



Liver

Enhanced recovery in liver surgery decreases postoperative outpatient use of opioids



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ABSTRACT

Background: Pathways of enhanced recovery in liver surgery decrease inpatient opioid use; however, little data exist regarding their effect on discharge prescriptions and post-discharge opioid intake.

Methods: For consecutive patients undergoing liver resection from 2011–2018, clinicopathologic factors were compared between patients exposed to enhanced recovery vs. traditional care pathways. Multivariable analysis was used to determine factors predictive for traditional opioid use at the first postoperative follow-up. The enhanced recovery in liver surgery protocol included opioid-sparing analgesia, goal-directed fluid therapy, early postoperative feeding, and early ambulation.

Results: Of 244 cases, 147 enhanced recovery patients were compared with 97 traditional pathway patients. Enhanced recovery patients were older (median 57 years vs 52 years, $P = .031$) and more frequently had minimally invasive operations (37% vs 16%, $P < .001$), with fewer major complications (2% vs 9%, $P = .011$). Enhanced recovery patients were less likely to be discharged with a prescription for traditional opioids (26% vs 79%, $P < .001$) and less likely to require opioids at their first postoperative visit (19% vs 61%, $P < .001$) despite similarly low patient-reported pain scores (median 2/10 both groups, $P = .500$). On multivariable analysis, the traditional recovery pathway was independently associated with traditional opioid use at the first follow-up (odds ratio 6.4, 95% confidence interval 3.5–12.1; $P < .001$).

Conclusion: The implementation of an enhanced recovery in liver surgery pathway with opioid-sparing techniques was associated with decreased postoperative discharge prescriptions for opioids and outpatient opioid use after oncologic liver surgery, while achieving the same level of pain control. For this and other populations at risk of persistent opioid use, enhanced recovery strategies can eliminate excess availability of opioids.

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Introduction

The opioid epidemic continues to be a major public health concern both in the United States and abroad. Opioids are the source of greater than 60% of deaths related to drug overdose, and the death rate from prescription opioid use has quadrupled in the past 20 years.¹ In addition, the economic burden of this epidemic costs the United States an estimated US\$78.5 billion annually.² For

surgeons, the perioperative period is a critical setting for opioid prescribing and, thus, an area to target for intervention. Research has demonstrated that prescribing opioid medications to even opioid-naïve patients in the perioperative period can lead to long-term use, with rates of new persistent opioid use as great as 6.5%.^{3,4} Specific to the cancer population, recent literature has shown that 10%–15% of patients who had been opioid-naïve before undergoing oncologic surgery became new persistent opioid users.^{5,6}

Recently, Enhanced Recovery After Surgery (ERAS) efforts have improved perioperative outcomes after many types of operations.^{7–10} Specific to liver surgery, enhanced recovery efforts are reported to decrease overall complications and hospital duration of stay.¹¹ One of the pillars of a successful ERAS program is opioid-sparing analgesia. ERAS protocols have been demonstrated

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to decrease rates of inpatient opioid use^{12,13}; however, data are lacking on the ability of enhanced recovery programs to minimize opioid prescriptions at discharge and outpatient opioid use in hepatobiliary surgery. It is important to define strategies for elimination of excess opioids in patients undergoing hepatobiliary surgery, given the continued high proportion of open approaches, the magnitude of resections, the potential alterations to drug metabolism accompanying liver resection, and the frequent need for subsequent adjuvant therapies.

The primary objective of this study was to compare postoperative pain control and postoperative outpatient opioid requirements for patients undergoing hepatectomy, mostly for malignancy, based on whether the patient was managed with an evidence-based enhanced recovery in liver surgery (ERILS) protocol or a traditional recovery pathway. The secondary aim was to compare discharge prescription practices after liver resection between patients managed on the ERILS pathway and patients managed on a traditional recovery pathway.

