Impact of anaesthetic technique on survival in colon cancer: a review of the literature

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Abstract

An oncological surgical resection is the mainstay of treatment for potentially curable colon cancer. At the time of surgery, a large fraction of patients do harbour—although not visibly—minimal residual disease at the time of surgery. The immunosuppression that accompanies surgery may have an effect on disease recurrence and survival. Regional or neuraxial anaesthetic techniques like epidural anaesthesia may suppress immune function less than opioid analgesia, by reducing stress response and significantly reducing exposure to opioids. Consistent with this hypothesis, regional anaesthetic techniques have been associated with lower recurrence rates in breast cancer and prostate cancer. Results for colon cancer, however, are contradictory. In this review of the literature we describe all studies addressing the association of the use of epidural anaesthesia and survival in colon cancer surgery.

Key words: colon cancer; epidural anaesthesia; immunosuppression; survival

Introduction

An oncological surgical resection is the mainstay of treatment for potentially curable colon cancer. However, even in stage I and II colonic cancer, 10–30% will develop recurrence of disease. It is known that, even with the best surgical technique, surgery for cancer is associated with release of tumour cells. Also it is noteworthy that, at the time of surgery, a large fraction of patients do harbour minimal residual disease, although this may not be visible [1].

The idea that surgery itself can promote local cancer recurrence and metastasis is not novel and was described in the 19th century by Velpeau, a French anatomist and surgeon, who noticed that surgical removal of cancer could be associated with the return of the disease and that the operation possibly tended to accelerate tumour growth [2]. Whether this results in recurrence of clinical cancer or metastasis depends largely on the balance between the tumour’s ability to spread and the immunosurveillance of the patient [3]. General anaesthesia and
surgical stress may suppress immunity by directly affecting the immune system or activating the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system [4]. Pre-operative and post-operative opioids may inhibit cellular and humoral immune function in humans, and morphine itself might have a pro-angiogenic effect that promotes tumour growth [5].

Regional or neuraxial anaesthetic techniques may suppress immune function less than opioid analgesia by reducing stress response and significantly reducing exposure to opioids. Consistent with this hypothesis, regional anaesthetic techniques have been associated with lower recurrence rates of breast- and prostate cancer [5, 7]. Results for colon cancer, however, are contradictory [8]. In this review of the literature we describe all studies addressing the association of the use of epidural anaesthesia (EA) and survival in colon cancer surgery.

**Methods**

Relevant studies were sought in the Pubmed database (starting date January 1990 up to June 2014) using search terms as follows: (i) “regional anesthesia” or “regional anaesthesia” or “regional analgesia” or “anaesthetic technique” or “anaesthetic technique”, (ii) “recurrence” or “survival” and (iii) “colorectal cancer” or “colon cancer”. Also, we searched “related citations” and reference lists to identify other articles. Only full papers published in the English language were included. We did not define a minimum of patients to qualify for inclusion in the analysis.

The following information was gathered from the articles: (i) number of included patients, (ii) design of the study, (iii) age, (iv) type of tumour (colon and/or rectal), (v) tumour stage, (vi) follow-up, and (vii) effect of anaesthetic technique on overall survival and cancer recurrence.

**Results**

A total of seven studies was found addressing the impact of EA on survival in colorectal cancer surgery [8–14]. Table 1 shows the characteristics of each of these.

**Prospective studies**

Two of these seven studies were prospective. Christopherson et al. studied long-term survival after resection of colon cancer as a sub-analysis of a prospective randomized study. This Veterans Affairs Co-operative Study No. 345 was initially designed to compare the short-term effect of general anaesthesia with and without epidural anaesthesia and analgesia supplementation in patients undergoing abdominal surgery. Randomization was stratified for type of surgery, age and cardiac risk [13]. The second prospective study was the Multicentre Australian Study of Epidural Anaesthesia and Analgesia in Major Surgery (the MASTER trial), primarily designed to compare adverse outcomes in high-risk patients managed for major surgery with epidural block or alternative analgesic regimens with general anaesthesia in a multicentre randomized trial [14].

Of 446 patients in the MASTER trial, with a mean age of 70–71 years undergoing major abdominal surgery for different types of cancer, 112 underwent surgery because of stage I–III colon cancer. They did not find that the use of EA (n = 58) was associated with improved overall survival [14].

**Disease-free survival**

Of the two prospective studies, only the MASTER trial made a disease-free survival analysis. EA in this study was not associated with improved disease-free survival.

**Retrospective studies**

Five retrospective studies were included in this review. Of all reviewed literature, the largest retrospective study was the Surveillance, Epidemiology, and End Results (SEER)-based study, with a large cohort of 42,151 patients aged 66 years or older and diagnosed with non-metastatic colorectal carcinoma [8]. Holler et al. studied 749 stage I–IV colorectal cancer patients in their large retrospective analyses [12]. The Swedish study of Gupta et al., of a total of 655 colorectal patients with a mean age of 69 (rectal cancer) and 73 (colon cancer) years old, excluded emergency operations, laparoscopically-assisted resections and stage IV in their analysis [11]. Day et al. studied colon and rectal cancer patients with a mean age of 70 (no epidural) and 72 (epidural) years old [9]. All underwent a laparoscopic resection in this study. Patients received either an epidural (n = 107), spinal block (n = 144), or morphine, patient-controlled analgesia (PCA) (n = 173) for their primary post-operative analgesia. Gottschalk et al. analysed stage I–IV patients (n = 509), of which there were 283 with colon cancer, 202 with rectal cancer and 25 ‘others’ [10].

