Open versus Laparoscopic Resection of Primary Tumor for Incurable Stage IV Colorectal Cancer: A Large Multicenter Consecutive Patients Cohort Study

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Short running head: Open vs Lap resection for Stage IV CRC

Mini Abstract

Short- and long-term outcomes of laparoscopic and open resection for incurable Stage IV colorectal cancer were examined in a large cohort study. The effectiveness of laparoscopic surgery was clarified.

Abstract

Objective: To investigate the hypothesis that laparoscopic primary tumor resection is safe and effective when compared with the open approach for colorectal cancer patients with incurable metastases.

Summary and Background Data: There are only a few reports with small numbers of patients on laparoscopic tumor resection for Stage IV colorectal cancer.

Methods: Data from consecutive patients who underwent palliative primary tumor resection for Stage IV colorectal cancer between January 2006 and December 2007 were collected retrospectively from 41 institutions. Short- and long-term outcomes were compared between patients who underwent laparoscopic or open resection.

Results: A total of 904 patients (laparoscopic group: 226, open group: 678) with a median age of 64 years (range: 22-95) were included in the analysis. Conversion was required in 28 patients (12.4%) and most of the reasons for conversion (23/28: 82%) were bulky or invasive tumors. There was no 30-day postoperative mortality in either group. The complication rate (NCI-CTCAE Grade 2-4) after laparoscopic surgery (17%) was significantly lower than that after open surgery (24%) (P=0.02), and the difference was greater (4% vs. 12%; P<0.001) when we limited the analysis to severe (≧Grade 3) complications. The median length of postoperative hospital stay in the laparoscopic group was significantly shorter than that in the open group (14 vs. 17 days; P=0.002). In univariate analysis, overall survival for the laparoscopic group was significantly better than that for open surgery (Median survival time: 25.9 vs. 22.3 months, P=0.04), although no difference was apparent in multivariate analysis.

Conclusions: Laparoscopic primary tumor resection has advantages in the short term and no disadvantages in the long term, compared with open surgery. It is a reasonable treatment option for certain Stage IV colorectal cancer patients with incurable disease.

Introduction

Colorectal cancer is one of the most common neoplasms worldwide [1]. Approximately 20 to 25% of patients with colorectal cancer are reported to have metastatic disease at the time of first presentation [2, 3]. Of these, only about 20% of patients can undergo curative resection of the distant metastasis [4].

There are two controversies surrounding the treatment strategy for incurable Stage IV colorectal cancer. The first is whether or not we should remove the primary tumor in patients with incurable metastases. With the progress of chemotherapy for colorectal cancer in the last two decades, non-operative treatment has become one of the important treatment options for incurable Stage IV colorectal cancer [5-7]. Based on this opinion, National Cancer Network (NCCN) guidelines recommend non-operative treatment for incurable Stage IV colorectal cancer without symptoms [8]. On the other hand, some reports advocate the benefits of primary tumor resection as a treatment for Stage IV colorectal cancer [3, 9, 10]. Therefore there seems to be no consensus at this time regarding the effectiveness of palliative primary tumor resection for incurable Stage IV patients.

The second controversy is whether, if the primary tumor is to be resected, we should use an open or laparoscopic approach. The role of laparoscopic primary tumor resection for incurable Stage IV colorectal cancer has not been well evaluated, although randomized control trials have confirmed the feasibility and efficacy of laparoscopic surgery for localized colorectal cancer [11-14]. There have been several reports demonstrating the efficacy of the laparoscopic approach for Stage IV colorectal cancer compared to Stage I-III disease [15, 16], or to open surgery [4, 17], in terms of complication rate, hospital stay, or even survival time. However, these studies included relatively small numbers of patients and the evidence is limited and inconclusive.

Thus, in order to clarify the role of laparoscopic primary tumor resection in the treatment of Stage IV colorectal cancer, we conducted this multicenter observational study

including a large number of patients to compare the short- and long-term outcomes between open and laparoscopic primary tumor resection for exclusively “incurable” Stage IV colorectal cancer.