Methods

Study population and data collection

After approval by our Institutional Review Board (University of Texas MD Anderson Cancer Center, Houston), a prospectively maintained surgical database was queried for consecutive patients intended for liver resection from October 2011 through January 2018 ($n = 387$). Patients who underwent a simultaneous major multivisceral resection (most commonly a colorectal resection) were excluded to control for the potential confounding effects that a concomitant major operation could have on perioperative recovery, as were patients who were explored but determined to be oncologically unresectable. Baseline patient demographics including age, sex, body mass index ([BMI], kg/m²), and American Society of Anesthesiologists (ASA) classification were obtained. Performance status was prospectively collected using the Eastern Cooperative Oncology Group (ECOG) grading system.¹⁴ Perioperative details, including operative approach, operative time, estimated blood loss, and duration of stay, were collected.

Type of recovery pathway (ERILS versus traditional pathway) and use of a regional analgesia technique were noted. Techniques for regional analgesia included thoracic epidural analgesia (TEA) or transversus abdominis plane (TAP) block. Epidural catheters were placed between the 5th–10th thoracic interspinous levels and dosed according to current practices with hydromorphone 5–10 mcg/kg and 3–10 ml of 2% lidocaine (or 0.25% bupivacaine). Standard solutions for continuous infusion were hydromorphone 5 mcg/ml and bupivacaine (0.075%). TAP blocks included both preoperative ultrasonographic-guided injection (by the anesthesiologist) and intraoperative injection (by the surgeon) of long-acting liposomal bupivacaine. Major hepatectomy was defined as involving 3 or more contiguous liver segments.¹⁵ Complications were recorded and graded using the Accordion Severity Grading System. Complications that were grade III or greater were defined as major.¹⁶ Time-to-first postoperative follow-up visit was measured from the date of operation. The few patients with time-to-first-follow-up ≥ 30 days were excluded before statistical analysis.

Opioid use and patient-reported outcomes

Preoperative opioid use was defined as any patient reporting the use of any traditional oral opioid medication within 30 days of operation. In this study, the term “traditional opioid” refers to the semisynthetic oral opioids, including formulations of hydrocodone, oxycodone, and hydromorphone (Table I). Use of tramadol hydrochloride, a weak synthetic agonist of the μ -opioid receptor with

Table I
Classification and terminology of opioid medications

Classification	Opioids		
	Opiate	Traditional opioids	Opiate-like narcotic
Origin	Natural	Semi-Synthetic	Synthetic
Drugs	Morphine	Hydrocodone, oxycodone, hydromorphone	Tramadol

lesser addictive potential, was not included under the traditional opioid classification but was recorded separately and is reported throughout the Results section.¹⁷ In most cases, data on patient opioid use were collected through real-time interview by a dedicated research team. If the patient was not assessed directly by the research team, these data were captured via electronic medical record review of templated notes designed specifically to record opioid intake. All discharge prescriptions were also reviewed. Patient-reported pain scores were recorded from the first postoperative visit documentation, where the worst pain the patient had experienced in the past 24 hours was documented on a 0–10 scale.

Traditional liver surgery pathway

Postoperative management using a traditional pathway consisted of pain control at the discretion of the care team, most typically via intravenous and oral opiates and traditional opioids on an as-needed basis. Similarly, prescriptions for these medications were provided universally at discharge but without standardization of drug or amount.

ERILS pathway

The ERILS protocol has been well-described by Day et al.¹⁸ To be classified as using the ERILS pathway, a patient's perioperative care must have included at minimum: patient education, early oral feeding, goal-directed fluid therapy, multimodal analgesia, and early ambulation. When assessing the ERILS implementation phase, before the streamlined use of order sets that included all elements of the pathway, detailed chart review was performed to determine whether a patient was ERILS compliant. The ERILS analgesia component incorporated the use of a preoperative, multimodal oral regimen consisting of the following: a non-narcotic neuro-modulator (pregabalin), an anti-inflammatory nonsteroidal drug (ie, ibuprofen, or cyclooxygenase-2 inhibitors, ie, celecoxib), and tramadol, as well as regional anesthetic blocks.¹⁹ Postoperatively, patients were managed with similar scheduled multimodal adjuncts and traditional opioid administration only on an as-needed basis for pain uncontrolled by opioid alternatives and/or tramadol.

