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ORIGINAL ARTICLE

Chemotherapy within 30 days prior to liver resection does not increase postoperative morbidity or mortality

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Abstract

Background: Liver resections (LRs) are performed with increasing frequency for metastatic disease. To minimize the risk of postoperative complications, a period of 6 weeks between the last dose of chemotherapy and LR is typically recommended. The current study examines postoperative morbidity and mortality following LR in patients who received chemotherapy within 30 days prior to LR.

Methods: The merged 2005–2007 National Surgical Quality Improvement Program (NSQIP) Participant Use File was queried for perioperative risk factors, laboratory values and postoperative occurrences or complications in patients who underwent LR. Patients were grouped according to their receipt or non-receipt of chemotherapy within 30 days prior to LR and major postoperative complications.

Results: A total of 2331 patients underwent LR; 2147 did not receive chemotherapy within 30 days of resection (No Chemo group) and 184 received chemotherapy within 30 days prior to resection (Chemo group). The groups were similar with regard to preoperative co-morbidities and operative factors. The median NSQIP statistically computed morbidity probability was similar between the groups (No Chemo 0.32, Chemo 0.34; $P = 0.07$), whereas the median mortality probability was higher in the Chemo group (0.02) than the No Chemo group (0.014; $P = 0.001$). Thirty-day survival was similar between the two groups (No Chemo 97%, Chemo 98%; $P = 0.44$). Major complication rates did not differ between the groups (No Chemo 20%, Chemo 18%; $P = 0.51$). Factors associated with major complications in the Chemo group included: extent of resection; intraoperative transfusion; preoperative ascites, and preoperative haematocrit.

Discussion: Major morbidity was not increased in Chemo patients. The strongest predictors of major postoperative complications in the Chemo group were extent of resection and intraoperative red cell transfusion. Although the NSQIP dataset does not include data about tumour type or chemotherapy regimen, these data suggest that LR may be safely performed within 30 days of chemotherapy, thereby minimizing the length of time during which patients do not receive systemic treatment.

Keywords

liver resection, chemotherapy, morbidity, mortality

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Introduction

An increasing number of liver resections (LRs) are being performed in North America; several groups have reported a 1.5- to two-fold increase in hepatic resections.[1–3] It is likely that this increase largely reflects a growth in the number of LRs performed for colorectal hepatic metastases. In an era of highly effective chemotherapy for metastatic colorectal cancer, more patients are undergoing LR as part of a multimodal treatment plan designed to remove all their disease. Modern series of LRs for colorectal hepatic metastases indicate that the majority of patients receive systemic chemotherapy prior to LR.[2,4,5]

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Surgeons who perform LRs in patients following systemic therapy have reported both gross and histological changes in the liver parenchyma.[6–8] Several investigators have sought to determine whether these phenotypic changes are associated with a change in postoperative complications. Three recent studies have examined the impact of preoperative chemotherapy on postoperative complications following LR for colorectal metastases.[4,9,10] None of these studies found an increase in postoperative complications following preoperative chemotherapy. By contrast with these studies, reports by Karoui *et al.*[6] and Konopke *et al.*[11] found a greater than two-fold increase in postoperative complications in patients who received chemotherapy prior to LR.

Currently, there is no consensus regarding the risk of postoperative complications following use of systemic chemotherapy prior to major LR. Significant contributors to the conflicting findings cited include the retrospective nature of the majority of studies on this topic and a lack of standardized assessment of postoperative complications. We sought to address these two major limitations by using data available from a multi-institution database in which both preoperative co-morbidities and postoperative complications are evaluated and recorded according to a carefully prescribed protocol. The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was queried for postoperative complications following major LR. We compared postoperative morbidity and mortality in patients who did and did not receive systemic chemotherapy within 30 days of LR. The aims of the current study were: (i) to assess the potential impact of preoperative chemotherapy within 30 days of major LR on postoperative complications and mortality, and (ii) to identify patients at increased risk for postoperative complications following major LR and to determine if there are risk factors specific to patients who receive preoperative chemotherapy.

Materials and methods

Description of dataset

The ACS-NSQIP methodologies have been described previously.[12–16] Briefly, data were submitted to the ACS-NSQIP by 121 hospitals in 2005–2006. A total of 152 490 general and vascular surgery cases were included in the 2005–2006 dataset. Data were submitted by 183 hospitals in 2007, yielding a total of 211 407 cases. The data from the 2005–2006 and 2007 Participant Use Files were merged to produce a combined dataset incorporating all submitted cases over the 2005–2007 period. Each hospital utilizes a clinical nurse reviewer to collect preoperative patient characteristics, including risk factors, intraoperative variables and postoperative adverse occurrences (complications) that occur within 30 days following the surgical procedure. Cases submitted by each participating institution include the first 40 eligible general and vascular surgery cases performed in an 8-day cycle, with each 8-day cycle starting on a different day of the week. All clinical nurse reviewers have completed an in-depth training course on all study definitions. Data reliability is assured through periodic site visits by external nurse reviewers to confirm inter-rater reliability of captured data points. Outcomes for each case are determined on postoperative day 30 through nurse chart review, reports from morbidity and mortality conferences, and communication with each patient via letter or telephone call.

