Nationwide outcomes of simultaneous resection of primary colorectal cancer and synchronous liver metastases

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Abstract

Background

Of the few studies comparing simultaneous versus staged resection of primary colorectal cancer and synchronous liver metastases, most are limited to resections performed at the same facility. This study was performed to compare outcomes of simultaneous versus staged resection in these patients, including resections performed at a different center.

Methods

The Nationwide Readmissions Database was queried for all patients undergoing colorectal cancer and metastatic liver resections in the US from 2010 to 2014. Patients undergoing simultaneous resections were compared to patients who underwent liver and colon resections on separate admissions, both liver first and colon first. The outcomes of interest were in-hospital mortality, complications, and total cost.

Results

During the study period, there were 6,219 patients undergoing resection of primary colorectal cancer and synchronous liver metastases. Separate admission resection was performed at a different hospital in 45.8%. Compared to simultaneous resection, there was a reduced risk for mortality in patients undergoing colon first (OR 0.28, p<0.01) and there was no significant difference in performing liver resection first (OR 0.30, p=0.05). Simultaneous resection was associated with a decreased mean total cost of admissions compared to separate admission resection ($37,278 ±$34,353 versus $47,985 ±$ 28,342, p<0.01).

Conclusions

Nearly half of separate admission resections of primary colorectal cancer and liver metastases are performed at different hospitals and likely missed by single-center studies. Undergoing colon resection first on a separate admission is costlier, yet patients have more favorable outcomes. Further studies are needed to reveal the underlying factors responsible for these improved outcomes.
Keywords: colorectal cancer, metastatic colorectal cancer, liver metastases, colon resection, liver resection, synchronous

**Background**

Colorectal cancer is the third leading cause of cancer death in the United States in both men and women.\(^1\) Up to 50% of patients diagnosed with colorectal cancer will eventually develop liver lesions, and 22% of patients will have distant metastasis at the time of diagnosis, most commonly in the liver. These patients with advanced stage colorectal cancer (CRC) typically have a poor prognosis with a 5-year survival of only 14.2%.\(^2\)

Of patients with CRC with liver lesions discovered at or before diagnosis of the primary tumor (synchronous liver metastases, SLM), approximately 10-30% have potentially resectable disease at the time of diagnosis\(^3,12\), but the treatment algorithm for these patients is still controversial. Despite the addition of many new chemotherapeutic and biologic agents, overall survival even after medical treatment remains at an average of 18-24 months.\(^4\)

Recent studies have shown that patients who undergo surgical resection of liver metastases have improved outcomes, and successful surgical resection can improve overall 5-year survival rates to over 50%.\(^3\) Additionally, surgical resection of all neoplastic lesions is still considered the only curative therapy for long-term survival from colorectal cancer with liver metastases (CRCLM).

Treatment options most often favor a staged approach, typically with resection of the primary colorectal lesion first, followed by a variable number of cycles of chemoradiation, either before or after resection of the metastatic liver lesion(s). The preferred sequence of these events varies based on size and location of both primary and metastatic lesions, as well as the planned procedures to resect each lesion. More recently, treatment approaches have included simultaneous resection of both the primary lesion and the metastatic hepatic lesion.\(^5\) These single-stage procedures have the benefit of decreased length of stay and lower hospital costs due to single admissions rather than multiple.\(^17\).

Previous studies have evaluated some outcomes of simultaneous verses staged resection of hepatic lesions and colorectal primary lesions, but these studies often reflect the experience of a single institution or a small cohort. To date, few studies...
have compared simultaneous vs staged resection of hepatic metastasis from a nationwide sample. Thus, the purpose of this study was to compare outcomes of simultaneous versus staged resection of primary colorectal cancer and synchronous liver metastases nationwide, to include resections performed at multiple centers.

**Methods**

The Nationwide Readmissions Database (NRD) is the product of a collaborative effort to provide a national information resource, called the Healthcare Cost and Utilization Project, and is part of an assemblage that includes the largest collection of longitudinal hospital care data in the United States. The NRD contains data from 36 million weighted and 18 million unweighted discharges for all ages across hospital types, accounting for 60% of the total U.S. resident population and 58.2% of all U.S. hospitalizations.

The NRD was queried for all patients undergoing colorectal cancer and metastatic liver resections in the United States from 2010 to 2014. Patients undergoing resections simultaneously during the same admission were compared to patients who underwent liver and colorectal resections on separate admissions, both liver first and colon first. Hospital charges for each admission were queried used to calculate the total cost of each admission and readmission. Hospitals were grouped by volume into respective quartiles.

