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Review Article

Anesthetic technique and oncological outcomes in urology: A clinical practice review

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Abstract

Introduction: There is increasing awareness that different anesthetic and analgesic techniques may impact outcomes after oncological surgery, generally through modifying effects on the immune system but potentially via other mechanisms including mitigating the surgical stress response. This narrative review aims to summarize the mechanisms underlying the effect of perioperative factors on oncological outcomes, with an emphasis on the available urologic literature. *Methods:* Literature on anesthetic technique (i.e., general vs. regional) and oncological outcomes were reviewed with a particular focus on urological studies. *Results:* In prostate cancer surgery, the risk of mortality has been reported to be reduced with the use of regional (i.e., neuraxial) anesthesia, but there was no association between anesthetic technique and progression-free or biochemical recurrence-free survival. In nonmuscle invasive bladder cancer, regional anesthesia has been associated with lower recurrence rates and longer time to recurrence following transurethral resection of bladder tumor. *Conclusions:* This review highlights the role of regional anesthesia to improve oncoimmunological responses after surgery, potentially through decreased use of volatile anesthetics and opioids, decreased activation of the surgical stress response, and a direct local anesthetic-mediated anti-inflammatory effect. Available urological literature suggests an association of anesthetic type and outcomes for nonmuscle invasive bladder cancer and prostate cancer surgeries but the evidence is limited. Prospective studies are needed to further investigate the relationship between anesthetic technique and urologic oncological outcomes. © 2019 Elsevier Inc. All rights reserved.

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1. Introduction

The perioperative period is a critical time during which promotion of cancer progression or metastases may occur through direct cancer cell spillage at the time of surgery, suppression of the antitumor immune response, and direct stimulatory effects on tumor cells. Anesthetic agents commonly used in the perioperative period can also have a dramatic influence on the immune system, which can impact progression by disrupting the balance of cancer immune-editing. To date, the relationship between anesthetic technique and oncological outcomes has been studied in several cancer sites including melanoma, colorectal, lung, and breast cancer [1−5]. However, uniform results across malignancy type have not been seen and the relationship between anesthetic-induced immunosuppression and cancer recurrence remains unresolved. In the urological literature, several retrospective studies have examined the relationship between anesthetic technique and oncological outcomes [6−22]. The opportunity exists therefore to potentially improve perioperative patient care by utilizing anesthetic techniques and/or medications that may minimize immunosuppression. The goal of this review is to highlight the known cellular and molecular mechanisms that may underlie the effect of perioperative factors on oncological outcomes, based on a comprehensive analysis of the recent literature.

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2. Perioperative factors

2.1. Perioperative stress response

There are several changes that occur in response to the stress of surgery that impact the host immunologic response to cancer cells (Fig. 1, Table 1). The hypothalamic-pituitary-adrenal axis and sympathetic nervous system are key drivers of the surgical stress response [1,2,23]. Stimulation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system leads to release of catecholamines, glucocorticoids, prostaglandins and endogenous opioids, which would generally shift the balance from a type 1 T helper (Th1) to a type 2 T helper (Th2) cell milieu that would potentially favor tumor growth [24]. Catecholamines decrease the population of natural killer (NK) cells and cytotoxic T lymphocytes, both of which have the ability to modulate or inhibit tumor growth [25−27]. Catecholamines can lead to release of tumor-promoting cytokines (IL-4, IL-6, IL-8, IL-10) and a decrease key cytokines involved in cancer immune surveillance (IL-12, TNF-alpha, and IFN-gamma) [28−31]. Furthermore, catecholamines promote angiogenesis through increased production/release of proangiogenic factors (e.g., VEGF, MMP2, and MMP9), thereby favoring cancer proliferation [27,28,32,33]. These proangiogenic processes can mirror and exacerbate those tumor intrinsic pathways involving production of prostaglandin E2, stimulating myeloid-derived suppressor cells as well as tumor-associated macrophages [34].

2.2. Inhalational and intravenous anesthetics

Several studies have shown that anesthetic agents, both inhalational and intravenous, have effects on the immune system [25,35−44]. Inhalational agents inhibit cell-mediated immunity and are protumorigenic, in contradistinction to intravenous anesthetics which have been demonstrated to promote cell-mediated immunity and may have more antineoplastic properties. Retrospective studies in breast, colon, and rectal cancer have demonstrated inhalational anesthetics to be associated with decreased overall survival compared to total intravenous anesthesia with propofol (TIVA-propofol) [35−38]. In the largest retrospective study to date consisting of 5,214 propensity−matched individuals, use of inhalational agents during elective oncological surgery was associated with a hazard ratio (HR) of 1.46 for overall mortality over a 3-year follow-up period compared to intravenous anesthetics [37]. Similarly, a recent meta-analysis examining the effects of anesthetic agents on cancer outcomes demonstrated a significantly improved recurrence-free survival ($n = 7,866$) in a compilation of (breast, esophageal, and nonsmall cell lung) cancer types (pooled HR 0.78; 95% CI 0.65−0.94; $P < 0.01$), as well as overall survival ($n = 18,778$) (pooled HR 0.76; 95% CI 0.63−0.92; $P < 0.01$) with TIVA-propofol when compared to inhalational anesthetics [39]. The tumor-promoting effect of inhalational anesthetics is thought to occur, in

