

# Anaesthesia and cancer recurrence

Volume 1 Issue 3 - 2014

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**Abbreviations:** NK Cells, Natural Killer Cells; CTL, Cytotoxic Lymphocytes; STAT, Signal Transducer and Activator of Transcription; SNS, Sympathetic Nervous System; VEGF, Vascular Endothelial Growth Factor; HIF-1 $\alpha$ , Hypoxia Inducible Factor-1 $\alpha$ ; VGSC, Voltage Gated Sodium Channels; HPA, Hypothalamic-Pituitary Adrenal Axis

## Editorial

The incidence of cancer is increasing because of improved screening practices. Surgical resection of a tumor offers the best prospect for a good outcome in such patients. However, the risk of minimum residual disease and tumor seeding seems inevitable even after a carefully conducted procedure with wide margins of normal tissue resected.<sup>1,2</sup>

Recent clinical data have pointed towards a potentially devastating consequence of exposure to anaesthetic agents on cancer recurrence and metastasis.<sup>3-7</sup> During surgery bacterial contamination is inevitable but all the patients do not land up in sepsis. Similarly, inadvertent seeding of tumor cells during surgical procedure eventually leading to clinical metastasis is a complex dynamic process and depends on the delicate balance between host immune surveillance and tumor survival. The process of metastasis can be divided into four steps namely epithelial-mesenchymal transition, intravasation into blood vessels, migration of viable prometastatic cells (only 0.01% cells survive) and finally proliferation of these metastatic progenitor cells.<sup>8-10</sup> Survival of circulating tumor cells in circulation depends upon host immunity and inflammatory mediators released by immune cells in response. The surgical stress response, general anaesthesia with inhalation agents and opioids usage (especially morphine) in the vulnerable perioperative period leads to immunosuppression which has been implicated in promoting tumor recurrence.<sup>5,6,11</sup> Natural killer (NK) cells play a dominant role in eliminating cancer cells along with T helper 1 (Th1) cells and cytotoxic lymphocytes (CTL).<sup>12,13</sup> Proinflammatory cytokines, catecholamine and signal transducer and activator of transcription 3 (STAT 3) are implicated in cancer metastasis and recurrence. Activation of sympathetic nervous system (SNS) and hypothalamic-pituitary adrenal axis (HPA) plays a central role in immune suppression resulting from surgical stress. Prostaglandins secreted from tumour cells and catecholamines suppress NK cells, Th1 cells and CTL. They also shift the Th1/Th2 balance toward Th2 type immune response and promote angiogenesis.<sup>11-13</sup> Glucocorticoids increase apoptosis of immature T cells in thymus.

Along with surgical stress a number of perioperative factors like blood transfusion,<sup>14</sup> hypothermia,<sup>15</sup> hyperglycaemia,<sup>16</sup> hypotension,<sup>17</sup> hypoxia and postoperative pain<sup>18</sup> also suppress host immunity. Patients with malignancy undergoing major surgery are often anaemic and may often require perioperative blood transfusions. Intra-operative blood transfusion increases the risk of cancer recurrence by 74%.<sup>19</sup> This is due to the well known phenomenon of transfusion related immunomodulation (TRIM).<sup>14</sup> Thus, for cancer patients undergoing major surgery, optimising the nutritional status and use of erythropoietin to build up haemoglobin, may be

considered preoperatively (if feasible) to avoid/ reduce need for blood transfusion. But this may not be possible in all the cases due to urgent need of the cancer surgery. We must take measures to minimise blood loss like optimal surgical technique, maintain normothermia, use antifibrinolytic, and maintain the volume status with appropriate fluids till the transfusion threshold is reached. Stored blood and old erythrocytes release pro-tumour mediators. Leucodepleted blood may offer some protection but their use remains controversial.<sup>20</sup>

Hypotension activates SNS and HPA with its consequent immunosuppressive effects.<sup>17</sup> Hypoxia leads to Th-1 suppression and activates hypoxia- inducible factors in immune cells as well as cancer cells.<sup>18</sup> HIF inhibit NK cells and induces pro-angiogenic factors in tumour cell including VEGF and angiopoietin2. Number of hypotensive episodes during surgery found to be significant risk factor for recurrence after liver resection for metastatic colorectal cancer. Hypothermia also suppresses NK cell activity and increased risk of tumour progression, due possibly to SNS activation.<sup>15</sup> Hyperglycemia suppresses neutrophil and monocyte function, impairs phagocytosis and leads to increased production of proinflammatory cytokines.<sup>16</sup> The resulting immune-suppression may lead to increased tumour spread. So as anesthesiologist we should be cautious in the perioperative period and minimise such factors which may promote metastasis.

Another equally worrisome hypothesis which has been suggested is that the pro-tumor environment during anaesthesia for non-cancer surgery may activate dormant cancer cells in a patient where clinical malignancy would not have developed otherwise.<sup>21</sup> Also though effective pain management is known to improve the quality of life of the cancer patient, but chronic opioid administration for pain management may also lead to immunosuppression and subsequent metastasis and recurrence.

Opioids inhibit CTL and NK cell function and also increase angiogenesis which may promote tumor cell growth.<sup>22</sup> Various clinical studies have shown that in clinically used doses opioids promotes endothelial cell proliferation and migration in vitro. Pro angiogenic effect of opioids ( $\mu$  receptor agonists) is due to reciprocal activation of VEGF (vascular endothelial growth factor).<sup>23</sup> Further these  $\mu$  receptor agonists also induce a defect in the barrier function

**Received:** July 21, 2014 | **Published:** July 22, 2014

of cells which allows penetration and subsequent metastasis of tumor cells. Morphine sensitive  $\mu_3$ -receptor on immune cells is responsible for its immunomodulation effects.<sup>24</sup> So, use of peripherally acting  $\mu$  receptor antagonists (like methyl-naltrexone) in the perioperative period, which do not antagonise their central analgesic effect, may be beneficial in attenuating pro-tumor effects of opioids.<sup>25</sup> Synthetic opioids like fentanyl do not bind to  $\mu_3$ -receptor, so have less immunosuppressive effect than morphine.<sup>26</sup> Fentanyl augments NK cell activity and increases the number of NK cells.<sup>27</sup> Remifentanyl also does not impair NK activity.<sup>28</sup> The therapeutic potential of peripheral opioid antagonist remains to be explored in future.

