The American Journal of Surgery 218 (2019) 894–898

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Safety evaluation of simultaneous resection of colorectal primary tumor and liver metastasis after neoadjuvant therapy: A propensity score matching analysis

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ARTICLE INFO

Article history:
Received 29 May 2018
Received in revised form
10 September 2018
Accepted 18 September 2018

Keywords:
Colorectal cancer liver metastasis
Simultaneous resection
Neoadjuvant therapy

ABSTRACT

Background: Considering the surgical safety and perioperative complications, simultaneous resection after neoadjuvant therapy is not commonly recommended.
Methods: A total of 253 patients were included in study. Comparison of the short-term outcomes was performed after propensity score adjustment in Group A (n = 96) and Group B (neoadjuvant therapy, n = 96).
Results: There was no postoperative mortality. After matching, the differences from surgical confounders were well-balanced. Morbidity (15.6% vs. 15.6%, p = 0.981), and Clavien-Dindo grade of complications (p = 0.710) were similar. No difference was found when the complications were divided according to the origin (general, colorectal and hepatic). Length of the hospital stays also did not differ between the groups (p = 0.482). More importantly, there was no increase in the number of patients with delayed adjuvant treatment after surgery in Group B.
Conclusions: Neoadjuvant treatment did not increase morbidity, length of hospital stays and influence adjuvant treatment after simultaneous resection.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. In China, it is the fifth most common cancer and also the fifth most common cause of cancer-related death,[1–3] and approximately 40% of those who undergo curative surgery are likely to die of the disease. Liver metastasis is the most common cause of mortality.[4,5] The incidence of synchronous liver metastases, according to Manfredi's analysis of 13,463 patients with CRC, was estimated at 14%.[6]

In patients with colorectal liver metastases (CRLM), radical resection is the only curative therapy,[7] which can increase the 5-year survival to 50%. The strategy previously used for CRC presenting with synchronous CRLM was to resect the primary cancer, and then resect the hepatic tumors after chemotherapy. Due to improvements in the safety associated with hepatic surgery in recent years, the surgical management of synchronous disease has profoundly changed. Several experienced centers have reported the safety of combined procedures. Lesser et al. proved that the mortality and morbidity, as well as 3-year recurrence-free survival associated with simultaneous resection was similar to that noted in the case of staged resection.[8] Later, it was found that the long-term oncologic outcomes were also similar between the two types of resection.[9–13] Other benefits included low lengths of hospital stay or expenses, especially in cases of minor hepatectomy.[14,15] The CoSMIC study from the United Kingdom, that aims to compare the above approaches in patients with synchronous liver metastases, has been launched and the results are awaited.[16]

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https://doi.org/10.1016/j.amjsurg.2018.09.019
0002-9610/

Moreover, there is controversy surrounding the order of chemotherapy and surgery. Theoretically, synchronous resection is predominantly applied to those with minor CRLM (≤3 segments), while resection, mainly staged operation, combined with neoadjuvant therapy is used for those with major CRLM. Neoadjuvant therapy before surgery, however, is predominantly considered to increase surgical difficulty and morbidity in the case of the simultaneous approach and one-stage surgeries are not commonly applied in many centers. However, Clinical evidence is unwarranted. Regardless of the uncertain long-term prognosis, it is at least necessary to evaluate the surgical safety and short-term morbidity for this treatment approach.

In this study, we aimed to evaluate the surgical and perioperative safety in patients with synchronous CRLM, who underwent simultaneous resection after neoadjuvant therapy. To set up a comparison group, patients without preoperative treatment but with simultaneous resection were chosen. In order to avoid bias in evaluating the safety, possible confounders including basic condition and surgical procedures, were balanced using the propensity score matching.

