Does adjuvant chemotherapy compared to surveillance improve recurrence free and overall survival on stage 3 rectal cancer patients

The definitive treatment for locally advance rectal cancer is neoadjuvant radiotherapy or chemoradiotherapy followed surgical Total Mesorectal Excision (TME). The duration of radiotherapy is guided by a radiological assessment of Circumferential Resection Margin (CRM) involvement using magnetic resonance imaging (MRI). Short course radiotherapy (RT) with 25 Gray in 5 fractions over 5 days is recommended if the CRM is clear. Long course chemoradiotherapy (CRT) typically of 45-50 Gray in 25-28 fractions, with either oral capecitabine or infusional 5-fluorouracil (5-FU), is recommended if the CRM is threatened or involved.[[1]](#endnote-1)

While the combination of neoadjuvant RT/CRT and TME has reduced local recurrence, it has not reduced metastatic recurrence, which occurs in up to 30% of patients with localised disease within 10 years of radical treatment.[[2]](#endnote-2) Many patients who undergo neoadjuvant RT/CRT are also offered adjuvant chemotherapy following surgical resection with the aim or targeting micrometastatic disease. However, there is a lack of robust evidence for the benefit of adjuvant chemotherapy in this context and international guidelines and practices vary.

The randomised control trials and systematic review that have evaluated the benefit of adjuvant 5-FU based chemotherapy in patients with stage II and III rectal cancer who had undergone either RT/CRT and TME found no difference in overall survival (OS), disease-free survival (DFS) or distant recurrence.[[3]](#endnote-3),[[4]](#endnote-4),[[5]](#endnote-5),[[6]](#endnote-6) Subsequent randomised control trials evaluating the role of oxaliplatin-based chemotherapy regime showed conflicting results for a benefit in DFS.[[7]](#endnote-7),[[8]](#endnote-8) A meta-analysis of four of these studies found a significant difference in DFS but no difference in OS over a 3 year period. [[9]](#endnote-9) However, the authors advised interpreting the results with caution, citing the limitations and heterogeneity of the trials included.

Perhaps unsurprisingly, clinical guidelines on the role of adjuvant chemotherapy in rectal cancer following RT/CRT and TME differ. The National Comprehensive Cancer Network (NCCN) recommend oxaliplatin-based adjuvant chemotherapy in clinical stage II and III rectal cancer.[[10]](#endnote-10) The European Society of Medical Oncology (ESMO) non-prescriptively state that it is reasonable to consider adjuvant chemotherapy in rectal cancer patients with pathological stage III and high-risk stage II disease.[[11]](#endnote-11) They acknowledge the lack of evidence and unlikely benefit to OS and emphasise the importance of individualised decision-making.

In practice, the use of adjuvant chemotherapy in this context varies widely across the UK and comes down to local policies and individual clinician decision-making. The lack of consensus and divergent approaches make it an area of particular clinical interest. Further evaluation of local outcomes would inform future practice and contribute to the ongoing wider debate. The purpose of this retrospective analysis was therefore to examine real world data of patients with stage III rectal cancer in Kent over a 5-year period who have been treated with RT/CRT and TME and compare outcomes for those who have undergone adjuvant chemotherapy with those on surveillance.

**Materials and Methods**

This was a retrospective multi centre analysis which involved review of case records, imaging reports, multidisciplinary team meeting records and other electronic patient records. Cases were taken from oncology departments across Kent, England, UK which included (1) Maidstone Hospital, (2) Medway Maritime Hospital, (4) Darent Valley Hospital and (4) East Kent Hospitals (Queen Elizabeth the Queen Mother Hospital, Canterbury Hospital and William Harvey Hospital). The specific data collected included patient demographics, clinicopathological and radiological features at diagnosis. Other clinical data included surveillance imaging and outcome data to evaluate treatment outcomes in these treatment groups.

We retrospectively evaluated the records of patients with radically resected rectal cancer who had chemoradiotherapy (CRT), were downstaged, and then offered either surveillance (S) or adjuvant chemotherapy (AC) based on clinician’s judgement.

