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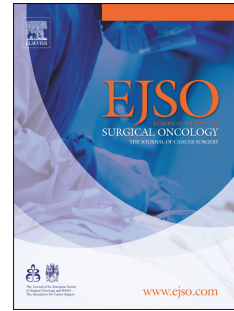
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Title page

Original article.

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Running title

Short course preoperative radiotherapy in rectal cancer.

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Abstract

Aim: The purpose of this study was to analyse the results of preoperative short course radiotherapy in a consecutive, national cohort of patients with rectal cancer.

Methods: Through a validated, prospective national database we identified 520 Danish patients who presented with high-risk mobile tumours in the lower two thirds of the rectum and were referred for preoperative radiotherapy with 5 x 5 Gy. The inclusion period was 56 months. Radiotherapy data was retrospectively collected.

Results: Of the 520 patients, 514 completed radiotherapy and 506 had surgery. Surgery was considered curative in 439 patients. The 3-year local recurrence rate was 4.0 % (95 % CI 2.5-6.5 %) and the distant recurrence rate at 3 years was 18.7 % (95 % CI 15.4-22.5 %). The 5-year disease free survival rate was 40.2 % (95 % CI 27.0-53.1 %) and overall survival 50.4 % (95 % CI 36.1-63.1 %). Most tumours (61 %) were classified as T3 or T4 and 41 % of the local recurrences occurred in patients with a fixed tumour at surgery.

Conclusion: This study confirms data from randomised studies that the short course 5 x 5 Gy regime is a feasible treatment for locally advanced rectal cancer even when applied in a population outside clinical trials.

Introduction

Most of the about 1200 new annual cases of rectal cancer in Denmark are readily resectable tumours. A small fraction consists of primary non-resectable, fixed tumours or otherwise inoperable patients. A middle group of mainly T3 tumours are considered resectable, but with a high risk of recurrence justifying peri-operative adjuvant treatment. A Swedish group introduced the preoperative so called "5 x 5 Gy" protocol as a fast, hypofractionated treatment followed by surgery without delay[1]. A phase II trial showed a 2-year local failure rate of no more than 5 % with few side effects[2]. Further documentation was delivered in a phase III trial where 1168 patients were randomised to either surgery alone or surgery with preoperative radiotherapy delivered as five daily fractions of 5 Gy[3]. Both local failure rate and overall survival were improved in the radiotherapy group.

The general introduction of total mesorectal excision (TME) during the 1990-ties caused a dramatic change in the surgical approach allowing a precise and nerve-sparing en bloc resection of the rectum and the mesorectal tissue, and the procedure resulted in a considerably lower local failure rate[4;5]. Therefore, the question arose if preoperative radiotherapy was still necessary in patients with resectable tumours[6-9]. In the Dutch study [10], patients were randomised to either TME alone or preceded by 5 x 5 Gy and a significant lower risk of local failure after preoperative radiotherapy was shown. In the recently published combined MRC CR07/NCIC-CTG C016 study[11], patients were randomised between preoperative radiotherapy versus selective postoperative radiotherapy. The preoperative regime was superior in terms of reducing the local failure rate. However, so far a significant survival benefit has not been reported.

Randomised clinical trials are the gold standard for evaluating new treatments. They may, however, give a too optimistic impression of the effect of the treatment if patients are selected and are younger or in better performance status than the patients met in daily clinic. It is important to support data from randomised trials with data from daily practice. The objective of the present study was therefore to analyse the outcome of preoperative short course radiotherapy and TME surgery in a consecutive, national cohort of patients with resectable rectal cancer.

Material and methods

Patients

All Danish patients with a high-risk, mobile rectal adenocarcinoma initiating preoperative 5 x 5 Gy radiotherapy in the period 2001-2005 were included. Treatment followed daily clinical practice based on the national guidelines' recommendations for preoperative evaluation, radiotherapy, surgery, and for the postoperative course.

Preoperative evaluation

Every rectal tumour should be biopsied and clinically classified by digital examination as fixed, adherent, or mobile within the pelvis. If curative resection was intended, magnetic resonance imaging (MRI) of the rectum was performed from 2004 to aid the classification. Chest X-ray and ultrasound of the liver or thoracoabdominal CT scan was performed to exclude metastatic disease.

