

Spinal anesthesia is associated with lower recurrence rates after resection of non-muscle invasive bladder cancer

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Heterogeneity of non-muscle invasive bladder cancer (NMIBC)

Bladder cancer is a common malignancy involving the urinary system, which can be categorized as non-muscle invasive and muscle invasive bladder cancer. NMIBC comprises of a heterogeneous population of tumor and includes pathological stage Ta (confinement to the epithelium or mucosa), T1 (invasion into the lamina propria without invasion into the muscularis propria) and CIS (Tis: flat, high-grade, non-papillary carcinomas confined to the urothelium). About 50–70% of all newly diagnosed bladder cancers are NMIBC and one third of the remaining cases show invasion into deeper layers but are still confined to the bladder (1). Of all newly diagnosed NMIBC, 70% present as stage Ta, 20% as T1 and 10% as CIS. Approximately 30–50% of low grade Ta tumor will recur and roughly 10–20% will progress to muscle invasive disease (2,3). In comparison with low-grade stage Ta tumor, T1 high-grade tumor has a higher recurrence rate around 69–80% and a 33% to 48% chance of progression to muscle-invasive disease. Thereby, T1 high-grade tumors should be considered as aggressive and potentially lethal diseases. In addition, re-resection (restaging) is required to identify whether unrecognized muscle-invasive disease remains after surgery (4). T1 tumors are often understaged by initial resection. Among T1 tumors, 4–25% shows muscle-

invasiveness in second staging.

Koumpan *et al.* (5) demonstrated that spinal block attenuated tumor recurrence significantly in the high-risk patients group but not in the low-risk group, which shows the heterogenetic characteristics of the bladder cancer. This result also suggests that analysis on specific risk category is required because the effects of spinal anesthesia may be different depending on tumor categorization within NMIBC.

Bladder tumor recurrence and anesthetic technique

An incomplete resection, tumor cell implantation, growth of microscopic tumors present at the time of the previous resection, and new tumor formation are four mechanisms underlying bladder cancer recurrence (6). A recurrence in the same location as the initial urothelial cancer most likely results from residual disease (via incomplete resection and tumor cell implantation). A distant recurrence most likely results from the growth of microscopic tumors present at the time of the previous resection and/or genuine new tumor formation. A high proportion of early urothelial cancer recurs at the site of the original resection, indicating possibility of incomplete resection or tumor cell re-implantation (7).

In literature, two retrospective studies reported that

compared to general anesthesia, spinal anesthesia decreased the risk of bladder cancer recurrence after surgery (5,8). Possible mechanisms were discussed as following. First, surgery under inhalational anesthetic agents impairs cell-mediated immune activity, especially that of natural killer (NK) cells, which controls cancer cell survival and tumor spread via chemokine receptor 2 signaling (9). Woods *et al.* (10) demonstrated that inhalational agents such as enflurane and halothane produced dose-dependent reduction in cytotoxicity of NK cells, which returned to normal within 1 hour of discontinuation of the anesthetics. On the other hand, Tai *et al.* (11) reported that surgery itself markedly reduced the number of NK cells in the spleen and tumor cell killing by NK cells were significantly reduced in surgically stressed mice. In the same study, human data confirmed that NK cell activity was indeed suppressed following the surgery and returns to baseline at postoperative day (POD) 28. Another study found that major surgery suppressed dopachrome tautomerase (DCT)-specific CD8+ T cell immunity beginning 24 hours after surgery and the suppression lasted for 7–10 days (12). Furthermore, in a study NK cell activity after hysterectomy, NK cell activity was maintained in patients who received extradural anesthesia, which suggests the effectiveness of neuraxial anesthesia in reducing surgical stress (13). In summary, inhalational anesthetic agents suppress NK cell activity but the effect does not last after the surgery. The suppression of NK cell activity after the surgery is likely due to the surgical stress, which may be blocked via spinal anesthesia. Thereby, regional anesthesia compared to general anesthesia may result in lower tumor recurrence due to mechanisms related to NK cell activity.

Second, local anesthetics may block the voltage-gated sodium channels (VGSC) that mediate cancer progression. Sodium channel-blocking anti-epileptic drugs such as carbamazepine, lamotrigine and topiramate are inversely associated with the risks of bladder cancer (14). Wang *et al.* (15) demonstrated that intraoperative lidocaine infusion was associated with the preservation of lymphocyte proliferation, attenuation of apoptosis, maintenance of the balance of Th1/Th2 cells and the decreased production of cytokines in patients undergoing radical hysterectomy. Obturator nerve block in transurethral bladder resection is usually performed with spinal anesthesia to prevent obturator reflex and avoid complications such as bleeding, bladder perforation, or incomplete tumor resection. Patients receive 10 mL 2% preservative free lidocaine along with

5 mL 0.5% bupivacaine during the procedure. Thereby, the additional local anesthetics may contribute to reducing recurrence to some degree. Third, volatile anesthetics have been shown to upregulate hypoxia inducible factors (HIF)-1 α and HIF-2 α activation, which is a transcriptional regulator of vascular endothelial growth factor (VEGF) expression mediating proliferation and angiogenesis. Overexpression of HIF-1 α is associated with enhancement of cell proliferation and cell migration (16,17).