During the postoperative hospitalization, ERILS patients returned to a multimodality oral regimen that typically included tramadol. At discharge, depending on the inpatient response to these agents and/or issues of outpatient prescription cost, the ERILS pain management strategy consisted of scheduled cyclooxygenase-2 inhibitors or over-the-counter ibuprofen and oral acetaminophen or a low-volume (<30 pills) tramadol prescription for breakthrough pain. Discharge prescriptions for traditional opioids were reserved for patients requiring consistent semisynthetic opioid administration within the past 24 hours of admission.

Patient education and engagement were also an integral part of the ERILS management plan. As such, beginning in August 2013, in conjunction with the phased ERILS implementation, all patients were contacted within 72 hours of hospital discharge and asked a standardized list of questions regarding their recovery. This

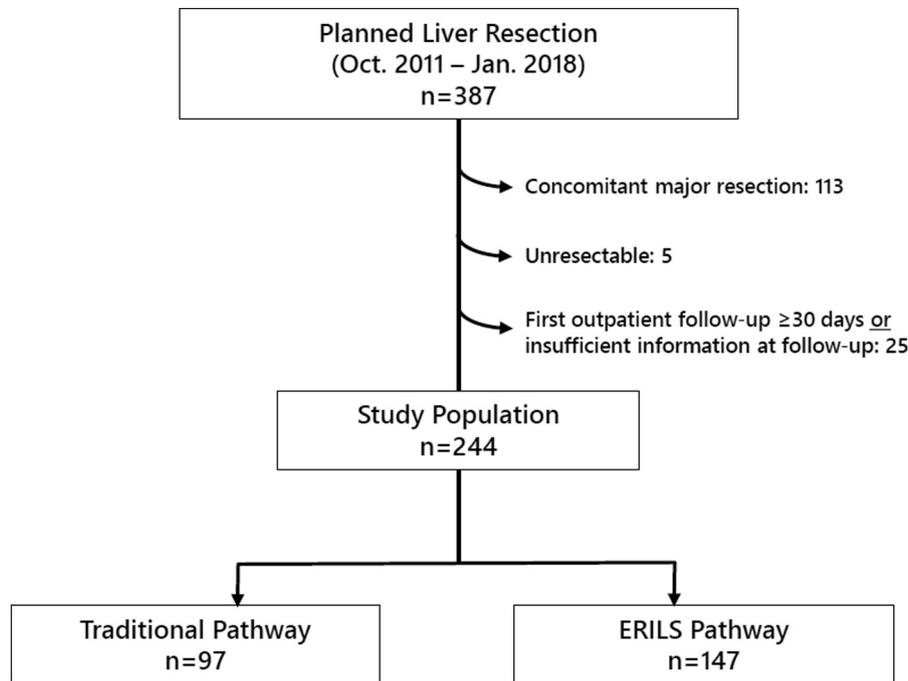


Figure. Study patient inclusion—enhanced recovery in liver surgery (ERILS).

interview included pain control needs and use of opioids and non-narcotic adjuncts.²⁰

Statistical analysis

Categorical variables are expressed as numeric figures and percentages and were compared using the χ^2 or Fisher exact test as appropriate. Continuous variables are expressed as median (interquartile range [IQR]) and were compared using Mann-Whitney *U* tests. All *P* values were two-sided and *P* < .05 was deemed statistically significant. Clinical factors with *P* < .1 on univariate analyses were included in the multivariable analysis that was performed using binary logistic regression and a backward stepwise variable elimination method. All statistical analyses were performed using JMP Pro software (v 12; SAS Institute Inc, Cary, NC).