Materials and methods

Patient selection

This is single-center, retrospective study. We reviewed a database of patients treated in the Department of Colorectal Surgery at the Shanghai Cancer Center, from June 2015 to March 2018. The study was approved by the Medical Ethics Committee of Fudan University Shanghai Cancer Center, and written informed consent was obtained from all participants. Patients who met the following criteria were selected: (a) initially diagnosed as having synchronous CRLM; (b) Eastern Cooperative Oncology Group status ≤2 and no surgical or chemotherapy contradictions; (c) available and complete clinical records, including pathologic diagnosis, treatment strategy, and laboratory data. The exclusion criteria included patients who had either malignant tumors in other organs, or systematic inflammatory or hematologic disease. Patients with complications before surgery, such as severe obstruction or hemorrhage, requiring emergent surgery, were also excluded.

Neoadjuvant therapies were applied to 122 patients. The chemotherapy regimen was mainly 5-FU based, including XELOX (N = 79), and mFOLFOX6 (N = 30). Thirteen patients received a FOLFIRI regimen. Targeted drug therapy (bevacizumab or cetuximab) were used for 20 patients. The number of chemotherapy cycles ranged from 3 to 10, according to the treatment reaction. Of those with low and cT3 rectal cancer, 13 also had long-term neoadjuvant radiotherapy. In addition, all patients underwent radical resection at least 30 days after the end of neoadjuvant therapy. Adjuvant chemotherapy was applied no more than 1 month after surgery. The contradictions of chemotherapy included patients with uncured complications, as well as abnormal routine blood tests and liver enzymes levels.

Evaluation criterion

Postoperative complications were evaluated for 30 days, following resection. Complications were graded according to Clavien's classification.[17] Patients with Grade I and II complications could be cured with or without pharmacological treatment. Grades III and IV were categorized as major complications, requiring intervention or surgery, and even intensive care unit management. Several blood biochemical indices were detected, including total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate transaminase (AST), lactic dehydrogenase (LDH), γ-glutamyl transpeptidase (GGT), and albumin (ALB). Fong's clinical risk score (CRS) was used to predict prognoses.[18] Traditionally, patients with a low risk of worse prognoses were marked as having a CRS of 0–2, and others as a CRS of 3–5.

Statistical analysis

A propensity score was then calculated by logistic regression with the factors, mainly basic condition and surgical procedures known to influence the postoperative safety. These factors included age, sex, body mass index (BMI), American Society of Anaesthesiology (ASA) score, and surgical approach (operation on primary and metastatic lesions), metastatic distribution, number, maximum diameter and blood loss). Patients with neoadjuvant therapy were matched 1:1 using nearest neighbor matching, based on the closest propensity score to those without preoperative treatment.

Statistical analysis was performed using IBM SPSS Statistics software version 22 (SPSS Inc) and R version 3.0.1. Chi-square tests and Fisher's exact tests were used to compare the categorical variables between the groups. The Kolmogorov-Smirnov test was used to verify the normal distribution of variables. The exploratory comparison of normally distributed and non-normally distributed independent groups was performed using t-tests and Mann-Whitney U tests (2 groups).

Results

Simultaneous resection of CRC and CRLM were performed in 253 patients, of whom 131 did not have neoadjuvant therapy (Group A) while another 122 (Group B) did. After matching, 96 patients each in Groups A and B were compared. All patients had R0 resection. Follow-up was in progress and none of the patients died from surgery-related complications.

The baseline characteristics of the patients before and after matching were summarized in Table 1. The median age was from 57 to 59 years old, after matching. The sex, BMI and ASA score were not significantly different between two groups. Patients in Group B had more severe CRLM, which was reflected in the distribution and median number. After matching, these differences were also balanced. The general surgical approaches (laparoscopic and open), and type of colorectal resection did not differ significantly between the groups. Minor resections of liver metastases were more frequently performed in Group A (74.8% vs 54.9%) and major resections were only applied in 25.2% of the patients. In order to compare the differences in surgical safety, this difference was also balanced. Besides, blood loss, intraoperative transfusion and temporary diverting stoma during surgeries also did not differ after matching.

