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Watch and wait after a clinical complete response in rectal cancer patients younger than 50 years

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Members of the International Watch & Wait Database Consortium (IWWD) are co-authors of this study and are listed in the *Supplementary material*.

Abstract

Background: Young-onset rectal cancer, in patients less than 50 years, is expected to increase in the coming years. A watch-and-wait strategy is nowadays increasingly practised in patients with a clinical complete response (cCR) after neoadjuvant treatment. Nevertheless, there may be reluctance to offer organ preservation treatment to young patients owing to a potentially higher oncological risk. This study compared patients aged less than 50 years with those aged 50 years or more to identify possible differences in oncological outcomes of watch and wait.

Methods: The study analysed data from patients with a cCR after neoadjuvant therapy in whom surgery was omitted, registered in the retrospective–prospective, multicentre International Watch & Wait Database (IWWD).

Results: In the IWWD, 1552 patients met the inclusion criteria, of whom 199 (12.8 per cent) were aged less than 50 years. Patients younger than 50 years had a higher T category of disease at diagnosis ($P = 0.011$). The disease-specific survival rate at 3 years was 98 (95 per cent c.i. 93 to 99) per cent in this group, compared with 97 (95 to 98) per cent in patients aged over 50 years (hazard ratio (HR) 1.67, 95 per cent c.i. 0.76 to 3.64; $P = 0.199$). The cumulative probability of local regrowth at 3 years was 24 (95 per cent c.i. 18 to 31) per cent in patients less than 50 years and 26 (23 to 29) per cent among those aged 50 years or more (HR 1.09, 0.79 to 1.49; $P = 0.603$). Both groups had a cumulative probability of distant metastases of 10 per cent at 3 years (HR 1.00, 0.62 to 1.62; $P = 0.998$).

Conclusion: There is no additional oncological risk in young patients compared with their older counterparts when following a watch-and-wait strategy after a cCR. In light of a shared decision-making process, watch and wait should be also be discussed with young patients who have a cCR after neoadjuvant treatment.

Introduction

Colorectal cancer is generally thought to be a disease of the elderly. However, together with the rise in older patients, the incidence in young patients (aged less than 50 years) has increased worldwide over recent decades[1]. Between 1990 and 2016, the incidence of rectal cancer in adults younger than 50 years in Europe increased annually from 1.6 to 3.5 per cent[2]. It is estimated that by 2030 nearly one in four diagnoses of rectal cancer will be in patients aged less than 50 years[3]. Young patients often receive more intensive treatment, presumably related to better overall performance status and possibly more advanced disease stage at presentation[4]. In addition, clinicians expect relatively more survival gain for young patients. Treatment of clinical stage II and III rectal cancers consists of total or partial mesorectal excision, often preceded by neoadjuvant treatment, resulting in complete disappearance of the rectal tumour and tumour-positive lymph nodes—termed a pathological complete response (pCR)—in 10–15 per cent of patients after chemoradiotherapy and almost 30 per cent of patients when smaller tumours are included[5]. This has led to the question of whether rectal resection could be considered overtreatment for this subgroup, as there is no longer evidence of tumour or involved lymph nodes. In addition, patients with a pCR have a particularly favourable oncological outcome, with a low risk of local or distant recurrences[5].

In an attempt to avoid potentially unnecessary surgery and its detrimental side-effects, a watch-and-wait strategy has been

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developed. Patients with a clinical complete response (cCR) on reassessment imaging after neoadjuvant therapy may avoid immediate surgery and be subjected to a strict surveillance strategy. Championed by Habr-Gama and colleagues[6] and followed by different cohort series[7,8], the safety and feasibility of watch and wait has been established in patients with a cCR after neoadjuvant therapy. The largest series of pooled individual data was published by the International Watch & Wait Database (IWWD) Consortium[9] in 2018, in an analysis of 880 patients worldwide with a cCR treated according to a watch-and-wait strategy. The 5-year overall survival rate was 85 per cent, corresponding to a disease-specific survival rate of 97 per cent, indicating that the vast majority of deaths were not cancer-related. Nevertheless, there may be more hesitance among treating clinicians to initiate watch and wait after a cCR in patients with young-onset disease than in older patients. It is questioned whether this approach would be oncologically safe for such young patients with a longer life expectancy, and thus potentially more considerable loss of life-years. The aim of the present study was to investigate the oncological outcomes of a watch-and-wait strategy in patients aged less than 50 years with a cCR after neoadjuvant therapy, and to compare them with outcomes among patients aged 50 years or older.