Radiotherapy

Short course preoperative radiotherapy was recommended in mobile T3 tumours located less than 10 cm from the anal verge and where the margin to the mesorectal fascia was not threatened. The patients received preoperative radiotherapy with a total dose of 25 Gy delivered as five daily fractions of five Gy to the gross tumour volume and the clinical target volume. The anatomic definition of the clinical target volume was not specified in the guidelines, but recommendations were based on Kapiteijn et.al.[12] Surgery should be performed within five days after termination of radiotherapy.

Surgery

Tumours in the lower two thirds of the rectum should have TME as part of an anterior resection (AR), Hartmann's procedure, or abdominoperineal resection (APR). In more proximal tumours, partial mesorectal excision was recommended. The surgery was considered curative if the margins

were free as assessed by the surgeon and the pathologist and no distant metastases were encountered before or during the operation.

Postoperative course

In general, neither postoperative radiotherapy nor adjuvant chemotherapy was recommended.

Follow up differed, but all patients had a follow up at least three years postoperatively.

Colonoscopy was recommended with a three to five years interval to detect metachronous neoplasia.

Data retrieval

A national colorectal cancer database was established in Denmark in 2001 by the Danish Colorectal Cancer Group. All patients with a primary adenocarcinoma of the colon or rectum are consecutively included. Demographic data and data concerning diagnosis, tumour localisation, stage, treatment, postoperative complications, and follow up are reported online from all surgical departments. The capture rate of the database is validated each month against the National Patients Register and lays steadily over 95%[13].

Detailed information concerning planning, dose, and fractionation was retrospectively retrieved from the six departments of oncology responsible for the radiotherapy. If the pre-planned follow up at three years was not reached, the surgical department was asked for a patient status concerning local failure, distant metastasis, and/or cause of death. Pre- and postoperative TNM classification as well as reporting of the circumferential margin (CRM) were adopted during the study period, thus not all patients were classified according to this system.

Statistics

Time-to-event analysis was handled according to the Kaplan Meier method. The starting point common for all patients was the date of diagnosis, and this date was used in calculations of local recurrence, distant recurrence, disease free survival, and overall survival. Local and distant

recurrence was calculated as the time to development and verification of local or distant recurrence, respectively. Disease free survival was calculated as the time to local or distal failure or death. Overall survival was calculated to the date of death. Patients were censored at the time of their last follow up. To minimise selection bias, all patients were included in the analyses and subsequently the estimates are more conservative. Univariate analyses of survival data were performed with the log rank test for categorical variables and with Cox proportional hazard regression for continuous variables. Other data was analysed with non-parametric methods. When using a test statistics, the level of statistical significance was set at 5 % double-sided. Quartiles or 95 % confidence interval (CI) were reported when appropriate. The statistical software STATA (StataCorp LP, College Station, Texas, USA) was used.

Results

Patients

During 56 months from 2001 to 2005, 1257 out of 5633 Danish rectal cancer patients were reported to the colorectal cancer database with a referral to preoperative radiotherapy. Three hundred and thirty four had a fixed tumour and were referred for long course radiotherapy[14]. Four hundred and four patients were excluded because they had an adherent tumour or a tumour not evaluable by digital examination, the radiotherapy was not initiated, or data was missing. Furthermore, patients with a mobile tumour treated with long course radiotherapy, mostly in phase II trials, were excluded. This leaves 520 patients with a mobile tumour who initiated short course radiotherapy.

Patient characteristics are show in Table 1. The median age was 67 years (range 30-91 years) and the majority were males (n=333). The tumour was localised in the upper third of the rectum in 10 patients, the middle third in 258 patients, the lower third in 235 patients, and unknown in 17 patients. Preoperative MRI, which was introduced between 2002 and 2004, was performed in 145 patients and classified the tumour as T2 in 8 patients, T3 in 126 patients, T4 in 8 patients, and Tx in 3.

Radiotherapy

The median time from diagnosis to initiation of radiotherapy was 34 days (quartiles 26-45 days). Target definition was based on CT scanning in 416 cases and conventional X-ray in 103. The method of treatment planning was unknown for one patient. Radiotherapy was delivered as five daily fractions of five Gy and was completed as planned in 514 patients. The caseload in the six departments undertaking radiotherapy ranged between 62 and 131 patients.

Surgery

Surgery followed radiotherapy in 506 patients after a median of four days (quartiles 3-5 days).

