

Editorial

## Need of Safer Anaesthetic Drug for Oncoanaesthesia

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### Editorial

The medical science has always looking not only for newer drugs but also for safer drugs having least adverse effects. This has prompted the research and development to look for the drug molecules with better safety profile. But in spite of improved safety profile, certain drugs has been implicated in some or the other adverse issues. Recently, there has been reports on implication of anesthetic drugs on increased incidence of cancer metastasis and cancer recurrence [1,2]. Such implications of cancer metastasis and recurrence due to drugs might not be acceptable. The oncoanaesthesia is always challenging in view of extensive surgical intervention superimposed on preexisting implications of chemotherapy and radiotherapy. The comorbidities and general status of cancer patients are also concern in perioperative management. With the improvement in surgical procedures, improved chemotherapy and radiotherapy, cancer patients are considered potential curable. However, if certain interventions during the management of cancer impose issues on increased risk of cancer recurrence or cancer metastases remains unacceptable. This mandates a search of a safe molecule for anaesthetic practice that may be considered absolute safe for cancer patients undergoing anaesthetic management for oncosurgical intervention.

The factors for cancer recurrence related to management in the perioperative period appear to be multifaceted and is not very clear. The reported factor responsible for cancer recurrence includes metabolic, hematological, inflammatory/immunological responses and neuroendocrine factors [2-4]. These body responses are protective and assist in elimination of tumor cells shed into the body during surgical intervention [5-8]. However, the perioperative and specially surgical stress leads to body immune suppression and thus obtundation of protective responses for prevention of tumor cell spread. This implies a tight balance of the metastatic potential of the tumour and the antimetastatic host defenses. The body response alteration is a lead factor for cancer recurrence or tumor metastasis [9,10]. Apart from these surgical response, certain anaesthetic drugs have been implicated for cancer recurrence or metastasis. This has been implicated due to alteration on body immunity response and effect on cellular mechanisms (e.g. cell apoptosis) or influence on the endocrine and sympathetic systems [11]. The various agents used in perioperative period like opioids, midazolam,  $\alpha_2$  agonists like clonidine, dexmedetomidine are prone of risk for cancer recurrence

[12]. Also, the drugs of similar groups like fentanyl and morphine among the opioids have different risk for cancer recurrence. On the other hand, agents like COX-inhibitor (ketorolac),  $\beta$  blockers has been reported to reduce cancer metastasis in oncosurgery [13-15]. Opioids promotes endothelial cell proliferation, migration of cells, increase angiogenesis and induce a defect in the barrier function of cells [16,17]. The angiogenic effect is due to reciprocal activation of VEGF (vascular endothelial growth factor) [17]. However, the peripherally acting  $\mu$  receptor antagonists attenuates pro-tumor effects of opioids [18,19]. So it appears there is a need of a molecule that blocks the tumor inducing effect of the opioid molecule. The future exploration needs to be done for therapeutic potential of peripheral opioid antagonist. Though the potential for cancer spread with volatile agents are conflicting, but some data regarding its relation has been reported [20,21]. The hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) promotes tumor cell survival and is up-regulated by the volatile agents [20]. The increased level of HIF-1 $\alpha$  leads to the possibility of relapse in breast cancer. In specific, isoflurane, a volatile anaesthetic agent is reported to have protective effect of colon cancer from [21,22]. So, again, the volatile agent molecule needs to have all protective effect against spread of cancer cells. The other anaesthetic agents have also been implicated in tumor cells. The midazolam and ketamine interfere with host immunity and thus may promote spread of tumor cell whereas propofol have protective effect [23,24]. These effects have been related to immunosuppression by ketamine and prevention of surgical stress induced immunosuppressant and promotion of T lymphocyte activities by propofol [24,25]. The morphine induced stimulation of COX-2 expression in tumour cells may be overcome by NSAIDs especially those with COX-2 selection inhibition [26]. The multimodal analgesic management in perioperative period balances the adverse profile of tumor spread related to drugs. The beneficial role of ketorolac by preventing recurrence after breast cancer surgery has been reported [26]. However, it would be interesting to look for a molecule with combined action i.e. opioid like analgesic action with COX inhibition. The local anaesthetics and beta blockers have also been reported to have protective effect by their action on voltage gated sodium channels, potassium or calcium channels and beta receptors (also by reducing surgical stress response) respectively [27,28].

Though these data of anaesthetic drugs and cancer recurrence are reported in literature but not in a robust randomized clinical trial. However, still it becomes essential this possible risk implicated due to anaesthetic drugs. Pharmacogenomics is an emerging concept for drug development. The occurrence of cancer recurrence due to implicated anaesthetic drugs is not universal [1,2]. There appears role of genetic factors in addition to various other factors related to surgery and anesthetic management in the perioperative period. This phenomenon is applicable for various anesthetics as well and emphasizes the need of newer drugs with better efficacy and lesser side effect profile [29]. Also the era of 'personalized medicine' and need of individualized drug therapy is an emerging concept [11]. It is dire need for the researches to look for anaesthetic drug molecule which

remains safer for its use in cancer surgery with regards to potential for cancer recurrence or metastasis. The literature mentions regarding the variability in response to anaesthetic agents like induction agents, opioids resulting from genetic factors [30]. In future the phenomenon of pharmacogenetics probably would identify patient at risk for cancer recurrence to a particular anaesthetic drugs.

To conclude, the implication of anaesthetic agents for spread of tumor cells leading to possibility of recurrence after cancer surgery cannot be ignored. A more robust data by well designed prospective randomized clinical trial of optimal sample size is desirable to assess the risk associated with various anesthetic drug molecule for its role in cancer recurrence and metastasis. The role of genetic factors for cancer recurrence or metastasis needs further elucidation. This may probably lead to development of cancer safe anaesthetic molecule in future.

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