Methods

Study design

The IWWD is an international multicentre, partly retrospective and partly prospective cohort database, established in 2014 to collect all available data to provide an understanding of the risks and benefits of a watch-and-wait strategy after achieving a cCR following neoadjuvant treatment. Data registration started in April 2015. Patient consent and ethical and institutional review board approval were handled according to the local requirements of participating centres. Data were entered online by local research staff or the participating investigator, and stored in a highly secured NEN7510 certified and encrypted research data server (ProMISe) (Leiden, the Netherlands). To analyse the data, a data set without identifiable patient parameters was extracted from PRoMISe in compliance with the General Data Protection Regulation (EU 2016/679). The Clinical Research Centre of the Leiden University Medical Centre was responsible for overall data management and performed data quality checks in case of missing or data irregularities. All participating centres retain full ownership of their data and responsibility for accuracy of the information provided.

Patients

Data registered in the observational IWWD from all patients achieving a cCR after neoadjuvant treatment, and not undergoing surgery, were analysed. Patients with distant metastases at diagnosis or concurrently with the start of watch and wait, and those for whom age was missing, were excluded. The indication for and type of neoadjuvant therapy, the decision to watch and wait, and all restaging and follow-up assessments were done according to the local protocol of the participating institutions. A cCR was defined by the absence of signs of residual tumour or involved lymph nodes at clinical reassessment after neoadjuvant therapy, which consisted of digital rectal examination, endoscopy, MRI, CT, and/or other imaging modalities according to each institution's policy. Local regrowth was defined as any reappearance of the tumour at the original tumour location or regional lymph nodes. Distant metastases were defined by the presence of radiological evidence or histological confirmation of metastatic disease.

Statistical analysis

Currently, most national screening programmes start from age 50 years[10]. Therefore, patients were divided into two groups: those younger than 50 years and patients aged 50 years or more. Baseline characteristics were described. Differences were tested with c^2 tests. Statistical analyses were performed using SPSS® version 25.0 (IBM, Armonk, NY, USA). Data on all imaging modalities at baseline were combined to determine stage, with MRI as the leading modality. The reverse Kaplan–Meier method was used for calculation of median follow-up. All survival analyses were done using the Kaplan–Meier survival method in Stata® version 16.1 (StataCorp, College Station, TX, USA). Differences were assessed by means of the log rank test. Hazard ratios (HRs) and 95 per cent confidence intervals were computed using Cox regression. Patients alive and disease-free at last follow-up were censored. To evaluate overall survival, disease-specific survival, the development of local regrowth, and the development of distant metastases from the moment a cCR was diagnosed, the date of decision to watch and wait was used as starting point for all survival analyses.

Results

Of 1924 patients registered in the IWWD between 14 April 2015 and 9 April 2021, 1552 met the inclusion criteria for the present study. Median follow-up was 3.2 (i.q.r. 1.8–5.1) years. In total, 199 patients (12.8 per cent) were aged less than 50 years. Before 2011, 17.3 per cent of patients (34 of 196) were younger than 50 years, between 2011–2015 this was 11.7 per cent (69 of 592 patients), and after 2015 this was 12.6 per cent (96 of 764 patients). Baseline characteristics are shown in *Table 1*. Patients younger than 50 years had fewer co-morbidities and a higher T category at diagnosis. Baseline diagnostics in this group more often consisted of digital rectal examination and CEA measurement, whereas those

