Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in Central Sweden

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Editor’s key points

- Epidural analgesia (EDA) may be associated with better long-term outcome after cancer surgery than patient-controlled analgesia (PCA).
- A retrospective analysis of 655 patients with colorectal cancer with a mean follow-up of 2.6 yr.
- EDA was associated with lower mortality in rectal but not in colonic cancer patients.
- Large-scale prospective studies are required to address this important aspect of cancer care.

Background. There is some evidence that epidural analgesia (EDA) reduces tumour recurrence after breast and prostatic cancer surgery. We assessed whether EDA reduces long-term mortality after colorectal cancer surgery.

Methods. All patients having colorectal cancer surgery between January 2004 and January 2008 at Linköping and Örebro were included. Exclusion criteria were: emergency operations, laparoscopic-assisted colorectal resection, and stage 4 cancer. Statistical information was obtained from the Swedish National Register for Deaths. Patients were analysed in two groups: EDA group or patient-controlled analgesia (PCA group) as the primary method of analgesia.

Results. A total of 655 patients could be included. All-cause mortality for colorectal cancer (stages 1–3) was 22.7% (colon: 20%, rectal: 26%) after 1–5 yr of surgery. Multivariate regression analysis identified the following statistically significant factors for death after colon cancer (P<0.05): age (≥72 yr) and cancer stage 3 (compared with stage 1). A similar model for rectal cancer found that age (≥72 yr) and the use of PCA rather than EDA and cancer stages 2 and 3 (compared with stage 1) were associated with a higher risk for death. No significant risk of death was found for colon cancer when comparing EDA with PCA (P=0.23), but a significantly increased risk of death was seen after rectal cancer when PCA was used compared with EDA (P=0.049) [hazards ratio: 0.52 (0.27–1.00)].

Conclusions. We found a reduction in all-cause mortality after rectal but not colon cancer in patients having EDA compared with PCA technique.

Keywords: analgesia, epidural, patient controlled; complications, death; surgery, colorectal
Methods

We obtained permission from the Regional Ethics Committee in Linköping, Sweden, before the start of this study. All patients undergoing surgery for colorectal cancer from January 2004 to January 2008 at the University Hospitals in Linköping and Örebro were included in the study. Exclusion criteria were: emergency operations, laparoscopic-assisted colonic and rectal resection, and stage 4 cancer (distant metastases) determined at the time of surgery. We verified the list of patients who were finally included in the data analysis through the Regional Cancer Register in Uppsala, for patients operated upon in Örebro, and in Linköping, for patients operated upon in Linköping. These Regional Centres record and maintain information about all patients with cancer. Medical records of all the patients included were obtained and data extracted by research nurses who were not involved with the study or data analysis. Specialist anaesthetists assisted them with data extraction when necessary. Specialist colorectal surgeons were consulted when there was a discrepancy between hospital records and those obtained from the Swedish Cancer Register or when staging of cancer was unclear from the medical records. In addition, we obtained statistical information from the Swedish National Register for Deaths to verify mortality data obtained from hospital records. The quality of the data extracted was verified through random sampling by the authors.

Patients were allocated to two groups, those receiving EDA perioperatively and those receiving i.v. patient-controlled analgesia (PCA group) as the primary method of analgesia. This is discussed in further detail below.

The anaesthetic technique is standardized for patients undergoing surgery for colorectal cancer in both hospitals and consisted of induction with fentanyl and propofol, muscle relaxation using a non-depolarizing agent, and maintenance with inhalation anaesthesia using either sevoflurane or desflurane. Anaesthetic concentrations were maintained in order to achieve adequate depth of anaesthesia using either clinical signs or monitoring of depth of anaesthesia. In patients with an epidural, perioperative analgesia was maintained either with local anaesthetic (LA) and fentanyl (Linköping) or LA alone (Örebro). In patients without an EDA, fentanyl was administered intermittently perioperatively as required for analgesia, and anaesthesia maintained using inhalation anaesthesia as described above. At the end of surgery, muscle relaxation was reversed using a combination of glycopyrrolate and neostigmine and the patients were transferred to the post-anaesthesia care unit where they were observed for 4–6 h until they were fully awake and had minimal pain and subsequently transferred to the general surgical ward. Postoperative EDA analgesia was attained by either a combination of LA with fentanyl (Linköping) or LA and morphine (Örebro). Patients in the PCA group received a patient-controlled i.v. analgesia pump with morphine (1 mg bolus dose, lockout time 6 min) as required. These methods were usually used for 2–5 days after operation until the patient had satisfactory analgesia (VAS <3–4) on oral medication. All patients received paracetamol 1 g, four times a day, which was routine in our hospitals.

