Patients with rectal cancer receiving adjuvant chemotherapy have an increased survival: a population-based longitudinal study

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Background: The aim of this study was to investigate whether or not the use of adjuvant chemotherapy in stage III rectal cancer varies between regions and over time, and if this has had an effect on survival rates.

Patients and methods: Patients from the Uppsala/Örebro region below 75 years-of-age, operated 1995–2002 and registered in the Swedish Rectal Cancer Register, were monitored between 1995 and September 2008. A multivariate Cox proportional hazard regression model was used for analysis. Overall survival was described using the Kaplan–Meier method.

Results: Four hundred and thirty-six patients with stage III rectal cancer were included. Adjuvant chemotherapy was given to 42% of the patients (proportions varying from 13% to 77% among counties), and there were substantial variations between counties.

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increases over time. The 5-year overall survival was 65.8% [95% confidence interval (CI) 50–84] for patients having adjuvant chemotherapy compared with 45.6% [95% CI 39–52] for patients not treated with chemotherapy. The multivariate hazard ratio for death was 0.65 (95% CI 0.5–0.8) for patients treated with adjuvant chemotherapy.

**Conclusions:** The use of adjuvant chemotherapy for rectal cancer has increased, but varies considerably between hospitals/counties. In this cohort, those having adjuvant chemotherapy had a longer overall survival.

**Key words:** adjuvant, chemotherapy, rectal cancer

**introduction**

Adjuvant chemotherapy increases survival in stage III colon cancer patients [1, 2]. Already in 1990 and 1991 the ‘National Institute of Health (NIH) Consensus Conference’ and the National Cancer Institute (NIH) [3, 4] recommended that adjuvant chemotherapy should be standard treatment of rectal cancer patients based upon the results of a few small trials in the USA [5–7]. These conclusions have been criticised since the evidence was considered not strong enough to support the recommendations. The trials behind the recommendations were all under powered and patients were included before the total mesorectal excision (TME) technique was introduced, and complementary radiotherapy was, if given, delivered postoperatively.

Nowadays, radiotherapy is frequently used as preoperative treatment in a selected patient group. Several randomised trials have shown that short-course preoperative 5 × 5 Gy reduces local recurrence rates [8–11]. Long-course chemoradiotherapy probably results in the same gain [12, 13]. Improved overall survival was only seen in the pre-TME era, although a cancer-specific survival benefit has been shown after longer follow-up in stage III patients [14]. Based on these results, preoperative irradiation is now considered the gold standard if preoperative staging indicates that the patient is at sufficient risk for developing a local recurrence [15]. The adjuvant chemotherapy mostly used in the early rectal cancer studies was 5-fluorouracil (5-FU) in combination with methyl-CCNU (semustine, Santa Cruz Biotechnology, USA), which is no longer used. A combination of 5-FU with the biomodulator leucovorin, or capecitabine [16], is now considered baseline treatment of colorectal cancer [17]. Based on the evidence of efficacy in patients with stage III colon cancer [18, 19], combinations of 5-FU and oxaliplatin have also replaced the use of 5-FU alone as treatment in rectal cancer patients.

Three recent trials have explored the use of concomitant chemotherapy and radiotherapy in more advanced cases of rectal cancer, and all three demonstrated a reduction in the local recurrence rate [20–22]. A survival gain was seen in the trial including the most locally advanced cases [22]. In one of the other two trials [20], a subgroup analysis showed a survival benefit in the good-prognosis patient group, presumed to have had a down-staging (ypT0–2) [23]. A pooled analysis of five trials reported that patients who received adjuvant chemotherapy had better long-term survival than those who did not [24]. However, despite many published trials, none has yet been able to reveal an overall survival benefit, and the value of adjuvant chemotherapy for patients with stage III rectal cancer is still not clear [25, 26].

The aim of this study was to explore how the use of adjuvant chemotherapy in the routine management of stage III rectal cancer varies between regions and over time in a defined Swedish population, and to see if this has had an effect on overall survival and recurrence.

