

A Multicenter Analysis of Short-term and Long-term Outcomes Following Laparoscopic Multivisceral Resection for Advanced Colorectal Cancer

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Abstract. *Background/Aim:* Recent research has demonstrated that laparoscopic multivisceral resection (MVR) for advanced colorectal cancer is safe, practicable, and yields satisfactory oncological results, which is in line with the growing usage of laparoscopic surgery. The effectiveness of laparoscopic MVR is still debatable, though. The goal of this study was to compare the short- and long-term results of patients with advanced colorectal cancer treated with open MVR with laparoscopic procedures. *Patients and Methods:* Data on 3,571 consecutive patients hospitalized at the Kyushu University National Kyushu Cancer Center for colorectal cancer surgery between 2004 and 2020 were gathered retrospectively. In the end, 84 individuals with advanced colorectal cancer who had a colectomy with MVR were examined. We evaluated invasiveness in terms of complications, blood loss, and operating time. *Recurrence-free survival rates and overall 5-year survival were among the oncological outcomes. Results:* Of the 84 patients examined, 29 underwent laparoscopic treatment, and 55 underwent open treatment. The laparoscopic surgery group experienced shorter

hospital stays (15 vs. 18 days, $p < 0.05$) and much less blood loss (median volume: 167 vs. 1,058 g, $p < 0.005$) than the open surgery group. Following the exclusion of patients with stage IV colorectal cancer from the study (groups undergoing laparoscopic surgery, $n = 25$; open surgery, $n = 38$), the groups displayed comparable pathologic results and no discernible variations in either the 5-year overall survival ($p = 0.87$) or recurrence-free survival ($p = 0.86$). *Conclusion:* In certain individuals with advanced colorectal cancer, a laparoscopic method of manipulation with MVR may be less invasive than an open method without compromising the prognosis.

Due to progress in surgical techniques, advancements in instrumentation, and enhanced understanding of colorectal cancer anatomy, the invasiveness of surgical procedures has diminished. Laparoscopic colectomy is applicable across a broad spectrum of conditions – from early to advanced cancer and from colon cancer to rectal cancer. Findings from extensive randomized controlled trials and meta-analyses have indicated that laparoscopic surgery for colorectal cancer is equivalent to or better than open surgery with regard to safety, feasibility, blood loss, postoperative pain, cosmesis, length of hospital stay, and oncological outcomes (1-4).

Locally advanced colorectal cancers may occasionally infiltrate or attach to neighboring organs. In these cases, identifying whether adhesions between the tumor and adjacent structures or organs stem from malignant invasion or benign inflammatory changes can pose a diagnostic challenge; consequently, radical removal requires an en bloc multivisceral resection (MVR) with a safe margin (5, 6). For these cases, various guidelines, including those from the European Association of Endoscopic Surgery, the Society of American Gastrointestinal and Endoscopic Surgeons, and the French Society of Digestive Surgery, recommend opting for open surgery. This is due to the association of serious