Patients and Methods

Patients with incurable Stage IV colorectal cancer who underwent primary tumor resection at 41 institutions participating in the Japan Society of Laparoscopic Colorectal Surgery from January 2006 to December 2007 were included in this study. All the surgeons were experienced and skilled in open surgery and had experience of more than 100 open surgery cases, and most of the surgeons (32/38) had experience of more than 100 laparoscopic colorectal surgeries. Four surgeons had performed less than 30 laparoscopic colorectal surgeries and 2 of these performed only open surgeries in this study. This study included only patients who underwent “palliative” primary tumor resection and excluded those who underwent resection of metastases with curative intent, irrespective of whether this was simultaneous or two-stage. The choice of operative approach (open or laparoscopic) was at the surgeon’s discretion. According to a questionnaire requesting information on treatment strategies for incurable Stage IV colorectal cancer from each institute participating in this study, the first choice of treatment was systemic chemotherapy in 11, open resection in 4, laparoscopic resection in 3 and in the remaining 23 institutes, the treatment selection depended on the patients’ condition. After approval of each institution’s ethical committee, the consecutive patients’ demographic and clinicopathological data including operating time, blood loss, conversion, intraoperative complications, residual tumor sites, chemo/radiotherapy, tumor pathology, length of hospital stay, postoperative complications, and survival times were collected retrospectively. Tumor location was defined according to the Japanese Classification of Colorectal Carcinoma Second English Edition [18]. “Tumor stenosis” was defined as the condition where colonoscopy could not

pass through the tumor region.

The primary endpoint was overall survival. Secondary endpoints included length of hospital stay, oral intake on the day after the operation, increment of C-reactive protein (CRP) and increment of white blood cell count (WBC) on the first postoperative day, complication rate, and postoperative febrile period.

The sample size required for calculating 2-year overall survival with adequate accuracy was estimated as 600 using imaginary data (imaginary 2-year survival: 20%).

Statistical Analysis

Overall survival was calculated from the date of operation until death from any cause or the date of the last follow-up. Survival curves were estimated using Kaplan-Meier's method, and comparison was performed with a log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model for multivariate analysis. Categorical variables were compared with Fisher's exact test. Continuous variables were compared using t-tests. All *P* values were two-sided and *P* values less than 0.05 were considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

During the study period, data from 972 patients were collected. Nine patients were excluded from analysis because of the exclusion criteria. Emergency operation was carried out in 59 patients. Most of the emergency operations except one case were open resections, and they were also excluded from the analysis set to reduce bias between the groups. Thus, a total of 904 patients were used for analysis. Of these, laparoscopic resection was performed in 226 cases (laparoscopic group), and open resection was performed in 678 cases (open group).

Patient clinicopathological characteristics in both groups are shown in Tables 1 and 2. There was no difference between the groups in terms of age, American Society of Anesthesiologists (ASA) class, tumor location, and rate of tumor stenosis. The proportion of rectal cancer was similar between the two groups (open: 137/677 (20.2%), laparoscopic: 42/226 (18.6%)). In this series, 412 (47%) patients had stenotic disease and 210 (23%) patients suffered from preoperative anemia (Hb <10.0). Twenty-eight cases (12.4%) of the laparoscopic resections needed conversion to open surgery. Most of the reasons for conversion (23/28: 82%) were bulky or invasive tumors. Six intraoperative complications including five cases of bleeding and one splenic injury were observed exclusively in the open group. Operative times were significantly longer in the laparoscopic group (222 vs. 175 minutes; *P*=0.002). However, estimated blood loss was less in the laparoscopic group compared with the open group (50 vs. 180 g; *P*<0.001). The proportion of patients who had metastases involving multiple organ sites was higher in the open group than in the laparoscopic group (37.6% vs. 28%; *P*=0.008).

Short-term outcomes are shown in Table 3. The laparoscopic group showed significantly lower white blood cell counts on the first postoperative day, earlier first oral intake, shorter periods of postoperative fever (≧37℃), and shorter lengths of postoperative hospital stay. Postoperative complications (NCI-CTCAE ver. 3.0 ≧Grade 2) occurred less frequently in the laparoscopic group (16.8%) compared with open resection (24.2%; *P*=0.02). When we limited analysis to severe complications (Grade 3 or 4), the difference became more obvious (4.4% vs. 11.9%; *P*<0.001). There was no 30-day mortality after operation in either group.