**methods**

**patients**

All 2400 patients from the Uppsala/Örebro Regional Oncological Centre (ROC), and registered 1995–2002 in the Swedish Rectal Cancer Register, were traced. The completeness of the follow-up of rectal cancer patients diagnosed between 1995 and 2002 is almost 100%. The patients were followed up from 1995 until September 2008.

It was not possible to determine from the register whether the patients were operated with TME throughout this period, although Swedish guidelines from 1995 recommended TME surgery, indicating that the majority had a TME procedure. Tumours were defined as low if they were located 0–5 cm from the anal verge; middle 5–10 cm, and high if they were located 10–15 cm from the verge.

Postoperative adjuvant chemotherapy, if given, consisted of 5-FU combined with leucovorin. The first cycle of 5-FU plus leucovorin commenced a maximum of 8 weeks following surgery and was given either as the Nordic regimen [27] or the bolus/infusion de Gramont Lv5FU2 regimen [28]. Both drugs were administered for 2 consecutive days every 14 days for a total of 12 courses. The dose of 5-FU for subsequent courses was reduced if substantial toxicity occurred.

**outcome measures**

The primary outcome measure was overall survival. Overall survival was defined as the time from operation to death from any cause. Secondary outcomes were the local recurrence and appearance of distant metastases. Local recurrence was confirmed by biopsy sample or positive imaging. It was defined as recurrent disease in the pelvis. Distant metastases were defined as recurrent disease outside the lesser pelvis. Date of first site was computed, and disease-free survival was defined as time to first event (local recurrence, distant metastasis or death).

**statistical analyses**

SPSS (IBM, NY, USA; Version 17.0) was used for statistical analysis. The \( \chi^2 \) test was applied in cases of dichotomous response parameters and to test differences in proportions between groups. The Kaplan–Meier method was used to describe the cumulative survival rate. Differences in survival between groups were tested for significance by the log-rank method.

Relative risk (RR) analyses were calculated with 95% confidence intervals (CIs). The possible determinants were first tested in a univariate and then in a multivariate Cox proportional hazard regression model where the hazard ratio (HR) was considered as an estimate of the RR. Analyses were performed from a treatment initiation perspective.
ethics

The study was approved by the Ethics Committee of Uppsala University (Dnr 2006/250).

results

Of the 2400 patients operated for rectal cancer between 1995 and 2002, 712 patients had stage III disease. Of these, 447 were younger than 75 years. Eleven were excluded since their medical records could not be retrieved. Thus, a total of 436 were eligible for further analyses (supplementary Figure S1, available at Annals of Oncology online). Fifty-eight percent were males. The median age for the study population was 66.5 (57.6–75.3) years. The median tumour level was 7.9 (3.67–12.1) cm from the anal verge. The types of surgery performed in the study cohort were anterior resection (N = 273, 63%), abdominoperineal resection (N = 134, 31%), Hartmann’s operation (N = 19, 4.4%), and other (N = 1, 0.2%; Table 1). The mean range follow-up time of surviving patients was 9.7 years (5.8–13.7).

The medical records were scrutinised to validate the register data on preoperative radiotherapy and adjuvant chemotherapy. Seventy-six percent (331 of 436) received preoperative radiotherapy. Most of them, or 297 (90%) received 5 × 5 Gy, 18 (5%) received ∼50 Gy in 25–28 doses, 10 (3%) received radiochemotherapy of ∼50 Gy, and 8 (2.5%) did not fulfil the protocol for the planned treatment of 25 or 50 Gy (Table 2).

Adjuvant chemotherapy was given to 42% (185 of 436) of the patients. The median age was 61.8 years for patients who received adjuvant chemotherapy and 68.4 years for those who did not (P < 0.001).

The proportion of patients who received adjuvant chemotherapy in the Uppsala/Orebro region increased from 22% during the first year up to about 50% after 1998, with the exception of 2002 (35%, P < 0.01). The variation among counties was considerable. Södermanland County had the lowest proportion, 13%; whereas, Västmanland had the highest, 77% (Table 3).

The 5-year overall survival was 65.8% for patients receiving adjuvant chemotherapy compared with 45.6% for patients not treated with chemotherapy (P < 0.001).