part, to inhibition of NK cells with subsequent promotion of tumor growth and metastases [40]. In contrast, propofol does not reduce NK cell activity or inhibit cell-mediated immunity [36].

2.3. Regional anesthesia

A 2014 Cochrane review concluded that evidence for the benefit of epidural anesthesia on tumor recurrence is inadequate to draw definitive conclusions [41]. However, only 4 studies consisting of a total of 746 participants were available for review. All 4 studies were secondary data analyses of previously conducted prospective randomized controlled trials (RCTs) and the quality of evidence was graded low for overall survival and very low for both progression-free survival and time to tumor progression. In contrast, a separate meta-analysis of retrospective studies suggested that regional anesthesia improves overall survival after oncologic surgery, although a definitive effect on cancer recurrence was not confirmed [42].

Several studies have examined the effect of regional anesthesia on tumor growth [43−45]. Regional anesthesia is believed to (1) facilitate tumor responses by limiting afferent signals of the surgical insult sent to the central nervous system; (2) decrease the efferent activation of the sympathetic nervous system; (3) decrease endogenous opioid release, as well as perioperative opioid requirements; and (4) reduce inflammation through a direct local anesthetic anti-inflammatory effect [43−45]. Taken together, as stated in a recent review by the American and European Societies for Regional Anesthesia, non-neuraxial regional analgesia techniques might reduce metastases but the evidence is weak and only retrospective in nature [46]. Epidural analgesia, on the other hand, has slightly more robust evidence and has been shown in 5 RCTs to have a protective role on the immune response and inflammation, but evidence is lacking demonstrating a clinical impact on disease-free survival or recurrence [46].