Description of data subsets and variables used in the current study

Of the 363 897 cases in the merged 2005–2007 ACS-NSQIP database, 2331 cases were identified as involving a major open LR based upon the following principal Current Procedural Terminology (CPT) codes: 47120 (partial lobectomy, $n = 1357$); 47122 (trisegmentectomy, $n = 230$); 47125 (left hepatectomy, $n = 232$), and 47130 (right hepatectomy, $n = 512$). The analysis was limited to major open LRs because of the appreciable morbidity associated with partial lobectomy to extended hepatectomy (18–30%[10,17]) and because modern series of colorectal hepatic metastasectomies involve multisegment resections.[2,10,18]

Patients were then separated into two groups based upon their receipt or non-receipt of chemotherapy within 30 days of LR (No Chemo and Chemo groups). According to the ACS-NSQIP definition, patients were identified as having received chemotherapy if they 'had any chemotherapy treatment for cancer in the 30 days prior to surgery'. Chemotherapy included, but was not limited to, oral and parenteral chemotherapy agents. If treatment consisted solely of hormonal therapy, the patient was not considered to have received chemotherapy. The ACS-NSQIP database does not include any information about the specific type of chemotherapy received within 30 days prior to operation, the number of cycles of chemotherapy received, or the precise interval within the 30-day timeframe between the last dose of chemotherapy and the LR. Neither does the database indicate the histological type of malignancy for which the therapy was received. Patients in the No Chemo group included any patient who underwent a major open LE (as defined above) but did not receive chemotherapy within 30 days of resection. The indication for hepatectomy is not specified in the ACS-NSQIP database.

The preoperative variables collected for the ACS-NSQIP describe patient demographic characteristics and co-morbidities. The preoperative variables specifically analysed in the current study included: age; gender; race; current smoking history; current alcohol use; body mass index (BMI); American Society of Anesthesiologists (ASA) physical status classification; presence of diabetes mellitus; history of severe chronic obstructive pulmonary disease; ascites; congestive heart failure within 30 days of surgery; hypertension requiring medication; disseminated cancer; steroid use for chronic conditions; loss of >10% of body weight in the previous 6 months; transfusion of >4 units of packed red blood cells (pRBC) within the preoperative 72 h, and radiation therapy for malignancy within 90 days of operation. According to the ACS-NSQIP database protocol, a patient was considered to have disseminated cancer if it had 'spread to one site or more sites in

addition to the primary site' or if 'the presence of multiple metastases indicates the cancer is widespread, fulminant or near terminal'.

Ten preoperative laboratory values were examined: creatinine; albumin; serum glutamic oxaloacetic transaminase (SGOT); total bilirubin; alkaline phosphatase; white blood cell count (WBC); haematocrit; platelet count; partial thromboplastin time (PTT), and prothrombin time (PT). Absolute values were converted into normal and abnormal values based upon the following institutional reference ranges: creatinine 0.5–1.5 mg/dl; albumin 3.5–5.0 g/dl; SGOT 0–75 U/l; total bilirubin 0.1–1.2 mg/dl; alkaline phosphatase 25–165 U/l; WBC 4.5–11.0 k/μl; haematocrit 36–50%; platelet count 140–415 k/μl; PTT 0–36 s, and PT 0–15 s.

Operative variables analysed included the extent of LR, total operative time, and administration of pRBC transfusion. Partial hepatectomy was defined as CPT code 47120 and extensive hepatectomy as CPT codes 47122, 47125 or 47130.

Postoperative occurrences were assessed up to 30 days postoperatively, and included both in-hospital and out-of-hospital occurrences. Postoperative *infectious occurrences* included: superficial incisional infection; deep incisional infection; organ space infection; pneumonia; urinary tract infection (UTI); sepsis, and septic shock. The following *pulmonary occurrences* were analysed: unplanned intubation; need for ventilatory assistance >48 h postoperatively; pneumonia, and pulmonary embolism. *Cardiac occurrences* included: myocardial infarction, and cardiac arrest requiring cardiopulmonary resuscitation (CPR). Deep venous thrombosis and pulmonary embolism were recorded as *thromboembolic occurrences*. Additional occurrences noted included wound disruption, transfusion of pRBC within 72 h postoperatively, and return to the operating room within 30 days postoperatively.

