A prospective feasibility study evaluating the 5x-multiplier to standardize discharge prescriptions in cancer surgery patients

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ABSTRACT

Background: We designed a prospective feasibility study to assess the 5x-multiplier (5x) calculation (eg, 3 pills in last 24 hours × 5 = 15) to standardize discharge opioid prescriptions compared to usual care.
Methods: Faculty-based surgical teams volunteered for either 5x or usual care arms. Patients undergoing inpatient (≥48 hours) surgery and discharged by surgical teams were included. The primary end point was discharge oral morphine equivalents. Secondary end points were opioid-free discharges and 30-day refill rates.
Results: Median last 24-hour oral morphine equivalents was similar between arms (7.5 mg 5x vs 10 mg usual care, P = .830). Median discharge oral morphine equivalents were less in the 5x arm (50 mg 5x vs 75 mg usual care, P < .001). Opioid-free discharges included 33.5% 5x vs 18.0% usual care arm patients (P < .001). Thirty-day refill rates were similar (15.3% 5x vs 16.5% usual care, P = .742).
Conclusion: The 5x-multiplier was associated with reduced opioid prescriptions without increased refills and can be feasibly implemented across a diverse surgical practice.

INTRODUCTION

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It is estimated that there are 72–81 opioid prescriptions per 100 people in the United States and therefore a surplus of diverted opioids in the community that have triggered both state and national efforts to combat this public health crisis [1–4]. Although government-level interventions are well intentioned, these efforts could instead be refocused on

providers' opioid prescribing protocols, which are often discordant with patients' actual needs [5]. This would have a tremendous impact, as opioid prescriptions written by surgeons are often the initial exposure for patients with opioid dependence. Although surgeons are not solely responsible, new persistent opioid use has been identified in up to 10–15% cancer surgery patients [6–10]. Practices relying heavily on provider bias, rather than a patient-centered approach, are associated with excess opioid dissemination and potential community diversion [11–15].

We previously identified variations in opioid prescribing patterns among surgical providers and found that excess opioids were being prescribed across all our department's abdominal cancer sites [6,12,16,17]. This led to the creation of our "4 Pillars" of perioperative opioid reduction, which addressed (1) provider and patient education, (2) limiting the initial peak bolus of inpatient opioid use in the first 24 hours, (3) nonopioid bundles and purposeful weaning to zero or near-zero by the last 24 hours, and (4) standardizing discharge prescription volumes [10,18,19]. Our early efforts focused on the first pillar (education), which was associated with a dramatic shift in department-wide practice from the time we started these efforts in August 2018 to our first reassessment in summer 2019, with a reduction in median discharge oral morphine equivalent (OME) from 200 mg across our department in 2017 to 50 mg by summer 2019 [18,19].

Although progress was made in reducing initial inpatient opioid exposure (second pillar) and improving inpatient weaning (third pillar), one provider-based problem that remained was calculating discharge opioid prescriptions (fourth pillar). We then introduced a novel "5x-multiplier" calculation to tailor "right size" discharge opioid prescriptions based on each patient's last 24-hour opioid use, which was designed based on a March 2017 Centers for Disease Control and Prevention *Morbidity and Mortality Weekly Report* which demonstrated an inflection point at 5-day prescription length in predicting long-term opioid dependence in opioid-naive patients [20,21]. This, along with general recommendations in 2017 to limit prescriptions sizes to less than 1 week, led to the idea of multiplying actual use on the last inpatient day by 5. Our retrospective cohort study of hepatopancreatobiliary (HPB) patients treated in 2018–2019 demonstrated a 67% reduction in discharge opioid volumes compared to usual care, with no reflexive increase in 30-day refill rates [20], suggesting that adopting a patient-centered model for opioid volume calculations can overcome provider bias and variation in discharge opioid volumes.

To expand on our prior study and assess generalizability of the 5x-multiplier, we designed a prospective feasibility study within a quality improvement (QI) initiative to evaluate the 5x-multiplier in a broad, cancer surgery cohort of non-HPB patients. We hypothesized that a similar impact seen in our study of HPB patients would be realized across the full range of surgical oncology procedures and that the 5x-multiplier could be easily implemented across a diverse surgical practice. Furthermore, to address common concerns about underprescribing, we sought to measure refill rates and volumes to find if the 5x-multiplier can accurately estimate a patient's outpatient opioid needs.