Results

Study population

Of the 387 patients intended for liver resection during the designated time period, 244 patients met inclusion criteria (Figure). The median age for the entire cohort was 55 years (IQR 46, 62), 116 (48%) of whom were female. The median BMI was 27 kg/m², and the vast majority of patients (91%) had an ASA classification of III. A total of 95% of patients underwent liver resection for a malignancy, with 127 (52%) undergoing resection of colorectal liver metastases. The next most common indications were cholangiocarcinoma for 28 patients (11%) and hepatocellular carcinoma for 23 patients (9%). On final pathology, 11 patients (5%) had benign disease; however, 9 of these patients (82%) underwent resection out of concern for possible malignancy.

ERILS versus traditional pathway patients

Clinical characteristics comparing ERILS (147 patients) versus traditional recovery pathway (97 patients) are presented in Table II.

Baseline demographics were comparable between groups; however, ERILS patients were somewhat older (median age 57 years vs 52 years, *P* = .031) and more likely to have a higher ASA classification (ASA ≥ III for 96% ERILS vs 86% of traditional pathway patients, *P* = .010). Preoperative opioid use was similar between groups, including 17 ERILS (12%) and 14 traditional pathway (14%) patients (*P* = .523).

In regard to perioperative factors, ERILS patients more frequently had a regional anesthetic block compared with traditional pathway patients (85% vs 70%, *P* = .008). Of the 125 ERILS patients who received a block, 52% had a TEA and 48% received a TAP block; whereas 97% of the 68 traditional pathway patients who received a block had TEA and only 2 (3%) received a TAP block. A smaller percentage of ERILS patients (63%) underwent an open operative approach, compared with 84% of traditional pathway patients (*P* < .001). ERILS patients had a shorter hospital duration of stay (4 days vs 6 days, *P* < .001) and a lesser rate of major complications (2% vs 9%, *P* = .011). The rates of bile leak and wound infection were similar between the groups. There were no perioperative deaths in this patient cohort.

Postoperative outpatient opioid utilization

Only 38 (26%) ERILS patients were discharged from the hospital with a prescription for a traditional opioid compared with 76 (79%) of traditional pathway patients (*P* < .001). More ERILS patients were discharged with only tramadol (69% vs 21%, *P* < .001), and more ERILS patients were discharged with purely non-narcotic regimens (4% vs 0%, *P* = .043; Table III).

The median time to first follow-up visit was 10 days for both groups. Information about patient-reported pain scores was available for 129 patients (88%) in the ERILS group and 90 (93%) in the traditional pathway group. At outpatient follow-up, the average pain score for both groups was 2 out of a 10-point scale (ERILS [IQR 0, 3] versus traditional [IQR 0, 4]; *P* = .500). A total of 28 (19%) of ERILS patients reported a traditional opioid requirement at the first visit compared with 59 (61%) of traditional pathway patients

Table II
Patient factors, based on recovery pathway*

Factor	Traditional (n = 97)	Enhanced recovery (n = 147)	P value
Preoperative			
Age (years)	52 (44, 60)	57 (46, 63)	.031
Sex, female	51 (53)	65 (44)	.201
BMI (kg/m ²)	26 (24, 32)	27 (24, 32)	.501
ASA class			.010
II	13 (13)	6 (4)	
III	84 (87)	139 (95)	
IV	0 (0)	2 (1)	
ECOG performance status			.064
0	71 (73)	88 (60)	
1	25 (26)	57 (38)	
2	1 (1)	1 (1)	
3	0 (0)	1 (1)	
Opioid use	14 (14)	17 (12)	.523
Perioperative			
Regional anesthetic block	68 (70)	125 (85)	.008
Open approach	81 (84)	92 (63)	<.001
Major hepatectomy [†]	38 (39)	40 (27)	.054
Multivisceral operation [‡]	7 (7)	5 (3)	.178
Operative time (minutes)	271 (175, 337)	222 (157, 250)	.036
Estimated blood loss (cc)	150 (100, 250)	150 (75, 25)	.249
Duration of stay (days)	6 (5, 7)	4 (3, 6)	<.001
Postoperative			
Any complication	27 (28)	33 (22)	.340
Major complication [§]	9 (9)	3 (2)	.011
Bile leak	2 (2)	10 (7)	.094
Wound infection	6 (6)	6 (4)	.535
Organ space infection	6 (6)	1 (1)	.012
Mortality	0 (0)	0 (0)	—

Bold indicates $P < .05$.

