors Associated With Time to the Diagnosis of Distant Metastases

Distant metastases-free survival with conditional analysis for the entire cohort has been reported previously. Briefly, distant metastases-free survival for the entire cohort from the date of decision to watch and wait was 97.1% (95% CI, 96–98.3) at 1 year, 91.4% (95% CI, 89.3–93.5) at 3 years, and 88.9% (95% CI, 86.5–91.3) at 5 years, respectively.

In the present study, univariable analysis identified age, sex, cT baseline stage, cN baseline stage, final dose of radiotherapy, and local regrowth as candidates for the multivariable analysis ($p < 0.25$) (Table 1).

Development of local regrowth at any time and age were the only factors that remained statistically significant for worse distant metastases-free survival in the final Cox multivariable model. In fact, patients with local regrowth showed a 5-fold higher risk of developing distant metastases compared with those without local regrowth (HR 4.98; 95% CI, 3.20–7.78; $p < 0.001$), and a 2% increase in the risk of developing distant metastases for each year increase in age.

A comparison of patients with and without local regrowth is available in Supplemental Table 1 at http://links.lww.com/DCR/C55. The median time to diagnosis of distant metastases in patients with or without local regrowth was 22.5 and 19.2 months, respectively (p = 0.993).

Evolving Impact of Local Regrowth Over Time

Because of the relevant role of local regrowth in the development of distant metastases previously identified, further analyses were performed and additional results were obtained. Accordingly, distant metastases-free survival at 5 years for patients with cCR was 73.0% (95% CI, 66.1–79.8) for patients with local regrowth and 94.3% (95% CI, 92.2–96.3) for patients without local regrowth ($p < 0.001$) (Fig. 1).

TABLE 1. Clinical and radiological features according to the development of distant metastases

Clinical and radiological features	*Patients without distant metastases*	*Patients with distant metastases*	*Univariable analysis, HR (95% CI)*	*p value*
n	708	85		
Age (y), mean (SD)	63.7 (11.9)	65.4 (11.8)	1.0 (0.99–1.03)	0.089
Sex (male/female)	466/242 (65.8%/34.2%)	68/17 (80.0%/20.0%)	2.1 (1.22–3.53)	0.007
Tumor size (mm), mean (SD)	38.9 (14.3)	38.6 (13.6)	0.9 (0.81–1.20)	0.894
Distance from the anal verge (cm), mean (SD)	4.4 (3.1)	4.3 (2.7)	0.9 (0.91–1.1)	0.890
Initial CEA level (ng/mL), mean (SD)	4.1 (8.5)	4.0 (5.0)	1.0 (0.97–1.04)	0.636
Initial staging[a]				
cT				
1–2	199 (33.9%)	17 (25.8%)		
3–4[b]	388 (66.1%)	49 (74.2%)	1.5 (0.86–2.61)	0.148
cN				
–	251 (41.6%)	37 (52.1%)	0.7 (0.43–1.11)	0.124
+[b]	352 (58.4%)	34 (47.9%)		
Year of decision to WW				
<2010	149 (21.0%)	18 (21.2%)		
>2010	559 (79.0%)	67 (78.8%)	1.3 (0.78–2.28)	0.292
RT final total dose[c]				0.155
<50.4 Gy	218 (39.4%)	31 (47.0%)		
>50.4 Gy[b]	335 (60.6%)	35 (53.0%)	0.7 (0.43–1.14)	
RT final total dose (Gy), mean (SD)	49.6 (4.9)	49.9 (4.2)	1.0 (0.96–1.06)	0.606
Local regrowth				
No	547 (77.3%)	34 (40.0%)		
Yes[b]	161 (22.7%)	51 (60.0%)	4.8 (3.14–7.49)	<0.0001

RT = radiation therapy; WW = wait and watch.
[a]Initial cT staging was available for 653 patients, and initial cN staging was available for 674 patients.
[b]Reference category.
[c]RT final total dose was available for 619 patients.

Moreover, development of local regrowth at any time was identified as a risk factor for worse distant metastases-free survival already at the first year after the date of decision to watch and wait (distant metastases-free survival local regrowth 93.2% [95% CI, 89.7–96.6] vs no local regrowth 98.4% [95% CI, 97.4–99.4]; $p < 0.001$). Using conditional estimates, local regrowth remained as a significant risk factor over time: patients with local regrowth without distant metastases for 5 years remain at higher risk for development of distant metastases compared to patients without local regrowth (5-y conditional distant metastases-free survival: local regrowth 94.9% vs no-local regrowth 98.4%; $d = 0.24$) for 1 additional year (at 5 + 1 = 6 y) (Fig. 2A). Conditional distant metastases-free survival between these groups becomes similar after 6 years of follow-up without distant metastases from the time to decision to watch and wait (see Supplemental Figure 1 at https://links.lww.com/DCR/C54). Altogether, the data suggest that the number of events (distant metastases) among patients with local regrowth still develop in a significant number of patients beyond 5 years of follow-up.