METHODS

Study Design and Team Assignments. This prospective feasibility study was designed in summer 2019 and approved by all section chiefs in the Department of Surgical Oncology at The University of Texas MD Anderson Cancer Center. The protocol was approved in August 2019 by the institutional QI Assessment Board for a September 9, 2019, to December 31, 2019, study. Because this was a nonrandomized study of 2 discharge methods within the standard of care, informed consent was waived. The analyses and publication of these data were approved by the Institutional Review Board (PA17-0726). No changes were made to the study protocol during the study period.

There were 5 non-HPB specialties (sarcoma, colorectal, gastric/peritoneal, endocrine, general surgery) included. Inpatient provider teams (faculty, advanced practice providers [APPs], and fellows) were voluntarily assigned by individual faculty to the 5x or usual care (UC) arms and educated on the 5x-multiplier using a distributed slide deck with screen shots of our electronic health record's location of daily opioid use (to calculate the last 24 hours of inpatient use). A laminated pocket card showed all the faculty names and which arm each volunteered for so that APPs and fellows would know the faculty choice. Faculty who did not have an opinion were assigned based on predicted case volume to balance total patients in both arms. There was no attempt to balance all case metrics (eg, operative extent, open versus minimally invasive, expected hospitalization), as this was not a randomized clinical trial. Considering that this study was conducted to assess the feasibility of the 5x-multiplier in a convenience sample, no additional measures were taken to balance cohorts. Additionally, no mandate was given to inpatient APPs or fellows regarding compliance with the faculty-volunteered study arm, and crossover was allowed (ie, those in UC could be discharged with 5x-multiplier volumes and vice versa). UC was defined as the discharging provider's (APP or fellow) discretion, and 5x was defined as taking the last 24-hour OME and multiplying by 5 (eg, if the last 24-hour use was 3 tramadol pills, the discharge prescription would be $3 \times 5 = 15$ tramadol pills). The primary end point was median discharge OME. The secondary end points were opioid-free discharges, 30-day refill rates, and refill volumes. These were compared by intent-to-treat (by assigned arm) and by per-protocol analyses (by actual 5x or non-5x).

Patients and Discharge Process. Patients undergoing inpatient surgery were eligible for inclusion, and exclusion criteria included surgical hospitalizations with discharge <48 hours, discharge by a primary team not involved in the study (eg, inpatient rehabilitation team), or patients with duplicate encounters in the medical record for the same admission. Use of a standardized discharge summary (Supplementary Fig 1) was encouraged to assist with 5x OME calculations (in addition to a laminated pocket card with sample OME conversions) and to track opioid and multimodal pain medications (Supplementary Fig 1). Discharges were processed by APPs and fellows only.

Statistical Analyses and Reporting. Demographic, clinical, inpatient, and discharge medication prescriptions and 30-day opioid refill data were obtained through the electronic medical record. Last-24-hour, discharge, and 30-day refill opioid volumes were converted to OME with institutionally approved tables (eg, 7.5 mg OME = 5 mg oxycodone = 7.5 mg hydrocodone = 75 mg tramadol). Nonparametric statistical comparisons were performed with the Mann–Whitney U test for continuous variables and χ^2 test or Fisher exact test (when percentage < 5%) for categorical values using SPSS version 22 (IBM, Armonk, NY). Unadjusted analyses were performed given the nonrandomized, pragmatic nature of this study. All tests were 2-sided. Figures were assembled with GraphPad Prism version 8 (GraphPad Software, La Jolla, CA). The "Standards for QUality Improvement Reporting Excellence" 2.0 guidelines were used during the design of this study and as a framework for the reporting of our findings [22].