The data analysed included: cancer grade (1-3); stage (stage 2-3); presence of extramural vascular invasion (EMVI); whether the CRM was negative, threatened or involved; distance from the anal verge (< or >5cm ); post-radiotherapy and post-operative staging; resection margin status (R0,1 or 2); time between surgery and adjuvant radiotherapy; and the PFS (time to until local recurrence or distant metastasis) and overall survival (OS) at year 1 and 2 post treatment.

Normality was determined with the Kolmogorov Smirnov test. ANOVA was used to compare the differences between the three groups and Kaplan-Meier analyses to assess survival differences. Cox proportional hazard regression model was used to assess the impact of independent variables on survival outcomes. Mann Whitney, Chi Squared test, T test and Fishers exact test were also used where appropriate dependent upon data type. A p-value of <0.05 was regarded as statistically significant.

**Results**

172 patients with stage 3 rectal cancer that was down-staged following neoadjuvant chemoradiotherapy and total mesorectal excision were identified and included in this study. 98 patients (57%) received adjuvant chemotherapy and the remaining 75 patients (43%) did not receive adjuvant therapy. Patient demographics, tumour characteristics, and outcomes following neoadjuvant and surgical therapy are displayed in Table 1.

Patients who received adjuvant chemotherapy were younger than those who did not (median age 63 vs 70 years, p <0.001). Patients who received adjuvant chemotherapy had higher rates of circumferential resection margin involvement (88 vs 70%, p=0.01), higher rates of extramural venous invasion (73 vs 40%, p<0.001), and lower R0 resection rates (86 vs 95%, p=0.059). They had a higher tumour stage following radiotherapy (p=0.007; Stage 4: 1.3 vs 0%, Stage 3: 44 vs 31%, Stage 2: 43 vs 33%, Stage 1: 9.3 vs 33%, Stage 0: 2.7 vs 3.4%) and higher tumour stage post surgery (p<0.001; Stage 3: 33 vs 12%, Stage 2: 44 vs 25%, Stage 1: 15 vs 48%, Stage 0: 8.3 vs 15%. There was no significant difference in baseline histological grade (p=0.9), tumour regression grade (p=0.85), tumour distance from the anal verge (p=0.14), or time between radiotherapy and surgery (p=0.19).

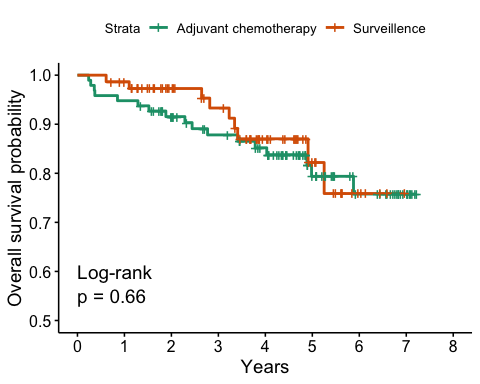
Disease recurrence was more frequent in the patients who had received adjuvant chemotherapy (24 vs 11%, p=0.026) with a trend towards a shortened recurrence free survival (p = 0.05) (Figure 1). There was no difference in overall survival between the groups (p=0.66) (Figure 2).

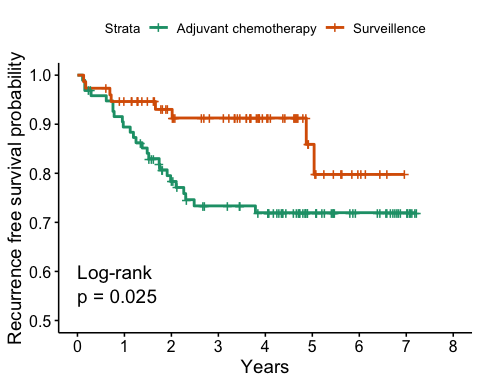
Independent risk factors for survival were identified with multivariable analysis of patient demographics, tumour characteristics, and outcomes following neoadjuvant and surgical therapy (Table 2). After adjusting for confounders, administration of adjuvant chemotherapy was no long significantly associated with worse DFS compared with surveillance (HR 0.25, C.I. 0.05 to 1.35, p=0.11). None of the variables studied were associated with risk of recurrence. On the other hand, incomplete resection the only significant predictor for poorer overall survival (R1 vs R0: HR 5.81, C.I. 2.09-16.2, p<0.001). Increased time between radiotherapy and surgery was also associated with poorer survival (HR 1.02, p=0.006). (Were any of the variables significant in univariate but not multivariate analysis?)