Other features were listed in Table 2 after matching. After neoadjuvant therapy, patients presented with lower N stage and size of primary tumors, possibly due to the effect from preoperative therapies. However, CRS score and T stage were similar between two groups. Considering that neoadjuvant therapy might lead to more tissue edema and bleeding, median operative time was a little longer in group B.

Data on surgical safety and morbidity are further analyzed in Table 3. Fifteen patients in each group had post-surgical complications, and the morbidity was similar (15.6%–15.6%, p = 0.981). According to the Clavien-Dindo grade of complications, no difference was observed in the complication severity between Group A and Group B (p = 0.710).

For further evaluation, we divided the complications into 3 categories: general (wound infection and hyperpyrexia), colorectal (complications of anastomoses and abdominal infection) and

Table 1
Comparison of characteristics before and after propensity score matching.

Variable	Before matching			After matching		
	Group A (N = 131)	Group B (N = 122)	p value	Group A (N = 96)	Group B (N = 96)	p value
Mean age, years, (range)	61.0 (29–80)	57.0 (28–77)	0.041	59.0 (29–80)	57.0 (28–74)	0.387
Sex, Male, (%)	71 (54.2)	76 (62.3)	0.192	53 (55.2)	58 (60.4)	0.465
BMI(Kg/m^2)	22.7 (16.9–34.4)	23.0 (15.3–34.1)	0.552	22.9 (16.9–34.4)	23.4 (17.3–34.1)	0.381
ASA Score ≥3, (%)	6 (4.6)	4 (3.3)	0.751	4 (4.2%)	4 (4.2%)	0.711
CRLM						
Distribution, unilobar, (%)	92 (70.2)	64 (52.5)	0.004	60 (62.5)	51 (53.1)	0.188
Median number, (range)	1 (1–14)	2 (1–12)	0.001	2 (1–14)	2 (1–11)	0.189
Median Maximum diameter, mm, (range)	30 (10–100)	30 (10–115)	0.230	30 (4–100)	27 (5–113)	0.679
Operation						
Surgical approach (%)			0.104			0.414
Totally laparoscopic	32 (24.4)	23 (18.9)		20 (20.8)	21 (21.9)	
Conversion to open	18 (13.8)	29 (23.7)		14 (14.6)	17 (17.7)	
Open	81 (61.8)	70 (57.4)		62 (64.6)	58 (60.4)	
Type of colorectal resection (%)			0.217			0.380
Right	60 (45.8)	41 (33.6)		42 (43.8)	34 (35.4)	
Left	19 (14.5)	17 (13.9)		13 (13.5)	13 (13.5)	
LAR	48 (36.6)	58 (47.5)		38 (39.6)	46 (47.9)	
APR	4 (3.1)	6 (5.0)		3 (3.1)	3 (3.1)	
Type of hepatectomy (%)			0.001			0.138
Minor (n < 3)	98 (74.8)	67 (54.9)		64 (66.6)	54 (56.3)	
Major (n ≥ 3)	33 (25.2)	55 (45.1)		32 (33.4)	42 (43.8)	
Median blood loss, mL, (range)	200 (50–2000)	300 (50–2500)	0.046	200 (50–2000)	300 (50–2500)	0.408
Intraoperative transfusion (%)	28 (21.4)	26 (21.3)	0.846	21 (21.9)	19 (19.8)	0.552
Temporary diverting stoma (%)	11 (8.4)	15 (12.3)	0.058	11 (11.5)	8 (8.3)	0.423

BMI, body mass index.
ASA, American Society of Anesthesiologists.
CRLM, colorectal liver metastasis.
LAR: low anterior resection.
APR: Abdominoperineal resection.

hepatic (infection around liver transection, cholangitis and severe pleural effusion) complications. Although the statistically result was similar between the groups ($p = 0.118$), different tendency could also be observed. Patients with preoperative treatment had more hepatic but less colorectal complications. However, the lengths of hospital stays did not differ (10 days vs 9 days, $p = 0.482$).