Volatile anaesthetics up-regulate the expression of hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), which is an important mediator for protection from ischemia. HIF system is also used by cancer cells to promote their own survival under condition of hypoxia.<sup>29</sup> The level of HIF-1 $\alpha$  has been found to correlate with early relapse in breast cancer. Isoflurane is found to protect colon cancer cells from tumour necrosis factor (TNF) induced apoptosis.<sup>30</sup> However, a recent study on sevoflurane failed to prove its association with increased risk of new cancer.<sup>31</sup> For nitrous oxide the results of various studies have been conflicting.<sup>32</sup> Certain anesthetic techniques and agents have been found to be associated with less immunosuppression and cancer recurrence in cancer patients. Minor innocuous modifications in the anaesthetic management may thus lead to significant long term impact on outcome of onco-patients.

Regional anesthesia (RA) ameliorates most of the aforesaid adverse consequences of surgery in a cancer patient primarily by reducing the neuroendocrine stress response, requirement of inhalation agents and use of opioids in the perioperative period.<sup>33,34</sup> Many large clinical trials have shown beneficial effect of RA to decrease the recurrence and improve survival,<sup>34-36</sup> but others have refuted the claims.<sup>37,38</sup> Benefit of epidural anaesthesia has been shown in trials that have tightly controlled pathological classification.<sup>39</sup> RA alone or supplemented with GA has well established role in improving quality of analgesia and decreasing postoperative morbidities. Thus, although not conclusively proven in reducing the incidence of recurrence of cancer, it thus seems justified to advocate its wider use in cancer surgery. Among the intravenous agents, midazolam<sup>40</sup> and ketamine<sup>41</sup> have been found to interfere with host immunity whereas propofol may have anti-tumour effect. Ketamine leads to profound immunosuppression because of its adrenergic activity. Propofol attenuates surgical stress induced immunosuppression and promotes T lymphocyte activities.<sup>42</sup> Propofol also has cyclooxygenase (COX-2) inhibiting property.<sup>43</sup> It has been found to inhibit lymphoma growth and the invasiveness of colon cancer cells. Thus, TIVA with propofol may be an attractive option for anaesthetising cancer patients.

COX-2 is over expressed in many types of cancers. It is critical for the production of prostaglandin PGE2 which promotes tumour progression. NSAIDs especially those with COX-2 selection inhibition, may prevent morphine induced tumour growth and metastasis since morphine stimulates COX-2 expression in tumour cells.<sup>44</sup> Also, by reducing the requirement of opioids, they can minimize opioid induced immunosuppression in the host. A clinical study showed that single dose of pre-emptive ketorolac significantly reduced recurrence after breast cancer surgery.<sup>45</sup> Other agents which may have a positive effect in preventing recurrence after cancer surgery are local anaesthetics<sup>46</sup> and beta blockers.<sup>47</sup> Local anaesthetics act by inhibiting voltage gated sodium channels (VGSC). These channels are highly expressed in a variety of cancer cells. These VGSCs are usually neonatal splice variants which are more sensitive

to lidocaine and phenytoin than their adult counterparts. VGSC  $\alpha$ -subunit levels correlate with the metastatic potential of the tumours. *In vitro* exposure of human fibroblasts to local anaesthetics impairs cell growth. Mesenchymal stem cells may be critical in tumour growth and metastasis. Anti-proliferative effects of local anaesthetics may be mediated by potassium or calcium channels. Clinical evidence of the effectiveness of local anaesthetics to decrease tumour growth is however limited. Large randomised trials are required to further substantiate this effect.

Animal studies have shown that metastasis rate is halved with the administration of beta blockers. In humans, beneficial effects have been found in hypertensive patients on chronic beta blocker therapy with operable breast cancer in terms of longer disease free survival rates. They may exert their anti-tumour effect by reducing surgical stress response. Also, VEGF secretion is reduced from ovarian tumours following beta blockade. They may provide an exciting area for future research in cancer treatment. Other factors which may be of importance to a cancer patient in this regard are perioperative immunonutrition, prevention of inadvertent intraoperative hypoxia, hypothermia, hypotension and hyperglycemia. There is some evidence that perioperative immunonutrition with arginine and omega-3 fatty acids can improve NK cell activity and shift the TH1/Th2 balance in favour of Th1 and thus reduce immunosuppression in cancer patients.<sup>48,49</sup>

## Conclusion

Perioperative period is highly conducive for dissemination of cancer cells and later establishment of metastasis. The possibility of certain anaesthetic agents leading to increased recurrence after cancer surgery is a grave one and cannot be discounted. Though studies in this field are mostly inconclusive and limited by multiple confounding factors and mostly retrospective, enough experimental and clinical evidence has been generated to create a platform for future larger prospective randomised trials which might provide us with better clinical guide. Till then based on available evidence we can modify our anaesthetic practice for cancer patients to include safer techniques and anaesthetic agents to optimize outcomes. Regional anaesthesia and analgesia should be widely incorporated in the management of cancer patients.

## Funding details

None.

## Acknowledgments

None.

## Conflicts of interests

Authors declare that there is no conflict of interest.

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