Using the date of local regrowth as "time zero," the risk of distant metastases (worse conditional distant metastases-free survival) remains higher for 1 additional year among patients with local regrowth even when patients are distant metastases-free for 1, 2, 3, and 4 years (see Supplemental Figure 2 at https://links.lww.com/DCR/C54). Conditional distant metastases-free survival for 1 additional year between patients with local regrowth only becomes similar to those without local regrowth when patients achieve 5 years of follow-up without distant metastases (5 + 1 = 6-y conditional distant metastases-free survival: local regrowth 100%) (Fig. 2B). Here, the data suggest that the number of events (distant metastases) among patients with local regrowth still develop in a significant number of cases up to 5 years from the date of local regrowth.

Results of conditional Cox regression analysis at different time points are in agreement with previous findings, demonstrating that local regrowth remains a statistically significant risk factor for the development of distant metastases even after the patients achieve 1, 2, 3, or 4 years (HR 3.0; 95% CI, 1.01–8.97; $p = 0.04$) of follow-up without distant metastases using the date of decision to watch and wait (Table 2).

DISCUSSION

Patients who achieve a cCR and are managed by watch and wait have excellent oncological outcomes.[4,7] Overall, the risk of distant metastases is low among this subgroup of patients. Distant metastases-free survival is 89% at 5 years, and once patients remain distant metastases-free for 3 years, conditional distant metastases-free survival

TABLE 2. Conditional Cox regression results according to years free of distant metastases

Baseline			
Local regrowth	*No. events (metastasis) (%)*	*HR (95% CI)*	*p*
Yes: 212 (26.7)	51 (24.1%)	4.98 (3.19–7.77)[a]	<0.001
No: 581 (73.3)	34 (5.9%)		
1-y distant metastases-free			
Yes: 188 (25.5)	38 (20.2%)	5.17 (3.12–8.57)[b]	<0.001
No: 549 (74.5)	25 (4.5%)		
2-y distant metastases-free			
Yes: 151 (23.3)	24 (15.9%)	6.19 (3.20–11.97)[b]	<0.001
No: 498 (76.7)	14 (2.8%)		
3-y distant metastases-free			
Yes: 120 (21.2)	16 (13.3%)	7.37 (3.15–17.22)[b]	<0.001
No: 445 (78.8)	8 (1.8%)		
4-y distant metastases-free			
Local regrowth	No. events (metastasis) (%)	HR (95% CI)	*p*
Yes: 95 (20.0)	6 (6.3%)	3.01 (1.01–8.97)[b]	0.047
No: 381 (80.0)	7 (1.8%)		
5-y distant metastases-free			
Yes: 66 (20.2)	5 (7.7%)	3.38 (0.98–11.69)[b]	0.054
No: 261 (79.8)	5 (1.9%)		
6-y distant metastases-free			
Yes: 48 (23.2)	2 (4.2%)	3.41 (0.48–24.23)[b]	0.220
No: 159 (76.8)	2 (1.3%)		

LR = local regrowth.
[a]HR adjusted by age.
[b]Crude HR because only LR remained in the final model.

for the following 2 years (3 + 2 = 5 y) is even better (98%). However, patients who achieve an initial cCR may include highly heterogeneous subgroups of patients. One group of patients with cCR may never develop local regrowth (and probably do not need intensive surveillance once cCR is sustained ≥5 y), whereas another group of patients will develop local regrowth during follow-up.[12] Patients who sustain a cCR have a very low risk for distant metastases over time, and the risk is increased among those who develop initial apparent cCR followed by a local regrowth.[3,11] In the present study, in patients with local regrowth at any time, distant metastases-free survival is already worse in the first year of follow-up compared to patients without local regrowth (93.2% vs 98.4%; $p < 0.01$).

Here, local regrowth was an independent risk factor associated with worse distant metastases-free survival. Although there is a chance that a proportion of distant metastases have been driven by worse biological behavior at baseline (leading to both local regrowth and distant metastases), the observation of a significant amount of late distant metastases (≥3 y from decision to watch and wait) suggests that additional mechanisms may have been drivers here.