We also evaluated if synchronous resection after neoadjuvant therapy would somewhat delay postoperative chemotherapy. However, post-surgical adjuvant treatment was delayed in only 10 patients in Group A and 9 in Group B due to complications or unrecovered blood tests. Similarly, no difference was detected either ($p = 0.425$).

We further detected the changes in several important blood indices and their recovery before adjuvant treatment (Table 4). However, none of the findings were statistically different between the groups.

Discussions

In this study, we investigated the safety of simultaneous surgery after neoadjuvant therapy. The morbidity and perioperative recovery for patients with synchronous CRLM were similar between patients with and without neoadjuvant therapy. This would somewhat support the choice of applying simultaneous resection after chemoradiation.

Apart from the unclear effects on prognoses, the major concern with regards to simultaneous resection after neoadjuvant therapy is the safety during and after surgery, in which adverse effects on liver function are important. Patients in our study predominantly received 5-Fu-based neoadjuvant chemotherapy. It has been reported that traditional 5-Fu-based chemotherapy is correlated with hepatocyte steatosis, as reflected in the increase in the morbidity, and infection-related complications.[19,20] Other regimens, like oxaliplatin and irinotecan could also cause hepatotoxicity and induce

Table 2
Comparision of other clinical characteristics.

Variable	Group A (N = 96)	Group B (N = 96)	p value
Pathologic T stage, (%)			0.153
T1-2	3 (3.1)	12 (12.5)	
T3	41 (42.7)	37 (38.5)	
T4	52 (54.2)	47 (49.0)	
Pathologic N stage, (%)			0.010
N0	24 (26.4)	34 (35.4)	
N1-2	72 (73.6)	62 (64.6)	
CRS range, 0–2, (%)	46 (47.9)	48 (50.0)	0.819
Primary tumor diameter, mm, (range)	35.0 (3–110)	26.0 (0–115)	0.001
Median Operative time, min, (range)	207 (120–378)	229 (91–900)	0.028

CRS: Fong's clinical risk score.

Table 3
Comparison of perioperative complications and recovery after propensity score matching.

Variable	Group A (N = 96)	Group B (N = 96)	p value
90-days mortality	0	0	
Morbidity (%)	15 (15.6)	15 (15.6)	0.981
Details of complications			
Clavien-Dindo grade			0.710
Grade I-II	8	10	
Grade III-IV	7	5	
Details of complication			0.118
General	3	5	
Wound Infection	1	2	
Unknown hyperpyrexia	2	3	
Colorectal	8	3	
Pelvic infection	3	3	
Anastomotic leakage	3	0	
Anastomotic bleeding	2	0	
Hepatic	4	7	
Bile duct infection	0	1	
Severe pleural effusion	1	4	
Abdominal infection	2	2	
Subphrenic abscess	1	0	
Median Hospital stay, days, (range)	10 (6–55)	9 (6–58)	0.482
Delayed Adjuvant Therapy, (n%)	10 (12.5)	9 (10.4)	0.425

"yellow liver" (steatohepatitis) and "blue liver" (sinusoidal obstruction syndrome), respectively.[21] However, accurate proof on the association between target drugs and hepatotoxicity was not obtained. Overall, the reported adverse liver drug reactions included steatosis, non-alcoholic steatohepatitis and sinusoidal dilation.[22] Although previous studies have elucidated its association with an increased 90-day mortality after hepatic surgery,[20] a worse hepatic reserve and a higher complication rate,[19,23] most of those studies are outdated; in addition, improvements in surgical techniques and perioperative treatments should also be taken into consideration. Therefore, whether pathologic changes could lead to a higher morbidity, in reality, differs between individuals.

