Impact of intraoperative opioid and adjunct analgesic use on renal cell carcinoma recurrence: role for onco-anaesthesia

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Editor—Renal cell carcinoma (RCC) is an immune-mediated disease. Surgery provides a critical window for oncological control of localised disease, though 20–30% of patients still develop metastases.[1] During the perioperative period, both surgical techniques and anaesthetic agents impact cell-mediated immune activity, potentially affecting oncological outcomes.[2]

Opioids have been negatively associated with cancer-specific outcomes in different cancer types.[3] Potential mechanisms include direct effects on tumour cells or altering perioperative immune responses.[4] Despite the immunogenic nature of RCC and the known impact of opioids on the immune system, the potential for anaesthetic agents to potentiate kidney cancer has not been explored. Therefore, we studied the relationship between intraoperative opioid exposure and adjunct analgesics on oncological outcomes after nephrectomy for localised RCC. After Institutional Review Board approval, we combined our institutional nephrectomy database with a database of intraoperative anaesthetic parameters. In this retrospective analysis, we included patients with localised kidney cancer treated between 2010 and 2018, excluding bilateral kidney surgeries, paediatric cases, and benign histologies. Intraoperative opioid dosages were converted into oral morphine milligram equivalents (MME),[5] measured as a continuous variable. This is presented per 10 MME, the equivalent of 50 μg of i.v. fentanyl. Adjunct analgesics were recorded as a three-level categorical variable: no adjunct, any ketamine, and any dexmedetomidine. Patients receiving both dexmedetomidine and ketamine (n=10) were included in either the dexmedetomidine or ketamine group based on the highest infusion dose (either longer duration or higher infusion rate [per weight per time]).

Intraoperative MME and adjunct administration were tested for associations with recurrence-free survival (RFS) and two secondary endpoints, cancer-specific survival (CSS), and overall survival (OS). Median follow-up duration and 95% confidence interval (CI) were estimated using the reverse Kaplan–Meier approach. By using continuous and multilevel categorical variables of interest, analyses were based on covariate-adjustments using Cox Proportional Hazards Regression models rather than propensity-score matching procedures. The model used a backwards selection process starting with clinical (age, BMI, comorbidities, etc.) and surgical (operative and anaesthetic duration, transfusions, open *vs* minimally invasive approach, etc.) factors with $P<0.1$ from univariable analyses and also included well-validated predictive variables regardless of statistical significance: T-stage, N-stage, histology, and tumour size. For all endpoints, non-linear relationships between continuous variables and outcomes were assessed using restricted cubic splines; there was no significant violation of the linearity assumption. All statistical tests were two-sided and $P<0.05$ was considered statistically significant. Extended methods are provided in the Supplementary material.

The cohort comprised 2775 patients, 67% male, median age of 60 yr and BMI of 29 kg m^{-2}. Some 71% of patients had radical nephrectomies, 65% had clear-cell histology, and 95% had negative margins. Opioid administration was non-normally distributed with a median of 68 MME (inter-quartile range: 50–94). Patients receiving adjunct analgesics had more advanced disease: larger tumours, higher stage, and more nodal disease.

During a median follow-up of 3.1 yr (95% CI: 3.0–3.2), 152 patients developed metastases and 176 died, 60 from kidney cancer. Five-year RFS was 88% (95% CI: 87–90), 5-year CSS was 97% (95% CI: 96–97), and 5-year OS was 91% (95% CI: 90–93). The distribution of MMEs summarised year-by-year from 2010 to 2018 indicated that MMEs administered intraoperatively decreased over time for both patients treated with and without opioid-sparing analgesics. Furthermore, the proportion of patients receiving adjunct analgesics increased over time ($P<0.001$). These temporal trends were not significantly associated with differences in patient or disease characteristics.