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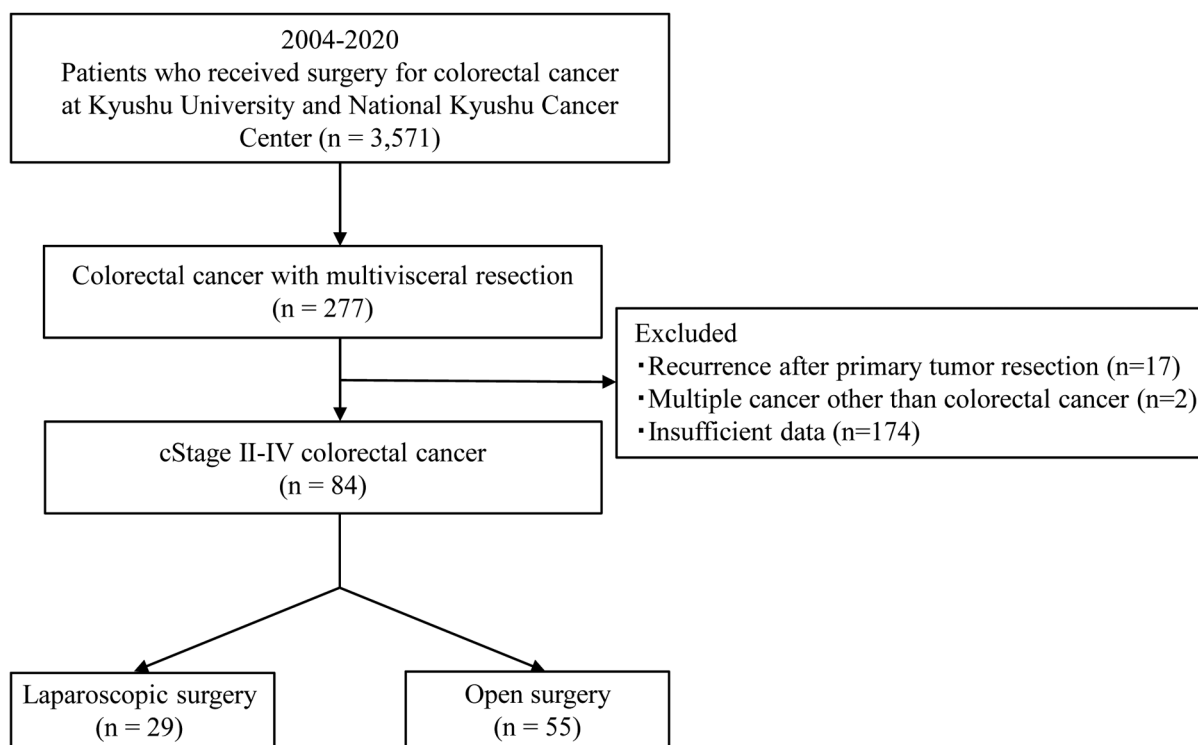


Figure 1. Flow diagram of patient selection.

complications with an extended en bloc MVR. Additionally, there is limited published evidence regarding the oncological outcomes associated with laparoscopic surgery (7-9). The Japanese Society for Cancer of the Colon and Rectum (JSCCR) emphasizes the importance of prudent consideration in determining the indications for utilizing laparoscopic surgery in the management of locally advanced colorectal cancers. This recommendation is derived from insights gained through the open-label, multi-institutional, randomized, phase III JCOG0404 trial (10). In light of the increasing adoption of laparoscopic surgery, recent studies have demonstrated that laparoscopic MVR is safe, feasible, and provides acceptable oncological outcomes (11, 12). However, the efficacy of laparoscopic MVR in the management of locally advanced colorectal cancer is a topic of ongoing debate, and there is a scarcity of publications addressing the long-term outcomes of laparoscopic MVR with an adequate median follow-up duration. Currently, there are available data on extended follow-up periods, encompassing long-term outcomes, such as survival and recurrence. Therefore, in the present study, we investigated the outcomes of patients with advanced colorectal cancer who underwent laparoscopic or open MVR and were followed for a median of >3 years. We compared these approaches on their short-term and long-term outcomes.

Patients and Methods

Patients. We retrospectively collected data on 3,571 consecutive patients admitted to the Kyushu University National Kyushu Cancer Center for surgical treatment of colorectal cancer between 2004 and 2020. We identified all patients who underwent a colectomy with MVR for cT4b advanced colorectal cancer that had infected or attached itself to nearby organs as shown on preoperative imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI). We excluded patients with recurrence of colorectal cancer after primary tumor resection (n=17), multiple cancers other than colorectal cancer (n=2), and insufficient data (n=174). The subjects of this study were 84 patients, who were divided into a laparoscopic surgery group (n=29) and an open surgery group (n=55) (Figure 1). Data on clinicopathological parameters [age, sex, body mass index (BMI), tumor diameter and location, preoperative treatment and therapy, type of surgery, depth of tumor invasion, lymph node metastasis, lymphatic invasion, venous invasion, pathological stage, resection margins, histological type, and recurrence site] were gathered by reviewing medical and pathology reports. Additionally, data on perioperative outcomes, such as operating time, amount of blood lost during surgery, removal of surrounding tissues and organs, switch to open surgery, problems after surgery, duration of hospital stay following surgery, and death, were gathered. Complications were defined as those that the Clavien-Dindo grading system ranked as grade III or higher. Physical examinations and blood testing were part of the follow-up, which was done every three months for the first three years following the procedure and

Table I. Characteristics of patients with colorectal cancer treated with laparoscopic or open multivisceral resection.