RESULTS

Rounding Teams and Operations. Twenty-two attending surgeons in 5 surgical specialties voluntarily enrolled to participate in either study arm (Supplementary Table 1). A total of 753 consecutive cases were performed by these surgeons participating in the predetermined study period of 4 months. Three-hundred and eight cases were excluded because of discharge in <48 hours or discharge by another primary team; 22 cases were excluded owing to being discharged by a surgical team in a different study arm; and 14 cases were excluded because of duplicate records for patients who underwent multiple procedures
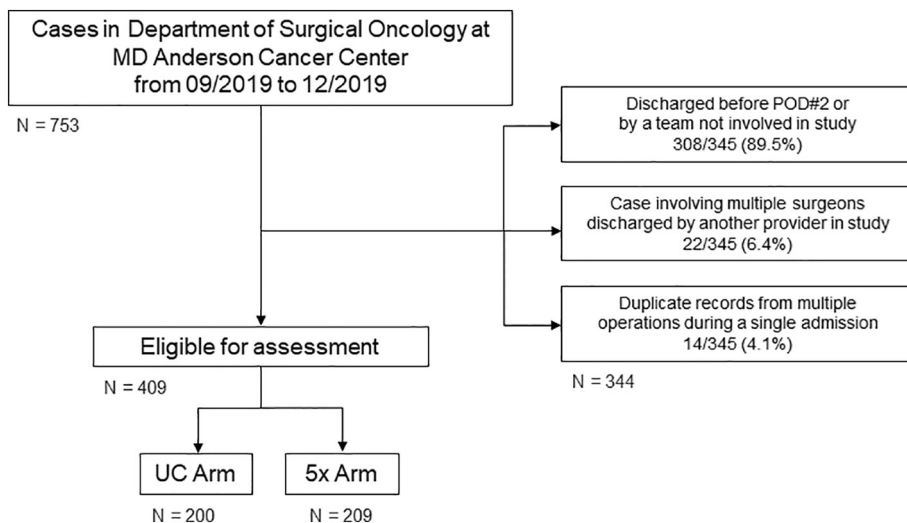
Fig 1. Flowchart of patients included in this prospective feasibility study of the 5x-multiplier in comparison to usual care to guide discharge opioid prescriptions. *POD*, postoperative day.

during the same admission. A total of 409 index hospitalizations were considered evaluable for this study, with 200 in the UC arm and 209 in the 5x arm (Fig 1).

Patients and Primary Analyses. Table 1 depicts the demographics and clinical characteristics for patients included in this feasibility study. Both groups had similar baseline demographics regarding age, sex, smoking status, and body mass index. There was a higher proportion of patients with preoperative opioid prescriptions listed in the medical record in the UC arm (45.0% UC vs 25.4% 5x, $P < .001$). A greater proportion of patients in the 5x arm underwent minimally invasive surgery (26.0% UC vs 39.7% 5x, $P = .003$) and received regional anesthetic blocks (41.0% UC vs 56.9% 5x, $P = .001$). There was no difference in 30-day readmission rates (10.0% vs 10.0%, $P = .999$). Median last-24-hour OME was still similar between groups (10 mg [interquartile range {IQR}: 0–20 mg] UC vs 7.5 mg [IQR: 0–20 mg], $P = .830$). For the

primary end point, median discharge OME was greater in the UC arm (75 mg OME [IQR: 25–150 mg] UC vs 50 mg OME [IQR: 0–100 mg] 5x; $P < .001$). Figure 2, *A* shows the difference in median discharge OME in both arms, with the 5x arm's IQR overlapping with zero. There were more 5x arm patients discharged opioid-free (18.0% UC vs 33.5% 5x; $P < .001$).

Compliance and Refills by Intent to Treat. We retrospectively assessed utilization of the 5x-multiplier and 30-day refill prescriptions in both study arms (Table 2). There were 58.4% cases in the 5x arm which used the 5x-multiplier to calculate discharge opioid prescriptions, 16.7% cases which were sub-5x, and 24.9% cases which were over-5x. In the UC arm, there were 28% patients who received actual 5x prescriptions, 17.5% cases sub-5x, and 54.5% over-5x. Opioid refill rates for the UC and 5x arms were similar at 16.5% and 15.3%, respectively ($P = .742$). By intent to treat, initial