Table 1 Baseline characteristics

	< 50 years (*n* = 199)	≥ 50 years (*n* = 1353)	*P*§
Age at diagnosis (years)*	45 (40–48, 21–49)	66 (60–73, 50–98)	
Sex			0.145
M	123 (61.8)	907 (67.0)	
F	76 (38.2)	446 (32.0)	
Co-morbidity			<0.001
Yes	30 (16.9)	453 (47.6)	
No	148 (83.1)	499 (52.4)	
Unknown	21	401	
Clinical tumour category†			0.011
cT0–1‡	0 (0.0)	22 (1.8)	
cT2	34 (20.5)	349 (28.1)	
cT3	119 (71.7)	789 (63.5)	
cT4	13 (8)	82 (6.6)	
Unknown‡	33	111	
Clinical node category†			0.198
cN0	54 (32.1)	477 (37.8)	
cN1	68 (40.5)	471 (37.4)	
cN2	46 (27.4)	313 (24.8)	
Unknown	31	92	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r., range). †Information from ultrasonography, CT, and MRI combined; MRI was the leading modality in determining stage. ‡A tumour was clearly present based on imaging, or other clinical examination (such as endoscopy). §χ^2 test.

aged 50 years and over underwent MRI of the pelvis more often. The same pattern was observed for reassessment after induction therapy (*Table 2*). Induction therapy was mandatory for inclusion in the IWWD, and the majority of patients received chemoradiotherapy. Among the patients younger than 50 years, 15 (7.5 per cent) received induction chemotherapy (7 combined with induction chemoradiotherapy and 8 with induction external beam radiotherapy). Of patients aged 50 years or more, 67 (5.0 per cent) received induction chemotherapy (34 combined with induction chemoradiotherapy, 24 with induction external beam radiotherapy, and 9 with only induction chemotherapy).

Three- and 5-year overall survival rates were higher among young patients (97 (95 per cent c.i. 93 to 99) and 93 (86 to 96) per cent respectively) in comparison to those in the older group (93 (91 to 94) and 85 (82 to 88) per cent) (HR 2.51, 95 per cent c.i. 1.36 to 4.63; $P = 0.003$) (*Fig. 1*). A statistically significant difference was no longer evident in the disease-specific survival rates in patients aged less than 50 years (98 (93–99) and 95 (88 to 98) per cent) compared with those aged 50 years or more (97 (95–98) and 92 (89–94) per cent) (HR 1.67, 0.76–3.64; $P = 0.199$) (*Fig. 2*). The cumulative probability of local regrowth at 3 and 5 years was 24 (18 to 31) and 25 (19 to 32) per cent respectively in patients younger than 50 years, compared with 26 (23 to 29) and 28 (25 to 31) per cent in those age 50 years or older (HR 1.09, 0.79 to 1.49; $P = 0.603$) (*Fig. 3*). Among patients younger than 50 years who developed local regrowth, this occurred during the first 6 months, the first year, and the first 2 years in 47.7, 75.0, and 90.9 per cent respectively; respective values in the older group were 37.1, 70.8, and 90.8 per cent (*Table 3*). At 3 and 5 years, the cumulative probability of distant metastases was 10 (6 to 16) and 11 (7 to 17) per cent in patients younger than 50 years, and 10 (8 to 12) and 13 (10 to 15) per cent among those aged 50 years or more (HR 1.00, 0.62 to 1.62; $P = 0.998$) (*Fig. 4*). At least 68.4 per cent of all distant metastases occurred in the first 2 years among patients under 50 years, compared with 62.5 per cent of those in the older group (*Table 3*). Of the young patients with local regrowth, 18 per cent (8 of 44) developed distant metastases, which was comparable to the 22 per cent (70 of 315) in the older group ($P = 0.543$).

Treatment of local regrowth in 44 young patients consisted of low anterior resection in 14 patients (93 per cent R0 rate), of whom three also received chemotherapy, abdominoperineal resection in 14 (R0 rate 71 per cent), of whom one also received brachytherapy and one chemotherapy, radiotherapy, and targeted therapy. Nine patients underwent local excision (100 per cent R0 rate), two had chemotherapy only, and information regarding treatment of local regrowth was not available for five patients.

Additional analyses demonstrated that patients who were diagnosed before 2010 accounted for the difference in diagnostic procedures between patients younger than 50 years and those aged 50 years or more. The statistically significant difference disappeared in the subgroup of patients who started watch and wait in 2010 or later. All survival analyses were repeated for patients enrolled from 2010 and staged by MRI. This selection did not change the outcomes.

