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ORIGINAL ARTICLE

Detours on the Road to Recovery: What Factors Delay Readiness to Return to Intended Oncologic Therapy (RIOT) After Liver Resection for Malignancy?

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Abstract

Background Poor recovery after oncologic hepatic resection delays Return to Intended Oncologic Therapy (RIOT) and shortens survival. In order to identify at-risk patients, this study was designed to determine which psychosocial and perioperative factors are associated with delayed RIOT readiness.

Methods A prospectively maintained database was queried to identify consecutive patients undergoing hepatectomy for malignancy from 2015 to 2017. Perioperative factors were compared between patients with early (≤ 28 postoperative days) vs. delayed (> 28 postoperative days) clearance to RIOT. Univariate analysis and multivariable logistic regression were performed.

Results Of 114 patients, 76 patients (67%) had an open surgical approach, 32 (28%) had a major hepatectomy, and 6 (5%) had a major complication, with no mortalities. Eighty-two patients (72%) had early and 32 patients (28%) had delayed RIOT readiness. Patients with high preoperative symptom burden were more likely to have delayed RIOT readiness (OR 3.1, 95% CI 1.1–8.4, $p = 0.024$). On multivariable analysis, open surgical approach (OR 6.9, 95% CI 1.4–34.7, $p = 0.018$), length of stay > 5 days (OR 3.6, 95% CI 1.4–9.4, $p = 0.010$), and any complication (OR 3.4, 95% CI 1.1–10.7, $p = 0.033$) were associated with delayed RIOT readiness. Postoperative factors associated with delayed RIOT readiness included nutritional and wound-healing parameters.

Conclusions This study highlights the previously under-described importance of preoperative patient symptom burden on delayed postoperative recovery. As a cancer patient's return to oncologic therapy after hepatectomy has a substantial impact on survival, it is critical to adhere to enhanced recovery principles and address all other modifiable factors that delay recovery.

Keywords Liver surgery · Postoperative outcomes · Multidisciplinary cancer care · Hepatectomy

Introduction

Since its inception nearly 20 years ago, the Enhanced Recovery After Surgery (ERAS®) program has led to a paradigm shift in the care of surgical patients. The driving principle behind this multidisciplinary, evidence-based perioperative care pathway is that reduction of surgical stress will enable patients to recover more reliably, rapidly and completely.[1, 2] As ERAS protocols have been incorporated into more surgical specialties, studies have confirmed that ERAS adherence correlates with reduced postoperative complications and hospital length of stay (LOS).[3–7] Although these outcomes are important, they are only surrogates for recovery. Given the increasing emphasis on personalized treatment and precision healthcare, the field of enhanced recovery has started to transition its focus to patient-centric outcomes that directly measure postoperative functional recovery.[8, 9]

Enhanced Recovery has the potential to play a particularly crucial role in the perioperative care of cancer patients. With the majority of oncologic diagnoses requiring a multidisciplinary treatment approach, ERAS pathways are key to ensuring rapid recovery from oncologic resection to avoid delays in other intended treatment modalities, most commonly but not limited to chemotherapy. A newly defined surgical oncology

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quality metric that directly comments on recovery in this patient population is Return to Intended Oncologic Therapy (RIOT).[10] Preliminary studies have determined that reporting of RIOT metrics is feasible, that failure to RIOT is associated with worse oncologic outcomes, and that ERAS protocols result in improved RIOT rates.[2, 9–11]

In practice, an important gap in our understanding of RIOT is exactly what factors impact a patient's ability to RIOT; in other words, what factors determine RIOT readiness. As a measure of functional recovery, RIOT readiness has value for all patients, regardless of the actual need for adjuvant therapy. It is known that ERAS protocols minimize perioperative stress, thereby reducing patient complications and improving functional recovery. However, the individual patient and operation-specific details leading to delays in RIOT have not been defined. To address this knowledge gap, this study was designed to analyze perioperative factors associated with early vs. delayed RIOT readiness in patients undergoing liver surgery for malignancy, including a determination of which factors assessed at the initial postoperative outpatient visit further potentiate or mitigate RIOT readiness.