In addition to the patient data, the following specific data were extracted from the medical records: preoperative general health status and chronic medications, amount of blood loss and transfusion, staging of cancer in accordance with international standards (stages I–III), and time to death after surgery. Data were collected up to the end of December 2009, ~1 yr after the last patient was recruited into the study. Thus, the follow-up period was 1–5 yr after surgery.

Data were analysed using the t-test for continuous variables, that is, age. Categorical variables were analysed with χ² test. In order to compare survival between the groups, the log-rank test was used. Proportional hazard modelling, Cox’s regression, was used in survival analyses in order to get adjusted estimates. To control for eventual confounding, we also performed a propensity score analysis. The propensity score, defined as the probability of receiving epidural anaesthesia predicted from all baseline variables, was calculated for each patient using logistic regression. The scores were then divided into 20 categories and this categorized score was inserted as a stratifying variable in the Cox regression. Statistical significance level was set to P<0.05. All analyses were done with Stata/MP v11.1 (StataCorp LP, College Station, TX, USA).

Results

From a total of 750 patients operated for colorectal cancer between the periods 2004–8, 655 were included into the study (Fig. 1). The patient and perioperative characteristics for rectal and colon surgery patients are shown in Table 1 and for EDA and PCA in Table 2. The total number of deaths during the period 1–5 yr after colorectal surgery for stages 1–3 cancer was 149 (22.7%) [colon: 72 (20%), rectal: 77 (26%)]. The majority of patients undergoing surgery for colorectal cancer had EDA for perioperative pain management. No differences were found in ASA classification, staging of cancer, number of patients receiving blood transfusions, or in the incidence of co-morbidities between the EDA and PCA groups. The total number of deaths during the period in the EDA group was 129 (23%) and in the PCA group was 20 (22%) (NS) (Table 2).

Multivariate regression analysis for independent risk factors and the hazards ratio for death identified, for colon cancer, age >72 yr (P=0.0001) and cancer staging 3 compared with stage 1 (P=0.013) (Table 3), and for rectal cancer, age >72 yr (P=0.005), use of PCA compared with EDA (P=0.049), and cancer staging 2 and 3 compared with stage 1 (P=0.005 and 0.002, respectively), were independently associated with a higher risk for death after operation (Table 4). After propensity analysis, the only significant factor associated with a higher risk for death was age >72 yr for colon cancer (P<0.0001) and the use of PCA for rectal cancer (P=0.025).

The Kaplan–Meier survival curves for colon and rectal cancer are shown in Figures 2 and 3, respectively, for patients in the EDA and PCA groups. No significant risk of death was

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found for colon cancer when comparing EDA with PCA ($P=0.23$), but a significantly increased risk of death was seen after rectal surgery when PCA was used compared with EDA ($P=0.02$).

**Discussion**

There is increasing evidence in recent years, suggesting that perioperative management may affect patient morbidity and mortality after surgery. The clinical events that may lead to altered immune response after surgical trauma includes: tissue injury, hypotension, blood transfusions, ischaemia, hyperglycaemia, endocrine mediator release, infection, and pain.\(^7\)–\(^{12}\) The main cause of this immune-compromised response is probably related to the neuroendocrine stress exerted through activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal axis (HPA axis). Postoperative pain is also known to activate the HPA axis,\(^1\)–\(^{12}\) which is suppressed by regional anaesthetic techniques. Surgery results in tissue injury, which in turn also leads to the activation of the stress response. The direct immunosuppressive effects of anaesthetics and analgesic agents are now thought, in part, to mediate this clinical situation in cancer patients after surgery.

As a number of perioperative events can affect immune suppression after surgery, there are several factors that need to be considered. The first question is whether mortality after colorectal surgery seen in the present study (22.7%) is comparable with other international studies. In a recent review,\(^{13}\) several studies with short- and long-term data were analysed. In one study with a median follow-up time for open colorectal surgery of 37 months, an overall mortality of 32.2% was found,\(^{14}\) while in another with a 7 yr follow-up found an overall mortality of 25.4%.\(^{15}\) The high overall mortality in the former study, despite a shorter follow-up period, is somewhat surprising and difficult to explain. Our patients, with a mean follow-up time of \(\sim\) 2.6 yr, had an overall mortality of 22.7%. A study of recto-sigmoid cancer surgery with a median follow-up of 4.4 yr found an overall mortality of 23.5%,\(^{16}\) which is similar to our own results, but our patients had a shorter follow-up period. Several confounding factors, which are difficult to control for, may explain some of the differences between these studies, but our mortality is essentially similar to recently published international data.