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

	< 50 years ($n = 199$)	≥ 50 years ($n = 1353$)	P†
Baseline			
Digital rectal examination	157 (78.9)	946 (69.9)	0.009
Endoscopy/rectoscopy	126 (63.3)	805 (59.5)	0.305
Endorectal ultrasound imaging	26 (13.1)	200 (14.8)	0.522
MRI of pelvis	163 (81.9)	1201 (88.8)	0.006
Carcinoembryonic antigen	147 (73.9)	860 (63.6)	0.004
Dissemination investigations*	187 (94.0)	1221 (90.2)	0.091
Reassessment after induction therapy			
Digital rectal examination	169 (84.9)	978 (72.3)	<0.001
Endoscopy/rectoscopy	180 (90.5)	1197 (88.5)	0.409
Endorectal ultrasound imaging	18 (9.0)	84 (6.2)	0.132
MRI of pelvis	152 (76.4)	1139 (84.2)	0.006
Carcinoembryonic antigen	76 (38.2)	354 (26.2)	<0.001
Dissemination investigations*	110 (55.3)	708 (52.3)	0.437

Values in parentheses are percentages. *At least one of the following: X-ray of thorax, CT of thorax, CT of abdomen, ultrasonography of liver, CT of liver, MRI of liver, CT of pelvis, PET. †χ^2 test.

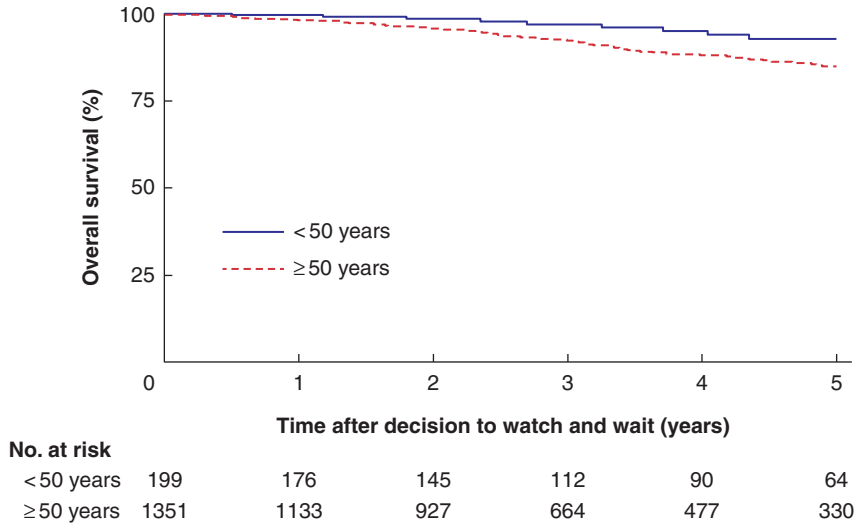
Discussion

The present study aimed to evaluate the outcome of a watch-and-wait strategy in patients younger than 50 years with a cCR after neoadjuvant treatment, compared with outcomes in patients aged 50 years or more. Based on current data from patients in the IWWD, the young patients had comparable disease-specific survival, and a risk of local regrowth and distant metastases similar to that of older patients undergoing watch and wait.

In line with the present findings, young patients often present with more advanced disease stage at diagnosis, more aggressive tumours, and unfavourable histopathological features[11]. As colorectal cancer is often perceived as a disease of the elderly, this now-frequent diagnosis in young patients may be overlooked by both patients and physicians. Young patients wait longer before the initial symptoms lead them to search for a healthcare provider. In addition, the duration of diagnostic evaluation is longer for young compared with older patients[11,12] owing to a low level of suspicion of malignancy. Symptoms as rectal blood loss are frequently ascribed to benign conditions such as haemorrhoids. In this study, patients younger than 50 years less often underwent diagnostic MRI of the pelvis, currently the most important staging modality[13]. However, this did not appear to affect survival compared with that of patients aged over 50 years. National screening programmes are helpful in identifying tumours at an early, asymptomatic stage. However, as the minimum age for inclusion in a national screening programme is 50 years in general, this will not help in identifying young-onset rectal cancer[10].