The survival curves differed significantly as seen in Figure 1. The median survival time was 8.5 years (95% CI 5.9–11.1) for patients receiving adjuvant chemotherapy compared with 4.3 years (95% CI 3.5–5.1) for those who did not.

Univariate and multivariate Cox proportional hazard regression analyses showed a significant influence of adjuvant chemotherapy on survival. The HR for death was 0.65 (95% CI 0.5–0.8) for patients who received adjuvant chemotherapy (Table 4).

Table 1. Operations performed in stage III rectal cancer patients included in the Swedish Rectal Cancer Register of the Uppsala/Orebro Regional Oncological Centre, 1995–2002

<table>
<thead>
<tr>
<th>Operation</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoperineal resection</td>
<td>134 (31)</td>
</tr>
<tr>
<td>Anterior resection</td>
<td>273 (63)</td>
</tr>
<tr>
<td>Hartmann’s operation</td>
<td>19 (4.4)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Missing data on type of operation</td>
<td>10 (2.3)</td>
</tr>
</tbody>
</table>

Table 2. The number of patients with stage III rectal cancer who received preoperative radiotherapy, and/or postoperative adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Yes [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative radiotherapy (total)</td>
<td>331 (76)</td>
</tr>
<tr>
<td>5 × 5 Gy</td>
<td>297 (90)</td>
</tr>
<tr>
<td>50 Gy</td>
<td>18 (5)</td>
</tr>
<tr>
<td>50 Gy + chemotherapy</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Did not fulfil treatment</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Postoperative chemotheraphy only</td>
<td>45 (10)</td>
</tr>
<tr>
<td>Both preoperative radiotherapy and postoperative chemotherapy</td>
<td>139 (32)</td>
</tr>
</tbody>
</table>

Figure 1. Overall survival analysis of patients operated for rectal cancer stage III 1995–2002. They were followed until 2008.
survival is shown in supplementary Figure S2, available at online. The 5-year disease-free survival was 58.8% for patients receiving adjuvant chemotherapy and 41.4% for patients not treated with chemotherapy ($P < 0.001$). Six patients were excluded due to missing data.

Age and site of tumour had an influence, whereas preoperative radiotherapy did not have an independent effect on survival (Table 4). The subgroup analysis showed that high tumours showed a survival benefit from adjuvant chemotherapy (HR 0.54; 95% CI 0.3–0.9, $P < 0.05$), but not tumours located 5–10 cm (HR 0.67; 95% CI 0.4–1.0, $P = 0.07$), or low tumours 0–5 cm (HR 0.97; 95% CI 0.6–1.6, $P = 0.9$). Five patients were excluded due to missing data. The year of surgery did not affect survival (Table 4). The analysis of data with patients divided into age groups showed that age groups 50–60, and over 70 years, treated with adjuvant chemotherapy appeared to gain most benefit (supplementary Table S1, available at Annals of Oncology online).

There were no statistically significant differences in recurrence or metastatic spread between the groups with or without adjuvant chemotherapy (Table 5). Disease-free survival is shown in supplementary Figure S2, available at Annals of Oncology online. The 5-year disease-free survival was 58.8% for patients receiving adjuvant chemotherapy and 41.4% for patients not treated with chemotherapy ($P < 0.001$). Six patients were excluded due to missing data.

### Table 4. Multivariate analysis of factors related to survival in patients <75 years operated for stage III rectal cancer included in the Swedish Rectal Cancer Register of the Uppsala/Orebro Regional Oncological Centre, 1995–2002 ($n = 436$)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>0.98</td>
<td>0.77–1.26</td>
<td>0.84</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03</td>
<td>1.01–1.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>0.99</td>
<td>0.75–1.31</td>
<td>0.98</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>0.65</td>
<td>0.50–0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Year of surgery</td>
<td>0.97</td>
<td>0.92–1.03</td>
<td>0.32</td>
</tr>
<tr>
<td>Site of tumour</td>
<td>0.95</td>
<td>0.92–0.98</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Effect Hazard ratio 95% Confidence interval $P$-value