Differences in patient characteristics, cancer staging, or preoperative co-morbidities between the groups may explain the overall difference in mortality between the groups in our study. Although the number of patients in the PCA group was small, no differences were seen in the age or sex distribution, ASA physical status classification, or cancer staging and therefore it is likely that the patient population is representative and not different in the two groups. In addition, known pre-existing co-morbidities that have been shown to be associated with a higher risk of postoperative death such as cardiac status, previous stroke, diabetes mellitus, and renal insufficiency were similar between the groups. Therefore, none of these factors would appear to account for the differences in mortality seen between the
two groups. It is also important to consider other factors that may affect metastases and long-term mortality after cancer surgery such as blood transfusion, perioperative hypothermia, hyperglycaemia, and hypotension. However, because our study was retrospective, these factors could not be controlled and therefore it is possible that one or several of these factors may have affected the results and consequently future prospective studies should also take into consideration these compounding factors.

The question therefore remains whether anaesthetic technique may play a significant role in determining overall mortality after colorectal surgery. Recently, anaesthesia and anaesthetic techniques have been the focus of a number of studies on cancer-related morbidity and mortality. A comprehensive review of perioperative anaesthetic management of patients with cancer has recently been published. Specifically, the use of regional anaesthetic techniques has been found to be associated with a lower incidence of cancer recurrence after breast surgery and a lower risk for increase in prostate-specific antigen, a marker for metastases, after radical prostatectomy. A recently published study, however, did not find any difference in mortality after radical prostatectomy in patients with epidurals compared with those without, thus questioning previous findings. Studies in patients undergoing colorectal surgery have, however, found mixed results. In one study, where data in patients with colorectal cancer were retrospectively analysed from a prospective, randomized study, the authors found that epidural supplementation was associated with enhanced survival among patients without metastases within 1.46 yr. However, epidural anaesthesia had no effect on survival of patients with metastases. In another study published recently, the authors found that the use of EDA for perioperative pain control during colorectal cancer surgery was not associated with a decreased cancer recurrence, but a potential benefit was observed in older patients. In our study, we found that patients with rectal cancer...
cancer and who received epidural anaesthesia had a significantly lower mortality than those with PCA. However, no significant differences were seen in patients with colon cancer. These findings persisted after propensity analysis matching and therefore our findings confirm previous studies on the protective effects of regional anaesthesia. These observations are interesting and important, in that the type of tumour (colonic or rectal) may also play an important role in determining outcome. Indeed, in the study described above, there were a greater number of patients with rectal cancer in the epidural group, which may have accounted for the lack of differences found when combining data for colorectal cancer surgery. Our results on mortality were similar when we pooled data for colonic and rectal cancer. Thus, the benefit of regional anaesthesia on cancer recurrence may depend on the specific type of tumour (i.e. how aggressive), the age of the patient, and the site of the tumour (colonic or rectal). Older patients, possibly with less aggressive tumours, may have some benefit from epidural anaesthesia. Patients with very aggressive tumours may not benefit to the same extent as those with slow-growing tumours.

The anaesthetic technique used in the two hospitals in Sweden varied slightly but was nevertheless standardized, in that low thoracic epidural anaesthesia was used for colonic surgery and either low thoracic epidural (Linköping) or high lumbar (Örebro) was used for rectal surgery. The latter often involves surgery in the sacral segments, which are difficult to anaesthetize using a low thoracic epidural

<p>| Table 3 | Hazards ratio (95% confidence intervals) and their corresponding P-values using Cox’s multivariable model before and after matching using propensity scores are shown (see the Methods section for further details). PCA, patient-controlled analgesia |
| Factor | Before matching | After matching |</p>
<table>
<thead>
<tr>
<th></th>
<th>Hazards ratio</th>
<th>P-value</th>
<th>Hazards ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural (vs PCA)</td>
<td>1.63 (0.76–3.47)</td>
<td>0.210</td>
<td>0.82 (0.30–2.19)</td>
<td>0.68</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.79 (0.50–1.23)</td>
<td>0.31</td>
<td>1.33 (0.58–3.07)</td>
<td>0.50</td>
</tr>
<tr>
<td>Age (&lt;72 vs &gt;72 yr)</td>
<td>4.05 (2.13–7.71)</td>
<td>&lt;0.0001</td>
<td>8.75 (2.98–25.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage of cancer (1 vs 2)</td>
<td>2.38 (0.95–6.00)</td>
<td>0.065</td>
<td>2.38 (0.28–20.04)</td>
<td>0.43</td>
</tr>
<tr>
<td>Stage of cancer (1 vs 3)</td>
<td>3.77 (1.32–10.80)</td>
<td>0.013</td>
<td>5.18 (0.62–43.64)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