The occurrence of any one of the following complications was classified as a *minor complication*: superficial incisional infection; deep wound infection; wound disruption, or UTI.

The occurrence of any one of the following complications was classified as a *major complication*: organ space infection; pneumonia; unplanned intubation; pulmonary embolism; ventilatory support >48 h; progressive renal insufficiency; acute renal failure; stroke; coma for >24 h; cardiac arrest requiring CPR; myocardial infarction; deep venous thrombosis; sepsis; septic shock, and return to the operating room within 30 days postoperatively.

Patients were grouped according to their receipt or non-receipt of chemotherapy within 30 days prior to LR and the occurrence or absence of a major postoperative complication.

Morbidity and mortality probability calculations

Risk-adjusted 30-day postoperative mortality and morbidity were calculated for each hospital by logistic regression analysis with 30-day postoperative mortality and morbidity as dependent variables and patient preoperative and perioperative risk factors as independent variables. Regression analyses included patients from all hospitals participating in the ACS-NSQIP. A mortality and morbidity probability was calculated for each patient and then summed to obtain an expected number of deaths or patients with complications for each hospital.

Statistical analysis

Student's *t*-test with equal variances was used for comparison of continuous variables and Pearson's chi-squared and Fisher's exact test were used for analysis of discrete variables. A stepwise forward logistic regression was used for multivariate model determination. The variables were retained if they significantly contributed to the model ($P < 0.15$) in the presence of other variables, as determined by the likelihood ratio test. Differences of $P < 0.05$ were considered significant. All analyses were performed using SPSS Version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Demographics and co-morbidities by chemotherapy group

The merged 2005–2007 ACS-NSQIP database contained a total of 2331 open major LRs. Of these, 2147 resections (92%) were performed in patients who had not received chemotherapy within 30 days of resection and 184 (8%) were performed in patients within 30 days of administration of chemotherapy. The demographics and co-morbidities of patients in the No Chemo and Chemo groups are summarized in Table 1. The average age in both groups was approximately 58 years. There were more men in the Chemo than the No Chemo group. The majority of patients in both groups were White, non-smokers, non-drinkers, had an average BMI of 27 and belonged to ASA classes 2 or 3. The two groups of patients were also well matched for co-morbidities, including diabetes mellitus, history of severe chronic obstructive pulmonary disease, congestive heart failure, hypertension, loss of >10% of body weight over the previous 6 months, steroid use and ascites. Significantly more patients in the Chemo group had disseminated cancer and had received radiotherapy for malignancy in the 90 days prior to LR.

Operative variables by chemotherapy group

An analysis of the operative variables revealed no differences in the extent of LR, total operative time, or units of pRBC received intraoperatively between patients who did and did not receive chemotherapy within 30 days of LR (Table 2). Slightly more than half the patients in both groups underwent a partial lobectomy, and the remainder of the patients underwent a hemihepatectomy or trisegmentectomy. Median operative time was a median of 21 min longer in the Chemo group. The median number of pRBC received intraoperatively was zero in both groups.

Morbidity and mortality probability and postoperative occurrences by chemotherapy group

The median values for ACS-NSQIP statistically computed morbidity probability were similar in both groups (No Chemo 0.32, Chemo 0.34; $P = 0.07$). This indicates that the risk-adjusted

Table 1 Demographics and co-morbidities of patients who did and did not receive chemotherapy within 30 days of liver resection

	No chemotherapy *n* = 2147 (%)	Chemotherapy *n* = 184 (%)	*P*-value
Age, years	58.4 ± 13.7	57.3 ± 10.6	0.30
Men	1045 (49)	104 (57)	**0.04**
Race			0.40
Indian/Alaskan	9 (0.4)	1 (0.5)	
Asian	89 (4)	5 (3)	
Black/Black Hispanic	170 (8)	10 (5)	
Hispanic/Hispanic unknown	73 (3)	2 (1)	
White	1650 (77)	156 (85)	
Unknown	156 (7)	10 (5)	
Current smoker	328 (15)	28 (15)	0.98
>2 alcoholic drinks/day	61 (3)	6 (3)	0.74
Body mass index, median	26.9	27.2	0.15
ASA physical status classification			0.72
1	35 (1.6)	3 (1.6)	
2	729 (34)	58 (31.5)	
3	1272 (59)	117 (64)	
4	110 (0.5)	6 (3)	
5	1 (0.04)	0 (0)	
Co-morbidities			
Diabetes mellitus			0.07
No	1825 (85)	168 (91)	
Oral hypoglycaemic treatment	228 (11)	11 (6)	
Insulin therapy	94 (4)	5 (3)	
History of severe chronic obstructive pulmonary disease	67 (3)	3 (2)	0.26
Congestive heart failure within the 30 days prior to surgery	8 (0.4)	1 (0.5)	0.72
Hypertension requiring medication	988 (46)	74 (40)	0.13
Loss of >10% of body weight in previous 6 months	114 (5)	12 (6.5)	0.49
Transfusion >5 units pRBC preoperatively	6 (0.3)	1 (0.5)	0.44
Steroid use for chronic condition	40 (2)	4 (2)	0.77
Ascites	31 (1)	2 (1)	0.69
Disseminated cancer	818 (38)	147 (77)	**<0.001**
Radiotherapy for malignancy in last 90 days	16 (0.7)	11 (6)	**<0.001**

