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# Adjuvant chemotherapy in patients with clinically node-negative but pathologically node-positive rectal cancer in the Netherlands: A retrospective analysis

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ABSTRACT

*Introduction:* Accurate clinical staging of rectal cancer is hampered by suboptimal sensitivity of MRI in the detection of regional lymph node metastases. Consequently, some patients may be understaged and have been withheld neoadjuvant (chemo)radiotherapy in retrospect. Although Dutch guidelines do not advocate adjuvant chemotherapy (ACT) in rectal cancer, some of these clinically understaged patients receive ACT according to local policy. We aim to assess the benefit of ACT in these patients.

*Methods:* Population-based data from patients with clinically node-negative (cN0) but pathologically node-positive (pN+) rectal cancer that underwent total mesorectal excision (TME) without neoadjuvant treatment between 2008 and 2018 were obtained from the Netherlands Cancer Registry. Missing data were handled by multiple imputation. Stabilised inverse probability treatment weighting (sIPTW) was used to balance clinical characteristics. Overall survival (OS) was compared in ACT and non-ACT patients.

*Results:* Of 34,724 patients, 13,861 had cN0 disease of whom 3016 were pN+ (21.8%). 1466 (48.6%) of these patients underwent upfront TME and were included. Median follow-up was 84 months (95% confidence interval [CI] 76–97) versus 79 months (95% CI 77–81) in patients that did (n = 290, 19.8%) and did not (n = 1176, 80.2%) receive ACT, respectively. After sIPTW adjustment, ACT was associated with improved OS (hazard ratio 0.70; 95% CI 0.49–0.99; p = 0.04). The estimated 5-year OS rate was 74.2% versus 65.3%, respectively.

*Conclusion:* In this population-based cohort of patients with cN0 but pN+ rectal cancer who underwent upfront TME, ACT was associated with a significant OS benefit. These data support to discuss ACT in this population.

## 1. Introduction

The benefit of adjuvant chemotherapy (ACT) in rectal cancer has not been clearly established. A Cochrane meta-analysis of 21 randomised controlled trials that investigated the benefit of ACT in patients with rectal cancer showed a significant benefit in disease-free survival and overall survival [1]. However, most trials were preceded with the widespread use of high quality surgery by total mesorectal excision (TME), which is associated with improved local control and survival rates [2]. More recently, four randomised phase III trials investigated postoperative chemotherapy compared to observation after preoperative (chemo)radiotherapy [3–6]. In a meta-analysis of these trials, no improvement in overall survival, disease-free survival, or distant recurrence rate was observed [7]. Based on these data, Dutch guidelines do not advocate ACT in rectal cancer patients.

Neoadjuvant treatment is recommended in patients with locally advanced rectal cancer, predominantly to reduce the risk of local recurrence [8,9]. For patients with early and intermediate rectal cancer,

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the risk of local recurrence is low and surgery alone with a radical TME is appropriate according to the ESMO guideline [8]. However, clinical staging of rectal cancer is hampered by suboptimal sensitivity of MRI, and a proportion of patients clinically staged with lymph node negative (cN0) disease may prove to have positive lymph nodes after pathologic review of the surgical specimen (pN+) [10]. Some of these clinically understaged patients receive ACT according to local policy. Previous retrospective studies with data from American databases indicated an overall survival benefit for any form of adjuvant treatment in this subgroup of patients [11,12].

In this study, we assessed the impact of ACT on overall survival in patients with cN0 but pN+ rectal cancer, who had not been treated with neoadjuvant (chemo)radiotherapy, in a large nationwide cohort of Dutch patients diagnosed with rectal cancer between 2008 and 2018.

## 2. Methods

### 2.1. Study design and database

This retrospective cohort study was designed to assess the effectiveness of ACT in patients with cN0 but pN+ rectal cancer who were treated with upfront TME. With population-based data we conducted a comparative analysis using stabilised inverse probability treatment weighting (sIPTW) to adjust for the potential confounding effects of patient baseline demographics and clinical characteristics.