2.4. Opioids

The hypothetical benefits attributed to regional anesthesia techniques are thought to stem, as least in part, from the effect of local anesthetics in (1) inhibiting the neuroendocrine stress response to surgery; (2) limiting the perioperative volatile and opioid requirements; and (3) reducing inflammation through a (local anesthetic) intrinsic anti-inflammatory effect [44]. Opioids can directly inhibit immunologic responses to cancer cells [47,48] and therefore the benefits of regional techniques might be mitigated (or even completely negated) when performed with opioids alone. Indeed, this was tested in a recent matched-cohort analysis, Chipollini et al. evaluated 430 patients undergoing radical cystectomy for nonmetastatic urothelial bladder carcinoma under perioperative epidural analgesia (primarily dosed with sufentanil) and general anesthesia (epidural
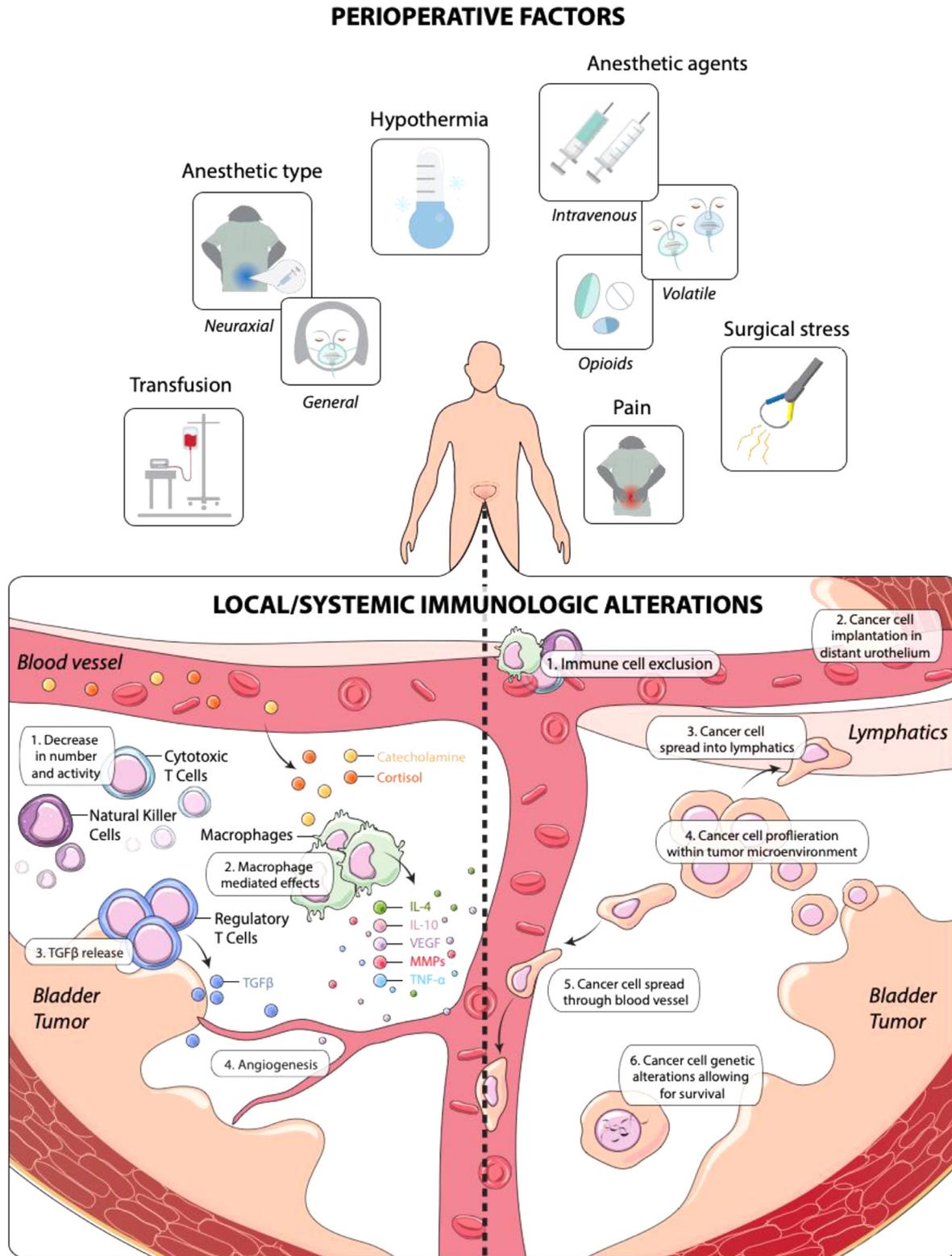
Fig. 1. The impact of perioperative factors on immunological control of cancer cell proliferation. Release of catecholamines caused by the surgical stress response promotes oncogenesis through (1) a decrease in the number and activity of natural killer cells and cytotoxic T lymphocytes, (2) a shift from M1 to M2 macrophages which release cancer-promoting cytokines (IL-4, IL-10) and proangiogenic factors (VEGF, MMPs); and (3) release of TGF beta from macrophages and T regulatory cells, which further promotes immunosuppression and angiogenesis.

Table 1
Factors implicated in tumor immunology

	Tumor-suppressing	Tumor-promoting
Innate	Natural killer cells	Neutrophils
	M1 macrophages	M2 macrophages
	Type 1 NKTs	Type 2 NKTs
		Myeloid-derived cells
		Tumor associated macrophages
Adaptive	Th1 CD4 cells	Th2 CD4 cells
	Cytotoxic CD8 cells	B lymphocytes
		CD4 regulatory cells

group) vs. general anesthesia (GA group) alone [49]. In this analysis, the epidural group received higher median intravenous morphine equivalents when compared to the GA group (75 mg vs. 50 mg respectively; $P < 0.0001$), and had an elevated 2-year recurrence rate compared to GA patients (25.2% vs. 20% respectively; Gray test $P = 0.0508$) [49]. In addition, sufentanil-alone epidural analgesia was a significant predictor of worse recurrence-free survival (adjusted HR = 1.67, 1.14−2.45; $P = 0.009$) and cancer-specific survival (HR = 1.53, 1.04−2.25; $P = 0.030$) on multivariable analyses [49].

Opioids (morphine in particular) reduce NK cell activity against cancer cells and enhance tumor growth and angiogenesis through activation of VEGF [47,48]. Retrospective studies in breast and nonsmall-cell lung cancer have shown an association of intraoperative opioid use with decreased survival [50,51]. In a retrospective study of 593 patients with metastatic prostate cancer, higher mu-opioid receptor expression and greater opioid requirements were associated with shorter progression-free survival and decreased overall survival [6].