Fourteen patients did not undergo surgery due to refusal (3), deterioration (7), and unknown cause (4). Peroperatively, metastatic disease such as liver metastasis or peritoneal seeding was found in 16 patients.

Surgery was performed in 28 different departments each treating between one and 28 patients.

The tumour was resected in 490 patients and in 439 cases it was considered curative.

Peroperatively, 52 tumours were fixed even though they appeared mobile at digital examination, but could be resected with a curative intention in 43 patients. In 31 cases, neighbouring organs such as vagina, uterus, prostate, or adnexae were resected. The intraoperative bleeding amounted to a median of 600 ml (quartiles 300-600 ml). An anastomosis was performed in 232 patients. Anastomotic leak occurred in 35 patients and 14 had a reoperation while 21 were treated with drainage only. The 30-day postoperative death rate was 4 % (19 patients with 15 deaths from surgical complications and 4 from unknown cause), and the median length of stay was 12 days after surgery (quartiles 9-20 days).

Pathology

Histopathological exam included TNM classification[15] in 404 patients with ypT1-2 in 109 cases, ypT3 in 253 cases, ypT4 in 26 cases, and missing in 16 cases. Most patients, 211, had ypN0, 95 ypN1, 63 ypN2, 2 ypN3, and in 33 cases data was missing. Twenty-seven patients had distant metastasis, M1. The corresponding distribution of stages is shown in Table 1. The CRM was reported for 450 patients with a value above one millimetre for 389.

Outcome

During a median follow up of 37 months (quartiles 27-38 months), 22 patients developed a local recurrence. Nine of the local recurrences occurred among patients with a fixed tumour at surgery. Kaplan-Meier analysis (Figure 2) taking into account the varying length of follow up resulted in a 3-year local recurrence rate of 4.0 % (95 % CI 2.5-6.5 %). The latest local failure was observed after

52 months and only eight patients were followed for five years or more resulting in a 5 years local failure rate estimate of 11.4 % with a wide 95 % CI of 5.9-21.6 %. Ninety-six patients developed a distant recurrence of which 16 were discovered at the time of surgery. Figure 2 also shows the distant recurrence rate, which at 3 years was 18.7 % (95 % CI 15.4-22.5) and at 5 years 27.3 % (95 % CI 20.7-35.4). Ten patients developed both a local and a distant recurrence. Five, four and one developed the local recurrence before, synchronously, or after the distant recurrence, respectively.

DFS is illustrated in Figure 3. The median DFS was 53 months and the 5-year DFS rate was 40.2 % (95 % CI 27.0-53.1 %). At the end of follow up, 141 patients of the entire study population had died. Eighteen patients died from postoperative complications, 79 patients died of or with cancer, 20 patients of other causes, and in 24 patients the cause of death was unknown. The 5-year overall survival rate was 50.4 % (95 % CI 36.1-63.1 %) (Figure 3). Survival was independent of sex ($p=0.86$) and tumour localisation in the rectum ($p=0.21$), but inversely correlated with age ($p<0.001$).

Univariate analyses of predictors (sex, calendar year of diagnosis, age, tumour localisation, stage, and CRM) for local recurrence revealed that only CRM was a significant predictor ($p<0.001$). For distant recurrence, only stage and CRM were significant predictors ($p=0.005$ and $p<0.001$, respectively). Disease free survival and overall survival were correlated with stage and age ($p<0.001$ in all instances).

Discussion

This study presents the results of short course preoperative radiotherapy in rectal cancer when applied in a population of patients with advanced but resectable tumours. It is based on a validated national database with prospective data collection supplemented with retrospective collection of radiotherapy data. By reflecting daily practice, this study adds important data to the randomised studies by evaluating the quality of the treatment of rectal cancer in Denmark.

Inter-study comparisons of clinical outcomes should be done with caution because of known and unknown differences in the study populations and treatment. Nevertheless, it may provide a rough estimate of potential differences. The main outcome measure for preoperative radiotherapy in rectal cancer is the local recurrence rate.

As the standard procedure during our study period was TME, appropriate studies to compare with are the Dutch TME trial and the British/Canadian CR07/C016 study. These two studies reported local recurrence rates at three years of 2.4 % [10;16] and 4.4 % [11], respectively, for patients having preoperative short course radiotherapy. Correspondingly, the number in our study was 4.0 % at three years. Note that nine local recurrences (41 %) in our study was seen in tumours peroperatively judged by the surgeon to be fixed. Furthermore, only 2 % of the patients had tumours in the more favourable, proximal localisation (10-15 cm above the anal verge) compared to 30% and 14% in the Dutch study and CR07/C016 study, respectively.