Factor	Laparoscopic (n=29)	Open (n=55)	p-Value
Age, years			
<65	10 (34.5)	27 (49.1)	0.20
≥65	19 (65.5)	28 (50.9)	
Sex			
Male	19 (65.5)	26 (47.3)	0.11
Female	10 (34.5)	29 (52.7)	
BMI, kg/m ²	22.2 (16.1-30.8)	20.8 (14.4-31.0)	0.98
Maximum diameter of tumor, mm	60 (30-120)	69 (30-170)	0.08
Tumor location			
Right side	7 (24.1)	7 (12.7)	0.18
Left side	22 (75.9)	48 (87.3)	
Preoperative stoma creation	2 (6.9)	2 (3.6)	0.50
Preoperative therapy			
Chemotherapy	4 (13.8)	10 (18.2)	0.94
Chemoradiotherapy	2 (6.9)	1 (1.8)	
Clinical stage			
II-III	27 (93.1)	37 (67.3)	<0.05
IV	2 (6.9)	18 (32.7)	

Note: Data are expressed as n (%) or median (range), as indicated. BMI: Body mass index.

then every six months after that. A CT scan was done every six months. The period of time from the date of operation until the date of death from all causes was called overall survival (OS). The period of time between surgery and the date of the disease's recurrence was called recurrence-free survival (RFS). For the purpose of this study, every patient provided written informed consent. The Institutional Review Board for Studies in Humans approved this research (Kyushu University; approval number #28-382 and National Kyushu Cancer Center; approval number #2013-102). This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable standards.

Surgical techniques. Open or laparoscopic surgery were used to perform radical resections. Both patients underwent a central vascular ligation, and all lymph nodes surrounding the tumor's supplying vasculature as well as the whole mesocolon were excised. Our institution's standard protocol for colorectal cancer laparoscopic surgery was previously reported (13). The surgeons choose between a laparoscopic and an open operation. The number of cases undergoing laparoscopic MVR has increased over time, as our technical abilities have developed and the spectrum of applications for laparoscopic surgery has grown. In actuality, open MVR predominated over laparoscopic MVR at our institution until 2012 (the ratio of laparoscopy was 10.0%). Nonetheless, the percentage of laparoscopies has increased (to 56.8%) since 2013. The surgeon made the intraoperative decision to convert to open surgery. Since elective surgery has fewer postoperative complications and death rates than emergency surgery, stoma formation has been employed as a bridge to surgery in cases of intestinal obstruction (14). The JSCCR guidelines state that a thorough evaluation of each patient's clinical circumstances was used to determine whether to execute a drastic resection of the main tumor with distant metastases. These evaluations covered the following: prognosis, risk of surgical

complications, impact of resection, general patient condition, metastatic status, and symptoms associated with the initial tumor, such as bleeding or bowel obstruction (15).

Statistical analysis. JMP Pro 16 software (SAS Institute, Cary, NC, USA) was used for statistical analysis. Fisher's exact test or χ^2 tests, as applicable, were used to examine significant differences between groups. The Kaplan–Meier method was used to examine OS and RFS, and the log-rank test was used to evaluate any differences between the two groups. $p < 0.05$ was regarded as significant.

Results

Patient characteristics. This study included a total of 84 patients who underwent a colectomy with MVR for cT4b colorectal cancer. Of these patients, 29 underwent laparoscopic surgery, and 55 underwent open surgery. The patients in the laparoscopic and open surgery groups were not significantly different with regard to age, sex, and BMI (Table I). The two groups had similar distributions of tumor diameters and tumor locations and proportions of preoperative treatments and therapies. The number of patients diagnosed with cStage IV disease was higher in the open surgery group than that in the laparoscopic surgery group ($p < 0.05$).

Perioperative outcomes. The two groups had similar median operating times ($p = 0.17$), but the laparoscopic surgery group experienced significantly less blood loss ($p < 0.005$) (Table II). Four cases (13.8%) required conversion to open surgery due to extensive adhesion ($n = 1$), liver invasion ($n = 1$), and difficulty to secure a field of view because of large tumor

Table II. Perioperative oncological outcomes of patients with colorectal cancer treated with laparoscopic or open multivisceral resection.