BMI, body mass index; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.

* Values presented as number (percentage) or median (interquartile range [IQR]).

[†] Defined as resection of ≥ 3 contiguous liver segments.

[‡] Defined as minor concomitant operations involving an additional (non-liver) organ/structure.

[§] Accordion Severity Grading System, grade ≥ 3 .

($P < .001$). On subanalysis of the patients not requiring traditional opioids at the first postoperative visit, 60 (50%) of ERILS patients were taking tramadol for pain compared with 17 (45%) of traditional pathway patients ($P = .603$). More ERILS patients (41%) were either taking no analgesic medication or only anti-inflammatory medications compared with 22% of traditional pathway patients ($P = .002$).

On subanalysis of only patients who underwent open-incision liver resection, nearly all patients (99%) received either a traditional opioid prescription or tramadol at discharge; however, ERILS patients were discharged on traditional opioids less frequently compared with non-ERILS pathway patients (34% vs 79%, $P < .001$). At first postoperative visit, only 25% of open-approach ERILS patients reported using a traditional opioid compared to 63% of non-ERILS patients ($P < .001$). There was no obvious difference in the number of open-incision ERILS patients who reported using only anti-inflammatory medications or no analgesia compared to traditional pathway patients (28% vs 20%, $P = .193$) concerning using only anti-inflammatory medications or no analgesia. As with the whole cohort, patient-reported pain scores were equivalent with a median score of 2/10 for both groups.

Multivariable analysis for factors contributing to traditional opioid requirement at the first postoperative outpatient visit is presented in Table IV, showing all factors with $P < .1$ on univariate analysis for postoperative opioid use. Factors found to be independently predictive of traditional opioid use at the first outpatient follow-up visit were preoperative opioid use (odds ratio [OR] 6.1, confidence interval [CI] 2.5–15.9; $P < .001$), traditional recovery

Table III
Postoperative opioid prescriptions and use based on recovery pathway*

	Traditional (n = 97)	Enhanced recovery (n = 147)	P value
Discharge prescription[†]			
Traditional opioid [‡]	76 (79)	38 (26)	<.001
Tramadol	20 (21)	100 (69)	<.001
Anti-inflammatory only/no medication	0	6 (4)	.043
First postoperative visit pain medication use			
Traditional opioid [‡]	59 (61)	28 (19)	<.001
Tramadol	17 (18)	59 (40)	<.001
Anti-inflammatory only/No medication	21 (22)	60 (41)	.002
Pain score [§]	2 (0, 4)	2 (0, 3)	.500
Time to visit	10 (9, 13)	10 (9, 12)	.049

Bold indicates $P < .05$.

* Values presented as number (percentage) or median (interquartile range [IQR]).

[†] Data available for 96 traditional patients (99%) and 144 ERILS patients (98%).

[‡] Includes oxycodone, hydrocodone, hydromorphone.

[§] Data available for 90 traditional patients (93%) and 129 ERILS patients (88%).

pathway (OR 6.4, 95% CI 3.5–12.1; $P < .001$), and open surgical approach (OR 2.6, 95% CI 1.2–5.6; $P = .011$).