3. Anesthesia effects and urologic cancer surgery

3.1. Prostate cancer

Studies assessing the effect of GA vs. regional anesthesia on prostate cancer outcomes have had mixed conclusions with most trials reporting negative results. A 2015 systematic review included 10 studies with 6,261 patients receiving GA and 7,504 patients receiving either neuraxial anesthesia alone or in combination with GA [7]. Of these studies, one was a secondary analysis of a prospective RCT and the remainder were retrospective cohort studies [7−17]. Median follow-up time of these studies was 3.2 to 16.2 years. Three studies were positive [8−10], while 7 were negative [11−17]. There was no difference in overall survival, biochemical recurrence-free survival, or progression-free survival [7]. A number of these studies, however, did not utilize propensity matching, which may have led to significant unmeasured confounding. When only studies with propensity matching were included, use of regional anesthesia was associated with a 19% reduction in the risk of mortality, significantly improving overall survival (HR

of 0.81; 95% confidence interval 0.68−0.96; $P = 0.016$) [7]. The authors suggested that the risk of mortality was significantly reduced with the use of regional anesthesia, but there was no association between anesthetic technique and progression-free or biochemical-free survival restricting any conclusions of the study [7].

There are several limitations of these previous studies that make interpretation difficult. The retrospective nature and lack of randomization in all but one of the studies may have led to significant residual confounding despite propensity matching. In 7 of the 10 studies, use of GA in both treatment groups is another confounder. In the 3 studies that compared GA to spinal anesthesia alone, there was no difference in biochemical recurrence-free, progression-free, or overall survival [15−17]. Furthermore the patient populations studied (mostly low risk) and historical definitions utilized for recurrence limit any conclusions and relevance to contemporary practice.

Finally, a major limitation of these retrospective studies is the lack of standardized anesthetic protocols for general and regional anesthesia treatment groups. Variations in practice pattern will always exist among anesthesiologists, making it difficult to control the type and dose of drugs used in retrospective studies. Although less opioid is generally used with regional anesthesia, this may not always be the case. In a study done by Scavonetto et al., improved progression-free and overall-survival were seen in patients receiving combined epidural and GA compared to those receiving GA alone [10]. However, in a subsequent study published by the same group, no difference was seen between those receiving GA and epidural anesthesia [16]. This was attributed to prolonged infusion of epidural fentanyl in the latter group, which was absorbed systemically. Furthermore, use of anti-inflammatory and opioid medications pre- and postoperatively were left uncontrolled limiting any conclusions given their contribution to the perioperative immunologic responses.

Taken together, the impact of anesthesia technique on prostate cancer outcomes remains unclear. The risk of unidentified confounding factors is significant in these retrospective studies, making interpretation difficult. Prospective RCTs with standardized protocols may help eliminate variation in perioperative anesthesia practice. However, low recurrence rates and prolonged time to recurrence in prostate cancer, together with the substantial numbers required to identify a small relative reduction in recurrence, make prospective RCTs in this disease group somewhat impractical. Moreover, as use of minimally invasive techniques for radical prostatectomy becomes more commonplace, the minimal requirement for opioids, combined with less activation of the surgical stress response and less immune suppression may further limit the ability to detect an effect of anesthetic technique on outcome. Indeed, there is significant preclinical as well as prospective trial evidence of differences in early inflammatory and anticancer immunological responses between open and laparoscopic

approaches to cancer surgery, although none of these include investigations in prostate cancer [52,53].

3.2. Bladder cancer

Most bladder cancers are nonmuscle invasive bladder cancer (NMIBC) at the time of presentation and, given the high recurrence rates and generally intensive local therapies, NMIBC represents a highly prevalent and a resource-intensive cancer to manage [54]. The high recurrence rates, short time to recurrence, and ability to readily perform transurethral resection of bladder tumors (TURBTs) under GA or regional anesthesia, make this an ideal model to evaluate the effect (if any) different anesthetic techniques may have on oncological outcomes.

To date, 3 retrospective studies have evaluated the impact of anesthetic technique on outcomes after TURBT, all of which were published in the last 3 years [18−21]. The first study was a retrospective analysis of 137 and 24 patients who underwent TURBT under spinal and GA respectively. This showed a partial correlation between increased 5-year survival and spinal anesthetic, but no difference in 5-year recurrence rates [18]. Important limitations of this study were that the authors: (1) did not control for pathological grade between groups; (2) did not record use of adjuvant therapy; and (3) did not clearly define recurrence. Two more recent studies did find an association between spinal anesthesia and decreased recurrence rates following TURBT [19,20]. Choi et al. examined 5-year recurrence rates in 534 and 156 propensity-matched patients who underwent TURBT under spinal and GA respectively [19]. After a median follow-up time of 35 months, spinal anesthesia was associated with a lower incidence of recurrence (HR 0.64; 95% confidence interval 0.498−0.826; $P < 0.001$) and longer time to recurrence (41.1 vs. 35.5 months; $P < 0.001$) compared to GA [19]. Similarly, in a cohort of 231 patients who underwent TURBT, Koumpan et al. showed that spinal anesthetic was associated with a lower incidence of recurrence on multivariable analysis (OR 2.06, 95% CI 1.14−3.74; $P = 0.017$) and longer time to recurrence compared to GA (42.1 vs. 17.2 months; $P = 0.014$) after controlling for European Organization for Research and Treatment of Cancer risk group (amalgam of tumor grade, stage, size, and number of lesions) and use of adjuvant therapy [20]. Limitations of the latter 2 studies include their retrospective design and relatively small sample sizes; furthermore, they did not report specific perioperative medication protocols for each group.