Population-based data from patients with non-metastatic rectal cancer treated with surgery in the Netherlands between January 2008 and December 2018 were requested from the Netherlands Cancer Registry (NCR). ICD-O-3 topography codes C209 (rectum) and C199 (rectosigmoid) were included. The NCR registers all newly diagnosed malignancies in the Netherlands and covers the total Dutch population of over 17 million people. Main notifications of the NCR are linked to the automated pathology archive comprising all histologically confirmed cancer diagnoses, and the National Registry of Hospital Discharge Diagnoses. Trained data managers collect patient, tumour, and treatment characteristics from medical records. Follow-up on vital status occurs through annual linkage between the NCR and National Municipal Personal Records Database, which contains information on vital status of all Dutch inhabitants. The most recent linkage occurred on February 1st 2023. Surviving patients were censored at this date.

During the study period, Dutch guidelines for rectal cancer recommended clinical staging by MRI, and surgery according to TME. No clear definition of the rectum was provided by the guidelines. The most used pragmatic definition was $\leq$ 15 cm from the anal verge, determined by MRI and/or endoscopy [13]. ACT or adjuvant radiotherapy was not recommended for any subgroup. The 2008 guidelines were revised in 2014 and included the following changes: the safe margin of the tumour to the mesorectal fascia was changed from $\geq$ 5 mm to $>$ 1 mm, the criteria for a tumour-positive lymph node on MRI was changed from a diameter $\geq$ 5 mm to a diameter of $\geq$ 5 mm plus at least one malignant feature (round, blurred boundary, and /or inhomogeneous aspect) or $\geq$ 9 mm. As to neoadjuvant therapy, until 2014 short course (5x5 Gy) radiotherapy was recommended for all cT2-T4 tumours (with the possible exception for proximal cT2) and/or cN1 tumours. Long course chemoradiotherapy with capecitabine 825 mg/m$^2$ twice daily was indicated for cN2 disease and/or circumferential resection margin (CRM) involvement. After 2014, short course radiotherapy was recommended for cT1–3N1 tumours or cT1–3N0 tumours with $>$ 5 mm extramural invasion, both with $>$ 1 mm distance to the mesorectal fascia. Long course chemoradiotherapy was indicated for cT4 and/or cN2 disease, or tumours with $\leq$ 1 mm distance to the mesorectal fascia.

### 2.2. Patients

Patients with adenocarcinoma histology, cN0 but pN+ disease, and primary TME (including total proctocolectomy) were included. Patients were excluded if they received neoadjuvant (chemo)radiotherapy or adjuvant radiotherapy, if they underwent a sigmoidectomy (considered to have colon cancer), or if the pathological stage was unknown.

### 2.3. Outcomes

The primary outcome was overall survival in patients who were treated with ACT versus who received no ACT according to the sIPTW analysis. Overall survival time was defined as the time between diagnosis and death due to any cause. Subgroup analyses to evaluate the effect of ACT according to pathological T-stage, pathological N-stage, histological grade of the primary tumour, distance of the primary tumour to the anal verge, and year of diagnosis (2008–2014 versus 2015–2018) were secondary outcomes. Data on chemotherapy regimens, disease recurrence and cause of death are not routinely registered in the NCR. Disease-free survival, disease-specific survival or the effect of the chemotherapy regimen on overall survival could therefore not be analyzed.

### 2.4. Statistical analysis

To describe the study population per cohort, continuous variables were displayed as median with interquartile range (IQR) and categorical variables as counts and percentages. Comparisons between baseline characteristics between the two groups were done using the standardised mean difference (SMD). Unbalanced characteristics have a mean SMD $>$ 0.10. Median follow-up was calculated using the reverse Kaplan-Meier method. Missing values were handled by multiple imputation using a substantive model compatible fully conditional specification (SMC-FCS) approach, assuming missingness at random. The substantive model was a Cox proportional hazards analysis for overall survival with the following variables: age, sex, distance to the anal verge, type of surgery, differentiation grade, year of diagnosis, pathological T and N stage, and the outcome (overall survival). Twenty iterations were used, and multiple datasets were generated based on the percentage of patients with any missing data in the predictors used for sIPTW. sIPTW was used to construct a weighted sample in which the patient baseline demographics and clinical characteristics were balanced between treated and untreated patients [14]. First, the propensity score was estimated using multivariable logistic regression with type of treatment as the dependent variable and age, sex, distance to the anal verge, type of surgery, differentiation grade, year of diagnosis, pathological T and N stage as covariates. CRM, mesorectal fascia involvement and extramural vascular invasion (EMVI) were not available in the NCR for the total study period, so could not be added. Using the propensity score, a stabilised weight was calculated for each patient. Then, the balance of covariates after matching was assessed with the mean SMD. The mean SMDs before and after sIPTW were graphically displayed in a plot. Next, the average treatment effect was calculated by including the weights in a Cox proportional hazards regression model. The obtained hazard ratio (HR) was reported with a 95% confidence interval (CI). The adjusted 5-year overall survival rate was predicted using the sIPTW Cox proportional hazards model. For subgroup analyses, patients with missing data of the variable of interest were excluded, after which other missing values were imputed with multiple imputation using the above-mentioned methods, and again sIPTW was used to evaluate the unbiased treatment effect. A CI of 99% was used for subgroup analyses. Each measure was determined for each imputed dataset and pooled using Rubin's rules. A 2-sided p $\leq$ 0.05 was considered statistically significant. All analyses were performed in R (version 4.2.2).