Discussion

In this study of patients undergoing mostly oncologic liver resection, the use of an enhanced recovery pathway resulted in decreased opioid use at the time of the first postoperative follow-up. A decrease in outpatient utilization of traditional opioids from 61% to 19% translates into the elimination of 1,860 pills with high addictive potential prescribed to a cohort of 147 patients. It is important to note that, despite the lesser opioid intake, both minimally invasive and open-approach ERILS patients had similarly low patient-reported pain scores as the patients managed via the traditional recovery pathway. On multivariable analysis, the type of recovery pathway was the most significant factor contributing to opioid use, with patients treated on a traditional pathway having greater than 6 times the odds of requiring traditional opioids at the time of postoperative follow-up compared with those treated on the ERILS pathway.

Other reports have demonstrated the ability of enhanced recovery programs to decrease inpatient opioid utilization across various surgical specialties.^{21–25} ERAS in the setting of liver resection, specifically, has been shown to decrease inpatient opioid use.^{12,13} To our knowledge, the present study is the first to analyze the effect of an enhanced recovery program on opioid use at the time of the first postoperative outpatient follow-up. Likewise, in regard to the effect of ERAS on opioid discharge practices, there are very little published data, and the effect has been mixed.^{26–28} For example, a recent study by Brandal et al²⁷ determined that implementation of an ERAS program at their institution had no effect on opioid prescribing at discharge after colectomy despite substantial decreases in inpatient total morphine equivalents compared with pre-ERAS. In fact, 70% of patients in their study who had both low pain scores and low inpatient opioid use (without a preoperative opioid requirement) were still discharged with an opioid prescription. Other studies have demonstrated considerable variation and overprescription of opioids after surgery.^{29,30} According to a 2017 systematic review of studies using patient-reported data, postsurgical patients are highly unlikely to take the majority of opioid pills prescribed, which creates opportunities for community exposure to massive amounts of opioids.³¹

Table IV
Factors contributing to postoperative traditional opioid use*

Factor	Opioid use (n = 87)	No opioid use (n = 157)	Univariate	Multivariable	Odds ratio	95% CI
Age ≤50 (years)	41 (47)	46 (29)	0.005	0.146		
Preoperative opioid use	21 (24)	10 (6)	<0.001	<0.001	6.1	2.5–15.9
Traditional recovery pathway	59 (68)	38 (24)	<0.001	<0.001	6.4	3.5–12.1
Open approach	74 (85)	99 (63)	<0.001	0.011	2.6	1.2–5.6
Major hepatectomy [†]	36 (41)	42 (27)	0.021	0.366		
Multivisceral operation [‡]	7 (8)	5 (3)	0.093	0.300		
Major complication [§]	8 (9)	4 (3)	0.030	0.703		

Bold indicates $P < .05$ on multivariable analysis.

* Designated as the time of the first postoperative follow-up visit (median 10 days, IQR 9–13). Only variables with $P < .1$ on univariate analysis are presented. "Traditional opioid use" includes use of semisynthetic opioids (hydrocodone, oxycodone, hydromorphone).

[†] Defined as resection of ≥ 3 contiguous liver segments.

[‡] Defined as minor concomitant operations involving an additional (nonliver) organ/structure.

[§] Accordion Severity Grading System, grade ≥ 3 .

To be fully effective, the opioid-sparing component of ERAS must carry over into the discharge and postdischarge phases of care. In this study, ERILS patients were substantially less likely to require a traditional opioid prescription at the time of discharge, demonstrating that this is a feasible goal. After ERILS implementation, opioid minimization became the standard of care, with patients requiring traditional opioids at discharge becoming the exception rather than the rule. This change of mindset resulted in the substantial differences in opioid prescribing observed in this study.