Use of regional analgesia in combination with GA at time of cystectomy for muscle invasive disease has not been associated with improved cancer-specific or overall survival, although there are limited studies [21,22,49]. Weingarten et al. found no difference in rates of cancer recurrence, cancer-specific survival, or overall survival between patients who underwent cystectomy with addition of spinal anesthesia ($n = 195$) and those who had GA alone ($n = 195$) [21]. This was despite significantly less opioid use in the regional anesthesia group, which would be expected to allow for a more robust immunologic response. Similarly, Doiron et al. found that use of thoracic epidural analgesia was not associated with reduced cancer-specific or overall survival in 1,628 patients undergoing cystectomy over a 5-year observation period [22]. Limitations of these studies include their retrospective nature, lack of controlled perioperative medication protocol, and confounding use of GA in addition to regional anesthesia.

In summary, for patients with bladder cancer, regional (spinal) anesthesia was associated with lower recurrence rates and longer time to recurrence following treatment with TURBT for NMIBC in retrospective studies, but this has not been demonstrated for cystectomy for muscle-invasive disease. Studies in muscle-invasive bladder cancer were limited however by confounding use of GA and lower incidence of the primary outcome (cancer-specific or overall mortality) compared to TURBT studies (primary outcome recurrence). Few studies in other cancer types have shown differences in oncological outcomes (rather than overall survival) with regional anesthesia compared to GA [42]. The high recurrence rates, short time to recurrence, and ability to readily perform TURBTs under regional anesthesia alone, may support the findings of improved cancer-specific outcomes in these studies with NMIBC as compared to other cancer sites.

4. Emerging trials

To date, the results of studies comparing GA and regional anesthesia have been limited by relatively small sample size, retrospective nature, and lack of randomization between experimental groups. However, there are multiple emerging studies that are attempting to overcome these limitations, some of which are particularly relevant to the scope of this review.

Multiple retrospective studies have demonstrated an association between intraoperative opioid use and decreased survival in patients with breast, nonsmall-cell lung, and prostate cancers [6,47,48]. This proposed link is currently being evaluated in a RCT being conducted in 146 patients undergoing radical prostatectomy (NCT03212456). The primary objective is to evaluate tumor biochemical recurrence after radical prostatectomy in patients undergoing opioid anesthesia compared to patients anesthetized without opioids. Additionally, this study will evaluate the quality of analgesia between the 2 techniques, patient satisfaction with perioperative period, quality of anesthetic recovery, and adverse effects (nausea, vomiting, pruritus, and drowsiness).

As previously described, inhalational anesthetics are thought to promote tumor growth through the inhibition of NK cells, which normally function to inhibit tumor growth [40]. Meanwhile, the intravenous anesthetic propofol

purportedly does not reduce NK cell activity nor does it inhibit cell-mediated immunity [36]. In an attempt to validate this hypothesis, a phase IV RCT is examining the immunomodulatory effects of volatile and TIVA-propofol for patients with renal cell cancer (NCT03514550). For this study, patients that are scheduled for nephrectomy are randomized to receive either TIVA with propofol or inhalation anesthesia with sevoflurane. The trial's primary outcome is the expression of CD16 on NK cells as measured on postoperative day 1. This trial will also use flow cytometry based analysis of lymphocyte populations (CD3+, CD4+, CD8+, CD16+, CD19+, CD25+, and HLA-DR+) at baseline, end of surgery, and on postoperative days 1, 3 to 4, and 7 in a cohort of 20 patients.

There have been 3 recent studies examining the relationship between the anesthetic technique and outcomes after TURBT [18−20]. However, these studies have been limited by their lack of specific perioperative medication protocols and their retrospective nature. To address this, a randomized phase II study is evaluating the difference in 2-year recurrence rate based on the anesthetic method used during TURBT for NMIBC (NCT03597087). This study will randomize 289 patients into either a spinal anesthesia group or a GA group in a 1:1 ratio, where the spinal group will receive intrathecal bupivacaine and the GA group will receive propofol. Postoperatively, patients will undergo surveillance cystoscopy every 3 months, for 2 years. The primary outcome will be 2-year recurrence-free survival rate.