ASA, American Society of Anesthesiologists; pRBC, packed red blood cells
P-values shown in bold are significant at $P < 0.05$

30-day frequency of postoperative occurrences was predicted to be similar between the two groups based upon a statistical model that included patient preoperative risk factors as independent variables and individual hospital risk-adjusted 30-day postoperative morbidity as the dependent variable. The median mortality probability was higher in the Chemo group (0.02) compared with the No Chemo group (0.01; $P = 0.001$), indicating a higher predicted mortality among patients undergoing LR following preoperative chemotherapy.

Minor complications occurred in 10% of patients in the No Chemo group and 12% of patients in the Chemo group (P = non-significant [NS]). Major complications occurred in 20% of patients in the No Chemo group and 18% of patients in the Chemo group (P = NS). The frequencies of wound-related, infectious, pulmonary, cardiac, thromboembolic, and overall minor and major complications in the Chemo and No Chemo groups are illustrated in Table 3. There was no difference in the occurrence of any of the infection-related complications between the two groups. The need for an unplanned intubation was more common in the No Chemo group (84/2147, 4%) compared with the Chemo group (2/184, 1%; $P = 0.05$). Cardiac and thromboembolic complications were similarly uncommon in both groups. In both groups, 1% of

Table 2 Operative variables in patients who did and did not receive chemotherapy within the 30 days prior to liver resection

	No chemotherapy *n* = 2147 (%)	Chemotherapy *n* = 184 (%)	*P*-value
Extent of liver resection			0.99
Partial lobectomy	1250 (58)	107 (58)	
Hemihepatectomy/trisegmentectomy	897 (42)	77 (42)	
Total operative time, min	251.7 ± 122.5	267.7 ± 119.1	0.09
Median, min	229	250	
Units of pRBC given intraoperatively	0.9 ± 5.6	1.3 ± 3.8	0.30
Median	0	0	

pRBC, packed red blood cells

Table 3 Postoperative occurrences in patients who did and did not receive chemotherapy within the 30 days prior to liver resection

	No chemotherapy *n* = 2147 (%)	Chemotherapy *n* = 184 (%)	*P*-value
Minor complications	224 (10)	22 (12)	0.52
Major complications	432 (20)	33 (18)	0.56
Infectious complications			
Superficial incisional infection	110 (5)	14 (8)	0.15
Deep incisional infection	23 (1)	0	0.16
Organ space infection	133 (6)	6 (3)	0.11
Pneumonia	86 (4)	7 (4)	0.89
Urinary tract infection	19 (1)	7 (4)	0.78
Sepsis	149 (7)	6 (3)	0.06
Septic shock	77 (4)	10 (5)	0.20
Pulmonary complications			
Unplanned intubation	84 (4)	2 (1)	0.05
Ventilatory assistance >48 h	101 (5)	5 (3)	0.21
Wound disruption	19 (1)	2 (1)	0.78
Cardiac complications			
Myocardial infarction	8 (0.4)	0	0.41
Cardiac arrest requiring cardiopulmonary resuscitation	24 (1)	1 (0.5)	0.47
Thromboembolic events			
Deep venous thrombosis	44 (2)	5 (3)	0.54
Pulmonary embolism	33 (1.5)	5 (3)	0.23
Transfusion of red blood cells within 72 h postoperatively	22 (1)	2 (1)	0.94
Return to operating room within 30 days	105 (5)	11 (6)	0.52

patients required a pRBC transfusion in the 72 h following LR. Approximately 5% of patients in both groups required a return to the operating room within 30 days of the initial LR. Thirty-day survival was similar between the two groups: 97% of patients in the No Chemo group and 98% of patients in the Chemo group were alive at 30 days post-surgery ($P = 0.44$)

Univariate correlates of major postoperative complications: all subjects

Patients were separated into two groups based upon the occurrence of a major postoperative complication (e.g. pulmonary embolism, sepsis, need for re-intubation) (Table 4). The following demographic and co-morbidities were more common among patients with major complications: older age; male gender; current smoking history; higher ASA class; history of severe chronic obstructive pulmonary disease; loss of >10% of body weight in the previous 6 months, and ascites. Neither disseminated cancer nor the receipt of radiotherapy for malignancy within 90 days prior to LR were associated with developing a major postoperative complication. Patients who developed a major complication were more likely to have abnormal laboratory values for all of the variables examined than patients without a