Distant metastases remain the major cause of morbidity and mortality in rectal cancer patient and is not likely to be influenced by preoperative radiotherapy. Likewise, a benefit with respect to improved overall survival has not been shown[3;10;11]. However, encouraging population based data suggest a significant improvement in overall survival over time. Overall survival at 5-years was improved from 56 % before the Dutch TME trial to 65 % after and both TME surgery and preoperative radiotherapy seemed to improve survival[17]. In our study, which compares to the post-trial period, the 5-years survival rate was 50.4 % (Figure 3). Survival from rectal cancer is less favourable in Denmark compared to other western countries, but has been rising in recent

years[18]. This underscores the importance of a multidisciplinary approach based on clinical trials for improving the treatment of rectal cancer.

When radiotherapy is considered an option in rectal cancer, preoperative treatment is preferred to postoperative treatment[19] and two major approaches exist for preoperative radiotherapy. Either short course approach as in this study or long term therapy sometimes combined with chemotherapy[20;21]. Whether short or long course preoperative radiation is preferred depends on effect and toxicity. No trials have given the definite answer yet, but several studies highlight some of the advantages and disadvantages of the two approaches. A randomised Polish study compared the rate of sphincter preservation in short course radiotherapy and long course concomitant chemo-radiotherapy and found no difference[22;23]. Other outcomes reported in that study should be interpreted with caution, but the study showed no major clinical relevant difference between the treatments regarding efficacy. The rate of tumour downsizing was higher with long course chemoradiation, but on the other hand this modality was related to more acute toxicity. Even though underpowered to detect small differences, the possible increase in late toxicity in the hypofractionated regime[24], was not seen in that study.

The encouraging results from recent phase III studies[21;25] with increased effect of adding chemotherapy to long course radiation have caused a shift away from short course radiotherapy in many institutions, as it is not combined with chemotherapy. When tumour down sizing is important, i.e. if the tumour is fixed or the mesorectal fascia is threatened; long course chemo-radiotherapy has become the treatment of choice. However, retrospective data suggest that the 5 x 5 Gy regime can cause down sizing and complete response if surgery is delayed[26]. Prospective evaluating of the timing of surgery after 5 x 5 Gy is ongoing in Sweden together with a comparison to long course[27]. It will remain an unanswered question whether the nine patients in our study with a preoperatively fixed tumour and later local failure would have benefitted from delayed surgery or long course radiation.

Most late adverse effects are due to the surgical procedure, but 5 x 5 Gy radiotherapy causes increased bowel related late dysfunction compared to surgery alone[28]. Late adverse effects depend among other parameters on the volume of irradiated normal tissue and whether it is possible to avoid other critical structures such as the rectal sphincter. Earlier studies where larger volumes were irradiated with more simple radiotherapy techniques reported higher rates and more serious late effects than observed with conformal radiotherapy[29-31]. Most of the patients in our study received CT planned conformal radiotherapy aimed at reducing the volume of irradiated normal tissues while retaining a sufficient dose to the target.

The 5 x 5 Gy schedule has many advantages such as tolerability, reduction of local recurrence and low consumption of time and resources both for the patients and the health care system. Many questions regarding basic radiobiology, effect of concomitant chemotherapy, and timing of surgery are still to be answered. Hypofractionation is hampered with historical mistakes that might be accounted for by modern techniques, but special attention should be paid to long term adverse effects[32].

Both short course and long course preoperative radiation are valuable options in the management of rectal cancer[33], and the real challenges in the future will be to avoid over- and under-treatment by improved patient selection and to prevent distant recurrence[34].

In conclusion, this population based study showed a 3-year local failure rate and distant metastasis rate of 4.0 % and 18.7 %, respectively. The 5-year overall survival rate for all patients was 50.4 %. The study confirms data from randomised trials that the short course 5 x 5 Gy regime is a feasible treatment for locally advanced rectal cancer and may be applied in an unselected population.

Conflict of interest statement

None declared.

ACCEPTED MANUSCRIPT

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Legends

Figure 1.

Patient flow and illustration of the study population in a national cohort of Danish patients referred for short course preoperative radiotherapy for rectal cancer in the period 2001-2005.

Figure 2.