Table 1. Patient characteristics

| Characteristic | N | Adjuvant chemotherapy | Surveillance | p-value1 |
| --- | --- | --- | --- | --- |
| **n** |  | 98 | 75 |  |
| **Age at diagnosis, Median (IQR)** | 172 | 63 (55 – 70) | 70 (62 – 78) | **<0.001** |
| **CRM, n (%)** | 145 |  |  | **0.010** |
| pos |  | 71 (88) | 45 (70) |  |
| neg |  | 10 (12) | 19 (30) |  |
| **R status, n (%)** | 164 |  |  | 0.059 |
| R0 |  | 77 (86) | 70 (95) |  |
| R1 |  | 13 (14) | 4 (5.4) |  |
| **TRG status, n (%)** | 79 |  |  | 0.92 |
| TRG3 |  | 12 (27) | 11 (32) |  |
| TRG0 |  | 0 (0) | 1 (2.9) |  |
| TRG1 |  | 5 (11) | 3 (8.8) |  |
| TRG2 |  | 24 (53) | 16 (47) |  |
| TRG4 |  | 2 (4.4) | 2 (5.9) |  |
| TRG5 |  | 2 (4.4) | 1 (2.9) |  |
| **Distance from anal verge, Median (IQR)** | 148 | 3.00 (1.00 – 6.00) | 4.00 (2.00 – 6.00) | 0.14 |
| **EMVI, n (%)** | 119 |  |  | **<0.001** |
| neg |  | 18 (27) | 31 (60) |  |
| pos |  | 49 (73) | 21 (40) |  |
| **Time between radiotherapy and surgery, Median (IQR)** | 170 | 86 (77 – 99) | 89 (77 – 118) | 0.19 |
| **Baseline histological grade, n (%)** | 163 |  |  | 0.85 |
| G3 |  | 12 (13) | 10 (14) |  |
| G2 |  | 80 (87) | 61 (86) |  |
| **Cancer staging post surgery, n (%)** | 169 |  |  | **<0.001** |
| stage\_3 |  | 32 (33) | 9 (12) |  |
| stage\_0 |  | 8 (8.3) | 11 (15) |  |
| stage\_1 |  | 14 (15) | 35 (48) |  |
| stage\_2 |  | 42 (44) | 18 (25) |  |
| **Cancer staging post radiotherapy, n (%)** | 133 |  |  | **0.007** |
| stage\_3 |  | 33 (44) | 18 (31) |  |
| stage\_0 |  | 2 (2.7) | 2 (3.4) |  |
| stage\_1 |  | 7 (9.3) | 19 (33) |  |
| stage\_2 |  | 32 (43) | 19 (33) |  |
| stage\_4 |  | 1 (1.3) | 0 (0) |  |
| 1Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test | | | | |

# Figure 1. Overall Survival (top) & Recurrence-free survival (bottom)











## Table 4. Multivariate analysis of Risk factors for overall survival

TRG status, EMVI and cancer stage post radiotherapy were observed to display more than 20% missingness and thus excluded from multivariate analysis. Note data was pre-processed such that within each categorical variables, groups with very small number of samples (<2) were removed.