The median follow-up time for all patients was 30 months. The median survival time of patients who underwent laparoscopic surgery (25.9 months) was significantly longer than that for open surgery (22.3 months; *P*=0.04) (Figure 1). The proportions of patients who underwent chemotherapy after laparoscopic and open surgery were 85% and 82%

respectively, and median lengths of the initiation of chemotherapy after operation were 28 (range: 6-753) and 33 (range: 8-746) days respectively. In multivariate analysis using the Cox regression hazard model, ASA class, age, Carcinoembryonic antigen (CEA) level, and number of metastatic organs had a significant impact on overall survival. Overall survival for the laparoscopic approach was not inferior to that for the open approach even by adjustment of these covariates (Hazard Ratio (HR): 0.91; *P*=0.37) (Table 4).

Discussion

Approximately 20 to 25% of patients diagnosed with colorectal cancer have synchronous metastasis (Stage IV) at the time of first presentation [2, 3]. These patients generally have a poor prognosis, unless all metastatic disease is removed completely. Unfortunately, the proportion of such patients is only around 20%, and the role of surgery for the majority of Stage IV patients still remains palliative [4].

For patients with synchronous “incurable” metastases, it is generally accepted that the primary tumor should be removed, if possible, when it is causing symptoms, *i.e.*, stenosis or bleeding. However, it is controversial whether or not primary tumors should be removed in the absence of symptoms. Non-operative treatment including systemic chemotherapy is recommended by the NCCN guidelines [8] as a first treatment for incurable Stage IV colorectal cancer without symptoms. This is based on the opinion that, with the advancement of systemic chemotherapy, primary tumor resection is not necessary for most patients without symptoms at their first presentation [5, 19]. Poultsides et al. [7] reported that the use of chemotherapy without tumor resection for asymptomatic disease is appropriate standard practice; however 11% of patients required intervention during the treatment. In contrast Cook et al. [3] reported using the SEER database that more than 60% of patients with Stage IV colorectal cancer in practice underwent primary tumor resection, and that their prognosis was better than that of patients without resection (median survival time

(MST) of colon cancer patients: 11 vs. 2 months; MST of rectal cancer patients: 16 vs. 6 months). Ruo et al. also retrospectively investigated the outcomes of patients with asymptomatic Stage IV colorectal cancer who did or did not undergo palliative primary tumor resection [10]. They demonstrated that the resection group showed a survival advantage compared with the non-resection group, although the number of distant metastatic sites involved and the volume of hepatic replacement by tumor was smaller in the resection group (MST 16 vs. 9 months). At this time, there is no conclusive evidence regarding the effectiveness of palliative primary tumor resection for incurable Stage IV patients. More than half of the patients in this study had stenotic disease or were anemic (Hb<10.0), and the results were similar with or without symptoms, though because we don't have data on patients who were excluded from surgery, we cannot comment on the effectiveness of palliative primary tumor resection. We feel that the operative indications for incurable Stage IV patients may depend on various factors including the patient's general condition, estimated life expectancy, local advancement of the primary tumor, and the invasiveness of surgery.

Laparoscopic surgery offers perioperative clinical benefits for patients with localized colon cancer compared with open surgery [11-14]. However the evidence concerning its benefits as a treatment for Stage IV colorectal cancer is still lacking. There are several reports that advocate the use of laparoscopic resection for Stage IV colorectal cancer. Two reports comparing the surgical and/or oncological outcomes after laparoscopic colorectal resection, between localized disease (Stage I-III) and metastatic disease (Stage IV) [15, 16], demonstrated that laparoscopic surgery for selected Stage IV colorectal cancer can be successfully performed without increasing the incidence of complications, despite the inclusion of larger and more invasive tumors in the Stage IV group. Law analyzed the data from 200 colorectal cancer patients with metastases who underwent primary tumor resection (77 laparoscopic and 123 open resection), and reported that the survival times of

patients with laparoscopic and open resection were similar (MST: 16.0 vs. 16.4 months) [4]. However, these studies were not conclusive due to their small sample size.