Methods

Setting and Participants

After Institutional Review Board approval, a prospectively maintained hepatobiliary surgery database was queried for consecutive patients on an enhanced recovery protocol undergoing liver resection from January 2015 through November 2017 ($n = 149$). Operations intended for liver biopsy or intraoperative ultrasound only were excluded. Patients without postoperative follow-up with a surgeon in the first 30 days were excluded ($n = 7$). Patients determined at surgery to be oncologically unresectable were included and analyzed as "intention to treat," given these patients are in the greatest need for timely RIOT. All patients were treated on an ERAS pathway that included standardized preoperative patient assessment and education, opioid-sparing analgesia, goal-directed fluid therapy, and early postoperative ambulation and oral feeding as previously published.[9]

Data Collection

Preoperative factors included in outcomes analysis were the use of blood thinners (including anti-platelet agents) or opioid medications, weight loss (characterized as a loss of greater than 10% of a patient's body weight within 6 months of presentation), a previous diagnosis of cirrhosis, and the receipt of preoperative chemotherapy. Laboratory values and performance status based on the Eastern Cooperative Oncology Group (ECOG) grading system were obtained.[12] Perioperative factors included extent of resection, surgical approach, operative time, estimated blood loss, and the total number of liver tumors resected and maximum liver tumor diameter. Major hepatectomy was defined as involving three or more contiguous liver segments.[13] It was noted if there was a concurrent multivisceral operation performed at the same time as the liver resection. Immediate postoperative variables included hospital length of stay (LOS) and the need for a postoperative blood transfusion. Complications were recorded and graded with the Accordion Severity Grading System.[14] Complications that were grade III or higher were classified as major. Bile leakage was defined as Grade A, B, or C per International Study Group of Liver Surgery standards.[15] Factors captured at the initial postoperative visit were wound status, opioid use, laboratory values, and ECOG performance status.

Patient-Reported Outcome Measures

The validated patient-reported outcomes (PRO) assessment tool used in this study was the gastrointestinal-specific version of the MD Anderson Symptom Inventory (MDASI).[16] This tool is composed of 24 questions, each answered on a numerical rating scale from 0 to 10 (Fig. 1). The questionnaire includes a 13-question core symptom assessment, which is common to all versions of the MDASI. The gastrointestinal version (MDASI-GI) contains an additional five questions pertaining to symptoms specific to GI cancers, such as constipation, swallowing, or feeling bloated. Finally, there is a symptom-interference section comprised of six questions targeting the impact that the patient's symptoms have on daily function and well-being. Responses were scored as total numerical score for each section and total overall numerical score. In addition, severe symptoms were defined as a MDASI-GI score ≥ 7 of 10 for any question.[17, 18] The intent was to administer the PRO tool to every patient in the preoperative and postoperative setting.

Determination of RIOT Readiness

All postoperative patients were seen by an experienced surgical oncologist and assigned a time of RIOT readiness. This was based on a holistic review of all postoperative information available for the patient via subjective and objective assessments from the electronic health record. RIOT readiness was determined in all patients, even those for whom further oncologic therapy was not indicated or recommended. Patient recovery was classified as early RIOT readiness if they were ready to RIOT at ≤ 28 postoperative days and delayed RIOT readiness at > 28 postoperative days. This breakpoint designation was made based on the cohort's median RIOT readiness time and the practical need for the RIOT tool to be utilized within the context of the typical patient's postoperative follow-up schedule.