The outcomes of interest were in-hospital mortality, complications, and total cost. Univariable comparison was performed and significant variables (P<0.05) were used for multivariable logistic regression for each outcome. Results were weighted for national estimates.

**Results**

During the study period, there were 6,219 patients undergoing resection of primary colorectal cancer and synchronous liver metastases. Characteristics of the study population are listed in table 1. Simultaneous resection was performed in 63.6%, colon resection was performed first in 30.7%, and liver resection was performed first in 5.7%.

Separate admission resection was performed at a different hospital in 45.8%.
The overall in-hospital mortality rate was 2.0%. Compared to simultaneous resection, there was a reduced risk for mortality in patients undergoing colon first (OR 2.8, P<0.01) and there was no significant difference in performing liver resection first (OR 0.30, p=0.05).

The overall rate of complications was 26.8%, as listed in table 2. An increased risk for complications was found in patients undergoing liver resection first (OR 1.42, p<0.01) and there was no difference in patients undergoing colon resection first (p=0.08).

Simultaneous resection was associated with a decreased mean total cost of admissions compared to separate admission resection ($37,278 +/- $34,353 versus $47,985 +/- $28,342, p<0.01). Patients were at increased risk for being in the highest cost quartile if they underwent colon resection first (OR 2.45, P<0.01) or liver resection first (3.32, p<0.01).

Discussion

Simultaneous resection has been proven to be a safe and effective means of treating patients with colorectal cancer with synchronous liver metastases, with multiple studies showing no differences in morbidity or mortality compared to patients undergoing staged resection. Simultaneous resection has also been shown to decrease costs to both hospitals and patients. With this in mind, a growing body of literature is demonstrating a higher percentage of patients undergoing simultaneous resection, compared to years past, and some authors are advocating for this to be the new standard of care.

Despite the proven benefits of simultaneous surgery, it is important to understand that not all patients are eligible for combined surgery. Specific patient and tumor characteristics must be taken into account to determine the best candidates for a simultaneous approach. Some limitations to simultaneous resection may include patient age and comorbidities, lesions requiring extended or anatomically difficult resections or multi-stage hepatectomy, larger distribution, total number or size of liver metastases, and patients in suboptimal preoperative condition.

Multidisciplinary discussion facilitates the development of individualized, comprehensive treatment plans specific to each patient, and has been shown to
improve outcomes in patients with metastatic colorectal cancer. Additionally, treatment facilities require the appropriate resources to adequately care for and potentially “rescue” patients undergoing a combined procedure should they experience complications.

Of patients undergoing staged resection in this study, the majority had their colon resection performed first. This likely represents adherence to the traditional strategy of attempting to control or prevent symptoms of local invasion prior to addressing metastatic disease. Many authors also advocate colon-first surgery as a temporizing measure, while patients are given a trial of chemotherapy to assess response of the liver metastases and thus determine resectability of their liver lesion(s).

A small subset of patients in our study (5.7%) had their liver lesions resected first. This could represent the percentage of patients presenting with locally advanced rectal tumors, which not only require a more technically challenging surgical resection, but also in which neoadjuvant chemoradiation is typically preferred in an attempt to down-stage lesions and improve chances of R0 resection. Additionally, current studies note that patients undergoing liver-first surgery often require a major hepatectomy (involving three or more segments), usually due to a higher burden of hepatic disease compared to patients undergoing simultaneous resections.

Liver-first surgery is a fairly new entity in the treatment of metastatic colorectal cancer. Due to advances in both surgical and adjunct techniques, such as embolization, radio frequency ablation and two-stage hepatectomy, patients now have more options to address liver metastases, however, combining a major hepatectomy with a major colorectal resection is generally discouraged, as it increases both complications and mortality.

Separate admission resection was performed at a different hospital in 45.8% of patients in this study. This shows that nearly half of patients undergoing staged resection are potentially being excluded from single-center studies. Patients undergoing staged resections typically require more complex procedures, therefore it can be assumed that at a number of these patients may require referral to a surgical sub-specialist at a second institution or hospital, depending on the acuity and resources available at the index institution.

Recent studies have also shown that single-center, multidisciplinary management of patients with CRCLM results in better outcomes. Comprehensive management
at hepatobiliary referral centers has been shown to provide better disease control, fewer delays in care, fewer surgical procedures, less post-operative morbidity, and longer survival\textsuperscript{15}; therefore efforts should be made to arrange for single-center management in these facilities whenever possible.

The overall mortality rate for the patients in this study was 2.0%, which is consistent with other similar studies, which report mortality rates ranging from 0 to 3.5\%.\textsuperscript{6,9} Colon-first surgery incurred the lowest risk of mortality, but there was no significant difference in mortality between simultaneous and liver-first surgery.