<p>| Table 4 | Hazards ratio (95% confidence intervals) and their corresponding P-values using Cox’s multivariable model before and after matching using propensity scores are shown (see the Methods section for further details). PCA, patient-controlled analgesia |
| Factor | Before matching | After matching |</p>
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Epidural (vs PCA)</td>
<td>0.52 (0.27–1.00)</td>
<td>0.049</td>
<td>0.45 (0.22–0.90)</td>
<td>0.025</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.98 (0.61–1.56)</td>
<td>0.93</td>
<td>0.92 (0.54–1.58)</td>
<td>0.77</td>
</tr>
<tr>
<td>Age (&lt;72 vs &gt;72 yr)</td>
<td>1.93 (1.22–3.04)</td>
<td>0.005</td>
<td>1.68 (0.79–3.57)</td>
<td>0.18</td>
</tr>
<tr>
<td>Stage of cancer (1 vs 2)</td>
<td>2.78 (1.36–5.69)</td>
<td>0.005</td>
<td>1.43 (0.69–2.99)</td>
<td>0.36</td>
</tr>
<tr>
<td>Stage of cancer (1 vs 3)</td>
<td>3.63 (1.59–8.27)</td>
<td>0.002</td>
<td>0.43 (0.13–1.41)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Thus, the benefit of regional anaesthesia on cancer recurrence may depend on the specific type of tumour (i.e. how aggressive), the age of the patient, and the site of the tumour (colonic or rectal). Older patients, possibly with less aggressive tumours, may have some benefit from epidural anaesthesia. Patients with very aggressive tumours may not benefit to the same extent as those with slow-growing tumours.

The anaesthetic technique used in the two hospitals in Sweden varied slightly but was nevertheless standardized, in that low thoracic epidural anaesthesia was used for colonic surgery and either low thoracic epidural (Linköping) or high lumbar (Örebro) was used for rectal surgery. The latter often involves surgery in the sacral segments, which are difficult to anaesthetize using a low thoracic epidural

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Fig 2 The Kaplan–Meier survival curves for patients with colon cancer. PCA, patient-controlled analgesia. X-axis: number of years; Y-axis: proportion surviving.
unless large doses of LAs are used. However, lumbar epidurals may prevent adequate postoperative mobilization and may not provide adequate analgesia for abdominal surgery involving the thoracic segments. Thus, the requirements for good pain relief during rectal surgery are somewhat conflicting and, to the best of our knowledge, studies comparing these two methods are not available. In one small study in patients undergoing oesophagectomy, the authors inserted two epidural catheters in order to reduce the neuroendocrine response to thoracic and abdominal surgery but found no reduction in inflammatory markers. This could be because, during major surgery such as oesophagectomy, the operative trauma is very severe in relation to the protective effect of EDA. Thus, good pain relief may not be adequate to reduce the neuroendocrine response during such major surgery. Finally, it is possible that the type of tumour plays an important role in cancer recurrence and metastases, and even cancer-related and overall mortality. Thus, patients with rectal cancer may be more susceptible to the protective effects of epidurals than those with colon cancer. This needs to be explored in prospective studies randomizing patients to epidurals or PCA.

The most important limitation of this study is that it is retrospective and therefore has all the problems and flaws associated with such studies. Although the surgical technique has remained the same during the time this study was conducted (2004–8) and the perioperative management remains similar in our hospitals, it is possible that some other factors unknown to us today may have influenced outcome. Therefore, prospective, controlled studies need to be performed in order to further reduce these effects through randomization. Another limitation of our study is that the exact cause of death is unknown. Although there is always a death certificate available in Sweden, many of patients died at home and in hospices after a period of illness and therefore it was impossible to confirm the cause of death without an autopsy. This is rarely performed in Sweden in patients with known cancer, unless death was premature or unexpected. Thus, whether death was a direct consequence of cancer or not is impossible to establish. Finally, the number of patients in the PCA group was small. Since the routine for management of these patients in our hospitals has been EDA, some patients may not have received epidurals due to the inability to insert an epidural, patient reluctance to have an epidural or co-morbidities that prevented epidurals from being inserted. Specifically, the latter may have been a cause of increased risk in patients not having epidurals. However, this would not explain the differences seen between colonic and rectal cancers.

In conclusion, we found a significantly lower mortality in patients receiving an epidural for management of postoperative pain and operated for rectal but not colonic cancer, compared with those having patient-controlled morphine analgesia. These differences between rectal and colonic cancer could be due to the type of tumour and the protective effects of an epidural on the neuroendocrine response to surgery. Prospective, randomized studies are needed to answer the exact role of epidurals in preventing cancer-related morbidity and mortality during colorectal surgery.

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Conflict of interest

None declared.
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