In this study, we demonstrated the benefits of laparoscopic surgery over open surgery by analysis of data from 904 incurable Stage IV patients. Regarding safety, there was no 30-day operative mortality in this series. The frequency of postoperative complications in the laparoscopic group (16.8%) was low compared with the open group, and when we limited analysis to severe complications (≧Grade 3), the frequency was only 4.4%. Although the definition of complication is somewhat different, this rate compares favorably with previous reports from other groups [4, 15]. Interestingly, these complication rates are comparable to the previous report from the Japanese multicenter study of laparoscopic resection for Stage I-III colorectal cancer [20]. Therefore, we feel that the laparoscopic approach is, if performed by an experienced surgeon, safe and feasible even for colorectal cancer patients with synchronous incurable metastases. On the other hand, the conversion rate of 12.6% in this series seems to be higher than that of around 4% in Kitano's series [20]. The major reason for conversion in this study was the presence of advanced tumor. Indeed, Moloo described the major factor associated with conversion in Stage IV patients to be tumor fixation, a different pattern from that seen in Stage I-III, and stated that this should influence decision-making when offering a laparoscopic resection for patients with Stage IV colorectal cancer [15], because conversion may negate the benefits of laparoscopic surgery [21]. The length of postoperative hospital stay in the laparoscopic group was 14 days, significantly shorter than in the open group (17 days), but possibly somewhat longer than in previous reports from other countries; this may be due to differences in health insurance systems between Japan and other countries.

Although overall survival time after laparoscopic resection was significantly longer than that after open resection in univariate analysis, the difference was no longer apparent when multivariate analysis was applied. This seems be due to the selection bias (*e.g.* the

proportion of patients with metastasis in only one organ was higher in the laparoscopic group). However, the results of multivariate survival analysis indicate that laparoscopic surgery produced at least equivalent long-term outcomes in comparison to open surgery. In previous studies of primary tumor resection for Stage IV colorectal cancer, survival outcomes were less favorable, and median survival time (MST) did not reach 20 months. In this series, in spite of including exclusively “incurable” metastatic colorectal cancer, the MST of both the open group (22.3 months) and the laparoscopic group (25.9 months) were much longer than those previously reported for similar patients undergoing operations for incurable cancer. We believe that the laparoscopic approach will enhance the benefits of primary tumor resection (*i.e.* reduction of tumor-associated complications induced by chemotherapy, including perforation or bleeding) without increasing the risk of surgery.

This is a retrospective cohort study, and the choice of operative approach was at the surgeon’s discretion. Therefore, selection biases are the most important drawback of this type of study. A randomized controlled study would be ideal to confirm the efficacy of laparoscopic compared with open resection, though it seems difficult to balance the various factors involved in Stage IV patients. We believe this study may provide the best available evidence to determine the treatment strategy for incurable Stage IV colorectal cancer.

Conclusion

The laparoscopic approach has advantages in the short term and no disadvantages in the long term, compared with open surgery. Laparoscopic primary tumor resection is a reasonable treatment option for certain Stage IV colorectal cancer patients with incurable disease.