We examined all-cause, nonfatal in-hospital morbidity which was then grouped into categories. These categories included mechanical wound complications, infections, urinary, pulmonary, gastrointestinal tract, cardiovascular, systemic, and complications during the surgical procedure. The overall complication rate was 26.8\%, with liver-first surgery resulting in a higher risk for complications.

Patients undergoing liver-first surgery often require a much more technically challenging procedure, precluding a simultaneous approach.\textsuperscript{9} Also, these patients often have longer procedures with higher blood loss than patients having colon-first surgeries.\textsuperscript{10} Major blood loss and transfusions have been shown to be risk factors for poorer surgical outcomes, therefore it is likely beneficial to consider a staged procedure in patients in whom major blood loss is anticipated.

Other studies of liver-first surgery report morbidity rates of 20-31\% with no significant differences in morbidity, mortality, overall and disease-free survival compared to simultaneous or traditional colon-first approaches.\textsuperscript{19} Currently no randomized controlled trials have been performed to compare these different approaches, as each strategy is highly dependent on specific patient and tumor characteristics.

Simultaneous resection is associated with decreased mean total cost compared with staged resection. This is likely due to costs associated with multiple hospital admissions and multiple surgical procedures versus one single admission and one combined operative experience. Similar studies have shown comparable results of increased cost with staged resections, despite no differences in intra-operative blood loss, post-operative complications, 30-day readmissions and overall mortality.\textsuperscript{17,18}
Strengths of this study include factors of a nationwide sample, irrespective of insurance type or payor status, and inclusion of readmissions across multiple institutions.

There are several limitations to this study. Firstly, this study cannot control for selection bias, as it is retrospective, and patients were not randomized to specific procedures or sequence of surgical treatment. Secondly, the data included was obtained from the Nationwide Readmissions Database (NRD), which is constructed from state databases, and therefore may exclude readmissions across state lines. Furthermore, variations in costs across institution, state, and regional lines as well as cost changes due to inflation rates are not accounted for in this paper.

Conclusions

This study demonstrates that simultaneous resection for patients with colorectal cancer with synchronous liver metastases is a safe and effective option for a select subgroup of patients, but care must be taken to select the appropriate patient, pathology and treatment facility for a combined procedure.

Nearly half of the patients in this study had a portion of their staged resection performed at a different hospital, but this did not significantly affect mortality. If possible, attempts should be made to manage patients at a single hepatobiliary center with a multidisciplinary team, in efforts to reduce delays in care and number of surgical procedures, and increase overall survival.

Liver-first surgery is also an option in the appropriate patients. Although it does increase risks for complications, there are no major differences in mortality, morbidity, or survival with this approach.

List of Abbreviations

CRC colorectal cancer; SLM synchronous liver metastases, CRCLM colorectal cancer with liver metastases, NRD nationwide readmissions database
Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

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Authors’ contributions:
KB – Major contributor in writing the manuscript
AR – Contributed to data interpretation and drafting of the manuscript
JP – Acquired, analyzed and interpreted the patient data
AC – Contributed to the project design, conception and editing of the manuscript

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Table 1. Characteristics of patients undergoing simultaneous or staged resection for colorectal cancer with synchronous liver metastases.

| CHARACTERISTIC           | TOTAL (%) | OVERALL MORTALITY |
|--------------------------|-----------|-------------------|
|                          | n (%)     | p                 |
| TOTAL                    | 6219 (100%) | 122 (2%)     |
| RESECTION ORDER          |           |                   |
| Simultaneous             | 3954 (63.6%) | 107 (2.7%) | <0.01    |
| Liver first              | 353 (5.7%) | * (0.8%)   |
| Colon first              | 1912 (30.7%) | 12 (0.6%)  |
| SURGERY                  |           |                   |
| Proctectomy              | 3054 (49.1%) | 60 (2%)  | <0.01    |
| Sigmoidectomy            | 1384 (22.3%) | 20 (1.4%)  |           |
| Left colectomy           | 571 (9.2%) | * (1.4%)   |           |
| Transverse colectomy     | 235 (3.8%) | 15 (6.4%)  |           |
| Right colectomy          | 911 (14.6%) | 16 (1.8%)  |           |
| Total colectomy          | 64 (1%)   | * (6.3%)   |           |
| AGE GROUP (YEARS)        |           |                   |
| 18-44                    | 872 (14%)  | * (0.2%)  | <0.01    |
| 45-64                    | 3453 (55.5%) | 65 (1.9%)  |           |
| ≥ 65                     | 1893 (30.4%) | 55 (2.9%)  |           |
| ADMISSION TYPE           |           |                   |
| Emergent                 | 1250 (20.1%) |               |           |
| Elective                 | 4969 (79.9%) | 95 (1.9%)  | 0.57     |
| GENDER                   |           |                   |
| Male                     | 3568 (57.4%) |               |           |
| Female                   | 2651 (42.6%) | 27 (1%)   | <0.01    |
| BED SIZE OF HOSPITAL | Count | Complications | p-Value |
|----------------------|-------|---------------|---------|
| Small                | 585 (9.4%) | * (0.3%) | <0.01 |
| Medium               | 951 (15.3%) | 32 (3.4%) |       |
| Large                | 4682 (75.4%) | 88 (1.9%) |         |