Table 1
Demographics and clinical characteristics

Characteristic	Usual care (n = 200)		5x Multiplier (n = 209)		P value
Age (y), IQR	58	48–69	59	51–70	.144[*]†b, ‡c
Sex					
Male	106	53.0%	109	52.2%	.864[†]
Female	94	47.0%	100	47.8%	
BMI, range	26.48	17.05–57.73	27.96	17.04–48.94	.058[*]
Preoperative prescription					
Opioid	90	45.0%	53	25.4%	<.001[†]
Tylenol	70	35.0%	61	29.2%	.208[†]
NSAID	56	28.0%	51	24.4%	.408[†]
Muscle relaxer	18	9.0%	9	4.3%	.072[‡]
Gabapentin	25	12.5%	16	7.7%	.138[‡]
Smoker	8	4.0%	11	5.3%	.641[‡]
Minimally invasive	52	26.0%	83	39.7%	.003[†]
Regional block	82	41.0%	119	56.9%	.001[†]
Epidural	52	26.0%	14	6.7%	<.001[†]
Major complication (ACC 3 +)	14	7.0%	15	7.2%	.999[‡]
Readmission (30 d)	20	10.0%	21	10.0%	.999[‡]
LOS (d), range	5	2–79	4	2–31	.001[*]
2 + Multimodal at discharge	127	63.5%	131	62.7%	.864[†]
Last-24-h OME median (IQR)	10	0–20	7.5	0–20	.830[*]
Discharge OME median (IQR)	75	25–150	50	0–100	<.001[*]
Proportion discharge OME = 0	36	18.0%	70	33.5%	<.001[†]

BMI, body mass index; *NSAID*, nonsteroidal anti-inflammatory drug; *ACC*, Accordion Classification; *LOS*, length of stay.

[*] Mann–Whitney *U* test.
[†] χ^2 test.
[‡] Fisher exact test.
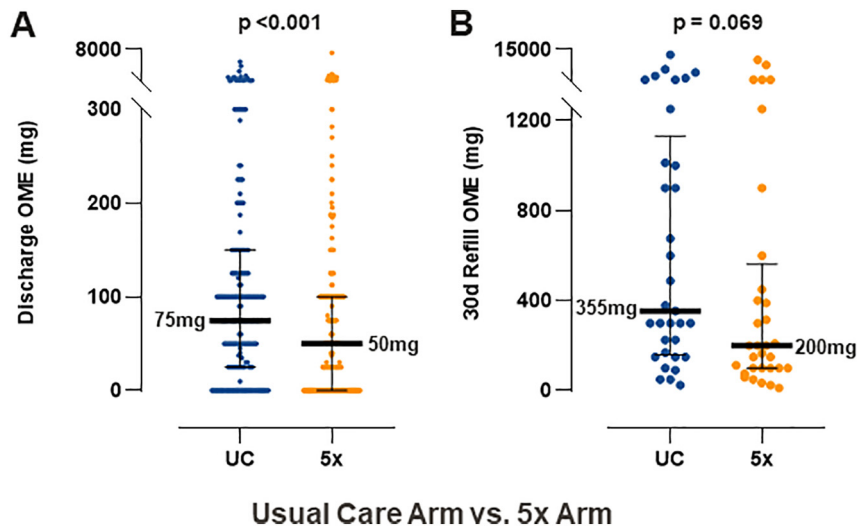
Fig 2. Comparison of opioid prescribing metrics and refill volumes by study arm, with median and IQR represented. A, Median discharge OME was lower in the 5x arm in comparison to the UC arm (50 mg [IQR: 0–100 mg] 5x vs 75 mg [IQR: 25–150 mg] UC; $P < .001$). B, Median 30-day refill OME was lower in the 5x in comparison to the UC (355 mg [IQR: 169–1013 mg] 5x vs 200 mg [IQR: 100–525]; $P = .069$).

opioid refill size was median 355 mg in the UC arm vs 200 mg OME in the 5x arm, not accounting for crossovers ($P = .069$). Figure 2, B shows the difference in the point estimates with narrower IQR in the 5x arm.

***Actual* Prescriptions and Associated Refills.** To assess the impact of 5x-standardized prescriptions on discharge OME and prescription volumes agnostic of study arm, patients receiving 5x prescriptions in both study arms were compared to those who received non-5x prescriptions. Patients receiving actual 5x prescriptions had a median discharge OME of 0 mg (IQR: 0–100 mg) compared to 100 mg (IQR: 50–200 mg) for patients receiving non-5x prescriptions ($P < .001$, Fig 3, A). In Table 2, 30-day refill rates were lowest in patients receiving actual 5x-multiplier prescriptions (14.3% UC arm; 11.5% 5x arm). Again, accounting for crossover, 30-day refill sizes were lowest (with narrower IQR) in patients receiving actual 5x prescriptions in both study arms (159 mg [IQR: 75-225 mg]

UC arm; 106 mg [IQR: 50–200 mg] 5x arm). Figure 3, B depicts the 30-day refill OME for patients (pooling both arms) who received actual 5x discharges in comparison to non-5x discharges, showing both a lower median refill OME and narrower IQR in patients receiving actual 5x prescriptions (131 mg [IQR: 60–200 mg]) compared to any non-5x prescriptions (488 mg [IQR: 210–1800 mg]) ($P < .001$). Postdischarge opioid (first-time) filling rates for patients who were discharged opioid-free were 2.8% (1/36) in the UC arm and 7.1% (5/70) in the 5x arm (Table 2).

