

## Regional analgesia and cancer outcomes: Our current understanding in 2024

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Cancer is one of the two leading causes of death globally, with metastatic or recurrent disease and/or complications related to treatment being the leading cause of death.<sup>[1]</sup> Surgery remains the mainstay of therapeutic options for non-metastatic disease for solid tumours as it offers the best chance for long-term survival. However, surgical interventions by themselves could contribute to cancer recurrence by disruption of the stromal tissue, shedding of tumour cells, or the release of inflammatory mediators and immunosuppressive factors with tissue damage and activation of the hypothalamic-pituitary-adrenal axis (HPA) axis.<sup>[2]</sup>

There has been significant interest in evaluating the choice of anaesthetic techniques or strategies and determining whether regional analgesia/anaesthesia could remarkably reduce the neuro-humoral responses to surgical stress and tissue damage and improve oncologic outcomes.<sup>[3]</sup> The use of local anaesthetics in high-volume regional blocks or as part of continuous catheter techniques is believed to have local effects on cancer tissue, inhibiting tumour growth, proliferation, and metastasis in animal models.<sup>[4]</sup> Furthermore, *in vitro* studies have demonstrated that local anaesthetic agents in clinically used dosing schedules are associated with preserving immune function.<sup>[5]</sup> Therefore, there was a rational basis for the interest and enthusiasm in the study and use of regional anaesthesia to decrease cancer recurrence.<sup>[6]</sup>

Several retrospective studies investigated the potential survival benefit of regional anaesthesia in curative resection surgery with mixed results.<sup>[7-9]</sup> Park *et al.*<sup>[10]</sup> published the results of a multicentre, randomised study in 2008 to determine whether epidural anaesthesia and postoperative epidural analgesia decreased the incidence of death and major complications during and after intra-abdominal surgical procedures. They showed no difference in 30-day mortality and morbidity rates between epidural-supplemented versus general anaesthesia. However, a sub-study of the parent randomised controlled trial (RCT) evaluated if epidural analgesia could decrease cancer recurrence following colon cancer resection. The authors found a beneficial association between epidural analgesia and improved survival in patients without metastases at 1.46 years, while there was no survival benefit for patients with metastases.<sup>[11]</sup> Rigg *et al.*<sup>[12]</sup> observed no overall difference in mortality or major morbidity between patients randomly assigned to general anaesthesia with intraoperative and postoperative epidural therapy or general anaesthesia with other anaesthetic and analgesic regimens for major abdominal or thoracic surgery (MASTER trial). A sub-study of this MASTER trial was performed to investigate cancer-free survival and all-cause mortality differences between the two arms. The authors found no differences in 5-year recurrence and mortality rates.<sup>[13]</sup>

Sessler *et al.*<sup>[14]</sup> published the first RCT results to evaluate the differences in cancer survival between regional and general anaesthesia in 2019. In this trial, 2,108 women undergoing primary breast resection were randomised into the regional anaesthesia-analgesia group (mostly paravertebral blocks) or general anaesthesia (mostly sevoflurane)-opioid analgesia group to assess local and metastatic cancer recurrence rates in the two groups. No difference was noted in breast cancer recurrence (Hazard ratio (HR): 0.97 [95% confidence interval (CI): 0.74, 1.28]) between the groups. Further, Yu *et al.*<sup>[15]</sup> published the results of a RCT in 526 women demonstrating no recurrence free survival (RFS) benefit in women having a pectoral nerve block (PEC) for mastectomy procedures (HR: 0.9 [95% CI: 0.76, 1.32]). Karmakar *et al.*<sup>[16]</sup> reported no difference between the thoracic paravertebral block and general anaesthesia groups for women (n = 180) undergoing modified radical mastectomy with a 5-year follow-up.

Xu *et al.* investigated the effects of general anaesthesia plus epidural versus general anaesthesia alone on RFS and overall survival (OS) in patients undergoing video-assisted thoracoscopic procedures for lung cancer resection. In this RCT of 400 patients, the authors found no differences in RFS (HR: 0.90, 95% CI: 0.60, 1.35) or OS (adjusted HR: 1.12; 95% CI: 0.64, 1.96) between the two groups.<sup>[17]</sup> Two other recent RCTs showed no benefits with regional analgesia in RFS in thoracic and abdominal cancer surgeries<sup>[18]</sup> or disease-free survival and overall survival at 5 years after elective colon resections.<sup>[19]</sup> Li *et al.*<sup>[20]</sup> recently published a systematic review and meta-analysis with trial sequential analysis of 15 RCTs comparing regional anaesthesia (RA) to general anaesthesia on RFS and OS after oncology surgeries involving 5981 participants. Compared to general anaesthesia, RA had no positive effect on RFS (HR, -0.02; 95% CI, -0.11 to 0.07), OS (HR, -0.03; 95% CI, -0.28 to 0.23), time to tumour progression (0.11; 95% CI, -0.33 to 0.55), 5-year RFS (risk ratio (RR), 1.24; 95% CI, 0.88 to 1.76), and 5-year OS (RR, 1.11; 95% CI, 0.85 to 1.44). Sub-group analysis based on study design, patient characteristics, and tumour types also showed no effect of RA on RFS or OS.

While the rationale and the initial enthusiasm on the cancer recurrence and disease-related survival benefits of regional analgesia were promising (mostly from retrospective studies), to date, data from the five randomised controlled trials and a meta-analysis

of randomised controlled trials offer no benefits for regional anaesthesia with regards to oncological outcomes. However, regional analgesia provides other benefits, with minimising opioid-related adverse events, better dynamic pain control, patient's ability for increased ambulation and pulmonary rehabilitative exercises, minimised postoperative pulmonary and thrombotic complications, and enhanced patient experience and satisfaction.<sup>[21]</sup>

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