Higher MME use was associated with adverse RFS in univariable (hazard ratio [HR] 1.06 per 10 MME, 95% CI: 1.03–1.09; $P<0.001$) and multivariable analysis (HR 1.04 per 10 MME, 95% CI: 1.01–1.07; P=0.018) (Fig. 1a). Furthermore, the adverse 5-year RFS predicted for incremental MME increases is illustrated for a low- and high-risk patient (Fig. 1b). Compared with no adjuvant analgesic, ketamine exposure was not

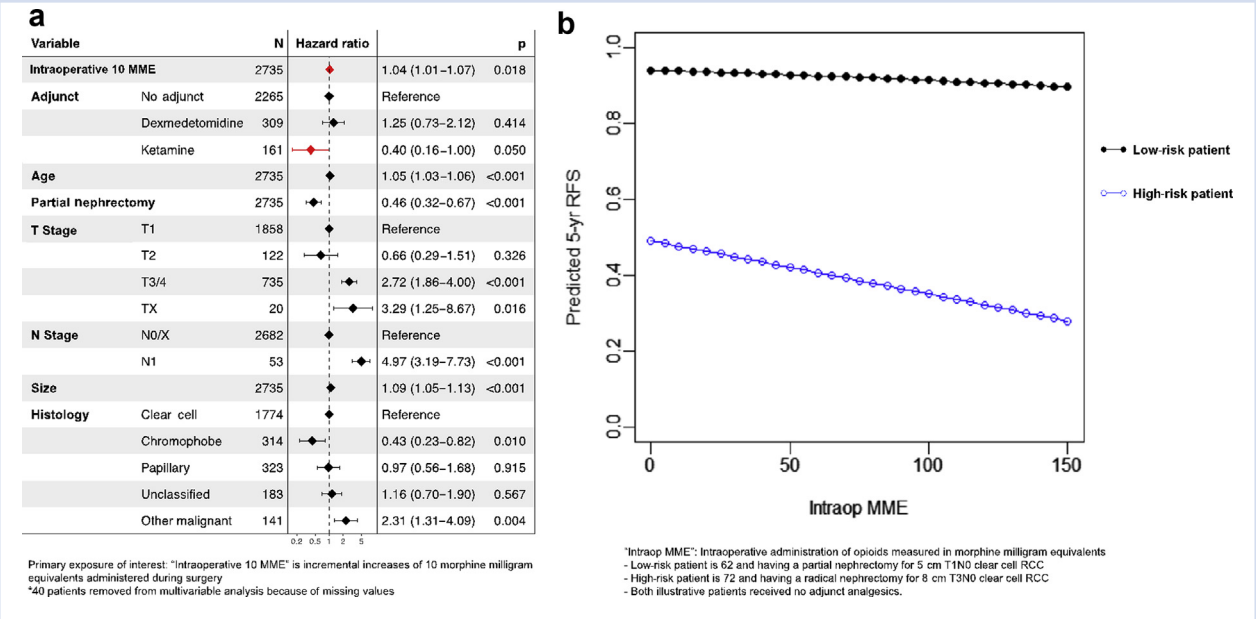

Fig 1. (a) Forest plot of the Multivariable Cox proportional hazards regression model for recurrence-free survival (RFS). (b) Predicted 5-yr RFS by increments of intraoperative morphine milligram equivalents (MME) of two illustrative patients with low vs high risk factors.
(a) Primary exposure of interest: "intraoperative 10 MME" is incremental increases of 10 morphine mg equivalents. 40 patients removed from multivariable analysis due to missing values.
(b) Intraop MME: intraoperative administration of opioids measured in morphine mg equivalents. Low risk patient is 62 yr and having a partial nephrectomy for 5 cm T1N0 clear cell RCC. High risk patient is 72 yr and having a radical nephrectomy for 8 cm T3N0 clear cell RCC. Both illustrative patients received no adjuvant analgesics. RCC, renal cell carcinoma.

significantly associated with RFS on univariable analysis, but was associated with improved RFS on multivariable analysis (HR 0.40, 95% CI: 0.16–1.00; P=0.050). There was no association between dexmedetomidine and RFS compared with no adjunct analgesics.