Age and site of tumour had an influence, whereas preoperative radiotherapy did not have an independent effect on survival (Table 4). The subgroup analysis showed that high tumours showed a survival benefit from adjuvant chemotherapy (HR 0.54; 95% CI 0.3–0.9, $P < 0.05$), but not tumours located 5–10 cm (HR 0.67; 95% CI 0.4–1.0, $P = 0.07$), or low tumours 0–5 cm (HR 0.97; 95% CI 0.6–1.6, $P = 0.9$). Five patients were excluded due to missing data. The year of surgery did not affect survival (Table 4). The analysis of data with patients divided into age groups showed that age groups 50–60, and over 70 years, treated with adjuvant chemotherapy appeared to gain most benefit (supplementary Table S1, available at Annals of Oncology online).

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### Table 5. Local recurrence and distant metastases in stage III rectal cancer patients who received adjuvant chemotherapy or not

<table>
<thead>
<tr>
<th>Local recurrence (No)</th>
<th>Adjuvant chemotherapy</th>
<th>Adjuvant chemotherapy</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>217</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (16%)</td>
<td>15 (9%)</td>
<td>0.069</td>
</tr>
<tr>
<td>Metastatic spread (No)</td>
<td>167</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>85 (51%)</td>
<td>64 (53%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

$\chi^2$ test between groups (Fisher’s exact test).

Discussion

In this survey from a population-based register, patients treated with adjuvant chemotherapy had almost twice as long median overall survival as patients not receiving chemotherapy. A small, non-significant, reduction in the number of patients with local recurrence but not distant metastases was noted. Furthermore, the use of adjuvant chemotherapy in patients operated for stage III rectal cancer differed considerably between the seven counties in the Uppsala/Orebro region. Time-trend analysis showed that the number of patients who received adjuvant chemotherapy increased.

However, one should be careful when interpreting results based on register data. An association between adjuvant chemotherapy and survival is shown, but this does not necessarily mean that there is a causal relationship. One could argue that there was a selection of more healthy patients for adjuvant therapy since the register does not include data on comorbidity. On the other hand, it could be that patients with a more aggressive tumour (poor differentiation, vessel invasion, higher N-stage etc.) were more often offered adjuvant chemotherapy. If so, this could decrease the difference in survival benefit between the groups. The survival benefit of adjuvant chemotherapy appears to be great. This difference is so large that it could hardly be explained by the selection bias alone. Furthermore, patients receiving adjuvant chemotherapy were significantly younger, but this could only to a minor degree explain the survival benefit and was compensated for in the Cox regression analysis.

The strength of the present study is that virtually 100% of all patients operated for rectal cancer are included in the Rectal Cancer Register, assuring that data show the true population-based outcome. Furthermore, the survival data are validated. Thus, the medical records of each patient have been scrutinised to assure that data on adjuvant chemotherapy and recurrence pattern are correct.

The survival rate of colon and rectal cancer increased throughout the study period due, at least in part, to improved diagnostic techniques, which has lead to a more correct staging, and also due to improvement in surgical techniques which might indicate a stage migration. However, it is not likely that this phenomenon is only seen among those having chemotherapy. The local recurrence rate has decreased as an effect of the TME technique [29] and preoperative radiotherapy [10]. It is possible that the evolution of novel chemotherapy regimens has also contributed.

Early studies, published in the late 80s and early 90s on adjuvant treatment of rectal cancer patients, evaluated postoperative radiotherapy with or without chemotherapy. A survival benefit was shown in the GITSG [5], NSABP [6], and NCCTG trials [7]. More recent studies have focused on preoperative (neo-adjuvant) therapy, in a setting of combined radio- and chemotherapy [24]. Two randomised trials in intermediate stage rectal cancer compared the use of preoperative radiochemotherapy with or without postoperative chemotherapy; the FFCD 9203 study [21] and the EORTC 22921 trial [20]. No significant difference was seen in overall survival in these two studies. Although the EORTC 22921 trial included 1011 patients, each group contained relatively small numbers of patients; which could explain the difficulty in showing a difference between the groups in terms of survival. In the two trials, only 73% and 43% respectively received the planned postoperative chemotherapy. This might also contribute to the negative results.