Factor	Laparoscopic (n=29)	Open (n=55)	p-Value
Operating time, min	302 (194-699)	322 (125-811)	0.17
Blood loss volume, g	167 (10-2,950)	1,058 (35-13,097)	<0.005
Open conversion	4 (13.8)		
Resected structures or organs			
Solid	25 (86.2)	34 (61.8)	<0.05
Multiple	4 (13.8)	21 (38.2)	
Complications (CD≥3)	2 (6.9)	9 (16.4)	0.19
Anastomotic leakage	1 (3.5)	1 (1.8)	
Intrabdominal abscess	0	4 (7.4)	
Ileus	1 (3.5)	1 (1.8)	
Surgical site infection	0	2 (3.6)	
Bleeding	0	1 (1.8)	
Mortality	0	0	
Postoperative stay, days	15 (8-45)	18 (6-100)	<0.05
Adjuvant chemotherapy			
Yes	12 (48.0)	23 (60.5)	0.32
Recurrence			
Present	5 (20.0)	9 (23.7)	0.67
Liver	3	2	
Lung	2	1	
Distant lymph node	2	3	
Peritoneum	1	1	
Brain	0	1	
Spleen	1	0	
Other local recurrence	1	3	

Note: Data are expressed as n (%) or median (range), as indicated. In some patients, the recurrence sites overlapped. CD: Clavien–Dindo Classification.

size (n=2). The number of patients who required removal of a solid structure or organ was 25 (86.2%) in the laparoscopic surgery group and 34 (61.8%) in the open surgery group. Two or more structures or organs were removed in four patients (13.8%) in the laparoscopic surgery group and in 21 patients (38.2%) in the open surgery group. These data suggested that more advanced cases were included in the open surgery group. The patients in the laparoscopic surgery group tended to have fewer complications compared with those in the open surgery group, but the difference was not significant ($p=0.19$). Compared to the open surgery group, the laparoscopic surgery group had shorter hospital stays ($p<0.05$). There were no deaths within 30 days of surgery in either group. The two groups included similar proportions of patients who received adjuvant chemotherapy. Recurrence rates were similar between the two groups (20.0% in the laparoscopic surgery group vs. 23.7% in the open surgery group; $p=0.67$), and the most common recurrence sites were the liver and distant lymph node in these groups, respectively. The most common adjacent structures or organs removed in the laparoscopic and open surgery groups, respectively, were the uterus (4 vs. 15), bladder (3 vs. 14), ovary (3 vs. 14), and small intestine (8 vs. 7) (Table III).

Table III. Structures or organs resected en bloc with the primary tumor.

Structure or organ	Laparoscopic (n=29)	Open (n=55)
Uterus	4	15
Bladder	3	15
Ovary	3	14
Small intestine	8	7
Prostate gland	1	9
Seminal vesicle	0	8
Abdominal wall or peritoneum	3	4
Vagina	2	4
Other parts of colorectum	1	4
Ureter	1	2
Omentum	2	0
Duodenum	1	1
Pararenal fascia	1	1
Diaphragm	1	1
Stomach	0	1
Liver	1	0
Levator ani muscle	1	0
Skin	1	0
Hypogastric nerve	0	1
Urachus	0	1
Coccyx	0	1

Note: In some patients, there was some overlap.

Table IV. Pathologic outcomes (Stage IV excluded) of patients with colorectal cancer treated with laparoscopic (Lap) or open (Open) multivisceral resection.

Factor	Laparoscopic (n=25)	Open (n=38)	p-Value
Depth of tumor invasion			
T3	13 (52.0)	15 (39.5)	0.23
T4a	1 (4.0)	7 (18.4)	
T4b	11 (44.0)	16 (42.1)	
Lymph node metastasis			
Positive	11 (44.0)	18 (47.4)	0.79
Negative	14 (56.0)	20 (52.6)	
Lymphatic invasion			
Positive	6 (24.0)	7 (18.4)	0.59
Negative	19 (76.0)	31 (81.6)	
Venous invasion			
Positive	13 (52.0)	13 (34.2)	0.16
Negative	12 (48.0)	25 (65.8)	
Pathological stage			
II	14 (56.0)	20 (52.6)	0.76
III	11 (44.0)	18 (47.4)	
R0 resection rate	22 (88.0)	37 (94.8)	0.32
Histological type			
tub1, tub2, pap	22 (88.0)	34 (89.5)	0.73
por, muc	3 (12.0)	4 (10.5)	

Note: Data are expressed as n (%). NA: Not available; muc: mucinous carcinoma; pap: papillary adenocarcinoma; por: poorly differentiated adenocarcinoma; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma.