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

M. D. Anderson Symptom Inventory (MDASI - GI)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours.* Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

Core Items:	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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MDASI-GI - October 2009

Fig. 1 MD Anderson Symptom Inventory, Gastrointestinal Version (MDASI-GI)

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

GI Items:	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **diarrhea, or watery stools via stoma (abdominal opening)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **swallowing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **change in taste** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **feeling bloated** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items **in the last 24 hours:**

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
19. General **activity**?	○	○	○	○	○	○	○	○	○	○	○
20. **Mood**?	○	○	○	○	○	○	○	○	○	○	○
21. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
22. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
23. **Walking**?	○	○	○	○	○	○	○	○	○	○	○
24. **Enjoyment** of life?	○	○	○	○	○	○	○	○	○	○	○

MDASI-GI - October 2009

Fig. 1 (continued)

Statistical Analysis

Categorical variables are expressed as number of patients with percentages and were compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables are expressed as median with interquartile range (IQR) and were compared using Mann-Whitney U test. All p values were two-sided and $p < 0.05$ was deemed statistically significant. Logistic regression was performed as multivariable analysis, using variable selection based on a $p < 0.05$ on univariate analysis. Multicollinearity was avoided when possible and factors with low frequency (≤ 5 occurrences) were excluded from the model. Statistical analysis was performed using JMP Pro software (version 12; SAS Institute Inc., Cary, NC).

Results

Study Population

A total of 114 patients met inclusion criteria for this study, with a median age of 55 years (IQR 46, 62) and equal gender distribution. The vast majority of cases were performed for malignancy (93%), with 56 resections (49%) for metastatic colorectal adenocarcinoma and 30 resections (26%) for hepatocellular carcinoma or cholangiocarcinoma. The study includes eight patients who underwent an operation based on findings concerning for malignancy, but ultimately had benign pathology. Three patients (3%) were deemed oncologically unresectable: one patient determined by diagnostic laparoscopy and two patients after laparotomy. Most operations (76%) were performed via open approach and 32 cases (28%) were major hepatectomies. Nineteen cases (17%) involved a combined multivisceral operation, including colectomy for 8 patients, small bowel resection for 4 patients, en bloc sarcoma resection for 2 patients, gynecologic procedure for 2 patients, axillary dissection for 1 patient, genitourinary resection for 1 patient, and adrenalectomy for 1 patient. A sensitivity analysis excluding patients with a multivisceral operation produced similar overall results compared to the entire cohort. The overall complication rate was 19%, with major complications occurring after six operations (5%). Bile leak occurred in 10 patients (9%) and required intervention (Grade B/C) in only one patient. There were no mortalities in the series. Based on disease status, stage, operative findings, and pathology review, the majority of patients (57%) were recommended to receive postoperative systemic chemotherapy. The median time to RIOT readiness was 28 days (IQR 21, 35).

Preoperative and Perioperative Factors Associated With Delayed RIOT Readiness

Baseline factors for both early and delayed RIOT readiness groups are shown in Table 1. The only preoperative factor found to be significantly associated with delayed RIOT readiness on univariate analysis was severe symptom burden on the MDASI PRO assessment tool, with 11 (44%) delayed RIOT readiness patients having severe symptom burden compared to 13 (20%) of early RIOT readiness patients (OR = 3.1, 95% CI 1.1–8.4, $p = 0.024$). Regarding perioperative factors, patients with delayed RIOT readiness were more likely to undergo a major hepatectomy (47% vs. 21%, $p = 0.006$) and have an open rather than minimally-invasive surgical approach (94% vs. 56%, $p < 0.001$). The delayed group had a longer median operative time (289 vs. 220 min, $p = 0.004$) as well as higher estimated blood loss (200 cc vs. 150 cc, $p = 0.021$) and a longer length of stay (6 vs. 4 days, $p < 0.001$). In regard to postoperative complications, the delayed RIOT readiness group had a significantly higher complication rate (34% vs. 13%, $p = 0.011$), but major complication rates were low and comparable between the early and delayed cohorts (9% vs. 4%, $p = 0.347$). Five patients (16%) in the delayed group suffered a wound infection compared to only two patients (2%) with early RIOT readiness ($p = 0.018$).