Table 4 (A) Univariate correlates of major postoperative complications following liver resection in all subjects. (B) Univariate correlates of major postoperative complication following liver resection in the chemotherapy group

(A)	No complications *n* = 1866 (%)	Major complications *n* = 465 (%)	*P*-value
Age, years	58.0 ± 13.6	59.5 ± 13.1	**0.03**
Age ≥65 years	632 (34)	182 (39)	**0.03**
Men	882 (46)	267 (57)	**<0.001**
Race			0.53
Indian/Alaskan	7 (0.4)	3 (0.6)	
Asian	77 (4)	17 (4)	
Black/Black Hispanic	140 (7)	40 (9)	
Hispanic/Hispanic unknown	58 (3)	17 (4)	
White	1441 (77)	365 (78.5)	
Unknown	143 (8)	23 (5)	
Current smoker	260 (14)	96 (21)	**<0.001**
>2 alcoholic drinks/day	52 (3)	15 (3)	0.64
Body mass index, median	26.9	27.1	0.73
ASA physical status classification			**<0.001**
1	33 (2)	5 (1)	
2	664 (36)	23 (26.5)	
3	1099 (59)	290 (62)	
4	70 (4)	46 (10)	
5	0	1 (0.2)	
Co-morbidities			
Diabetes mellitus			0.24
No	1606 (86)	387 (83)	
Oral hypoglycaemic treatment	186 (10)	53 (11)	
Insulin therapy	74 (4)	25 (5)	
History of severe chronic obstructive pulmonary disease	40 (2)	30 (6.5)	**<0.001**
Congestive heart failure within 30 days before surgery	6 (0.3)	3 (0.6)	0.40
Hypertension requiring medication	839 (45)	223 (48)	0.25
Loss of >10% of body weight in previous 6 months	89 (5)	37 (8)	**0.008**
Transfusion >4 units pRBC preoperatively	5 (0.3)	2 (0.4)	0.63
Steroid use for chronic condition	31 (2)	13 (3)	0.13
Ascites	17 (1)	16 (3)	**<0.001**
Disseminated cancer	776 (42)	184 (40)	0.46
Chemotherapy	151 (8)	33 (7)	0.56
Radiotherapy for malignancy in last 90 days	24 (1)	3 (0.6)	0.34
Preoperative laboratory variables	*n*/% abnormal	*n*/% abnormal	
Creatinine	75 (4)	33 (7)	**0.009**
Albumin	169 (10.5)	83 (20)	**<0.001**
Total bilirubin	82 (5)	43 (10)	**<0.001**
SGOT	125 (8)	56 (14)	**<0.001**
Alkaline phosphatase	216 (13)	112 (27)	**<0.001**
White blood cell	126 (7)	58 (13)	**<0.001**
Haematocrit	317 (17.5)	121 (27)	**<0.001**
Platelets	138 (7.6)	52 (11.5)	**0.01**
Partial thromboplastin time	67 (5)	31 (8)	**0.02**
Prothrombin time	63 (4)	34 (9)	**0.001**
Operative variables			
Extent of liver resection			**<0.001**
Partial lobectomy	1138 (61)	219 (47)	
Hemihepatectomy/trisegmentectomy	728 (39)	246 (53)	
Operative length, min	238.3 ± 111.4	311.8 ± 6.6	**<0.001**
Unites of pRBC given intraoperatively	0.6 ± 5.1	2.2 ± 6.6	
Median	0	0	**<0.001**

Table 4 Continued

(B)	No complications $n = 151$ (%)	Major complications $n = 33$ (%)	*P*-value
ASA physical status classification			**0.05**
1	3 (2)	0	
2	52 (34)	6 (18)	
3	93 (62)	24 (73)	
4	3 (2)	3 (9)	
5	0	0	
Co-morbidities			
Congestive heart failure within 30 days before surgery	0	1 (3)	**0.03**
Transfusion >4 units pRBC preoperatively	0	1 (3)	**0.03**
Ascites	0	2 (6)	**0.002**
Preoperative laboratory variables	N/% abnormal	N/% abnormal	
Creatinine	2 (1)	3 (9)	**0.04**
Albumin	11 (8)	6 (19)	0.09
Total bilirubin	3 (2)	3 (10)	0.08
SGOT	3 (2)	4 (13)	**0.02**
Alkaline phosphatase	13 (10)	5 (16)	0.33
White blood cell	16 (11)	7 (22)	0.14
Haematocrit	30 (20)	13 (41)	**0.02**
Platelets	18 (12)	6 (19)	0.39
Partial thromboplastin time	4 (3.5)	3 (11.5)	0.12
Prothrombin time	2 (2)	2 (7)	0.16
Operative variables			
Extent of liver resection			**0.02**
Partial lobectomy	94 (62)	13 (39)	
Hemihepatectomy/trisegmentectomy	57 (38)	20 (61)	
Operative length, min	254.9 ± 108.4	326.1 ± 147.8	**0.002**
Units of pRBC given intraoperatively	0.8 ± 2.1	3.7 ± 7.5	**<0.001**