Zaborowski and colleagues[4] evaluated cancer-specific outcomes of patients with stage III or high-risk stage II rectal cancer, treated with neoadjuvant long-course chemoradiotherapy, total mesorectal excision, and optional postoperative chemotherapy, and compared patients younger than 50 years with those aged 50 years or older. Although young patients were more often diagnosed with stage III disease and more often received neoadjuvant and postoperative therapy, disease-free survival rates at 1, 3, and 5 years were similar in the two age groups: 96, 87, and 81 per cent in the younger group, and 95, 85, and 81 per cent in the older group ($P = 0.711$); this is consistent with the present findings. Nevertheless, the present cohort had favourable tumour biology as the patients responded well to neoadjuvant treatment, and were even capable of obtaining a cCR. Patients with a cCR have better overall survival, comparable to that of patients with a pCR.

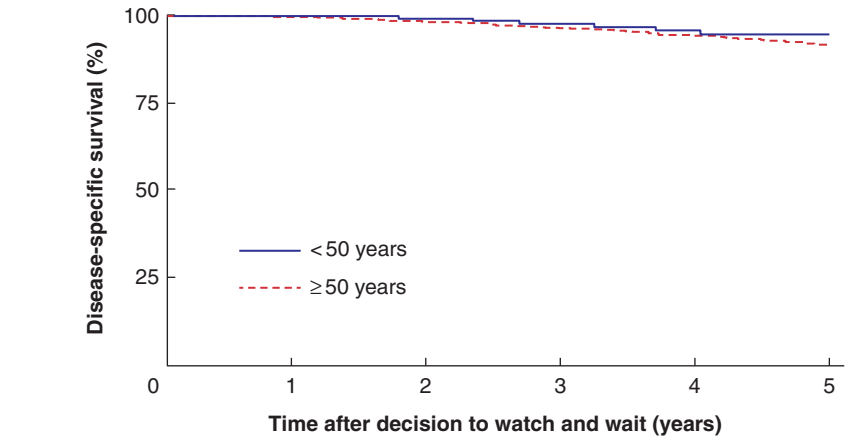
Offering watch and wait to patients with a cCR after neoadjuvant treatment is very appealing. Nonetheless, there might be an additional oncological risk, which is not yet entirely known. In a systematic review and meta-analysis, Socha and co-workers[14]



No. at risk						
<50 years	199	176	145	112	90	64
≥50 years	1351	1133	927	664	477	330

Fig. 1 Overall survival after the decision to watch and wait

$P = 0.003$ (log rank test).



No. at risk						
<50 years	199	176	145	112	90	64
≥50 years	1351	1133	927	664	477	330

Fig. 2 Disease-specific survival after the decision to watch and wait

$P = 0.199$ (log rank test).

calculated that patients treated according to a watch-and-wait strategy have a risk of developing distant metastases of between 0 and 6.5 per cent owing to the omission of immediate surgery. However, they suggested that the maximum risk of 6.5 per cent might be overestimated because of assumptions made in the calculation. In a pooled analysis of patients with a pCR after chemoradiation for rectal cancer, Maas *et al.*[5] reported a 5-year distant metastasis-free survival rate of 89 per cent. This is close to the risk of distant metastases found in the present study. It is likely that the additional risk of distant metastases resulting from omission of immediate surgery is very small. In the present study, the risk of metastases was similar in both age groups, despite a higher T category at initial diagnosis among younger patients. Achieving a cCR after neoadjuvant therapy may be a stronger prognostic factor than baseline stage on MRI. A recent study[15] has shown that, when patients have a sustained cCR for 3 years, the probability of developing local regrowth or distant metastases is less than 3 per cent.

For young patients, considerations regarding the choice of surgery or organ preservation by watch and wait may be different from those for the elderly. Postoperative morbidity and mortality rates are lower in young patients, favouring surgery[16]. Therefore, it feels more logical to operate on these patients as surgery provides more oncological certainty. However, urinary and sexual dysfunction can seriously affect quality of life for an excess of life-years, which may be highly relevant for younger patients. In addition, patients managed by a watch-and-wait strategy have a significantly better 3-year colostomy-free survival rate than those who undergo immediate surgery[8]. Having a stoma can affect body image and lead to less self-confidence because of the shame and fear of being stigmatized by others. In contrast, specific to young patients is that they may have children who are