Multivariable analysis was performed using logistic regression, and all factors in the model are shown in Table 2. Extent of resection and open surgical approach were both included given the different potential etiologies for delayed recovery between these two factors (i.e., risk of liver failure vs. wound healing). Among the perioperative factors, open surgical approach (OR 6.9, 95% CI 1.4–34.7, $p = 0.018$), length of stay > 5 days (OR 3.6, 95% CI 1.4–9.4, $p = 0.010$), and any complication (OR 3.4, 95% CI 1.1–10.7, $p = 0.033$) were independently associated with delayed RIOT readiness. The adequacy of the multivariable analysis was assessed and indicated an appropriately fit regression model (likelihood ratio test; chi-square statistic 31.7, $p < 0.001$).

Postoperative Factors Associated With Delayed RIOT Readiness

Comparisons of factors assessed at the first postoperative visit between early and delayed RIOT readiness groups are detailed in Table 3. The median time to first postoperative visit was 10 days (9–13 days) for the entire cohort, with those in the delayed group having a slightly longer time to first follow-up (13 vs. 10 days, $p = 0.009$). At this visit, patients with delayed RIOT readiness were more likely to have wound-healing issues (28% vs. 4%, $p < 0.001$). The vast majority of these were related to delayed healing with drainage in the absence of

Table 1 Clinicopathologic factors based on timing of RIOT readiness

Factor	Total	Early RIOT	Delayed RIOT	*P* value
No. of patients	114	82	32	--
Preoperative				
Age	55 (46, 62)	54 (46, 61)	57 (44, 66)	0.285
Gender, female	57 (50)	42 (51)	15 (47)	0.835
BMI (kg/m^2)	26 (24, 32)	27 (24, 32)	26 (23, 29)	0.255
ECOG performance status				0.381
0	51 (45)	40 (49)	11 (34)	–
1	61 (54)	40 (49)	21 (66)	–
2	1 (1)	1 (1)	0 (0)	–
3	1 (1)	1 (1)	0 (0)	–
Use of opioids	17 (15)	11 (13.4)	6 (19)	0.560
Use of blood thinners	17 (15)	9 (11)	8 (25)	0.079
Weight loss	5 (4)	2 (2)	3 (9)	0.134
Cirrhosis	7 (6)	5 (6)	2 (6)	1.000
Preoperative chemotherapy	60 (53)	44 (54)	16 (50)	0.835
Hemoglobin (gm/dL)	13.1 (12.1, 14.3)	13.2 (12.1, 14.3)	12.9 (11.6, 13.9)	0.379
White blood cell count (K/μL)	5.6 (4.7, 7.3)	5.5 (4.6, 7.1)	5.9 (5.0, 7.6)	0.137
Neutrophil/lymphocyte ratio	2.3 (1.6, 3.5)	2.3 (1.6, 3.3)	2.8 (1.9, 3.8)	0.258
Platelet count (K/μL)	214 (165, 259)	212 (167, 260)	222 (163, 260)	0.726
Albumin (gm/dL)	4.3 (4.1, 4.5)	4.3 (4.1, 4.5)	4.2 (4.0, 4.5)	0.062
Severe symptom burden[a]	24 (27)	13 (20)	11 (44)	*0.024*
Perioperative				
Open approach	76 (67)	46 (56)	30 (94)	*< 0.001*
Major hepatectomy[b]	32 (28)	17 (21)	15 (47)	*0.006*
Number of liver tumors	1 (1, 3)	1.5 (1, 3)	1 (1, 4)	0.267
Largest tumor diameter	3.1 (1.5, 5.2)	2.4 (1.3, 4.5)	5.9 (2.8, 8.6)	*< 0.001*
Multivisceral operation	19 (17)	10 (12)	9 (28)	0.052
Postoperative transfusion	6 (5)	6 (7)	0 (0)	0.183
Length of stay (days)	5 (3, 6)	4 (3, 5)	6 (5, 8)	*< 0.001*
Postoperative				
Any complication	22 (19)	11 (13)	11 (34)	*0.011*
Major complication[c]	6 (5)	3 (4)	3 (9)	0.347
Bile leak	10 (9)	5 (6)	5 (16)	0.140
Emergency room visit[d]	12 (11)	5 (6)	7 (22)	*0.036*
Wound infection	7 (6)	2 (2)	5 (16)	*0.018*