ASA, American Society of Anesthesiologists; pRBC, packed red blood cells; SGOT, serum glutamic oxaloacetic transaminase
P-values shown in bold are significant at $P < 0.05$

major complication. The most common laboratory abnormalities in the complication group were an elevated alkaline phosphatase and a low haematocrit (27%), followed by a low albumin (20%). Subjects who developed a major complication were more likely to have undergone an extensive LR. The average operative time was longer among subjects who developed a major complication and the number of pRBC received intraoperatively was an average of four-fold higher.

Univariate correlates of major postoperative complications: Chemo group

In order to determine which variables may uniquely predict the risk of a major complication among patients in the Chemo group, we separately examined the relationship between the preoperative variables and major postoperative complications in this group. Major complications occurred in 33 (18%) of patients in the Chemo group. Complications were associated with the following preoperative factors: higher ASA class; congestive heart failure within 30 days preoperatively; transfusion of >4 units preoperatively, and presence of ascites. Of these four variables, preoperative congestive heart failure and transfusion were unique risk factors for postoperative complications in the Chemo group. The true impact of congestive heart failure and preoperative transfusions on major complication rates in the Chemo group is uncertain, given that the difference between the No Chemo and Chemo groups reflects the fact that a single patient in the Chemo group had each of these risk factors. Patients who developed a major complication were more likely to have abnormal creatinine, SGOT and haematocrit values compared with those who did not develop a complication. The most common laboratory abnormality was a low haematocrit (41%).

When more stringent criteria were used to determine the impact of neutropenia (WBC count ≤5.0 k/μl, $n = 692$), anaemia (haematocrit ≤24%, $n = 13$) and thrombocytopenia (platelet

count ≤100 k/μl, $n = 61$) on major postoperative complications, thrombocytopenia, but not neutropenia, was associated with a higher rate of complications. A total of 23 (38%) patients with thrombocytopenia developed a major complication compared with 428 (19.5%) patients with platelet counts >100 k/μl ($P = 0.001$). A total of 18% of patients with neutropenia developed complications compared with 21% of patients with WBC >5.0 k/μl ($P = 0.17$). No analysis was performed for anaemia because only a small number of patients met the criteria for this complication.

Similar to findings for the group as a whole, subgroup results showed that patients who received preoperative chemotherapy and developed a postoperative complication were more likely to have undergone extensive LRs, had longer operative times and received more units of pRBC intraoperatively.

Multivariate predictors of major postoperative complications

Clinical variables from the univariate analysis of postoperative complications with a P-value < 0.15 were entered into a binary logistic regression analysis to identify independent predictors of postoperative complications. These variables included: age <65 or ≥65 years; gender; current smoker; ASA class 1–2 or 3–5; history of severe chronic obstructive pulmonary disease; loss of >10% of body weight in the previous 6 months; ascites; extent of LR (partial or extensive); steroid use for a chronic condition, and receipt of pRBC intraoperatively. Independent predictors of a major postoperative complication following LR are summarized in Table 5 and include: gender; history of severe chronic obstructive pulmonary disease; ascites; extent of LR, and receipt of pRBC intraoperatively. We were unable to perform multivariate analysis separately for patients in the Chemo group because of the small number of patients in this group who developed a major complication.

Table 5 Multivariate analysis of major postoperative complications following liver resection

	Odds ratio	95% CI	*P*-value
Age	1.14	0.91–1.43	0.26
Male gender	1.4	1.13–1.74	**0.002**
ASA class	1.21	0.95–1.54	0.12
Diabetes mellitus	1.09	0.81–1.47	0.57
History of chronic obstructive pulmonary disease	2.8	1.7–4.7	**<0.001**
Loss of >10% of body weight in previous 6 months	1.4	0.91–2.13	0.12
Ascites	2.9	1.4–5.9	**0.004**
Steroid use for chronic condition	1.3	0.64–2.6	0.48
Extent of liver resection	0.65	0.52–0.80	**<0.001**
Intraoperative pRBC transfusion	2.6	2.1–3.2	**<0.001**

