Peer Review File

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Responses to Reviewers' Comments

Reviewer A Comments	Responses to Reviewer A
I would like to congratulate the authors for taking a critical look at what we call in my country a purple crocodile: i.e. a potentially unnecessary registration burden.	Thank you for this supportive summary and fun reference! We too had this concern, which was one of the primary impetuses of this project as there was no other data on this issue for oncologic patients.
My main objection is: is the PDMP intended to monitor acute opioid use at all? Would it not have been wiser to look at, say, 6-month figures rather than 3-month figures?	We too agree that 6 months is a proper timepoint and used this in constructing the evaluate of the 3-month post-radiation interval. With the 2 months during radiation and 3-month follow-up visit this allows us to capture roughly 6 months of data from initial consultation. We thought about extending the follow-up duration thereafter to 6 months post-RT or a total of 9 months of on study; however, this starts to become an issue of acute (during treatment and 90 days thereafter) vs late toxicity (>90 days) and we wanted to try to isolate to the active treatment phase from chronic opioid use. This is valuable information and we look to further evaluate chronic opioid utilization in future cohorts. We have added the following clarification to the manuscript, "As radiotherapy treatment schedules were delivered over 6 to 7 weeks, the total study period for an individual patient from initial consultation to end of evaluation spanned nearly 6 months. 3 months was chosen as the endpoint as defined as the acute period for treatment toxicity (PMID: 12903007; 7713792)."
I would like more explanation from the	The calculation for MME was the total

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authors about the extremely high opioid doses in my experience (also with the target group). In our clinic, even during radiotherapy, we are at most around 240 MME.	amount for the prescription. This has been further clarified in the revision as such, "Patients were provided education on supportive care at the start of radiotherapy and the use of over-the-counter analgesics including acetaminophen and ibuprofen for those who did not receive concurrent chemotherapy or have other contraindications. All patients were provided viscous lidocaine 2% to use for oral mucositis and dysphagia on treatment. Opioids were not started unless indicated by failure to control pain with alternatives. The typical initial opioid prescription included oxycodone 5mg to 10mg with 60 to 90 tablets for and then personalized for baseline characteristics, degree of pain and individual usage."
The authors also mention the limitations of this study: far too few inclusions. Can the authors indicate how many patients should be included in order to draw definitive conclusions?	Because of the heterogeneity in head and neck cancer patients, our sample was limited to the most homogeneous population possible to reduce confounding variables and underscore that with a retrospective study, larger sample size is always preferred because any estimation and inference is more stable and reliable. However, with our current sample size of 64 patients, we maintain that our response rate is at least a reasonable approximation that could be confirmed with a much larger cohort of patients achievable only through a future multi-center collaboration and expanding the timeframe for analysis.
Why is the word opiate (the naturally occurring opioids morphine and codeine) used instead of the whole group of opioids?	This has been corrected.
Lines 66 - 67: rephrase text: "Evaluate changes in acute opiate analgesic prescribing in head and neck cancer patients before and after PDMP during radiotherapy.	This has been corrected, and changed to more accurately reflect the significance of the cohort, "This is the first reported evaluation of acute opioid analgesic prescribing patterns in head

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	and neck cancer patients undergoing radiotherapy before and after the implementation of a mandated PDMP."

Reviewer B Comments	Responses to Reviewer B
Thank you for presenting an insightful analysis that raises an important question on the impact of PDMPs.	Thank you for your encouraging comments.
Please provide more details on implementation of state required PDMP, was it mandatory to be utilized by a certain date? Is it electronically integrated into the EMR, more insight into how it could pose a hurdle to opiate prescription practices is needed. Since it is being termed an "intervention" more discussion is needed, also were you able to audit if PDMP was accessed for all postintervention patients?	The details regarding the state statute house bill (HB) 21 regarding the PDMP have been added as follows: "While cancer patients were excluded from law, HB 21 required that prior to prescribing or dispending any controlled substance to a patient 16 or older, the prescribing practitioner must first check the Florida Prescription Drug Monitoring Program (E-FORSCE) multi-state database. Additionally, Schedule II opioids intended for acute pain was given a maximum for 3-days or up to 7-days with exception. Additional continuing education requirements as well as documentation in the medical record and within the prescription indicating the lack of alternatives or "non-acute pain" exceptions were required. Electronically sent prescription were required by law with an initial phase in period and the PDMP system for our institution was not integrated into the electronic medical record for the radiation oncology clinic and required a separate login for each encounter. Documentation of all prescriptions was performed via review of the medical record as the PDMP is restricted only to clinical use and a request to audit for research was denied." The auditing is a limitation of the study. All providers were in compliance with the state monitoring system at the present time. The state restricts the PDMP to clinical purposes

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	and specifically restricts any access for purely research intention. We asked the state for permission but were denied access, therefore this is a limitation that we must use prescribed prescriptions rather than verified audit of what was filled at the pharmacy, which may overstate actual use as noted in the limitations.
In regards to pain management you touched on the use of gabapentin, were topical analgesics utilized? Or photobiomodulation?	Because this was a retrospective evaluation, it was more difficult to track over the counter analgesics. We have updated to include in the methods that our standard practice does include administration of 2% viscous lidocaine and that patients who are not on chemotherapy are recommended to take acetaminophen and ibuprofen at the time of pre-treatment education. This description has been added to the revision as noted in the response to reviewer A. A limitation, however, is that this was not trackable given the limitations of the study methods. We do not currently use photobiomodulation, but have added it to the discussion as follows: "Over-the-counter medications and prescription-based products, such as nonsteroidal anti-inflammatories [25], doxepin (PMID: 30990550), and photobiomodulation (PMID: 32666214), and gabapentin, have shown promise."
While MME and DVRS are your primary indicators of pain. Please comment on frequency of other surrogates such as PEG tube placement, IV hydration, ER visits, hospitalization.	This has been updated in the manuscript as follows: Regarding acute toxicity, there was no significant differences between the two cohorts. In total, feeding tubes (or parenteral/IV nutritional support) were indicated in 10/64 (16%), hospitalization occurred in 9/64 (14%). Grade 3+ nutritional toxicities (dry mouth, xerostomia, salivary duct inflammation, nausea and vomiting, trismus, anorexia, dysphagia and mucositis) was seen in 12/64 (19%) and 10/64 (16%) as

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	measured by CTCAE version 3 and 4, respectively.