**Overall survival**

Four of the retrospective studies assessed overall survival analysis. The large SEER-based study found a significant association between EA and improved overall survival (HR 0.91 (95% CI 0.87–0.94); P < 0.001) [8]. A significantly better overall survival was also found by Holler et al. in 442 patients who received EA (5-year survival rate with EA was 62%, but only 54% without EA; HR 0.73; P < 0.02) [12]. The positive impact in this study was the most significant in high-risk patients defined as American Association of Anaesthesiologists (ASA) classification 3–4 (P = 0.006) [12]. The Swedish study found a reduction in all-cause mortality in rectal cancer patients (n = 295) who received EA (HR 0.45 (95% CI 0.22–0.90); P = 0.025) [11]. Day et al. found no overall survival difference in their analysis [9].

**Disease-free survival**

In the study by Gottschalk et al. during median follow-up of 1.8 years, EA was associated with a lower cancer recurrence in 248 patients older than 64 years (P = 0.01), but not in younger patients (n = 261) [10]. The SEER-based study adjusted for demographic and clinical covariates and did not find a significant difference in the odds of recurrence between the groups during a mean follow-up of 5 years [8]. Also no recurrence-free survival difference was found in the study by Day et al. [9].

**Discussion**

Because the anticancer immune response is a primary determinant of cancer progression, it is logical to hypothesize that interventions aimed at reducing exposure to immunosuppressive factors would improve patient outcomes after a potentially curative cancer resection. Although EA is theoretically supposed
| First author | Year of publication | Study design | No. of patients | Mean age (years) | Cancer type | Stage | Follow up (years) | OS benefit from EA | RFS benefit from EA |
|--------------|---------------------|--------------|----------------|-----------------|-------------|-------|------------------|-------------------|-------------------|
| Christopherson | 2008 Prospective | 177 EA: 85 No EA: 92 | 69 Colon | I–IV | Up to 10 years | Better OS in stage I–II; No benefit in stage III–IV |
| Gottschalk | 2010 Retrospective | 509 EA: 256 No EA: 253 | 64 Colon (n = 283) Rectal (n = 202) ‘others’ (n = 25) | I–IV | Median, 1.8 | Not assessed |
| Gupta | 2011 Retrospective | 655 EA: 562 No EA: 93 112a EA: 58 No EA: 54 | 73 (colon) 69 (rectal) | I–III Mean, 2.6 | Better OS in rectal cancer |
| Myles | 2011 Prospective | 112a EA: 58 No EA: 54 | 71 (epidural) 70 (no-epidural) | I–III | Up to 12 years | No benefit |
| Day | 2012 Retrospective | 424 EA: 107 (251 including spinal) No EA: 173 | 72 (epidural) 70 (PCA) 70 (spinal) | I–III (?) Not clearly described | Median, 3.1 (epidural) 2.3 (PCA) 1.4 (spinal) | No benefit No benefit |
| Cummings | 2012 Retrospective | 42,151 EA: 9670 No EA: 32,481 | ≥66 Colon (n = 33 390) Rectal (n = 8761) | I–III | Up to 14 years | Better OS |
| Holler | 2013 Retrospective | 749 EA: 442 No EA: 307 | Not available Colon (n = 369) Rectal (n = 380) | I–IV | Up to 8 years | Better OS (especially in ASA classification 3 to 4) |

aAs a part of 446 patients undergoing major abdominal surgery for different types of cancer
EA = epidural anesthesia; OS = overall survival; PCA = patient-controlled analgesia; RFS = recurrence-free survival
A recent meta-analysis stated that laparoscopic surgery for colon cancer does not differ from open surgery in terms of overall survival [19]. None of the prospective studies in our review stratified for the type of surgery (laparoscopic vs. open).

Finally, the effect of EA might not only be anti-tumour, but also favour other mechanisms. Although cancer recurrence will determine survival to a large extent, other putative mechanisms include a reduction in perioperative cardiac-, respiratory- and thromboembolic events, but this effect mainly influences short-term survival [20]. A recent Cochrane review concluded that, compared with general anaesthesia, a central neuraxial block may reduce the 0–30-day mortality for patients undergoing surgery with intermediate-to-high cardiac risk [21].

In conclusion, this review of seven heterogeneous studies shows that the association between EA and survival of colon and rectal cancer is not clear, as conflicting results are described in the literature—although none of the studies showed a negative influence of EA on survival. Randomized, prospective, well-stratified studies are needed to determine whether the association between EA and (cancer-specific) survival is causative.

Conflict of interest statement: none declared.

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