Supplementary Figure 2 depicts the slope (the multiplier) of the line representing the real-world multiplier of the x axis (last-24-hour OME) to calculate the discharge prescriptions (y axis). Using the 5x-multiplier blunts the rate of rise by objectively calculating discharge OME based on the last-24-hour OME (x axis) regardless of the actual value. The stack of blue dots (UC arm patients) in the left corner of Supplementary Figure 2 also shows the number of patients who despite being opioid-free in the last 24 hours still received discharge opioids.

Table 2
Use of 5x in both arms and associated refill prescriptions

Characteristic	Total (N = 409)		Usual care (n = 200)		5x Multiplier (n = 209)		P value
	n	%	n	%	n	%	
Compliance with 5x							<.001[†]
Sub-5x	70	17.11%	35	17.50%	35	16.70%	
5x	178	43.52%	56	28.00%	122	58.40%	
Over-5x	161	39.36%	109	54.50%	52	24.90%	
Opioid refill	65	15.89%	33	16.50%	32	15.30%	.742[†]
Refill for actual sub-5x	15	21.43%	7	20.00%	8	22.9%	.771[†]
Refill for actual 5x	22	12.36%	8	14.30%	14	11.50%	.597[†]
Refill for actual over-5x	28	17.39%	18	16.50%	10	19.20%	.671[†]
Refill given for discharge OME = 0	6	5.66%	1	2.80%	5	7.10%	.661[†]
	Median	IQR	Median	IQR	Median	IQR	P value
Discharge OME (intent to treat)	75	0–125	75	25–150	50	0–100	<.001[*][†][b]
Discharge OME when actual sub-5x	55	25–100	60	25–90	50	25–100	.859[*]
Discharge OME when actual 5x	0	0–100	0	0–100	0	0–100	.738[*]
Discharge OME when actual over-5x	120	75–225	120	75–225	113	75–276	.707[*]
Initial refill size OME	300	113–900	355	169–1013	200	100–525	.069[*]
Refill size for actual sub-5x	600	200–1800	600	300–2475	607.5	150–3375	.728[*]
Refill Size for actual 5x	131	60–200	159	75–225	106	60–200	.493[*]
Refill Size for actual over-5x	439	255–1525	581	300–1250	345	150–1800	.501[*]
Refill size for DC OME = 0	62.5	25–165	25	25–25	100	25–165	.553[*]

DC, discharge.
[*] Mann–Whitney U test.
[†] χ^2 test.
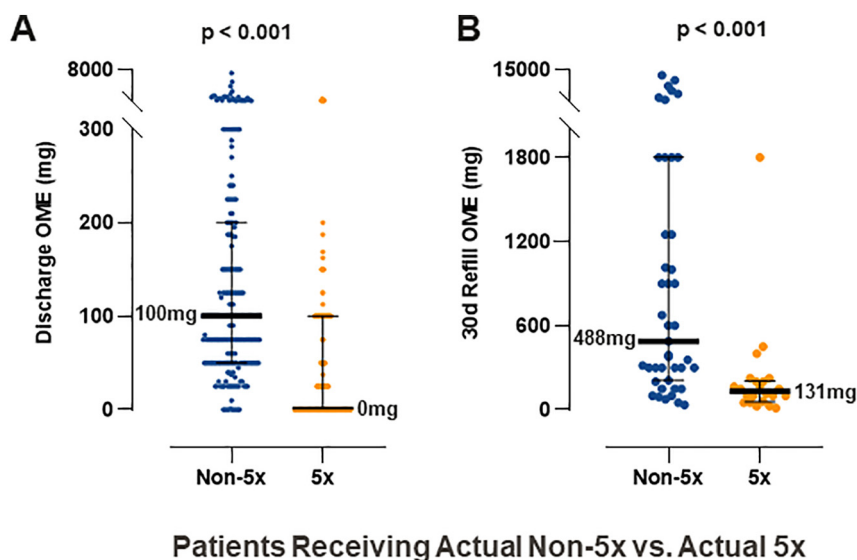
Fig 3. Comparison of opioid prescribing metrics and refill volumes by actual discharge volumes, with median and IQR represented. A, Median discharge OME was lower in patients receiving actual 5x prescriptions in comparison to non-5x prescriptions (0 mg [IQR: 0–100 mg] 5x vs 100 mg [50–200 mg] non-5x). B, Median 30-day refill OME was lower in patients from both study arms receiving actual 5x prescriptions in comparison to non-5x prescriptions (131 mg [IQR: 60–200 mg] 5x vs 488 mg [IQR: 210–1800 mg] non-5x; *P* < .001). *30d,* 30-day.