Conditional survival estimates suggest that the risk of distant metastases after local regrowth is not transient or restricted to the initial years after development of local regrowth. In addition, Conditional Cox regression analysis showed that local regrowth remains as a significant risk

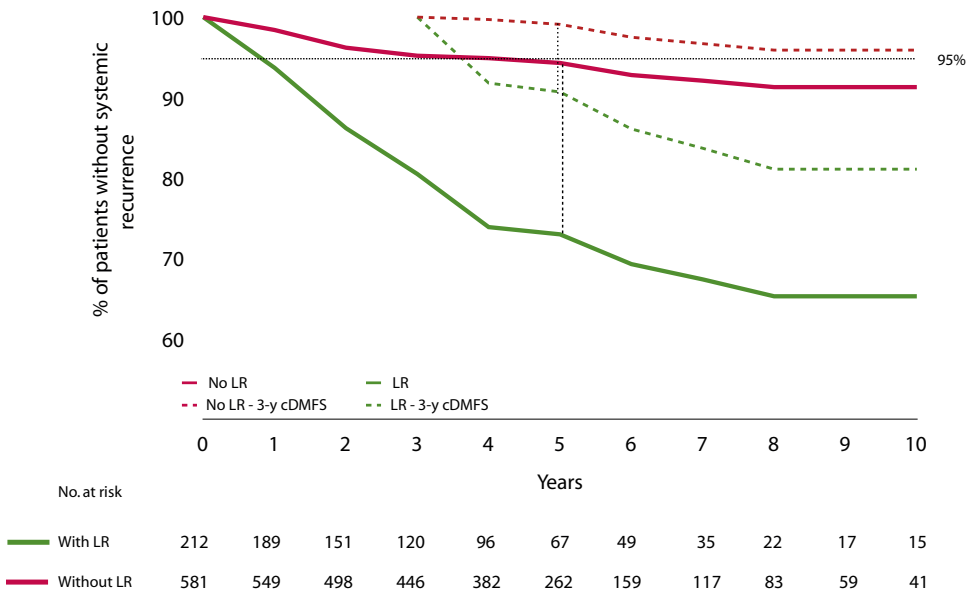

FIGURE 1. Kaplan-Meier curves show a significant difference in 5-y distant metastases-free survival between patients with and without LR after achieving a cCR and undergoing watch and wait (distant metastases-free survival: LR 73.0% [95% CI, 66.1–79.8], vs no LR 94.3% [95% CI, 92.2–96.3]; $p < 0.01$). Once patients with cCR achieve 3 y without distant metastases (frequently considered as the most critical time interval for the development of distant metastases), patients who develop LR are still at higher risk for worse cDMFS for the following 2 y (5-y cDMFS: LR 90.6% vs no LR 98.4%; $d = 0.24$). This suggests that patients with LR still sustain a significant risk for development of distant metastases beyond the typical and critical 3-y interval. cCR = clinical complete response; cDMFS = conditional distant metastases-free survival; LR = local regrowth.