Pathological outcomes. The laparoscopic and open surgery groups included 25 and 38 patients, respectively, after excluding stage IV cases (Table IV). We did not observe any significant differences in pathologic parameters between groups in depth of tumor invasion, lymph node metastasis, lymphatic invasion, venous invasion, pathological stage, R0 resection rate, or histological type.

The median follow-up period was significantly shorter in the laparoscopic surgery group (36.4 months, range=1.6-99.3 months) than in the open surgery group (58.6 months, range=1.6-195.1 months; $p<0.05$). This was possibly due to the increase in the use of the laparoscopic approach for MVR in recent years. The laparoscopic and open surgery groups did not differ significantly in terms of 5-year OS ($p=0.87$; Figure 2A) or RFS ($p=0.86$; Figure 2B).

Discussion

Laparoscopically assisted colectomy has been proven to be equally safe and efficacious compared to open colectomy in patients with colorectal cancer (16). However, it has been reported that the long-term outcomes of laparoscopically assisted colectomy were unfavorable, and it was proposed that this was due to varying levels of proficiency among institutions (17). Only a few studies have assessed the long-term outcomes of laparoscopic MVR of advanced colorectal cancers. Nishikawa *et al.* reported that a laparoscopic approach was

non-inferior to an open approach in terms of RFS ($p=0.578$) (12). In another study, Takahashi *et al.* and Miyo *et al.* reported that OS and RFS were comparable between the laparoscopic and open surgery groups (18, 19). Mukai *et al.* also reported that the short-term and long-term outcomes of laparoscopic surgery were equivalent to those of open surgery (20). Our study presented detailed oncologic outcomes with a relatively long median follow-up period of 38.0 months. The 5-year OS and RFS rates for the laparoscopic and open surgery groups did not differ significantly in our study, similar to what was reported in previous studies.

Among patients undergoing MVR for colorectal cancer, reported rates of pT4b ranged from 28.2% to 70.0% (6, 12). Previous studies revealed that laparoscopic surgery was linked to a lower incidence of pT4b compared to open surgery (6, 12, 18). They suggested that the lower pT4b rate in the laparoscopic surgery group meant that more advanced cases were included in the open surgery group. However, our pT4b rates were similar, with 44.0% in the laparoscopic surgery group and 42.1% in the open surgery group. The fact that pT4b rates were comparable in our study might be the result of more aggressive laparoscopy procedures being used for advanced cancers.

Achieving an R0 resection is the most important factor in a curative approach to colorectal cancer with MVR (21). Previous studies on MVR reported R0 resection rates of 68.4%-100% with laparoscopic surgery and 68.8%-98.5% with