Values are reported as number (percentage) or median (interquartile range [IQR]); Values with $p < 0.05$ are indicated in italic

RIOT return to intended oncologic therapy, BMI body mass index, ECOG Eastern Cooperative Oncology Group

[a] This data was available for 89 (78%) patients, 64/82 early RIOT patients and 25/32 delayed RIOT patients. Severe symptom burden was defined as MDASI-GI symptom or symptom interference score 7/10

[b] Defined as resection of ≥ 3 contiguous liver segments

[c] Accordion Severity Grading System, Grade ≥ 3

wound infection, as only one patient in both groups had an infected-appearing wound requiring intervention (with antibiotics) at postoperative follow-up. Thirty-one percent of patients with delayed RIOT readiness had an ECOG performance status of 3 at their postoperative visit compared to 4% of patients in the early group ($p < 0.001$). Postoperative hemoglobin and albumin levels were substantially lower in the delayed RIOT readiness group (median hemoglobin 10.7 vs. 12.0 g/dL [$p = 0.004$] and median albumin 3.7 vs. 4.0 g/dL [$p < 0.001$]), compared to the early RIOT readiness group. The median neutrophil/lymphocyte ratio (NLR) was higher in the delayed RIOT readiness group (3.8 vs. 3.3, $p = 0.034$).

Table 2 Preoperative and perioperative factors associated with delayed RIOT readiness

Factor	Early RIOT ($n = 82$)	Delayed RIOT ($n = 32$)	Univariate	Multivariable	Odds ratio	95% CI
Major hepatectomy[a]	17 (21)	15 (47)	0.006	0.240		
Open approach	46 (56)	30 (94)	< 0.001	*0.018*	6.9	1.4–34.7
Length of stay (> 5 days)	15 (18)	18 (56)	< 0.001	*0.010*	3.6	1.4–9.4
Any complication	11 (13)	11 (34)	0.017	*0.033*	3.4	1.1–10.7

RIOT return to intended oncologic therapy

Values are reported as number (percentage). All factors included in the multivariable analysis are shown and were selected based on univariate analysis. Values with $p < 0.05$ are indicated in italic

[a] Defined as resection of ≥ 3 contiguous liver segments

Discussion

This analysis of clinical factors associated with delayed return to oncologic therapy in patients undergoing liver resection for malignancy identifies several novel areas for potential intervention. Regarding the analysis of preoperative factors, none of the traditionally studied variables were associated with delayed RIOT readiness; however, inclusion of PRO data showed that severe preoperative symptom burden may be associated with delayed RIOT readiness. On univariate analysis, those with severe preoperative symptom burden had three times the odds of delayed RIOT readiness compared to those with low symptom burden. Perioperative factors including an open surgical approach, a longer hospital length of stay, and having any complication were also strongly associated with delayed RIOT readiness.

These findings are relevant for several reasons. First, the previously under-described impact of preoperative symptom burden on postoperative outcomes highlights the importance of administering and studying patient-reported outcomes in liver surgery patients. Importantly, although only addressed with univariate analysis, symptom burden on PRO's was the sole preoperative factor associated with delayed recovery. This suggests that comorbidities and traditional measures of performance status alone may be insufficient to identify patients at risk for delayed recovery. As measured by the PRO