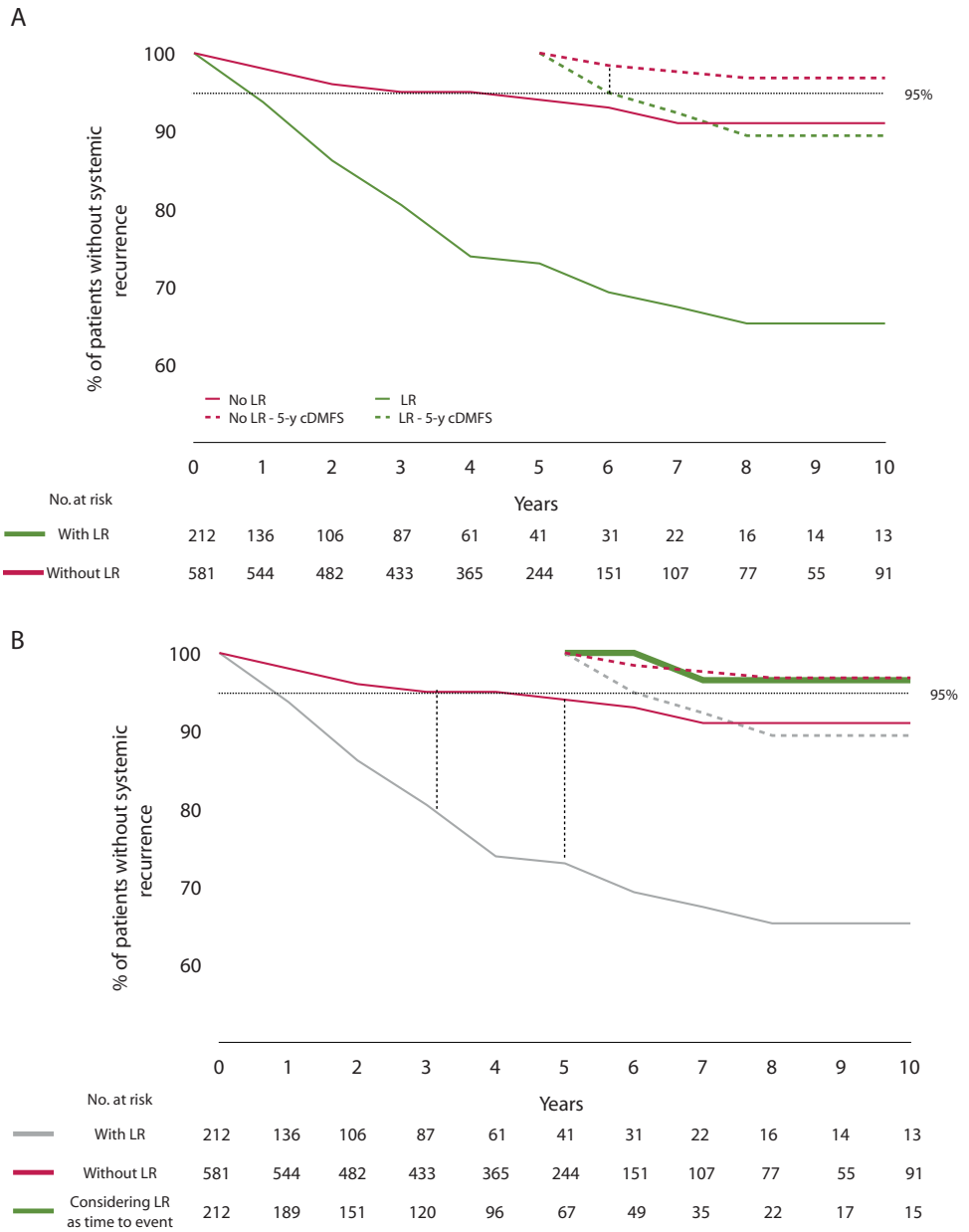

FIGURE 2. A, Considering the decision of watch and wait as baseline, patients with cCR managed by watch and wait and who develop LR at any time and are distant metastases-free for 5 y remain at higher risk for worse conditional distant metastases-free survival (5-y conditional distant metastases-free survival: LR 94.9% vs no LR 98.4%; $d = 0.24$). B, However, when distant metastases-free survival for patients with LR is estimated using time zero, the date of LR (instead of date of decision to watch and wait), after 5 y without distant metastases, conditional distant metastases-free survival becomes "similar" (curves are being superposed) to patients without LR. This suggests that the number of events (development of distant metastases) among patients with LR remain significant up to 5 y from the date of LR (and not restricted to 5 y from the date of decision to watch and wait). cCR = clinical complete response; LR = local regrowth.

factor for distant metastases until 5 years being distant metastases-free. The risk of distant metastases remains significant for a considerable amount of time after development of local regrowth and extends over the usual 5 years from initial treatment for the baseline primary tumor (achievement of cCR and date of decision to watch and wait). Instead, the risk of distant metastases for 1 additional year remains significantly higher in patients with local regrowth until 5 years from development of tumor regrowth. Finally, ascertainment and immortal time bias may have contributed to these findings.

Previous studies have suggested that patients who develop local regrowth were at higher risk for development of distant metastases and worse survival outcomes.[9,11] However, none of these studies were able to identify local regrowth as an independent risk factor.[10]

One hypothesis is that development of local regrowth may comprise a second event that increases the risk of

metastatic spread, perhaps by providing a (second) nidus (or "hit") for potential metastasis not present in the nonlocal regrowth group. The risk provided by primary cancer would be the first "hit." The risk provided by the development of local regrowth would constitute the second "hit." The second hypothesis is that inherent unfavorable biology at baseline is responsible both for an incomplete primary tumor response (despite the apparent initial cCR) and the development of distant metastases collectively. Although both of these mechanisms may play a role, it is impossible to distinguish the exact proportion of each one contributing to the risk of distant metastases. If the risk of metastatic disease was entirely related to aggressive baseline tumor biology, one would expect the vast majority of distant metastases to appear within 5 years from decision to watch and wait. However, the risk of metastatic disease remains higher long after development of local regrowth. Therefore, patients with a local regrowth may have to start counting time as to their oncological outcome and risk of distant metastases from the time of salvage surgery. Ultimately, by the time local regrowth is diagnosed, tumor volume, pathological features, and molecular features may substantiate the risk of metastatic disease similarly to a "new" second primary tumor.[18] Therefore, although the overall risk of distant metastases is still low, rates are distinct between patients who do and do not develop local regrowth at any time.