Failure rates for local and distant recurrence (n=520).

Figure 3.

Disease free survival and overall survival (n=520).

Table 1.

Patients characteristics. AR=anterior resection, APR=abdominoperineal resection, IRA=ileorectal anastomosis.

Figures

Figure 1.

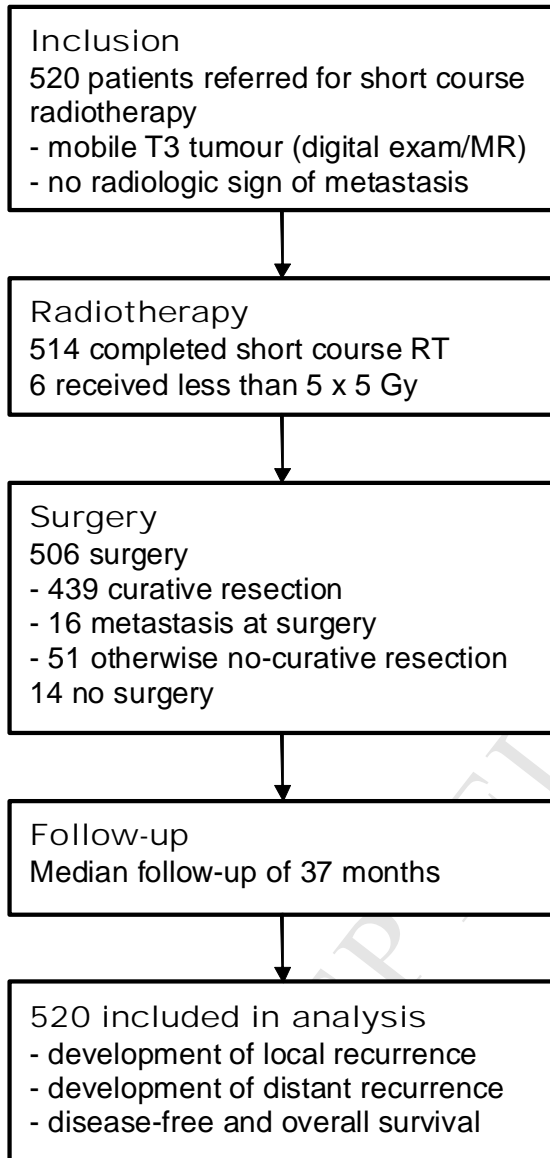


Figure 2.