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Figure legends

Figure 1: Long-term outcome: univariate analysis

Table 1: Patient characteristics

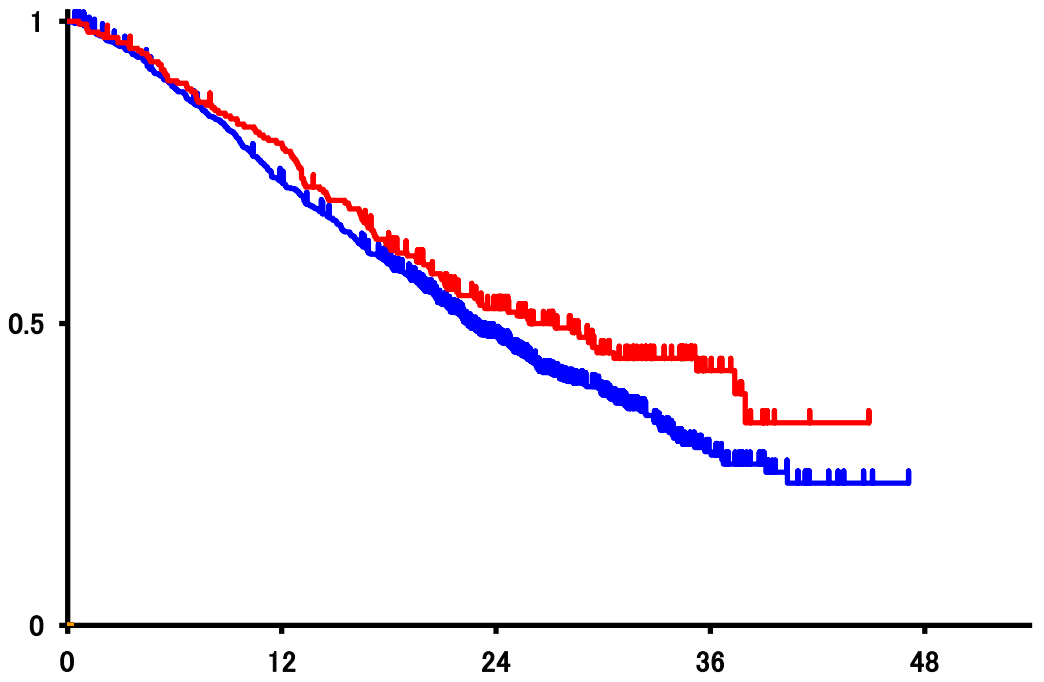
Table 2: Operative data

Table 3: Short-term outcomes

Table 4: Long-term outcome: multivariate analysis

Figure 1. Long-term outcome: univariate analysis

Analysis set: patients undergoing surgery except for emergency ones



	n	events	Median follow-up (months)	Median overall survival (months) 95%C.I.	
Open surgery	678	406	30.0	22.3 20.7-24.8	Logrank p=0.04
Laparoscopic surgery	226	117	30.0	25.9 21.1-35.2	

Table 1. Patients characteristics

Analysis set: patients undergoing surgery except for emergency ones

		Open surgery (n=678)		Laparoscopic surgery (n=226)	
			%		%
Age	Median	64		64	
	Range	26–95		22–87	
Gender	Male	403	59.5	114	50.4
	Female	274	40.5	112	49.6
Height	Median	160		160	
	Range	135–186		137–183	
Weight	Median	56		55	
	Range	29–120		33–85	
ASA-PS	″1/2″	618	92.0	211	94.2
	″3/4″	53	8.0	13	5.8
Other neoplasms	≧1	26	3.8	7	3.1
	none	652	96.2	219	96.9
Stenosis	−	343	52.1	125	56.6
	+	316	48.0	96	43.4
Previous laparotomy	+	151	22.7	67	30.2
	−	513	77.3	155	69.8
Tumor location	V/C/A/T	237	35.0	63	27.9
	D/S/RS	298	44.0	120	53.1
	other colon 99	5	0.7	1	0.4
	Ra/Rb/P	137	20.2	42	18.6
	total	677	100	226	100
Preoperative radiotherapy	+	9	1.3	1	0.4
	−	669	98.7	225	99.6
Preoperative chemotherapy	+	45	6.6	10	4.4
	−	633	93.4	216	95.6
CEA	Median	24.5		28.7	
	Range	0.09–15927		1–19046	
CA19-9	Median	41.0		29.8	
	Range	0.1–31410		0.1–113000	
WBC	Median	6780		6230	
	Range	690–23720		2300–14800	
Hb	Median	11.7		11.9	
	Range	5.1–17.4		5.0–16.5	
CRP	Median	0.6		0.3	
	Range	0–42.8		0–23.8	