Table 2. Rates of complications during either admission.
| Characteristic               | Total (%) | Complication during either admission | 95% Confidence Interval |
|-----------------------------|-----------|--------------------------------------|-------------------------|
|                             | n (%)     | p-value                              | OR                      |
| Total                       | 6219 (100%) | 1667 (26.8%)                          |                         |

**Resection Order**

| Resection Order | Total (%)    | Complication during either admission | 95% Confidence Interval |
|-----------------|--------------|--------------------------------------|-------------------------|
| Simultaneous    | 3954 (63.6%) | 1031 (26.1%)                          | <0.01                   |
| Liver first     | 353 (5.7%)   | 119 (33.7%)                           | 1.42 1.12 1.8           |
| Colon First     | 1912 (30.7%) | 517 (27%)                             | 0.08 1.12 0.99 1.27    |

**Surgery**

| Surgery            | Total (%)    | Complication during either admission | 95% Confidence Interval |
|--------------------|--------------|--------------------------------------|-------------------------|
| Proctectomy        | 3054 (49.1%) | 840 (27.5%)                           | <0.01                   |
| Sigmoidectomy      | 1384 (22.3%) | 303 (21.9%)                           | <0.01 0.74 0.63 0.86   |
| Left colectomy     | 571 (9.2%)   | 179 (31.3%)                           | 0.07 1.2 0.99 1.46     |
| Transverse colectomy | 235 (3.8%) | 87 (37%)                             | <0.01 1.58 1.19 2.1    |
| Right colectomy    | 911 (14.6%)  | 239 (26.2%)                           | 0.26 0.9 0.76 1.08     |
| Total colectomy    | 64 (1%)      | 19 (29.7%)                            | 0.54 1.19 0.69 2.05    |

**Age group (years)**

| Age group (years) | Total (%)    | Complication during either admission | 95% Confidence Interval |
|-------------------|--------------|--------------------------------------|-------------------------|
| 18-44             | 872 (14%)    | 200 (22.9%)                           | <0.01                   |
| 45-64             | 3453 (55.5%) | 875 (25.3%)                           | 0.22 1.12 0.94 1.34    |
| ≥ 65              | 1893 (30.4%) | 593 (31.3%)                           | 0.15 1.22 0.93 1.6     |

**Elective admission**

| Elective admission | Total (%) | Complication during either admission | 95% Confidence Interval |
|--------------------|-----------|--------------------------------------|-------------------------|
| Yes                | 4969 (79.9%) | 1340 (27%)                           | 0.57                   |

**Patient Sex**

| Patient Sex | Total (%) | Complication during either admission | 95% Confidence Interval |
|-------------|-----------|--------------------------------------|-------------------------|
| Female      | 2651 (42.6%) | 603 (22.7%)                           | <0.01 0.69 0.61 0.77    |
| Male        | 3568 (57.4%) |                                       |                         |
| Bed size of hospital | N (%) | N (%) | p-value |
|----------------------|-------|-------|---------|
| Small                | 585 (9.4%) | 143 (24.4%) | 0.36 |
| Medium               | 951 (15.3%) | 253 (26.6%) |
| Large                | 4682 (75.3%) | 1271 (27.1%) |

| Primary expected payor | N (%) | N (%) | p-value |
|------------------------|-------|-------|---------|
| Private insurance      | 3378 (54.3%) | 798 (23.6%) | <0.01 |
| Medicare               | 1890 (30.4%) | 598 (31.5%) | 1.39 | 1.11 | 1.74 |
| Medicaid               | 632 (10.2%) | 198 (31.3%) | <0.01 | 1.54 | 1.28 | 1.87 |
| Self-pay               | 155 (2.5%) | 37 (23.9%) | 0.63 | 1.1 | 0.75 | 1.61 |
| No charge / other      | 163 (2.6%) | 36 (22.1%) | 0.97 | 1.01 | 0.69 | 1.48 |