## 3. Results

### 3.1. Patient characteristics

Between 2008 and 2018, a total of 34,724 patients with

adenocarcinoma of the rectum who underwent TME were identified. 13,861 had cN0 disease, of whom 3016 were pN+ (21.8%). Of these patients, 1466 (48.6%) did not receive neoadjuvant (chemo)radiotherapy and were included in the analysis (Figure 1). 290 (19.8%) did and 1176 (80.2%) did not receive ACT. In the time period before the guideline revision (2008–2014), 466 patients were included of whom 132 (28.3%) were treated with ACT. In the time period 2015–2018, 1000 patients were included of whom 158 (15.8%) were treated with ACT. In the unadjusted cohort, patient, tumour and treatment characteristics differed between the groups that received ACT and no adjuvant treatment (Table 1). Patients treated with ACT were younger, had a more proximal primary tumour location, a higher pathological T and N stage, underwent a low anterior resection more often than an abdominal perineal resection, and the year of diagnosis was earlier.

Based on 19.2% of patients with missing data, 20 imputed datasets were generated. After sIPTW, patient, tumour and treatment characteristics were well balanced, with a mean standardised difference of $< 0.10$ for all covariates (Table 1; supplementary Figure 1).

### 3.2. Primary outcome

Median follow-up was 84 months (95% CI 76–97) in the ACT group and 79 months (95% CI 77–81) in the group that received no ACT. In the unadjusted analysis, median overall survival was not reached (NR) (95% CI 140-NR) in the ACT group and 106 months (95% CI 92–121) in the group that received no ACT (HR 0.59; 95% CI 0.47–0.74; $p < 0.001$). The 5-years overall survival was 75.0% versus 66.1%, respectively.

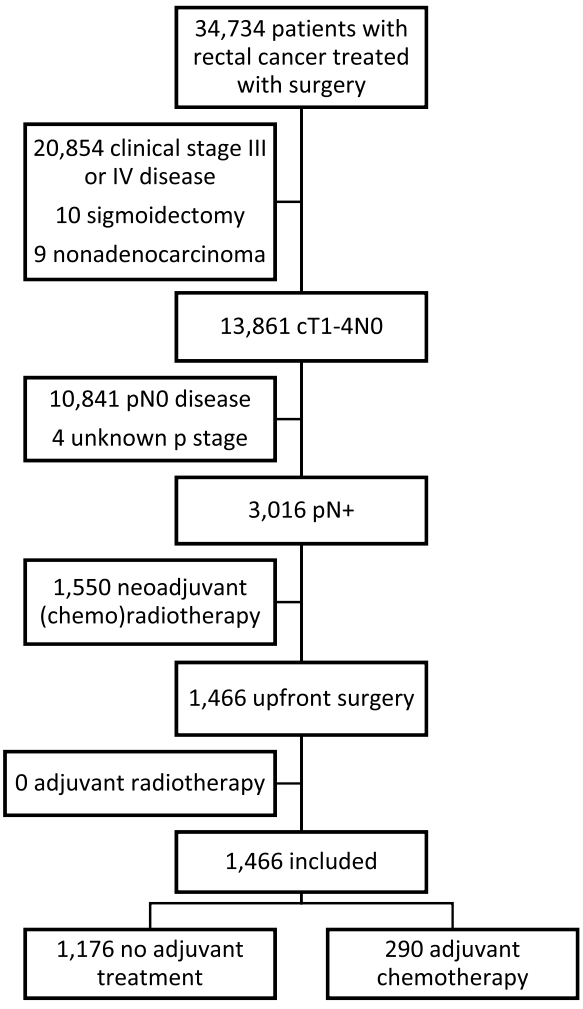


**Fig. 1.** Flow diagram of included patients.

**Table 1**
Patient characteristics. *ACT* adjuvant chemotherapy, *SMD* standardised mean difference, *sIPTW* stabilised inverse probability treatment weighting, *IQR* interquartile range, *LAR* low anterior resection, *APR* abdominoperineal resection.