| Characteristic | N | HR (95% CI)1 | p-value |
| --- | --- | --- | --- |
| Age at diagnosis | 92 | 0.99 (0.95 to 1.03) | 0.62 |
| CRM | 92 |  |  |
| pos |  | — |  |
| neg |  | 0.21 (0.002 to 1.84) | **0.19** |
| R status | 92 |  |  |
| R0 |  | — |  |
| R1 |  | 5.81 (2.09 to 16.2) | **<0.001** |
| Distance from anal verge | 92 | 1.08 (0.90 to 1.30) | 0.41 |
| adjuvant\_management | 92 |  |  |
| adjuvant\_chemo |  | — |  |
| surveillence |  | 0.94 (0.32 to 2.73) | 0.91 |
| Time between radiotherapy and surgery | 92 | 1.00 (0.99 to 1.01) | 0.61 |
| Baseline histological grade | 92 |  |  |
| G3 |  | — |  |
| G2 |  | 0.74 (0.21 to 2.64) | 0.64 |
| Cancer staging post surgery | 92 |  |  |
| stage\_3 |  | — |  |
| stage\_0 |  | 1.22 (0.28 to 5.40) | 0.79 |
| stage\_1 |  | 0.26 (0.03 to 1.94) | 0.19 |
| stage\_2 |  | 0.82 (0.30 to 2.22) | 0.70 |
| Cancer staging post radiotherapy | 92 |  |  |
| stage\_3 |  | — |  |
| stage\_1 |  | 2.68 (0.76 to 9.51) | 0.13 |
| stage\_2 |  | 1.21 (0.44 to 3.35) | 0.72 |
| 1HR = Hazard Ratio, CI = Confidence Interval | | | |

### Table 5. Multivariate analysis of Risk factors for recurrence- survival

This time, no significant difference was found in overall survival between surveillance and adjuvant chemotherapy group.

| Characteristic | N | HR (95% CI)1 | p-value |
| --- | --- | --- | --- |
| Age at diagnosis | 92 | 1.02 (0.96 to 1.08) | 0.58 |
| CRM | 92 |  |  |
| pos |  | — |  |
| neg |  | 0.49 (0.05 to 4.57) | 0.53 |
| R status | 92 |  |  |
| R0 |  | — |  |
| R1 |  | 4.41 (0.73 to 26.7) | 0.11 |
| Distance from anal verge | 92 | 1.07 (0.88 to 1.31) | 0.48 |
| adjuvant\_management | 92 |  |  |
| adjuvant\_chemo |  | — |  |
| surveillence |  | 0.25 (0.05 to 1.35) | 0.11 |
| Time between radiotherapy and surgery | 92 | 1.00 (0.99 to 1.01) | 0.72 |
| Baseline histological grade | 92 |  |  |
| G3 |  | — |  |
| G2 |  | 0.52 (0.06 to 4.43) | 0.55 |
| Cancer staging post surgery | 92 |  |  |
| stage\_3 |  | — |  |
| stage\_0 |  | 1.09 (0.08 to 14.8) | 0.95 |
| stage\_1 |  | 1.48 (0.21 to 10.4) | 0.69 |
| stage\_2 |  | 2.29 (0.42 to 12.5) | 0.34 |
| Cancer staging post radiotherapy | 92 |  |  |
| stage\_3 |  | — |  |
| stage\_1 |  | 2.35 (0.45 to 12.3) | 0.31 |
| stage\_2 |  | 0.45 (0.11 to 1.81) | 0.26 |
| 1HR = Hazard Ratio, CI = Confidence Interval | | | |

# Supplementary Figure 1. Missing data pattern

TRG status, EMVI and cancer stage post radiotherapy were observed to display more than 20% missingness and thus excluded from subsequent multivariate analysis.