95% CI, 95% confidence interval; ASA, American Society of Anesthesiologists; pRBC, packed red blood cells
P-values shown in bold are significant at $P < 0.05$

Discussion

Contemporary series of LRs for colorectal metastases reveal that the majority of patients currently receive systemic chemotherapy prior to resection.[2,4,5] Although surgeons and pathologists have noted morphological and histopathological liver changes induced by preoperative chemotherapy, it is unclear if these changes are associated with a difference in postoperative morbidity following LR. Some authors have reported no increase in postoperative morbidity in LRs performed following systemic chemotherapy,[4,9,10] whereas other investigators have recorded an increase in postoperative complications.[6,11]

To evaluate the impact of chemotherapy prior to LR on postoperative complications and mortality, we interrogated the ACS-NSQIP database for major LRs performed in the presence or absence of preoperative chemotherapy. A total of 2331 major LRs were included in the merged 2005–2007 ACS-NSQIP database. Of these, 8% ($n = 184$) were performed in patients who had received systemic chemotherapy within 30 days of resection. The two groups were similar with regard to age, ethnicity, and preoperative co-morbidities. Minor complications occurred in 10% of patients in the No Chemo group and 12% of patients in the Chemo group. Major complications occurred at a similar rate in the two groups: 20% in the No Chemo group and 18% in the Chemo group. There were no differences between the Chemo and No Chemo groups for any of the specific infection-related, pulmonary, wound-related, cardiac or thromboembolic occurrences analysed. The results of the current study confirm those of several other authors who did not demonstrate an increase in postoperative morbidity in patients who received chemotherapy prior to major LR.[4,5,7,9,10,19]

The 30-day mortality in the current study was 2–3% and did not differ between the Chemo and No Chemo groups. Vauthey *et al.*[10] reported an overall 90-day mortality of 2.7% in their study of 406 patients who underwent resection for colorectal hepatic metastases (248 received preoperative chemotherapy). They chose to report 90-day mortality in order to account for the deaths that can occur late in the postoperative course following hepatic resection as a result of progressive liver failure secondary to impaired hepatic regeneration. It is possible that the 30-day mortality value in the current study is an underestimate of overall postoperative mortality, given this possibility of late liver failure.

In addition to confirming a lack of increased morbidity following preoperative chemotherapy prior to LR, the results of the current study provide insight into a safe therapeutic window between systemic chemotherapy and LR. Because the ACS-NSQIP database specifically defines preoperative chemotherapy as therapy given within 30 days of the principal procedure, we may conclude that major LR can be safely performed within this timeframe. Traditionally, surgeons and oncologists have waited a

minimum of 6 weeks between the last administration of chemotherapy and a major surgical procedure in order to minimize the risk of postoperative complications. The current data suggest that LR may be safely performed within 30 days of systemic chemotherapy without increasing the risk of minor or major postoperative complications or 30-day mortality. Minimizing the interval between receipt of systemic chemotherapy and LR is desirable because this will result in at least a theoretical reduction in the time during which a patient is at risk of disease progression while between therapies (surgery and chemotherapy).

Several caveats must be considered when applying the results of the current study to a specific clinical scenario, however. The ACS-NSQIP database does not record the type of chemotherapy received, the number of cycles received, the precise interval (within the 30-day timeframe) between the last dose of chemotherapy and the LR, or the malignancy for which the chemotherapy was given. Consequently, there may be specific chemotherapeutic agents for which a longer delay (>30 days) between receipt of chemotherapy and LR is warranted. A recent study by Welsh *et al.*[18] found that neither the interval (in weeks) between finishing chemotherapy and undergoing LR nor the duration of chemotherapy (in months) impacted postoperative morbidity. However, they did note a reduction in complications with increasing time between the completion of chemotherapy and LR. Additionally, although it is likely that the majority of LRs performed following chemotherapy in the current study were performed for colorectal metastases (the most common metastatic liver tumour resected in the USA), this cannot be definitively determined in the current dataset. As a result, we are unable to make specific recommendations about LRs performed for a given tumour type.

The second aim of our study was to identify patients at increased risk for postoperative complications following major LR, and to determine if there are risk factors specific to patients who receive preoperative chemotherapy. For the group as a whole, major complications occurred more often in older patients (≥65 years), men, current smokers, patients with a higher ASA class, patients with a history of severe chronic obstructive pulmonary disease, patients who had lost >10% of their body weight in the 6 months prior to surgery, and those with preoperative ascites. Major complications in the Chemo group were associated with higher ASA class, congestive heart failure within the 30 days prior to surgery, transfusion of >4 units preoperatively, and preoperative ascites. Of these four preoperative variables, only preoperative congestive heart failure and preoperative transfusion were unique risk factors among patients who received preoperative chemotherapy. However, the differences between the No Chemo and Chemo groups were accounted for by a single patient with preoperative congestive heart failure and a single patient who received >4 units of pRBC preoperatively in the Chemo group. Consequently, we were not able to identify any preoperative risk factors for major postoperative complications unique to patients in the Chemo group.