| | No ACT (N = 1176) | ACT (N = 290) | Mean SMD | Mean SMD after sIPTW |
|---|---|---|---|---|
| **Sex** | | | 0.04 | 0.07 |
| Female | 435 (37%) | 102 (35%) | | |
| Male | 741 (63%) | 188 (65%) | | |
| **Age, median (IQR)** | 70 (63, 77) | 65 (58, 71) | 0.61 | -0.04 |
| **Distance to anal verge** | | | | |
| 0–5 cm | 338 (29%) | 16 (6%) | 0.63 | -0.03 |
| 5–10 cm | 430 (37%) | 56 (19%) | 0.27 | < 0.01 |
| > 10 cm | 288 (24%) | 127 (44%) | 0.79 | 0.02 |
| Missing | 120 (10.2%) | 91 (31.4%) | 0.54 | |
| **Pathological T stage** | | | | |
| 1 | 95 (8%) | 18 (6%) | 0.07 | -0.01 |
| 2 | 356 (30%) | 51 (18%) | 0.30 | -0.03 |
| 3 | 662 (56%) | 171 (59%) | 0.05 | 0.04 |
| 4 | 63 (5%) | 50 (17%) | 0.38 | < 0.01 |
| **Pathological N stage** | | | 0.32 | 0.01 |
| 1 | 962 (82%) | 197 (68%) | | |
| 2 | 214 (18%) | 93 (32%) | | |
| **Type of surgery** | | | | |
| Other | 63 (5%) | 7 (2%) | 0.15 | 0.01 |
| LAR | 922 (78%) | 272 (94%) | 0.46 | -0.01 |
| APR | 191 (16%) | 11 (4%) | 0.42 | -0.01 |
| **Differentiation grade** | | | | |
| Good | 27 (2%) | 5 (2%) | 0.04 | < 0.01 |
| Moderate | 996 (85%) | 239 (82%) | 0.08 | -0.02 |
| Poor | 87 (7%) | 30 (10%) | 0.11 | 0.02 |
| Missing | 66 (5.6%) | 16 (5.5%) | 0.00 | |
| **Year of diagnosis, median (IQR)** | 2016 (2014, 2017) | 2015 (2011, 2017) | 0.40 | -0.07 |
| 2008–2014 | 334 (28%) | 132 (46%) | | |
| 2015–2018 | 842 (72%) | 158 (54%) | | |

After sIPTW-adjusted analysis, the HR for overall survival was 0.70 (95% CI 0.49–0.99; $p = 0.04$). The estimated 5-year overall survival was 74.2% in patients treated with ACT versus 65.3% in patients not treated with ACT.

### 3.3. Secondary outcomes

Mean standardised differences of patient, tumour and treatment characteristics after sIPTW for the subgroup analyses are listed in the appendix (supplementary Table 1). Overall, baseline characteristics were well balanced in the larger subgroups, i.e. pT2, pT3, pT4, pN1, moderate differentiation grade, distance to the anal verge, and year of diagnosis. A consistent HR in favour of ACT versus no adjuvant treatment was observed generally across all subgroups examined (Figure 2). However, the upper limit of 99% CI's crossed 1.0 in the majority of subgroups.

## 4. Discussion

In this large retrospective cohort, we have demonstrated an overall survival benefit for ACT in patients with cN0 but pN+ rectal cancer who have not been treated with preoperative (chemo)radiotherapy.

After decades of clinical research, the role of ACT in rectal cancer remains unclear. To date, there are no data from randomised phase III studies supporting the use of ACT in patients treated with neoadjuvant (chemo)radiation [7]. A Cochrane meta-analysis indicated an overall survival benefit for adjuvant fluoropyrimidine-based chemotherapy after surgery alone [1]. The magnitude of benefit was only moderate (HR=0.83), but more importantly the applicability of its results to current clinical practice is very limited. Inter-trial variability was considerable and TME surgery was not routinely implemented in the majority