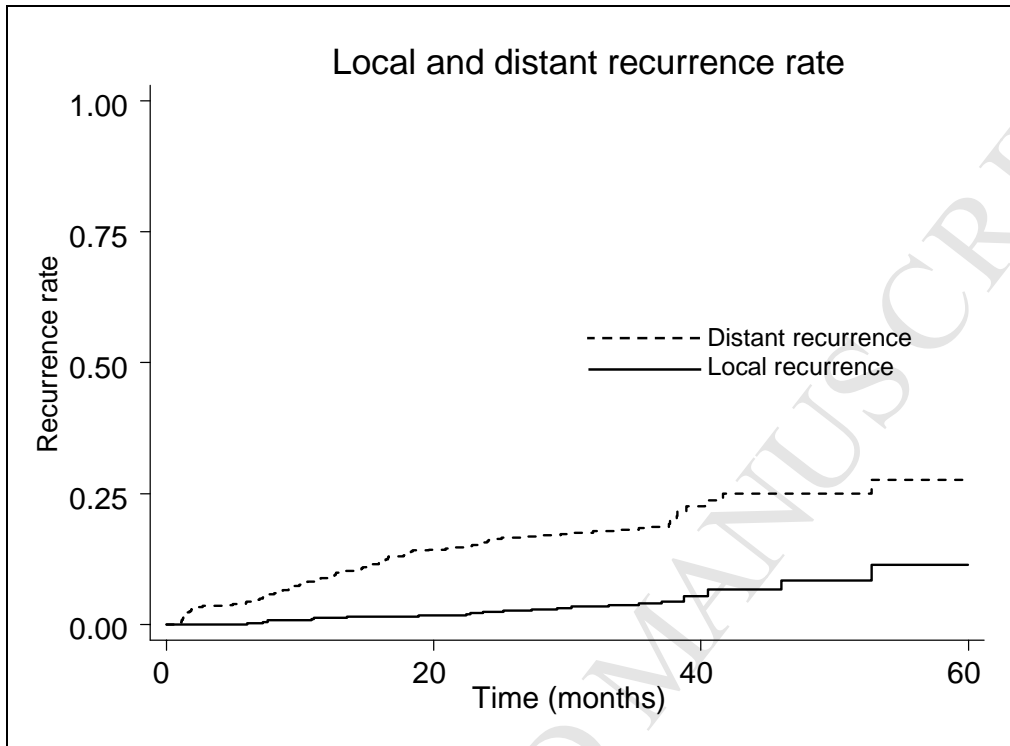
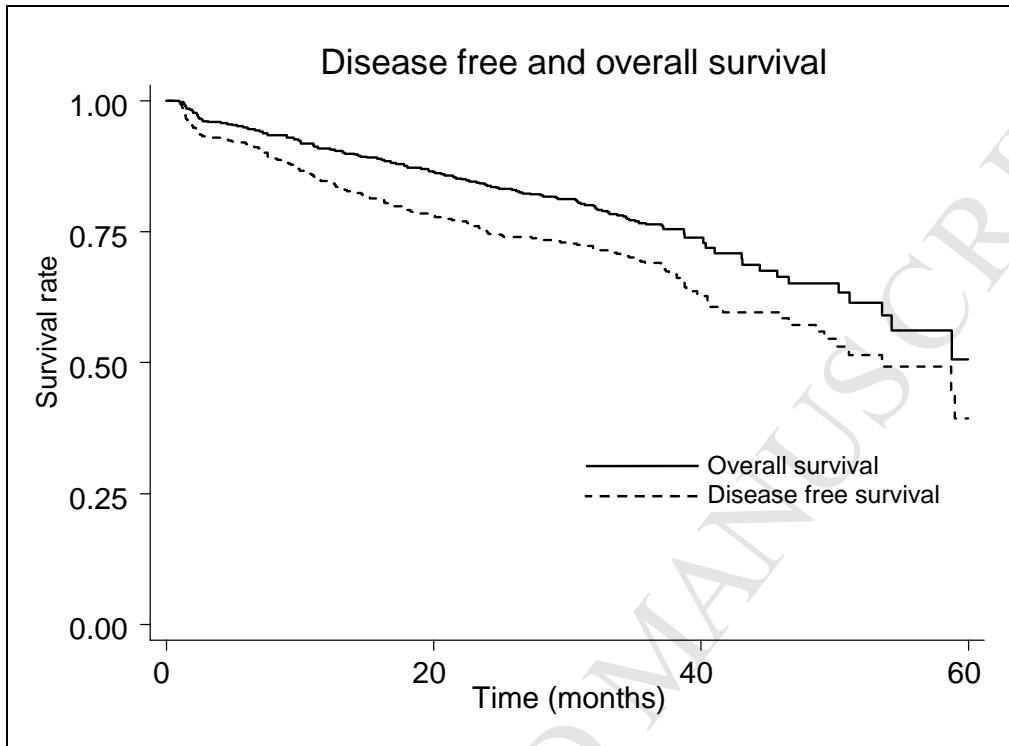


Figure 3.



Tables

Table 1.

Age, years	median range	67 30-91
Sex	female male	187(33 %) 333 (67 %)
Localisation, n (%)	0-5 cm 6-10 cm 11-15 cm missing	235 (47 %) 258 (51 %) 10 (2 %) 17
T stage at preoperative MRI* (n=145), n (%)	T1 T2 T3 T4 TX	0 (0 %) 8 (6 %) 126 (87 %) 8 (6 %) 3 (2 %)
Surgery, n (%)	AR APR Hartmann Colectomy + IRA Procto-colectomi Diversion only No surgery missing	231 (46 %) 187 (37 %) 58 (12 %) 1 (0 %) 3 (1 %) 9 (2 %) 14 (3 %) 17
Fixed tumour peroperatively, n (%)	yes no no surgery	52 (10%) 454 (87 %) 14 (3 %)
Curative resection, n (%)	yes no	439 (84 %) 81 (16 %)
TNM stage* (n=404), n (%)	I II III IV missing	82 (21 %) 136 (35 %) 144 (37 %) 27 (7 %) 13
CRM*	> 1 mm 0-1 mm missing	389 61 70
Dead within 30 days, n (%)	yes no no surgery	19 (4 %) 487 (93 %) 14 (3 %)

* adopted during the study period.