Table 2. Operative data

Analysis set: patients undergoing surgery except for emergency ones

			Open surgery (n=678)		Laparoscopic surgery (n=226)		Total (n=904)		# of missing values
				%		%		%	
Surgery	Right-sided colectomy	1	197	29.5	52	23.0	249	27.9	1
	Left-sided colectomy	2	96	14.4	44	19.5	140	15.7	
	Transverse colectomy	3	30	4.5	9	4.0	39	4.4	
	Anterior resection	4	117	17.5	54	23.9	171	19.1	
	Low anterior resection	5	112	16.8	41	18.1	153	17.1	
	Abdominoperineal resection	6	34	5.1	11	4.9	45	5.0	
	Hartmann's procedure	7	73	10.9	11	4.9	84	9.4	
	Others	9	8	1.2	4	1.8	12	1.3	
Open conversion	+				28	12.4			
	–				198	87.6			
Reason for Conversion	Tumor invasion				23	82.2			
	Adhesion				2	7.1			
	Bleeding				1	3.6			
	Narrow view				2	7.1			
Additional operation (複数回答可)	Liver resection		42	6.2	3	1.3	45	5.0	
	Lung resection		0		0		0		
	Cholecystectomy		10	1.5	4	1.8	14	1.5	
	Small bowel resection		21	3.1	2	0.9	23	2.5	
	Other operations		107	15.8	20	8.8	127	14.0	
	–		522	77.0	200	88.5	722	79.9	
Operative time (min)	Median		175		222		188		3
	Mean		207		234		214		
	Range		40-1220		63-650		40-1220		
Bleeding(g)	Median		180		50		134		8
	Mean		329		126		278		
	Range		0-4800		0-3220		0-4800		
Intraoperative complications	+		6	0.9	0				
		Bleeding	5						
		spleen injury	1						
	–		672	99.1	226	100			
fT	M		1	0.1	0				
	SM		2	0.3	1	0.4			
	MP		25	3.7	4	1.8			
	SS		310	45.7	114	50.4			
	SE		214	31.6	72	31.9			
	SI		73	10.8	20	8.8			
	A		35	5.2	11	4.9			
	AI		18	2.7	4	1.8			
fN	0		102	15.0	46	20.4			6
	1		218	32.2	73	32.3			
	2		197	29.1	72	31.9			
	3		147	21.7	30	13.3			
	X		10	1.5	3	1.3			
fM	0		380	56.0	127	56.2			9
	1		290	42.8	98	43.4			
Number of organs with residua tumor	1		423	62.4	163	72.1			
	≧2		255	37.6	63	28			

Table 3. Short-term outcomes

Analysis set: patients undergoing surgery except for emergency ones

			Open surgery (n=678)			Laparoscopic surgery (n=226)			*P*	# of missing values
			%			%				
Postoperative WBC(/μl)(1P	Median		9600			8600				3
	Mean		10001			9081			p<0.001	
	Range		2300-23200			1200-20100				
Postoperative CRP(mg/dl)	Median		6.9			5.2				58
	Mean		8.5			6.1			p=0.19	
	Range		0-680			0.8-26.8				
Water intake	Median		3.0			1.0				14
	Mean		3.4			2.2			p<0.001	
	Range		1-42			1-27				
Afebrile date	Median		4.0			3.0				42
	Mean		4.8			4.0			p=0.02	
	Range		0-62			1-30				
Longth of Stay	Median		17			14				8
	Mean		21			17			p=0.002	
	Range		1-142			6-77				
Blood transfusion	+		98		14.9	21		9.7	p=0.053	30
	-		559		85.1	196		90.3		
Postoperative complications ((+			164		24.2	38		16.8	p=0.02	
	-		514		75.8	188		83.2		
Postoperative complications ((+			81		11.9	10		4.4	p<0.001	
	-		597		88.1	216		95.6		
Postoperative complications	(CTCAE Grade)		Grade 2	Grade 3	Grade 4-5	Grade 2	Grade 3	Grade 4-5		
	Anastomotic leak	#	8	16	4	5	3			
	Ileus	#	17	25	1	6	1			
	Obstruction	#	4	4	1	1				
	Wound infection	#	35	8		13				
	Intra-abdominal infection	#	8	4	1	1	2			
	Urinary dysfunction	#	4	1		1				
	Bleeding	#	1	1			1			
	Stroke	#			2			1		
	Deep vein thrombosis	#		1						
	Lung infection	#	1	2	1					
	Others	#	13	11	7	2	2			
Multiple complications (cases)			16			2				

Table 4. Long-term outcome: multivariate analysis

Analysis set: patients undergoing surgery except for emergency ones

Factor		Hazard Ratio	95%CI	*P*
Approach	laparo/open	0.91	0.89-1.36	p=0.37
ASA-PS	2/1	1.17	0.97-1.40	p<0.001
	3/1	2.05	1.51-2.80	
	4/1	9.40	1.30-68.2	
Age	70-79/＜70	1.17	1.17-1.74	p<0.001
	≧80/＜70	1.62	1.62-3.00	
CEA	Q1/Q4	0.58	0.45-0.76	p<0.001
	Q2/Q4	0.62	0.49-0.79	
	Q3/Q4	0.80	0.63-1.01	
R2 organ	1/≧2	0.52	0.43-0.62	p<0.001