5. Conclusions

The perioperative period is a key time during which promotion of cancer metastasis may occur through direct tumor spillage at the time of surgery, suppression of the antitumor immune response, and direct stimulatory effects on cancer cells. Regional anesthesia is thought to improve the oncoimmunological response through decreased use of volatile anesthetics and opioids, decreased activation of the surgical stress response, and a direct local anesthetic-mediated anti-inflammatory effect. Current data are limited to retrospective studies, which lack controlled perioperative medication protocols and often employ adjunct use of GA, which may be confounding. The strongest association of anesthetic type and outcome appears to be that for NMIBC, as regional anesthesia was associated with lower recurrence rates and longer time to recurrence [19,20]. Prospective studies are needed to further investigate the relationship of anesthesia technique on oncological outcomes. The high recurrence rates, short time to recurrence, and ability to readily perform TURBTs under regional anesthesia alone, make NMIBC an attractive disease model to evaluate this association in a prospective manner. There are a number of RCTs ongoing including trials in NMIBC (NCT03597087), and it is likely that a positive result could be easily translated to routine practice and enhance the quality of care for these patients.

References

[1] Kim R. Anesthetic technique and cancer recurrence in oncologic surgery : unraveling the puzzle. 2017:159−177. doi:10.1007/s10555-016-9647-8

[2] Cassinello F, Prieto I, Oncology R, Anesthesiology O, Rivas S, Strichartz GR. Cancer surgery : how may anesthesia influence outcome ? J Clin Anesth 2015:1−11. https://doi.org/10.1016/j.jclinane.2015.02.007.

[3] Schlagenhauff B, Ellwanger U, Breuninger H, Stroebel W, Rassner G, Garbe C. Prognostic impact of the type of anaesthesia used during the excision of primary cutaneous melanoma. Melanoma Res. 2000 Apr [cited 2019 Apr 11];10(2):165−9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10803717.

[4] Tseng JH, Cowan RA, Afonso AM, Zhou Q, Iasonos A, Ali N, et al. Perioperative epidural use and survival outcomes in patients undergoing primary debulking surgery for advanced ovarian cancer. Gynecol Oncol. 2018 Nov [cited 2019 Apr 11];151(2):287−93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0090825818311545.

[5] Grandhi RK, Lee S, Abd-Elsayed A. The Relationship between regional anesthesia and cancer: a metaanalysis. Ochsner J. 2017 [cited 2019 Apr 11];17(4):345−61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29230120.

[6] Zylla D, Gourley BL, Vang D, Jackson S, Boatman S, Lindgren B, et al. Opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer. Cancer. NIH Public Access; 2013 [cited 2018 Nov 21];119(23):4103−10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24104703.

[7] Lee BM, Singh Ghotra V, Karam JA, Hernandez M, Pratt G, Cata JP. Regional anesthesia/analgesia and the risk of cancer recurrence and mortality after prostatectomy: a meta-analysis. Pain Manag 2015;5 (5):387–95. https://doi.org/10.2217/pmt.15.30.

[8] Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology 2008;109 (2):180–7. https://doi.org/10.1097/ALN.0b013e31817f5b73.

[9] Wuethrich PY, Schmitz SFH, Kessler TM, et al. Potential influence of the anesthetic technique used during open radical prostatectomy on prostate cancer-related outcome: a retrospective study. Anesthesiology 2010;113(3):570–6. https://doi.org/10.1097/ALN.0b013e3181e4f6ec.

[10] Scavonetto F, Yeoh TY, Umbreit EC, et al. Association between neuraxial analgesia, cancer progression, and mortality after radical prostatectomy: a large, retrospective matched cohort study. Br J Anaesth. 2014;113:95–102.

[11] Tsui BC, Rashiq S, Schopflocher D, et al. Epidural anesthesia and cancer recurrence rates after radical prostatectomy. Can J Anaesth. 2010;57(2):107–12.

[12] Forget P, Tombal B, Scholtes JL, et al. Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anaesthesiol 2011;28(12):830–5.

[13] Wuethrich PY, Thalmann GN, Studer UE, Burkhard FC. Epidural analgesia during open radical prostatectomy does not improve long-term cancer-related outcome: a retrospective study in patients with advanced prostate cancer. PLoS One 2013;8(8):e72873.

[14] Roiss M, Schiffmann J, Tennstedt P, et al. Oncological long-term outcome of 4772 patients with prostate cancer undergoing radical prostatectomy: does the anaesthetic technique matter? Eur J Surg Oncol 2014;40(12):1686–92.

[15] Tseng KS, Kulkarni S, Humphreys EB, Carter HB, Mostwin JL, Partin AW, et al. Spinal anesthesia does not impact prostate cancer recurrence in a cohort of men undergoing radical prostatectomy: an observational study. Reg Anesth Pain Med. [cited 2018 Nov 21];39(4):284−8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24918335

[16] Sprung J, Scavonetto F, Yeoh TY, et al. Outcomes after radical prostatectomy for cancer: a comparison between general anesthesia and epidural anesthesia with fentanyl analgesia: a matched cohort study. Anesth Analg 2014;119(4):859–66.