Higher MME use was associated with reduced CSS on univariable (HR 1.07 per 10 MME, 95% CI: 1.01–1.13; P=0.026) but not multivariable analysis, and with worse OS on univariable (HR 1.05 per 10 MME, 95% CI: 1.02–1.09; P=0.002) and multivariable analysis (HR 1.04 per 10 MME, 95% CI: 1.00–1.08; P=0.032). Neither ketamine nor dexmedetomidine were significantly associated with CSS or OS compared with no adjunct analgesic.

This is the first study that specifically investigates the relationship between opioid dose and RCC outcomes; validation studies, ideally prospective, are necessary to confirm these findings. The only prior studies of anaesthesia and RCC examined epidural use (but not opioid dose) reporting improved OS but not CSS.[6] Okhunov and colleagues[7] reviewed percutaneous renal cryoablation, finding borderline-significant reduction in RCC recurrence when using sedation and local anaesthesia compared with general anaesthesia and fentanyl. In our study, the few patients receiving an epidural did not demonstrate improved survival.

Mechanistically, cancer cells expressing μ-opioid receptors may facilitate tumorigenesis by enhancing immune-resistance and stimulating angiogenesis.[4] Indeed, clinical studies of other cancer types suggest an association between higher opioid doses and reduced RFS for Stage 1 non-small cell lung cancer.[8,9] However, separation of squamous and adenocarcinoma of the oesophagus showed that higher intraoperative opioid doses were associated with improved RFS and OS specifically in squamous variants.[10] This suggests that intraoperative opioid effects on the tumour microenvironment may be specific to tumour genetics.

Accounting for adjunct analgesics was important as opioids confer a somewhat paradoxical systemic effect. Opioids may suppress the antitumor immune response in CD4, CD8, and natural killer cells. However, in rat studies fentanyl minimises postoperative pain reducing lung cancer retention.[11] Therefore, it is essential to distinguish opioids attenuating the immune response from the importance of adequate analgesia protecting against tumour progression.

Study limitations for our study include the retrospective, non-randomised approach. We attempted to reduce bias by limiting the study to a focused cohort who are treated uniformly. Postoperative opioid administration data were unavailable and could provide additional insight. Furthermore, MME conversion potentially obscures the effects of specific opioids on outcomes,[2] although this is mitigated by fentanyl comprising most of our cohort's opioid exposure. Potential biases include higher proportions of patients with advanced tumours receiving adjunct analgesia and evolving intraoperative analgesic regimens coinciding with improved systemic therapy. This confounder is unlikely to pertain to RFS, as such therapies are utilised after metastatic recurrence.

In conclusion, reduced intraoperative opioid use was associated with improved RFS and OS after kidney cancer surgery. Future studies, particularly randomised trials, are required to validate this association. The potential RFS benefit of ketamine is novel and merits further study. Depending on the tumour type, intraoperative analgesics have been

implicated as protective, deleterious, or insignificant regarding oncological outcomes. Ultimately, akin to oncologists selecting the most efficacious systemic therapy by tumour-type, the field of onco-anaesthesia may evolve towards balancing analgesia based upon anticipated oncological impact. Pending prospective trials, this may mean reducing intraoperative opioid use for RCC.

Authors' contributions

Study design: AWS, MLH, JAC, RM, PR, KST, GWF, PJM, AAH, JSM
Analysis: AWS, MLH, JAC, KA, JRS, PR, KST, AAH, JSM
Drafting: AWS, RGD, JM, KST, JSM
Revising, final approval, agree to be accountable: all authors
Data acquisition: RM, RGD, JM, PR, KST, GWF, PJM, AAH, JSM

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.06.036.

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Persistence of intracranial blood flow on cerebral angiography in brain death

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