Table 3 Postoperative factors based on timing of RIOT readiness

Factor	Total	Early RIOT	Delayed RIOT	*P* value
No. of patients	114	82	32	
Time to postoperative visit (days)	10 (9, 13)	10 (9, 12)	13 (10, 17)	**0.009**
Wound status				**< 0.001**
Dry	102 (89)	79 (96)	23 (72)	
Drainage	10 (9)	2 (2)	8 (25)	
Infected	2 (2)	1 (1)	1 (3)	
Use of opioids	35 (32)	22 (28)	13 (42)	0.174
Hemoglobin (gm/dL)	11.5 (10.4, 12.8)	12.0 (11.0, 12.9)	10.7 (9.7, 12.6)	**0.004**
White blood cell count (K/μL)	7.3 (5.7, 9.1)	7.4 (5.9, 8.8)	7.2 (5.3, 10.6)	0.798
Neutrophil/lymphocyte ratio	3.4 (2.6, 5.2)	3.3 (2.4, 4.7)	3.8 (3.0, 6.6)	**0.034**
Platelet count (K/μL)	267 (224, 361)	267 (228, 369)	273 (201, 357)	0.711
Albumin (gm/dL)	3.9 (3.7, 4.2)	4 (3.8, 4.4)	3.7 (3.3, 3.8)	**< 0.001**
ECOG performance status				**< 0.001**
0	3 (3)	2 (2)	1 (3)	
1	36 (32)	34 (41)	2 (6)	
2	62 (54)	43 (52)	19 (59)	
3	13 (11)	3 (4)	10 (31)	
Adjuvant chemotherapy recommended	63 (55)	45 (57)	18 (56)	1.000

Values are reported as number (percentage) or median (interquartile range [IQR]); Values with $p < 0.05$ are indicated in bold.

RIOT return to intended oncologic therapy, ECOG Eastern Cooperative Oncology Group

tool used in this study, severe symptom burden reflects both socioeconomic stress and medical comorbidity. Recognizing these potentially modifiable risk factors creates an opportunity to preoperatively address them with the potential for concomitant improvement in timely RIOT.[19] In addition to increased utilization of physical prehabilitation in frail patients, early referral of patients with high symptom burden to supportive care services should be considered.[20, 21]

Second, the fact that an open surgical approach predicts delayed RIOT readiness strongly supports the use of minimally invasive approaches whenever it is oncologically appropriate and safe to do so.[22] Interestingly, open surgical approach remained associated with delayed RIOT readiness on multivariable analysis whereas major hepatectomy did not. This highlights the importance of measuring both surgical approach and magnitude of hepatectomy, as wound healing had more impact on recovery than postoperative hepatic insufficiency. Finally, these findings emphasize the importance of adherence to ERAS protocols, as they have been shown to effectively reduce two of the factors predictive of delayed RIOT: postoperative complications and hospital LOS.[3–7]

In addition to identifying important perioperative risk factors for delayed recovery, this analysis also identifies the specific postoperative factors that contribute to the surgeon's determination of time to RIOT readiness. Independent of specific complications and other issues related to the postoperative inpatient stay, the surgeon makes a determination on readiness to initiate other oncologic therapies almost exclusively on data acquired at the early postoperative visits. In this study, patients with poorly healing wounds and/or a poor performance status were more likely to have delayed RIOT readiness on univariate analysis. Similarly, lower hemoglobin and albumin levels and a higher median NLR were seen in the delayed group. While this is descriptive data, several of these factors are potentially modifiable with specific strategies. Appropriate preoperative skin preparation, meticulous care when closing a surgical incision, and thorough patient education regarding postoperative wound care have been demonstrated to reduce the rate of postoperative wound-healing complications.[23–27] While rates of wound infection at the initial postoperative visit were low in this cohort (2%), patients undergoing liver resection after receiving preoperative systemic chemotherapy are at high risk for slowly healing wounds due to a combination of malnutrition and direct effects on the immune system. Focusing on preoperative nutritional optimization and adhering to ERAS protocols (i.e., early postoperative feeding) can minimize catabolism and subsequent declines in albumin levels postoperatively.[1, 2, 4] In this study, preoperative immunonutrition was not used, and therefore may represent a valuable intervention study moving forward.[28–30]

The postoperative NLR reflects the complex relationship between the body's inflammatory response to malignancy and/or surgical trauma, and has been shown to be a poor prognostic indicator for various cancers.[31–33] In this study, the NLR was not used to determine RIOT readiness in real time. The association was only noted during retrospective factor analysis. This finding indicates that more information is needed to specifically determine what phenotypic presentation is expressed by an elevated NLR before it can be converted into an actionable and potentially modifiable factor. Nonetheless, given its relationship with delayed recovery in this oncologic cohort and its known long-term prognostic implications, it remains an interesting finding.