Patients who developed major complications were more likely to have abnormal values for all of the laboratory studies examined than patients without a major postoperative complication. The most common laboratory abnormalities were elevated alkaline phosphatase and low haematocrit (27%). Using more stringent criteria to define neutropenia and thrombocytopenia, we found that major complications were more common in patients with thrombocytopenia, but not in those with neutropenia.

In an earlier review of postoperative morbidity following LR by the Patient Safety in Surgery Study group,[20] elevated alkaline phosphatase, but not low haematocrit, was associated with postoperative complications. Of the three laboratory abnormalities that differed between subjects in the Chemo group with and without a major complication, the most common abnormality in the complication group was low haematocrit (41%). Our findings are in contrast to those of Melis *et al.*,[21] who reported that preoperative anaemia was not associated with an increased risk of postoperative complications following oesophagectomy. However, they did find that anaemic patients were more likely to receive a pRBC transfusion, which itself was an independent predictor of postoperative complications.[21] Given that major complications were more common among Chemo patients who were anaemic and among those who required >4 units of pRBC preoperatively, these may represent a group of patients who warrant additional attention prior to undertaking major hepatectomy in order to minimize postoperative morbidity. There may also be an increased risk for postoperative complications in LR patients with thrombocytopenia as this may be an indicator of portal hypertension and/or bone marrow suppression.

All three intraoperative variables examined (extent of LR, operative length, units of pRBC received intraoperatively) correlated with the risk of a major postoperative morbidity for the group overall as well as the Chemo group alone. Our results are in agreement with those of several other groups who found these three factors to be associated with an increased risk of complications following LR.[6,22,23] Konopke *et al.*[11] also reported that transfusion of 3–6 pRBC units was significantly associated with postoperative morbidity and temporary liver failure. Blood transfusions have been shown to increase morbidity in a variety of patient populations, including those undergoing colorectal, vascular and thoracic procedures.[24–26]

The results of our multivariate analysis revealed five factors independently associated with a major postoperative complication following hepatectomy: male gender; history of chronic obstructive pulmonary disease; preoperative ascites; extent of LR, and intraoperative pRBC transfusion. The correlation between extent of LR and perioperative blood transfusions on postoperative morbidity following LR has been discussed above. Recognition of male gender as an independent risk factor for postoperative complications following hepatic resection was previously reported by Fong *et al.*[27] and was noted in a study of postoperative complications following LR by Virani *et al.*,[20] but was not seen in the study by Karoui *et al.*[6] Neither ascites nor a

history of chronic obstructive pulmonary disease were found to be associated with postoperative morbidity following LR in the study by Virani *et al.*[20]

At least two significant limitations of the ACS-NSQIP database should be noted. The first is the absence of procedure- or specialty-specific complications. For example, incidences of postoperative bile leak and liver failure are not captured in the database. Additionally, ACS-NSQIP does not grade the severity of complications recorded. The importance of this additional layer of analysis is illustrated in the studies by Scoggins *et al.*[5] and Sahajpal *et al.*[9] The complication grading scale used by Scoggins *et al.*[5] classified complications according to the intervention required to manage them (e.g. local wound care, interventional radiology, drainage, etc.). The Clavien Scale[28] was employed in the study by Sahajpal *et al.*[9] They found that the majority of complications in their chemotherapy group were Clavien grade IIa, indicating 'potentially life-threatening complications with the need for intervention and prolonged hospital stay, requiring medical intervention only'. Patients in their No Chemo group were equally likely to have a Clavien grade I or IIa complication, suggesting that the severity of postoperative complications may be lower in patients who do not receive chemotherapy prior to LR.

This analysis reveals that hepatic resection can be safely performed in patients who receive chemotherapy during the 30 days prior to resection and that 30-day mortality and morbidity rates are comparable with those for patients who do not receive preoperative chemotherapy. Despite higher predicted mortality rates, patients who received chemotherapy had equivalent 30-day operative mortality. These observations suggest that a predetermined fixed recovery interval between chemotherapy and hepatic resection may not be required. We conclude that the timing of surgery should be based on individual patient characteristics with attention to the recovery of marrow suppression and restoration of red cell mass and the magnitude of the anticipated hepatic resection. Further, this study confirms that optimal outcomes are dependent upon intraoperative measures to minimize blood loss and the need for transfusions, principles that are linked to improved outcomes in all major elective and emergent abdominal procedures.

ACS-NSQIP data disclaimer

The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS-NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Conflicts of interest

None declared.

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