It should be noted that ERILS patients were more likely to be prescribed tramadol. Tramadol is classified as a synthetic opiate-like narcotic characterized by a notable decrease in euphoria compared with the effect of traditional opioid medications. Although tramadol does have the potential for abuse,³² its relatively lesser addictive potential compared with other agents has been proven in both animal and human studies that indicate an addiction risk in less than 3% of users and 0.1% of opiate-naïve users.^{17,33,34} The analysis presented in this study, which found that patients managed via the tramadol-associated ERILS pathway were substantially less likely to require traditional opioids and/or any opioids at postoperative follow-up supports the use of this medication within a multimodality, opioid-sparing regimen. The analysis further suggests that more widespread adoption of similar strategies could favorably impact the current nationwide opioid crisis by decreasing rates of opioid dependence in cancer surgery patients.^{5,6} In addition, increasing evidence that opioids stimulate cancer cell growth and activate metastatic pathways indicates the possibility that decreasing overall opioid use may contribute to improved cancer-specific survivals.^{35–37}

In addition to type of recovery pathway, preoperative opioid use and type of surgical approach were other factors predicting a greater likelihood of postoperative opioid requirement (OR 6.1 and OR 2.6, respectively). Although the finding that preoperative opioid use predicts postoperative opioid use is not surprising or novel,^{38,39} it does highlight the importance of a preoperative pain evaluation and presents an opportunity to identify patients at risk for continued long-term opioid use postoperatively.³⁸ More research is needed to determine the feasibility and effectiveness of preoperative opioid tapering before surgery, and multidisciplinary pain management teams should be formed to assist with this vulnerable population.³

Regarding the operative approach, the observed positive impact of minimally invasive surgery on opioid use is consistent with the current literature in liver surgery and other subspecialties and emphasizes that these approaches should be utilized whenever possible.^{40–42} Perhaps more importantly, subanalysis of only those patients who underwent an open approach determined that the impact of ERILS on the observed decrease in opioid use was retained. Because it is not always possible to use a minimally invasive approach in complex, often reoperative, oncologic surgery,

enhanced recovery strategies (including the use of regional nerve blocks) may be most beneficial in these patients, allowing the exposure necessary to safely and effectively complete the resection and replicating the recovery experience traditionally associated with a limited-incision approach.

The implementation of enhanced recovery programs has improved perioperative outcomes after oncologic surgery.⁴³ Our study emphasizes the importance of extending ERAS principles beyond discharge, which requires both education and compliance. Compliance measures need to be in place in order to accurately measure outcomes associated with ERAS implementation. One limitation of this study is that it includes our ERILS implementation "phase-in" period. To manage this issue, we performed a detailed chart review and used strict criteria to differentiate between the components of patients' perioperative care as described to declare a patient on the ERILS pathway. In addition, prior to the creation of the ERILS protocol, separate enhanced recovery components were being adopted. For example, 70% of patients in the traditional pathway received a regional anesthetic block. The implication is that traditional pathway patients were exposed frequently to individual elements of an enhanced recovery pathway. Given the magnitude of the effect on opioid utilization, the presence of partial pathway patients in the traditional cohort only strengthens the conclusion that complete pathway implementation has marked benefits.

Similarly, advances in both operative technique and other aspects of perioperative management may have played a role in the improvement in outcomes for ERILS patients. This effect is demonstrated both by the lesser percent of patients undergoing a major hepatectomy in the ERILS group in favor of parenchymal-sparing approaches, and the greater number of ERILS patients undergoing minimally invasive liver resections. Independent of these practice evolutions, this study demonstrated that a multimodal regimen incorporating regional blocks and patient education nearly eliminated traditional opioids from practice, while still providing excellent pain control.

Conclusions

In this analysis of patients undergoing liver resection at a major cancer referral center, patients managed with an enhanced recovery pathway were substantially less likely to require opioid medications at postoperative outpatient follow-up compared with patients managed on a traditional care pathway, with no increase in patient-reported pain. The direct impact of this finding is that adherence to enhanced recovery pathway has the potential to decrease persistent opioid dependence in this and other similar, at-risk patient populations. Likewise, with the enhanced recovery patients being substantially less likely to even receive an

at-discharge opioid prescription, the opportunity for excess unused opioids to enter and harm both the patient and the community can be avoided. Combined, these benefits further support the widespread implementation of enhanced recovery into surgical practice.

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Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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