[17] Ehdaie B, Sjoberg DD, Dalecki PH, Scardino PT, Eastham JA, Amar D. Association of anesthesia technique for radical prostatectomy with biochemical recurrence: a retrospective cohort study. Can J Anaesth 2014;61(12):1068–74.

[18] 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(1):4–9. https://doi.org/10.1186/s12871-016-0181-6.

[19] Choi W-J, Baek S, Joo E-Y, Yoon S-H, Kim E, Hong B, et al. Comparison of the effect of spinal anesthesia and general anesthesia on 5-year tumor recurrence rates after transurethral resection of bladder tumors. Oncotarget [Internet]. Impact Journals, LLC; 2017 [cited 2018 Nov 25];8(50):87667–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29152110.

[20] 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 2018;199(4):940–6. https://doi.org/10.1016/j.juro.2017.11.064.

[21] Weingarten TN, Taccolini AM, Ahle RNST, et al. Perioperative management and oncological outcomes following radical cystectomy for bladder cancer : a matched retrospective cohort study ´riope´ratoire et devenirs oncologiques apre ' s une Prise en charge pe´tude cystectomie radicale pour un cancer. 2016:584-595. doi:10.1007/s12630-016-0599-9

[22] Doiron RC, Jaeger M, Booth CM, Wei X, Siemens DR. Is there a measurable association of epidural use at cystectomy and postoperative outcomes? A population-based study. Can Urol Assoc J 2016 [cited 2018 Nov 25];10(9−10):321. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27800053.

[23] Oâ Dwyer MJ, Owen HC, Torrance HDT. The perioperative immune response. Curr Opin Crit Care 2015;21(4):336–42. https://doi.org/10.1097/MCC.0000000000000213.

[24] Talmadge JE, Fidler IJ. AACR centennial series AACR centennial series: the biology of cancer metastasis: historical perspective. 2010. doi:10.1158/0008-5472.CAN-10-1040

[25] Melamed R, Bar-Yosef S, Shakhar G, Shakhar K, Ben-Eliyahu S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. Anesth Analg 2003;97(5):1331–9. https://doi.org/10.1213/01.ANE.0000082995.44040.07.

[26] Pasero C, Gravis G, Granjeaud S, et al. Highly effective NK cells are associated with good prognosis in patients with metastatic prostate cancer. Oncotarget 2015;6(16):14360–73. https://doi.org/10.18632/oncotarget.

[27] Wong HPS, Ho JWC, Koo MWL, et al. Effects of adrenaline in human colon adenocarcinoma HT-29 cells. Life Sci 2011;88(25−26):1108–12. https://doi.org/10.1016/j.lfs.2011.04.007.

[28] Sood AK, Bhatty R, Kamat AA, et al. Stress hormone-mediated invasion of ovarian cancer cells. Clin Cancer Res 2006;12(2):369–75. https://doi.org/10.1158/1078-0432.CCR-05-1698.

[29] Bernabé DG, Tamae AC, ÉR Biasoli, Oliveira SHP. Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells. Brain Behav Immun 2011;25:574–83. https://doi.org/10.1016/j.bbi.2010.12.012.

[30] Yang E V, Kim S, Donovan EL, et al. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: Implications for stress-related enhancement of tumor progression. Brain Behav Immun 2009;23(2):267–75. https://doi.org/10.1016/j.bbi.2008.10.005.

[31] Calcagni E, Elenkov I. Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. Ann NY Acad Sci 2006;1069(1):62–76. https://doi.org/10.1196/annals.1351.006.

[32] Hormbrey E, Han C, Roberts A, Mcgrouther DA, Harris AL. The relationship of human wound vascular endothelial growth factor (VEGF) after breast cancer surgery to circulating vegf and angiogenesis. 2003 http://clincancerres.aacrjournals.org/content/clincanres/9/12/4332.full.pdf.

[33] Nakasaki T, Wada H, Shigemori C, et al. Expression of tissue factor and vascular endothelial growth factor is associated with angiogenesis in colorectal cancer. Am J Hematol 2002;69(4):247–54. https://doi.org/10.1002/ajh.10061.

[34] Obermajer N, Wong JL, Edwards RP, Odunsi K, Moysich K, Kalinski P. PGE 2 -driven induction and maintenance of cancer-associated myeloid-derived suppressor cells. Immunol Invest 2012;41(6−7):635–57. https://doi.org/10.3109/08820139.2012.695417.

[35] Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The choice of anaesthetic—sevoflurane or propofol—and outcome from cancer surgery: A retrospective analysis. Ups J Med Sci 2014;119(3):251–61. https://doi.org/10.3109/03009734.2014.922649.