When reviewing journals on the protective mechanisms of spinal anesthesia on tumor recurrence, confounding factors should be addressed and eliminated to validate the results of multivariate regression analysis. For example, the multiplicity of tumors can be a confounding factor because when bilateral bladder tumor resection is planned, general anesthesia may be preferred to regional anesthesia which requires spinal block with both obturator nerve blocks. Another possible scenario is that bilateral bladder tumor might have more lesion sites, which can accompany CIS or stage T1 more frequently compared to unilateral bladder tumor. These higher multiplicities can increase the possibility of incomplete resection and tumor reimplantation or unfounded microscopic focus, all which are sources of recurrence. Therefore, an association analysis between lesion numbers of bladder tumor and choice of regional anesthesia should be done to verify whether the association is significant.

Koumpan *et al.* (5) reported interesting findings on tumor recurrence. Seventy-two percent of patients who received intravesical bacillus Calmette-Guerin (BCG) had recurrence, but those who received postoperative chemotherapy showed protective effect on recurrence. This data mean that in patients who had general anesthesia, intravesical BCG did not show any effect on tumor suppression. This hypothesis is driven from following scenario. On intravesical application of BCG, live BCG attaches to the urothelium and is internalized by bladder cancer cells, owing to oncogenic aberrations that activate macropinocytosis. Following internalization, bladder cancer cells upregulate expression of MHC class II and ICAM-1 and secrete cytokines (18). Finally, NK cells and cytotoxic T cells migrate to the bladder cancer cells and eliminate the tumor cells. However, when surgical stress and inhalational anesthetics suppress the activity of NK cells and cytotoxic T cells, the effects of intravesical BCG may be not enough to kill the tumor cells. Activated macropinocytosis by intravesical BCG might rather aid tumor growth than

elimination because macropinocytic uptake of extracellular proteins provides the much-needed amino acids that fuel cancer cell metabolism and tumor growth (15). In this perspective, any steps to maintain the immunity after surgery should be taken into account. Recently, novel anticancer oncolytic vaccine was tried and showed promising result (12).

Conclusions

Recently, there has been surmounting evidence that supports anesthesia to have a significant effect on cancer progression. Thereby, because the method of anesthesia may also have critical effects in NMIBC, further prospective research is vital in unlocking the key to prevent bladder tumor recurrence.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49:466-5; discussion 475-7.
2. Anastasiadis A, de Reijke TM. Best practice in the treatment of nonmuscle invasive bladder cancer. *Ther Adv Urol* 2012;4:13-32.
3. Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. *J Urol* 2009;182:2195-203.
4. Nepple KG, O'Donnell MA. The optimal management of T1 high-grade bladder cancer. *Can Urol Assoc J* 2009;3:S188-92.
5. Koumpan Y, Jaeger M, Mizubuti GB, et al. Spinal anesthesia is associated with lower recurrence rates after resection of nonmuscle invasive bladder cancer. *J Urol* 2017. [Epub ahead of print].
6. Bryan RT, Collins SI, Daykin MC, et al. Mechanisms of recurrence of Ta/T1 bladder cancer. *Ann R Coll Surg Engl* 2010;92:519-24.
7. Schips L, Augustin H, Zigeuner RE, et al. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology* 2002;59:220-3.
8. Jang D, Lim CS, Shin YS, et al. A comparison of regional and general anesthesia effects on 5 year survival and cancer recurrence after transurethral resection of the bladder tumor: a retrospective analysis. *BMC Anesthesiol* 2016;16:16.
9. Iwasaki M, Zhao H, Jaffer T, et al. Volatile anaesthetics enhance the metastasis related cellular signalling including CXCR2 of ovarian cancer cells. *Oncotarget* 2016;7:26042-56.
10. Woods GM, Griffiths DM. Reversible inhibition of natural killer cell activity by volatile anaesthetic agents in vitro. *Br J Anaesth* 1986;58:535-9.
11. Tai LH, de Souza CT, Bélanger S, et al. Preventing Postoperative Metastatic Disease by Inhibiting Surgery-Induced Dysfunction in Natural Killer Cells. *Cancer Res* 2013;73:97-107.
12. Ananth AA, Tai LH, Lansdell C, et al. Surgical stress abrogates pre-existing protective T cell mediated anti-tumor immunity leading to postoperative cancer recurrence. *PLoS One* 2016;11:e0155947.
13. Tønnesen E, Wahlgreen C. Influence of extradural and general anaesthesia on natural killer cell activity and lymphocyte subpopulations in patients undergoing hysterectomy. *Br J Anaesth* 1988;60:500-7.
14. Takada M, Fujimoto M, Motomura H, et al. Inverse Association between Sodium Channel-Blocking Antiepileptic Drug Use and Cancer: Data Mining of Spontaneous Reporting and Claims Databases. *Int J Med Sci* 2016;13:48-59.
15. Wang HL, Yan HD, Liu YY, et al. Intraoperative intravenous lidocaine exerts a protective effect on cell-mediated immunity in patients undergoing radical hysterectomy. *Mol Med Rep* 2015;12:7039-44.
16. Zhao H, Iwasaki M, Yang J, et al. Hypoxia-inducible factor-1: a possible link between inhalational anesthetics and tumor progression? *Acta Anaesthesiol Taiwan* 2014;52:70-6.
17. Yang W, Cai J, Zabkiewicz C, et al. The effects of

anesthetics on recurrence and metastasis of cancer, and clinical implications. *World J Oncol* 2017;8:63-70.

18. Redelman-Sidi G, Glickman MS, Bochner BH. The

mechanism of action of BCG therapy for bladder cancer- a current perspective. *Nat Rev Urol* 2014;11:153-62.

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