Open Versus Laparoscopic Resection of Primary Tumor for Incurable Stage IV Colorectal Cancer: A Large Multicenter Consecutive Patients Cohort Study

Dear Sir/Madam

We read with interest the article by Hida *et al.* published in the May 2012 issue of Annals of Surgery.[1] We have discussed the paper in our journal club and would like to raise some points that we discussed. The choice of operation is subject to the surgeon's discretion, which adds to the selection bias inherent in these studies. The fact that only one-fourth of the population under study were subject to laparoscopy leads one to presume that significant selection criteria were at play in influencing the surgical approach. These criteria could have been explored further; for example a survey of how surgeons decide between laparoscopic and open approaches could have provided valuable information to the reader. Factors such as nutritional state and presence of symptoms have not been compared between the two groups, raising the question if these factors played a role in decision making and have biased the results in favour of laparoscopic surgery. In studies of this kind, it is important for readers to have an insight into the overall picture. For example, what is the distribution of presentation (by stage) of all patients with colorectal cancer in the centres involved? How many patients with stage IV disease were seen in this period and what proportion of these had surgery? The paper reports a 12.4% conversion rate from laparoscopic to open approach. However it is not clear in which group these patients were analysed, specifically whether they were analysed by intention to treat. This number could make a significant difference to the results to either group.

We noted the 0% 30-day mortality rates for both laparoscopic and open groups. This is extremely low for a cohort with such advanced disease undergoing major surgery. We wondered whether the in-hospital mortality rates was different, and whether that could have been reported alongside the 30-day mortality rates.

Judith E Ritchie, MBChB MSc
University of Sheffield
Sheffield, South Yorkshire UNITED KINGDOM
on behalf of Sheffield Surgical Journal Club

Reference

1. Hida K, Hasegawa S, Kinjo Y, et al. Open Versus Laparoscopic Resection of Primary Tumor for Incurable Stage IV Colorectal Cancer: A Large Multicenter Consecutive Patients Cohort Study. *Ann Surg*. 2012;255:929-934.

Reply to Letter: "Open Versus Laparoscopic Resection of Primary Tumor for Incurable Stage IV Colorectal Cancer: A Large Multicenter Consecutive Patients Cohort Study"

Reply to Dr. Judith E Ritchie:

We are pleased to have the opportunity to respond to the letter to the editor by Dr. Ritchie and would like to thank her and her journal club for their interest in our work. As Dr. Ritchie commented, the choice of operative approach was at the surgeon's discretion, so selection bias is the most important drawback in this type of study. However, as the potential biases in the decision-making process for surgical management of stage IV colorectal cancer are diverse, even a randomized controlled study would likely not have been sufficient for balancing the various factors involved in stage IV patients.

In our study, we asked 41 institutions about their treatment strategy for stage IV incurable colorectal cancer. Eleven selected chemotherapy and 7 selected surgical resection as the first-line treatment, and the remaining 23 informed us that it depends on patient condition. Symptomatic cases were always indicated for surgery. Regarding the operative approach, 9 institutes considered open surgery as a first-line treatment, while 16 considered laparoscopic surgery as a first-line treatment.

Although we did not compare nutritional state itself, we checked the factors representing the general condition of patients (height and weight, ASA physical status, and Hb levels). Concerning symptoms, we defined stenosis and anemia as tumor-derived symptoms[1]. Almost all patients with emergent disease received open surgery and were therefore excluded from our study, while other symptomatic patients who received laparoscopic surgery had better courses, as described in our other article[1]. The laparoscopic group included a 12.4% conversion and was analyzed by intention to treat.

Finally, we must apologize for an error in the mortality statistics; there were actually five 30-day mortalities in 678 open cases (0.7%) and one 30-day mortality in 226 laparoscopic cases (0.4%).

We hope that these data clarify the issues in question.

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Reference

1. Akagi T, Inomata M, Kitano S, et al. Multicenter study of short- and long-term outcomes of laparoscopic palliative resection for incurable, symptomatic stage IV colorectal cancer in Japan. J Gastrointest Surg. 2013;17:776-783.