[36] Lee JH, Kang SH, Kim Y, Kim HA, Kim BS. Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: a retrospective study. Korean J Anesthesiol 2016;69(2):126. https://doi.org/10.4097/kjae.2016.69.2.126.

[37] Wigmore TJ, Mohammed K, Jhanji S. Long-term survival for patients undergoing volatile versus IV anesthesia for cancer surgery. Anesthesiology 2016;124(1):69–79. https://doi.org/10.1097/ALN.0000000000000936.

[38] Cho JS, Lee MH, Kim S Il, et al. The effects of perioperative anesthesia and analgesia on immune function in patients undergoing breast cancer resection: a prospective randomized study. Int J Med Sci 2017;14(10):970–6. https://doi.org/10.7150/ijms.20064.

[39] Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B, Global Onco-Anesthesia Research Collaboration Group. Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia. Can J Anaesth. 2019 [cited 2019 Apr 11];66(5):546−61. Available from: http://link.springer.com/10.1007/s12630-019-01330-x.

[40] Inada T, Yamanouchi Y, Jomura S, et al. Effect of propofol and isoflurane anaesthesia on the immune response to surgery. Anaesthesia 2004;59(10):954–9. https://doi.org/10.1111/j.1365-2044.2004.03837.x.

[41] Os C, Kolodzie K, Cc A, Nl P. Anaesthetic techniques for risk of malignant tumour recurrence (Review). 2014;(11). doi:10.1002/14651858.CD008877.pub2. www.cochranelibrary.com

[42] Sun Y, Li T, Gan TJ. The effects of perioperative regional anesthesia and analgesia on cancer recurrence and survival after oncology surgery. Reg Anesth Pain Med. 2015 [cited 2018 Nov 21];40(5):589−98. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26263074.

[43] Ahlers O, Nachtigall I, Lenze J, et al. Intraoperative thoracic epidural anaesthesia attenuates stress-induced immunosuppression in patients undergoing major abdominal surgery. Br J Anaesth 2008;101(6):781–7. https://doi.org/10.1093/bja/aen287.

[44] Votta-Velis EG, Piegeler T, Minshall RD, et al. Regional anaesthesia and cancer metastases: the implication of local anaesthetics. Acta Anaesthesiol Scand 2013;57(10):1211–29. https://doi.org/10.1111/aas.12210.

[45] Chae B-K, Lee H-W, Sun K, Choi Y-H, Kim H-M. The effect of combined epidural and light general anesthesia on stress hormones in open heart surgery patients. Surg Today 1998;28(7):727–31. https://doi.org/10.1007/BF02484619.

[46] Missair A, Cata JP, Votta-Velis G, et al. Impact of perioperative pain management on cancer recurrence: an ASRA/ESRA special article. Reg Anesth Pain Med. 2019 [cited 2019 Mar 23];44(1):1328. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30640648.

[47] Lennon FE, Moss J, Singleton PA. The μ-Opioid receptor in cancer progression. Anesthesiology. 2012 [cited 2018 Nov 21];116(4):940−5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22357347.

[48] Aich A, Gupta P, Gupta K. Could perioperative opioid use increase the risk of cancer progression and metastases? Int Anesthesiol Clin [Internet]. NIH Public Access; 2016 [cited 2018 Nov 21];54(4):e1−16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27602710.

[49] Chipollini J, Alford B, Boulware DC, Forget P, Gilbert SM, Lockhart JL, et al. Epidural anesthesia and cancer outcomes in bladder cancer patients: is it the technique or the medication? A matched-cohort analysis from a tertiary referral center. BMC Anesthesiol. 2018 [cited 2019 Apr 11];18(1):157. Available from: https://bmcanesthesiol.biomedcentral.com/articles/10.1186/s12871-018-0622-5.

[50] Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology. 2006 [cited 2018 Nov 21];105 (4):660−4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17006061.

[51] Cata JP, Keerty V, Keerty D, Feng L, Norman PH, Gottumukkala V, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. Cancer Med. Wiley-Blackwell; 2014 [cited 2018 Nov 21];3(4):900−8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24692226.

[52] Okholm C, Goetze JP, Svendsen LB, Achiam MP. Inflammatory response in laparoscopic vs. open surgery for gastric cancer. Scand J Gastroenterol 2014 Sep;49(9):1027−34. https://doi.org/10.3109/00365521.2014.917698.

[53] Sammour T, Kahokehr A, Chan S, Booth RJ, Hill AG. The humoral response after laparoscopic versus open colorectal surgery: a meta-analysis. J Surg Res 2010 Nov;164(1):28–37. https://doi.org/10.1016/j.jss.2010.05.046.

[54] Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, et al. EAU guidelines on non−muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol. 2017 [cited 2018 Nov 25]; 71 (3):447−61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27324428.