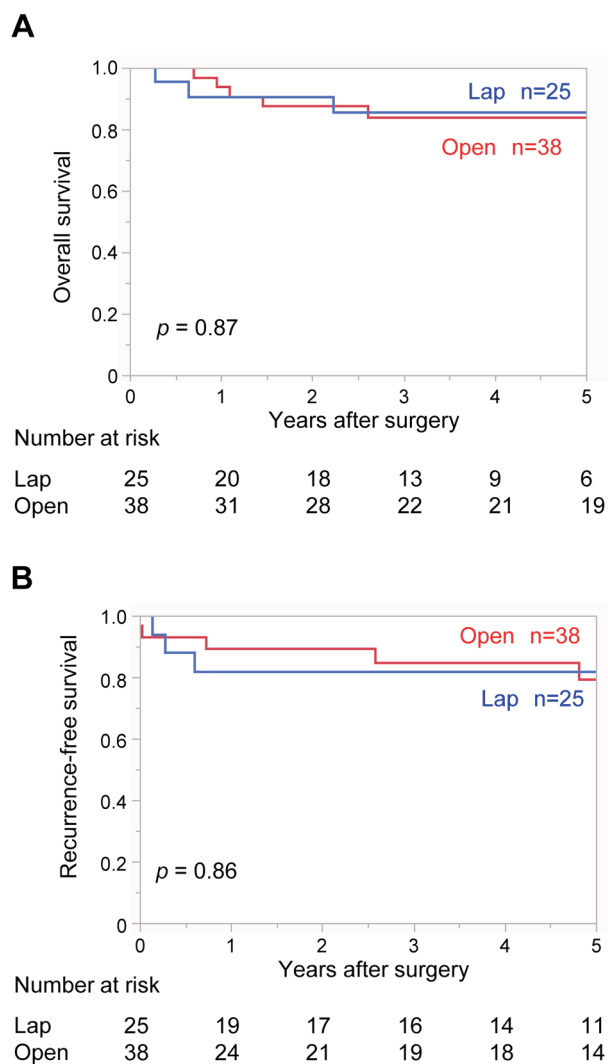


Figure 2. Kaplan–Meier curves of five-year survival after a laparoscopic (Lap) or open laparoscopic multivisceral resection (Open). (A) Overall survival. (B) Recurrence-free survival.

open surgery. Thus, our R0 resection rates were within the published range, with 92.0% in the laparoscopic surgery group and 94.8% in the open surgery group. Kim *et al.* reported that the local recurrence rates after MVR in the laparoscopic and open surgery groups were 7.7% and 27.3%, respectively (22). In our study, local recurrences occurred in two patients in the laparoscopic surgery group (8.0%) and in four patients in the open surgery group (10.5%), which suggested that our oncological clearance rate was acceptable. Our data support the notion that our laparoscopic surgery approach provided long-term outcomes similar to those provided with the open surgery approach, but with less invasiveness.

To prevent injury to vital organs, an early decision should be made about converting to an open procedure. Yang *et al.*

described the optimal timing for open surgery conversion (23). Though previous studies showed open conversion rates of 5.6%-23.0% with laparoscopic MVR, our open conversion rate, 13.8%, was within the range (24, 25). For bulky locally advanced colorectal cancer, a comprehensive preoperative evaluation of the peritumoral anatomy, coupled with a judicious and timely decision for potential open conversion during surgery, can mitigate the elevated risk of severe complications. To secure a circumferential resection margin, enhance the surgical field of view, or inhibit micrometastasis, the consideration of neoadjuvant chemotherapy is also viable.

Study limitations. First, the study was retrospective, therefore some bias was present. Second, the determination of the operation type, open or laparoscopic surgery, was inconsistent, because it was determined by the attending physician and team at each institution considering the tumor size and the number of invaded structures or organs. Third, although the clinical and pathological tumor stages were comparable between the laparoscopic surgery and the open surgery groups, patients in the open surgery group tended to have more aggressive tumors, as indicated by the fact that the open surgery group tended to have larger tumor sizes and a higher rate of removal of two or more structures than the laparoscopic surgery group. Fourth, laparoscopic MVR for advanced colorectal cancers has increased in popularity over the years, as over half of the MVRs have been performed laparoscopically in recent years. Therefore, the first half of this study period includes mainly patients who underwent open surgery. Additional evidence is necessary to confirm the utility of laparoscopic surgery in this subset of patients with colorectal cancer who require MVR.

Conclusion

For patients with locally advanced colorectal cancer, the short and long-term outcomes of laparoscopic and open MVR were equivalent. However, performing laparoscopic MVR should be considered only by a specialized team.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: Eiji Oki; Methodology: Sho Nambara, Ryota Nakanishi; Formal analysis and investigation: Sho Nambara, Ryota Nakanishi, Kentaro Nonaka; Writing – original draft preparation: Sho Nambara; Writing – Reviewing and Editing: Ryota Nakanishi, Yoshiaki Fujimoto, Qingjiang Hu, Tomonori Nakanoko, Masahiko Sugiyama, Mitsuhiko Ota, Yasue Kimura, Eiji Oki, Yasushi Toh, Tomoharu Yoshizumi; Funding acquisition: none, Resources: Sho

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