DISCUSSION

As an expansion of our work assessing the 5x-multiplier calculation to standardize discharge prescriptions in HPB surgical patients, we designed a prospective feasibility study to test the generalizability of this method in a diverse cancer surgery practice. Using the 5x-multiplier calculation of last-24-hour inpatient opioid use was associated with a 33% lower median discharge prescription opioid volume in comparison to usual care. Additionally, one third of patients in the 5x arm were discharged opioid-free vs 18% of UC arm patients. Similar to our previous retrospective HPB study [20], in this prospective feasibility study, there was no difference in 30-day opioid refill rates. And for the first time, we found additional evidence that using the 5x-multiplier was a "right size" calculation for most patients, as refills for patients in both arms receiving 5x prescriptions were dramatically smaller, highlighting how the patient-centered 5x multiplier's positive effects go beyond the initial opioid dissemination, and may provide guardrails for limiting the volume of refills as well. UC patients treated by crossover using a 5x-multiplier prescription derived benefits similar to patients assigned to the 5x arm, showing how a proverbial "rising tide" of a positive QI effort can lift all boats. These promising findings provide supporting rationale for studying the 5x-multiplier in a prospective, randomized fashion.

Standardization of discharge opioid prescriptions remains a pragmatic challenge, as it requires a departure from both the "procedure-specific" one-size fits all and the "provider-specific" usual care approaches [13,18,23]. Provider bias is one of the primary barriers to reducing the volume of opioids prescribed at discharge [12,24]. Hill et al were the first to publish that the amount of postdischarge opioids consumed at home was highly correlated with last-24-hour inpatient opioid usage, suggesting that a patient-centered approach for discharge opioid volumes could be satisfied by categorizing patients into a 3-tier discharge volume guideline [25]. Based on this concept of reviewing the actual opioid use in the last 24 hours, the 2016–2017 federal recommendations to limit initial prescriptions to ≤7 days, and Centers for Disease Control and Prevention data on increased long-term dependence in patients prescribed more than 5 days of initial volume [21], we introduced the 5x-multiplier in 2017–2018 [20].

The 5x-multiplier provides a patient-centered paradigm to simplify decision making and minimize both positive and negative biases of providers. It also removes the guesswork of the "optimal" time of weaning

off opioids, which can range from only a few days to 2 weeks [26]. Bleicher et al have published studies evaluating both "2x" and "4x" multipliers for patient-centered opioid prescribing practices [13,27]. In the present study, we found that there were nearly twice as many patients receiving zero opioids at discharge in the 5x arm (33.5%) in comparison to the UC arm (18.0%). Although this study did not allow for a direct comparison to other tiered (eg, prescribing 5–15–30 pills depending on which tier of use in last 24 hours) protocols for standardizing postoperative opioid prescriptions, one theoretical benefit of the 5x-multiplier over a tiered system is that for patients weaned to zero before discharge, they are not prescribed any outpatient opioids [28,29]. An "opt-in" strategy, as highlighted in the randomized clinical trial by Zhu et al, found that less than half of the patients undergoing cervical endocrine surgery opted in for opioid prescriptions, and of those who opted out, none required rescue opioid prescriptions, suggesting that patients who do not need opioids at discharge are unlikely to desire them later [30]. These findings support the goal of aggressively weaning patients to zero opioids by the day of discharge so that the multiplier results in an opioid-free discharge.