To our knowledge this is the first analysis that focuses on factors associated with delayed readiness to RIOT, a concept that itself is relatively new in the surgical and ERAS literature. The perioperative factors found to be associated with delayed RIOT readiness emphasize the opportunities for improvement through preoperative risk factor modification, symptom control, and adherence to ERAS protocols. Although less modifiable, also important are the factors present at the initial postoperative visit that reflect delayed recovery. Based on this analysis, future investigation should be focused on development of a predictive "RIOT score" that can be used to standardize the RIOT readiness assessment across providers. This would help identify patients at risk of delayed RIOT and illuminate opportunities for early intervention to prevent, or at least minimize, delayed initiation of postoperative adjuvant treatment. Future studies to refine the components of a RIOT score, perhaps incorporating adjunctive tools for the assessment of preoperative frailty, can also be investigated. Subsequently, validation of this score across a large population of oncologic patients treated by multiple providers should take place.

This study has several limitations. First, the study examines a relatively small sample size; therefore, the analyses with PRO data and of factors assessed at postoperative follow-up were descriptive in nature. Given the limited reporting of PRO's in the surgical literature, particularly in hepatobiliary surgery, these preliminary data may be significant and warrant further study. The multivariable analysis was limited to the recent cohort of patients for whom complete data were available; therefore, some potential confounders may not be accounted for. The smaller sample size of this component of the analysis is at least partially mitigated by the exploratory nature of the study, the recency of the cohort, and the homogeneity of the postoperative pathway implemented by a single care team. As such, all patients received standardized preoperative and postoperative assessments and treatment based on an established ERAS protocol implemented using standardized patient education and electronic medical record order sets. A second limitation is that sociodemographic factors (such as type of insurance or education level) that may play a role in recovery at a population level were not incorporated in this analysis. Instead, the resultant stressors derived from possible socioeconomic factors impacting each individual patient were captured by many of the PRO tool questions and were

integrated into the analysis. Third, the subjective nature of the PRO data and RIOT readiness interpretations could be seen as a limitation. However, the MDASI-GI has a high sensitivity for detecting patient disease severity and a high internal consistency of the symptom scales between assessments completed by a patient over his/her disease course.[16, 19] Further, assessments of RIOT readiness were made by a provider (TAA) with many years of experience. As no validated tools are available to make the assessments, the process of determining RIOT readiness took into account objective patient findings and was standardized between patients. Ultimately, this methodology is reflective of real-world practice, given that it is most often the operating surgeon who determines when a patient can proceed with further oncologic therapy by referral to adjuvant providers including medical oncology.

Conclusions

Evidence demonstrating the inpatient benefits of treating patients on ERAS protocols is rapidly accumulating, and the RIOT metric is emerging as an important quality measure that accounts for both perioperative and postdischarge variables to gauge patient-centric recovery of oncologic surgical patients. In this study of patients undergoing hepatic resection for malignancy who were treated on an ERAS protocol, several factors were found to predict delayed readiness to RIOT. To help prevent delays in therapy and the negative impact this has on long-term oncologic outcomes, efforts should focus on optimization of both preoperative and perioperative modifiable factors, including attention to preoperative symptom burden. Further investigation into the development of a RIOT score based on predictive factors present at postoperative follow-up, including PRO validation in a larger patient cohort, may further enable early identification of patients at risk of delayed RIOT.

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Statement of Author Contribution

- Substantial contributions to:
- The conception or design of the work: HL, RM, TA
- The acquisition, analysis, or interpretation of data for the work: HL, RM, BK, NN, CD, TA
- Drafting the work or revising it critically for important intellectual content: all authors
- Final approval of the version to be published: all authors
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors

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