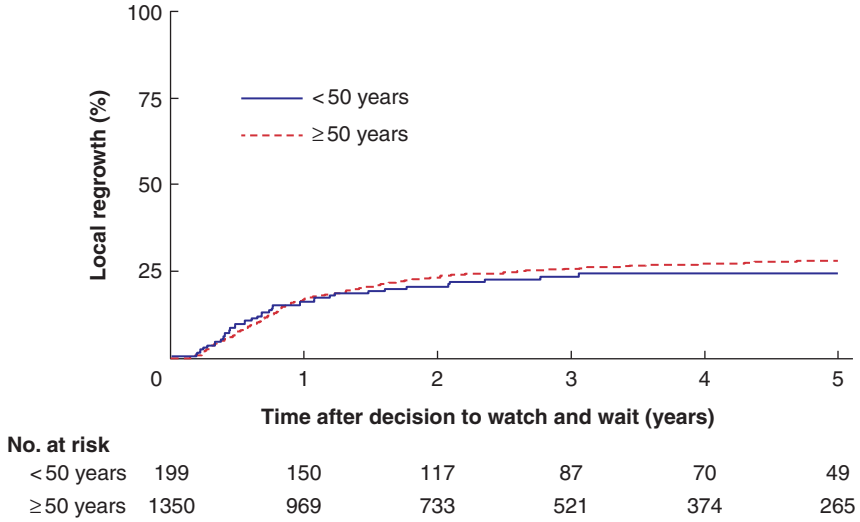


Fig. 3 Development of local regrowth after the decision to watch and wait

$P = 0.603$ (log rank test).

Table 3 Oncological outcomes

	< 50 years ($n = 199$)	≥ 50 years ($n = 1353$)	P‡
Follow-up after decision to watch and wait (years)*	3.5 (2.9, 4.2)	3.1 (3.0, 3.3)	
Alive at end of registered follow-up			0.016
Yes	188 (94.5)	1203 (88.9)	
No	11 (5.5)	152 (11.2)	
Local regrowth†			0.715
Yes	44 (22.1)	315 (23.3)	
Within 6 months	21 of 44 (48)	117 of 315 (37.1)	
Within 7–12 months	12 of 44 (27)	106 of 315 (33.7)	
Within 13–24 months	7 of 44 (16)	63 of 315 (20.0)	
After 2 years	4 of 44 (9)	28 of 315 (8.9)	
Timing unknown	0 (0)	1 of 315 (0.3)	
No	155 (77.9)	1038 (76.7)	
Distant metastases†			0.754
Yes	19 (9.5)	120 (8.9)	
Within 12 months	8 of 19 (42)	43 of 120 (35.8)	
Within 13–24 months	5 of 19 (26)	32 of 120 (26.7)	
After 2 years	0 (0)	6 of 120 (5.0)	
Timing unknown	6 of 19 (32)	39 of 120 (32.5)	
No	180 (90.5)	1233 (91.1)	

Values in parentheses are percentages unless indicated otherwise; *values are median (95 per cent c.i.). †Time calculated from decision to watch and wait. ‡χ^2 test.

still emotionally and financially dependent on them. It is known that the patient's quality of life can also influence the quality of life of their family[17]. As there is no histological confirmation of tumour response with a watch-and-wait policy, the inherent uncertainty about residual disease might reduce patients' willingness to take risks. However, with 3-monthly follow-up, which was considered acceptable by 95 per cent of patients a study by Gani and colleagues[18], 83 per cent of patients would consider deferral of surgery in the event of a cCR. Moreover, 94 per cent of patients would accept a local regrowth risk of 25 per cent, especially when facing permanent colostomy as an alternative. Kennedy and colleagues[19] found that patients were willing to accept a 20 per cent absolute increase in local regrowth and a 20 per cent absolute decrease in overall survival (from 80 to 60 per cent) if that would mean organ preservation instead of major surgery. In contrast, medical physicians were willing to accept a 5 per cent absolute increase in local regrowth and decrease in overall survival. This highly reflects the difference in point of view between patients and their treating physicians. Patients are willing to accept a higher oncological risk as they have other priorities. The option of watch and wait should, therefore, be discussed with the patient in a shared decision-making setting. It has been demonstrated that better understanding of a patient's situation after appropriate provision of information will help the patient to cope with cancer, and reduces stress, anxiety, and depression. This improved mental health also translates into better quality of life[20].