Japanese studies have shown a survival benefit of adjuvant chemotherapy in patients with rectal cancer [30, 31]. However, these data are difficult to extrapolate to the Western population since overall management is different.
To our knowledge, the only large European study that has shown a survival benefit from adjuvant chemotherapy in rectal cancer patients was published by the QUASAR group [32]. They mainly enrolled patients with stage II colorectal cancer (node negative) disease.

The lack of effect of radiotherapy on survival in the present study is somewhat surprising, since many studies have shown an effect on both recurrence and overall survival [9, 10, 14]. An explanation might be that the number of patients in this study is too small to reveal a significant difference.

There was no difference in local recurrence or distant metastases rates between the groups, indicating that reasons other than chemotherapy could have contributed to the survival benefit observed. In line with our findings, Kusters et al. [33] have shown that adjuvant chemotherapy prevents local recurrence rather than distant metastases, for advanced rectal cancer. In this study, short-course radiotherapy was given preoperatively and chemotherapy postoperatively. Many trials have compared neo-adjuvant radiochemotherapy treatment with adjuvant treatment, and these have shown an improved disease-free survival with preoperatively administered treatment [24, 25, 34]. In the EORTC 22921 trial, the authors concluded that chemotherapy, regardless of whether it is administered before or after surgery, confers a substantial benefit with respect to local recurrence [17]. In our study, there was a numeric difference, but the total number of patients included was presumably too small to show a statistically significant difference. Only a minor proportion received preoperative radiochemotherapy (3%).

The great variation among counties in the Uppsala/Orebro region regarding the frequency of patients receiving adjuvant chemotherapy is striking. It is presumably due to the lack of consensus in treatment recommendations. In Sweden, it is recommended that adjuvant chemotherapy should only be given to rectal cancer patients included in trials. However, in practice, local traditions decide whether or not adjuvant treatment is given.

The proportion of patients who receive adjuvant chemotherapy has slowly increased over the years. Data from the Uppsala/Orebro register between 2003 and 2010 show that 47% of stage III rectal cancer patients received adjuvant treatment, so the increase has not been dramatic. The great variation among counties remains (11–72%, ROC 2011).

In conclusion, the use of adjuvant chemotherapy in stage III rectal cancer has slowly increased with time but varies considerably among counties (and thus hospitals). Results indicate that adjuvant chemotherapy increases overall survival in rectal cancer patients by almost 50%. Further studies are required to see if this effect of adjuvant chemotherapy in prolonging survival in stage III rectal cancer patients remains when all relevant confounders are excluded.

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disclosure

The authors have declared no conflicts of interest.

references

Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: results from a randomized controlled trial

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¹Division of Upper Gastrointestinal Surgery, Department of Surgery; ²Department of Clinical Oncology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong SAR, China

Background: The aim of this study was to report on the 5-year survival outcomes of patients with resectable esophageal carcinoma who were treated by definitive chemoradiotherapy (CRT) or standard esophagectomy.

Patients and methods: Between July 2000 and December 2004, 81 patients with resectable squamous cell carcinoma of the mid- or lower thoracic esophagus were randomized to receive esophagectomy or definitive CRT. The primary outcome was the overall survival and secondary outcomes included disease-free survival, morbidities and mortalities.

Results: Forty-five patients received esophagectomy and 36 patients were treated by definitive CRT. The overall 5-year survival favors CRT but the difference did not reach statistical significance (surgery 29.4% and CRT 50%, \( P = 0.147 \)). A trend to improved 5-year survival was observed for patients suffering from node-positive disease (\( P = 0.061 \)). The 5-year disease-free survival also showed a trend to significance favoring CRT (\( P = 0.068 \)), particularly for patients suffering from node-positive disease (\( P = 0.017 \)). Both the stage of the disease and albumin level were significant predictors to mortality and disease-free survival.

Conclusions: Definitive CRT for squamous esophageal carcinoma resulted in comparable long-term survival to surgery.