A major barrier to adopting a patient-specific model to reducing discharge opioid prescriptions is the discharging provider's concern for increased refill requests or reduced patient satisfaction [12,31,32]. However, a systematic review by Bicket et al found that 67%–92% of surgical patients had unused opioids, suggesting that overprescription is the far greater problem [5]. The fear that standardizing opioid prescriptions can lead to increased refill requests contributes to overprescribing patterns, which may facilitate nonmedical use and/or community diversion. In this prospective feasibility study, 30-day refill rates were remarkably similar between arms (16.5% UC vs 15.3% 5x). As the 30-day refill rate serves as a surrogate for patient opioid needs, these findings support that the 5x-multiplier can be used without fear of excessive refill requests. Interestingly, we also found that patients who had actual 5x discharges in either study arm had both lower refill rates and substantially lower refill volumes (131 mg vs 488 mg, compared to sub-5x and over-5x), suggesting that 5x is "just right."

These results should be considered in the context of the opioid reduction education program in our department and at other institutions [33–35]. The current prospective feasibility study was initiated in September 2019, or about 1 year following our initial opioid reduction education program in August 2018, in an expanded spectrum of

inpatient cancer surgery to test its generalizability outside our institution. Even in the UC arm, the discharge OME was 75 mg (eg, 15 50-mg tramadol pills), which is a remarkably lower than the median 200 mg (40 pills) that we reported in the pre-education era before summer 2018 [19]. This suggests that the providers in both study arms in fall 2019 were already limiting opioid prescriptions. On top of these previous gains, further standardizing discharge opioids with the 5x-multiplier led to an even greater reduction in both initial (discharge) and secondary (refill) opioid volumes. Additionally, although this feasibility study was conducted in different surgical sections than our previous study of the 5x-multiplier in HPB surgery, it is possible that overlapping APP/fellows between services could have a positive "spillover" effect which may influence opioid prescribing practices [20].

There are inherent limitations to this prospective cohort study, designed with feasibility and pragmatic intent. The most salient is the nonrandomized design, which was chosen owing to lack of equipoise among department providers for a prospective randomized trial. Although we hypothesized that the 5x-multiplier would reduce discharge opioids, the most important result to show to our own colleagues was its feasibility. We did not attempt to balance the treatment arms or enforce compliance, and crossovers were allowed. Although this decision was intentional, it is reflected in the imbalance of study arm composition as there were differences in cohort composition (length of stay, minimally invasive versus open approach, and proportion of regional blocks to epidurals), which limit the ability to perform exact comparisons between arms. This heterogeneity may be attributable to differences in referral composition and/or surgeon pain management philosophy, and although each surgical section was relatively evenly distributed in both arms, there are certainly biases which remain. Also, discharge pain scores were not analyzed, but presumably, clinical decisions were made based on patient needs and satisfaction as seen in the crossover rates. A greater proportion of patients in the UC arm had preoperative opioid prescriptions listed in their charts [36,37], although we have found in reality that many of these "as needed" opioid prescriptions are either not used or rarely used and simply not updated in the medical record. There was crossover in both arms because there was no enforcement of final prescriptions, with 58% compliance in the 5x arm and 72% compliance in the UC arm. Although at first glance those numbers may seem disappointing in that they are not 90%, even in a recent prospective trial of a 3-tier discharge prescription model, the compliance for correct prescription volumes was 91% in the lowest opioid users but down to 61% in the highest users (>30 mg OME in last 24 hours). Thus, our real-world compliance of 58%–72% in a QI study seems reasonable and externally valid [28]. Lastly, there is a possibility that refill rates were underreported if occasional patients received opioid refills elsewhere (outside of our hospital), although this would be expected to be similar in both arms and is furthermore unlikely because most patients call their original surgeon for postoperative issues including refills. Despite these limitations, this study represents a first-of-its-kind, 22-team prospective evaluation of the 5x-multiplier concept across a diverse practice of cancer surgery within a pragmatic QI initiative that did not require mandatory compliance but still yielded dramatic results, validating the feasibility and positive outcomes of using the 5x-multiplier. Additionally, this pragmatic study sets up a potential randomized controlled trial comparing the 5x-multiplier to a 3-tier discharge protocol and/or provider choice (usual care) [28].

In conclusion, this prospective feasibility study within a QI initiative demonstrated that use of the 5x-multiplier to standardize discharge prescriptions was associated with reduced discharge OME, more opioid-free discharges, similar refill rates, and smaller refill volumes for patients undergoing inpatient cancer surgery. These findings provide evidence that the 5x-multiplier can be feasibly implemented across a spectrum of cancer surgery sites and provide clinical equipoise to justify its evaluation in a randomized clinical trial.

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