| Subgroup | ACT weighted sample size | No ACT weighted sample size | HR (99% CI) |
|---|---|---|---|
| pT stage | | | |
| pT1 | 5.3 | 91.4 | 0.54 (0.10-3.02) |
| pT2 | 15.1 | 341.5 | 0.26 (0.07-0.92) |
| pT3 | 72 | 583.2 | 0.74 (0.44-1.25) |
| pT4 | 29.8 | 41 | 0.39 (0.16-0.95) |
| pN stage | | | |
| pN1 | 59.3 | 889.4 | 0.70 (0.36-1.36) |
| pN2 | 13.2 | 173.8 | 0.48 (0.18-1.30) |
| Differentiation grade | | | |
| Good | 5 | 27 | 1.00 (0.15-6.70) |
| Poor | 94.7 | 877 | 0.75 (0.44-1.26) |
| Moderate | 10.9 | 75.2 | 0.86 (0.33-2.21) |
| Distance to anal verge | | | |
| 0-5 cm | 5.7 | 328.5 | 0.47 (0.11-1.95) |
| 5-10 cm | 38.2 | 417.5 | 0.55 (0.23-1.31) |
| >10 cm | 104.9 | 267 | 0.56 (0.32-0.98) |
| Year of diagnosis | | | |
| 2008-2014 (before new guideline) | 63.3 | 903.7 | 0.78 (0.41-1.51) |
| 2015-2018 (after new guideline) | 12.2 | 174.5 | 0.48 (0.17-1.33) |

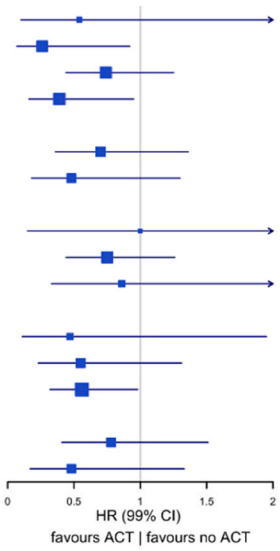


**Fig. 2.** Forest plot of overall survival by subgroup after stabilised inverse probability treatment weighting. ACT adjuvant chemotherapy, HR hazard ratio, CI confidence interval.

of included trials. As a result, the current postoperative rectal cancer population carries a lower risk of disease recurrence, which may reduce the impact of ACT on survival for the total population.

The uncertainty regarding the benefit of ACT is reflected by the varying recommendations in national and international guidelines. The current ESMO guideline encourages a risk-adapted treatment strategy [8]. For early and intermediate (which includes cN+ disease for tumours in the mid- or high rectum) rectal cancers, surgery alone is standard treatment if a good-quality TME can be assured. However, clinical nodal staging has shown to be unreliable, even when endoscopic rectal ultrasound, CT, and MRI are combined [10,15]. This is one of the main reasons that the NCCN guideline advocates total neoadjuvant therapy (TNT), i.e. short or long course (chemo)radiotherapy and 12–16 weeks of chemotherapy preoperatively, for patients clinically staged as cT3–4N0, or if the CRM (by MRI) is threatened or involved [9]. TNT is associated with high rates of pathologically complete responses and therefore holds the promise of organ preservation if that is a treatment goal, [16,17] but an overall survival benefit for neoadjuvant chemotherapy in cN0 disease has not been demonstrated. Hence, this approach carries the risk of substantial overtreatment.

Consistent with previous data, [18] a substantial proportion of patients in our cohort with cN0 disease appeared to be pN+ (21.8%). Comparing our overall survival results with historic prospective rectal cancer studies is challenging because studies that investigated ACT and were conducted after the widespread implementation of TME surgery included patients who were pretreated with neoadjuvant (chemo) radiotherapy. A single randomised phase II study showed an overall survival benefit for adjuvant oxaliplatin-based chemotherapy compared to fluorouracil monotherapy in a subgroup of patients with ypN2 disease [19]. These data are not sufficient to recommend ACT for all patients with (y)pN+ rectal cancer, and highlights the importance of our population-based study. When we compare our results with the benefit of adjuvant chemotherapy in stage III colon cancer, we observed a comparable reduction in the risk of death [20].

The strength of this study is the large sample size and inclusion of all Dutch patients who underwent TME for rectal cancer within the specified time period. Data on clinical and pathological N-stage were complete and follow-up for survival times was adequate. Missing data and differences in baseline characteristics were successfully accounted for through appropriate statistical methods. Additionally, our findings are in accordance with a previous retrospective study that included 1466 patients with cT1–2N0 but pN+ rectal cancer treated with upfront surgical resection from the American National Cancer Data Base. In this study, 37% of patients received ACT, 28% adjuvant chemoradiotherapy and 35% no adjuvant treatment. Both treatments were associated with an significant overall survival benefit as compared to observation alone [11].