Limitations of the present study should be considered carefully here. First, as it has been previously mentioned, the comparison of patients with local regrowth to those with sustained cCR is perhaps unfair in the sense that these tumors are potentially inherently and biologically different at baseline. It is very unlikely that development of local regrowth is the sole mechanism for development of distant metastases among patients who achieve a cCR after neoadjuvant treatment. A significant proportion of patients with cCR and distant metastases have never developed local regrowth. Among these patients, baseline features of primary cancer may have contributed to the development of distant metastases. In addition, there is a potential risk for ascertainment bias among patients who developed local regrowth. These patients may have been subjected to more intensive systemic restaging because of the presence of the detected local regrowth.

The considerably long study period and the presence of multiple centers entering data could also have taken into account significant heterogeneity in management of patients over time and according to treatment site. However, the year of decision was not identified as a risk factor associated with the development of distant metastases (Table 1). In addition, we found no differences in terms of outcomes when restricting to the subset of patients being managed after year 2010 (local regrowth remained as the sole independent predictor of distant metastases—data not shown). Distant metastases rates across the 3 most numerous institutional series were also similar (data not shown).

Still, a number of limitations inherently associated with registries and large databases may have contributed to many of the findings. Lack of detailed information regarding timing of regrowth, salvage procedures, final pathological findings, and use adjuvant chemotherapy could have further provided additional information regarding the risk of distant metastases among these patients. In the contemporary use of total neoadjuvant therapy regimens in attempting to reduce the risk of distant metastases among patients who achieve a cCR, there is a significant chance that routine adjuvant chemotherapy could have influenced distant metastases rate.[19–21] Also, inconsistencies and heterogeneity in the definitions of cCR, local regrowths, and surveillance strategies may also have influenced results. In contrast, this large data set of patients provides "real-world" data in terms of long-term oncological outcomes focused on the risk of distant metastases. In addition, the present study included patients with local regrowth, irrespective of decision for salvage treatment. Ultimately, patients with local regrowth not salvaged could have represented a subset of patients with an obvious even higher risk for development of metastatic disease. However, it is impossible to retrieve from the database the exact management of the local regrowth or the reasons for not providing salvage resection. Distant metastases itself could have been the reason for not salvaging these patients when synchronous distant metastases and local regrowth were detected. Finally, a number of patients with distant metastases being developed before or together with local regrowth were observed in the database. Curiously, very few patients had distant metastases detected before diagnosis of local regrowth. Considering the diagnosis of local regrowth is far more challenging than the detection of metastatic disease, one could argue that detection of distant metastases before detection of local regrowth merely reflects these diagnostic difficulties. The collection of high-quality data on local regrowths in future studies may help further understand the potential causal relationship between local regrowth and development of distant metastases.

Finally, the lack of a comparator group of patients managed by total mesorectal excision despite the achievement of a cCR could have provided further insight into the risk of distant metastases driven by development of local regrowth.

Despite the presence of inherent limitations frequently observed in large registry-based multicenter databases, current findings may have clinically relevant consequences to the management of patients who achieve a cCR enrolled in a watch and wait program. Considering that local regrowth is an independent risk factor (at least among identifiable risk factors) for worse distant metastases-free survival, attempts should be made to minimize the

risk for the development of local regrowth. Therefore, the use of strict clinical and radiological criteria for the selection of patients for organ preservation should be strongly recommended. Once a local regrowth is detected, patients should be considered at high risk for distant metastases development.

CONCLUSION

Development of a local regrowth at any time during follow-up after initial achievement of cCR among patients being managed by watch and wait is an independent risk factor for development of distant metastases over time. Conditional survival estimates that this risk factor remains significant over time although patients remain metastases-free for as long as 5 years from the diagnosis of local regrowth. Patients should be carefully advised of this potential disadvantage of watch and wait in the subset of patients who develop local regrowth, currently representing nearly 25% to 30% of all patients who achieve a cCR.

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