The EORTC 40983 study reported a postoperative complication incidence rate of 40% among 159 patients who underwent FOLFOX4 before resection, most cases of which were liver-related.[24] However, in the case of simultaneous resection, the concerns are totally different due to other situations, including the operation on primary lesions. Tranchart et al. reported a morbidity of 13% among 189 patients with simultaneous resection. Of the complications, most were general or colorectum-related, and only 31 patients underwent neoadjuvant therapy.[25] Yuan et al. presented an incidence rate of 17% of Grade II-IV complications in 60 patients, of whom 24 of them were pre-treated.[10] However, there were no clinical studies with large cohorts which detected the possible adverse effects of neoadjuvant therapy on simultaneous resection.

Theoretically, damage from chemical regimens was undoubtedly obvious during surgery, as reflected in the fragile texture and elevated incidence rate of hemorrhage, as well as in the dramatic elevation in the hepatic enzyme levels and risk of liver failure. However, with advances in surgical techniques and perioperative care, their practical effects on surgery and short-term outcomes require reconsideration. We have observed a higher incidence of hepatic complications in patients with neoadjuvant therapy. Notably most could be cured by conservative therapies. So whether the disadvantage was severe enough required more further studies. Interestingly, the overall incidence was similar between the two groups, which meant a lower incidence from colorectal surgery in patients with preoperative treatment could be observed. We believe that although the adverse impacts from radio-chemotherapies might increase operative difficulty or enlongate duration, this could be overcame by skilled surgery, and hemostasis technology. Besides, advantages like increased tumor shrink and resectability could also accurate tissues resection and tissues protection.

Overall, the mortality, morbidity, complication severity, and lengths of hospital stay did not differ between the two groups. In addition, we observed that the number of patients with adverse changes in the hepatic enzyme levels before and after resection was not higher. Most importantly, simultaneous resection after preoperative surgery did not delay patients' routine post-surgical treatment course. Our study's findings confirmed that this approach was comparatively safe and does not affect the post-surgical treatment course.

The present study had several limitations. Although we have balanced factors including the general conditions and cancer patterns, selection bias from subjective decision is still inevitable. For example, surgeions might be more careful to those with neoadjuvant chemotherapy during and after the operation. While these factors are non-quantifiable for analysis. Moreover, there were still some unanswered questions, pertaining to the identification of the risk factors for complications, such as the type of chemotherapy regimen and number of cycles, as well as the prognoses, which depended on the expansion of the case numbers and follow-up time. In many centers, neoadjuvant therapy is predominantly combined with a two-staged surgical approach. Apart from concerns about perioperative safety, the possible progression of primary lesions during neoadjuvant therapy, which would increase the rate of complications such as obstruction, bleeding and even perforation, is also a matter of concern. However, several studies have proven that this was over-estimated.[26,27] Considering the innate differences in the surgical trauma between the two approaches, we could not simply balance the gap and compare conditions at the same level. Our data could indirectly confirm the safety of simultaneous resection after neoadjuvant therapy.

Table 4
Changes in blood biochemical indexes.

Variable	Group A (N = 96) (N/%)	Group B (N = 96) (N/%)	p value
TBIL, post abnormal	42 (44.2)	40 (41.7)	0.770
DBIL, post abnormal	37 (38.5)	41 (42.7)	0.557
ALP, post abnormal	0	1	
ALT, post abnormal	78 (81.3)	72 (75.0)	0.295
AST, post abnormal	81 (84.4)	72 (75.0)	0.106
LDH, post abnormal	58 (60.4)	54 (56.3)	0.558
GGT, post abnormal	10 (10.4)	14 (14.6)	0.513
ALB, post abnormal	61 (63.5)	63 (65.6)	0.763

Conclusions

Simultaneous resection after neoadjuvant therapy was comparably safe. The preoperative neoadjuvant therapy did not increase morbidity and influence subsequent adjuvant treatment. So this may be done with equivalent morbidity to a group of patients who did not receive preoperative neoadjuvant therapy in carefully selected patients.

Funding sources

Funding: This work was supported by the National Natural Science Foundation of China (grant numbers 81472620, 81272307).

Declaration of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.09.019.

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