We also acknowledge some limitations. The retrospective nature of this study comes with intrinsic limitations. Unobserved variables cannot be addressed through sIPTW. These include histopathological features with prognostic value other than pN stage, for example CRM, pT substage, presence of extranodal deposits or extracapsular extension, lymphovascular invasion, EMVI, and perineural invasion [21]. Although MRI, which was recommended throughout the study period, is accurate in detecting EMVI, determining the T substage and the distance to the CRM, the unexpected presence of any of the abovementioned risk factors postoperatively may have influenced the adjuvant treatment strategy. Other potentially confounding missing variables are ECOG performance status, comorbidities, and surgery-related outcomes.

Regarding the clinical implications of our study, a few issues should be considered. Firstly, a new definition of rectal cancer has been proposed and embraced by the most recent Dutch colorectal cancer guideline [13,22]. During our study period, no clear definition of the rectum was provided by the guidelines. The most used pragmatic definition was $\leq$ 15 cm from the anal verge, determined by MRI and/or endoscopy [13]. In a retrospective analysis, the new definition of rectal cancer, the so-called sigmoid take-off definition, has shown to result in a reclassification from rectal to sigmoid cancer in 13.1% of patients [23]. In our subgroup analysis, the benefit of ACT is most robust in patients with a tumour $>$ 10 cm distance to the anal verge, some of whom would currently qualify as having sigmoid cancer and in whom the benefit of ACT is well established. However, the HR is comparable for patients with rectal cancers between 0 and 5 cm and 5–10 cm to the anal verge, indicating a benefit in all subgroups although subgroup analysis should be interpreted with caution due to small sample sizes. Secondly, the NCR does not routinely collect data on local or distant recurrences, and therefore did not allow us to analyze the effect of ACT on local recurrence rates and disease-free survival. However, since many patients

receiving ACT are being overtreated, either because they are cured by surgery alone or have disease recurrence despite ACT, overall survival is generally considered to be the most relevant endpoint for ACT. Thirdly, the NCR does not routinely register the chemotherapy regimen used, which hinders us to answer the practical question which regimen to apply when opting for ACT. Finally, non-operative organ preservation strategies such as short-course radiotherapy and chemoradiotherapy with or without transanal endoscopic microsurgery are gaining prominence in patients with early and intermediate rectal cancer [24]. Our results cannot be extrapolated to such patients who have to undergo completion TME and are found to have ypN+ disease.

These data warrant prospective evaluation of ACT, but given the challenges that adjuvant rectal cancer studies faced, randomised phase III trials investigating ACT with currently available cytotoxic drugs in rectal cancer should no longer be pursued [25]. A Trials within Cohorts design (TWiCs) may provide a feasible alternative [26]. Otherwise, research focus could be shifted to better selecting patients who may derive most benefit from ACT. For example, patients with colorectal cancer in whom circulating tumour DNA is detectable after surgery are associated with a very high risk of recurrence [27]. Studies investigating ctDNA guided approach in rectal cancer are ongoing (ACTRN12617001560381). Consensus Molecular Subtypes classification may also be a promising biomarker in this respect, but its predictive and prognostic value has yet to be determined in prospective trials [28].

In conclusion, in this retrospective cohort study we demonstrate that patients with cN0 but pN+ rectal cancer treated with upfront surgery may derive benefit from ACT. Our data support to discuss ACT with cN0 pN+ rectal cancer patients who have been treated with TME surgery alone.

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## CRediT authorship contribution statement

**Johannes J.M. Kwakman:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Marinde J.G. Bond:** Methodology, Software, Formal analysis, Data curation, Writing – review & editing. **Ramzi M. Demichelis:** Writing – original draft, Writing – review & editing. **Miriam Koopman:** Writing – review & editing. **Roel Hompes:** Writing – review & editing. **Marloes A.G. Elferink:** Resources, Data curation, Writing – review & editing. **Cornelis J.A. Punt:** Conceptualization, Writing – review & editing, Supervision.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CJAP has an advisory role for Nordic Pharma. This funding is not related to the current research. The remaining authors declare no potential conflicts of interest.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113466.

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