Chart, treemap chart, box and whisker chart

Description automatically generated

## Supplementary Table 1. Univariate Analysis of Risk factors for overall survival

| Characteristic | N | HR (95% CI)1 | p-value |
| --- | --- | --- | --- |
| Age at diagnosis | 170 | 1.00 (0.96 to 1.03) | 0.83 |
| CRM | 143 |  |  |
| pos |  | — |  |
| neg |  | 0.13 (0.02 to 0.99) | **0.049** |
| R status | 164 |  |  |
| R0 |  | — |  |
| R1 |  | 6.68 (2.91 to 15.3) | **<0.001** |
| TRG status | 79 |  |  |
| TRG3 |  | — |  |
| TRG0 |  | 0.00 (0.00 to Inf) | >0.99 |
| TRG1 |  | 2.07 (0.37 to 11.4) | 0.41 |
| TRG2 |  | 0.76 (0.20 to 2.83) | 0.68 |
| TRG4 |  | 0.00 (0.00 to Inf) | >0.99 |
| TRG5 |  | 0.00 (0.00 to Inf) | >0.99 |
| Distance from anal verge | 148 | 1.05 (0.90 to 1.22) | 0.53 |
| EMVI | 118 |  |  |
| neg |  | — |  |
| pos |  | 1.19 (0.47 to 3.02) | 0.72 |
| adjuvant\_management | 171 |  |  |
| adjuvant\_chemo |  | — |  |
| surveillence |  | 0.84 (0.37 to 1.88) | 0.67 |
| Time between radiotherapy and surgery | 170 | 1.00 (1.00 to 1.01) | 0.80 |
| Baseline histological grade | 161 |  |  |
| G3 |  | — |  |
| G2 |  | 0.41 (0.17 to 0.99) | **0.048** |
| Cancer staging post surgery | 169 |  |  |
| stage\_3 |  | — |  |
| stage\_0 |  | 0.48 (0.10 to 2.18) | 0.34 |
| stage\_1 |  | 0.18 (0.04 to 0.84) | **0.029** |
| stage\_2 |  | 0.95 (0.41 to 2.20) | 0.91 |
| Cancer staging post radiotherapy | 133 |  |  |
| stage\_3 |  | — |  |
| stage\_0 |  | 1.91 (0.23 to 15.5) | 0.55 |
| stage\_1 |  | 1.36 (0.40 to 4.66) | 0.63 |
| stage\_2 |  | 1.28 (0.46 to 3.53) | 0.63 |
| stage\_4 |  | 0.00 (0.00 to Inf) | >0.99 |
| 1HR = Hazard Ratio, CI = Confidence Interval | | | |

## Supplementary Table 2. Univariate Analysis of Risk factors for recurrence-free survival

| Characteristic | N | HR (95% CI)1 | p-value |
| --- | --- | --- | --- |
| Age at diagnosis | 170 | 0.98 (0.95 to 1.01) | 0.18 |
| CRM | 143 |  |  |
| pos |  | — |  |
| neg |  | 0.38 (0.11 to 1.26) | 0.11 |
| R status | 164 |  |  |
| R0 |  | — |  |
| R1 |  | 6.83 (3.14 to 14.9) | **<0.001** |
| TRG status | 79 |  |  |
| TRG3 |  | — |  |
| TRG0 |  | 0.00 (0.00 to Inf) | >0.99 |
| TRG1 |  | 5.13 (1.14 to 23.0) | **0.033** |
| TRG2 |  | 1.38 (0.36 to 5.33) | 0.64 |
| TRG4 |  | 0.00 (0.00 to Inf) | >0.99 |
| TRG5 |  | 0.00 (0.00 to Inf) | >0.99 |
| Distance from anal verge | 148 | 1.09 (0.95 to 1.25) | 0.21 |
| EMVI | 118 |  |  |
| neg |  | — |  |
| pos |  | 1.64 (0.63 to 4.28) | 0.31 |
| adjuvant\_management | 171 |  |  |
| adjuvant\_chemo |  | — |  |
| surveillence |  | 0.41 (0.19 to 0.92) | **0.030** |
| Time between radiotherapy and surgery | 170 | 1.00 (1.00 to 1.00) | 0.94 |
| Baseline histological grade | 161 |  |  |
| G3 |  | — |  |
| G2 |  | 0.59 (0.24 to 1.44) | 0.24 |
| Cancer staging post surgery | 169 |  |  |
| stage\_3 |  | — |  |
| stage\_0 |  | 0.20 (0.03 to 1.59) | 0.13 |
| stage\_1 |  | 0.57 (0.22 to 1.51) | 0.26 |
| stage\_2 |  | 1.12 (0.50 to 2.50) | 0.78 |
| Cancer staging post radiotherapy | 133 |  |  |
| stage\_3 |  | — |  |
| stage\_0 |  | 1.08 (0.14 to 8.30) | 0.94 |
| stage\_1 |  | 0.86 (0.30 to 2.44) | 0.77 |
| stage\_2 |  | 0.69 (0.28 to 1.69) | 0.42 |
| stage\_4 |  | 0.00 (0.00 to Inf) | >0.99 |
| 1HR = Hazard Ratio, CI = Confidence Interval | | | |

**Discussion- TBC**

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