A few limitations should be taken into account when interpreting the present results. The IWWD provides data on patients treated according to a watch-and-wait strategy in many centres worldwide. However, this also led to considerable variability between participating centres in baseline characteristics, neoadjuvant therapy, and imaging strategies[9]. Also important, it is unclear how many patients with young-onset rectal cancer with a cCR were actually treated according to a watch-and-wait strategy, possibly introducing a selection bias. The IWWD does not provide information on how many patients with or without a cCR were actually treated in each centre. Patients with late-onset rectal cancer could have been offered watch and wait in a more liberal fashion (owing to the high risk of postoperative morbidity/mortality), whereas patients with young-onset rectal cancer could have been selected more strictly. Another limitation could be the absence of baseline information regarding microsatellite stability status. It could be argued that a large population of patients aged below 50 years could actually represent those with microsatellite stability-high status/Lynch syndrome[4], a subgroup of cancers with distinct biological behaviour. In addition, no information on functional outcome and quality of life was available in the IWWD, although this is thought to be an important consideration for patients younger than 50 years when deciding on either organ preservation or surgery. It should also be kept in mind that the IWWD includes patients who started watch and wait in 1991. Over time, assessment modalities and neoadjuvant treatment strategies have evolved substantially, which might have

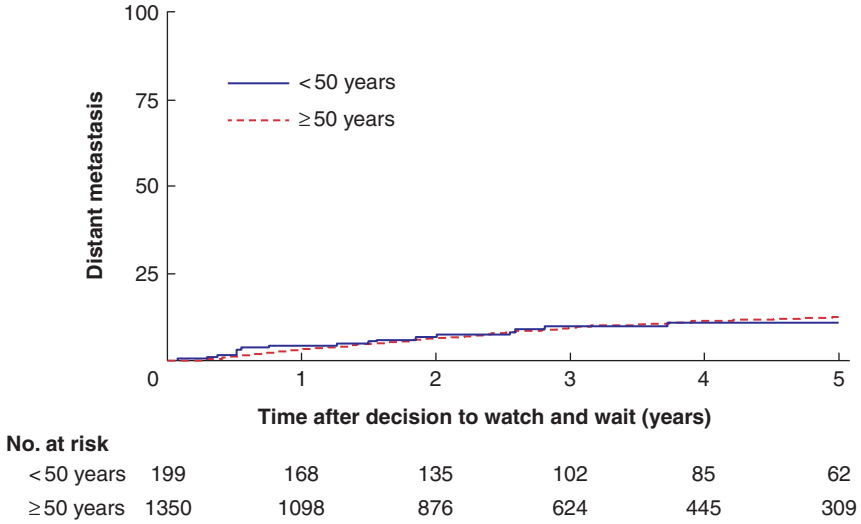


Fig. 4 Development of distant metastases after the decision to watch and wait

$P = 0.998$ (log rank test).

influenced oncological outcomes. Nevertheless, the IWWD is a proper reflection of real-world clinical practice.

The present analysis of oncological outcomes of a watch-and-wait strategy in patients younger than 50 years compared with older patients has highlighted aspects of proposing watch and wait in young-onset rectal cancer from different angles. Although patient preferences and concerns regarding different aspects will vary widely, the authors strongly believe that the possibility of organ preservation should always be discussed, even in young patients who have a longer life expectancy. They should be able to make their own decisions based on well founded information. Wishes and expectations of patients in the context of their future, taking into consideration their social life, family, career, and quality of life, should be discussed openly, enabling patients to make a well considered decision. However, it is critical that watch and wait is practised in a dedicated centre with the expertise to make a careful risk assessment and where sufficient follow-up modalities are available to ensure high quality of care.

When a cCR is determined after neoadjuvant treatment for rectal cancer, offering watch and wait as a treatment option may be consistent with the values and preferences of patients. There is no difference in oncological risk between young patients and older ones, so there should not be a reason to dissuade young patients from an organ-preserving treatment. A watch-and-wait strategy should certainly be considered and at least be discussed with the patient.

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Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

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