Surgical Oncology 35 (2020) 328–335

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: http://www.elsevier.com/locate/suronc

The role of surgery for locally recurrent and second recurrent rectal cancer with metastatic disease

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ARTICLE INFO

Keywords:
Locally recurrent rectal cancer
Distant metastases
Surgical indication

ABSTRACT

Background: The role of surgery for locally recurrent rectal cancer (LRRC) with resectable distant metastases or second LRRC remains unclear. This study aimed to clarify the influence of synchronous distant metastases (SDMs), a history of distant metastasis resection (HDMR), and a second LRRC on the outcome.

Methods: The long-term outcomes of 70 surgically treated patients with LRRC between 2006 and 2018 were compared by SDM (n = 10), HDMR (n = 17), and second LRRC (n = 7).

Results: Among the 10 patients with SDM, 4 patients underwent simultaneous resection, whereas the other 6 underwent staged resection with distant first approach. Recurrence developed in 9 patients, of which 2 patients with liver re-resection achieved long-term survival without cancer. The patients with and without SDM had equivalent 5-year overall survival rate (40.5% vs. 53.3%, $p = 0.519$); however, patients with SDM had a worse 3-year recurrence-free survival rate than those without SDM (10.0% vs. 37.5%, $p = 0.031$). Multivariate analysis showed that primary non-sphincter-preserving surgery, second LRRC, and R1 resection were independent risk factors for overall survival. Similarly, primary non-sphincter-preserving surgery, second LRRC, SDM, and R1 resection were risk factors for recurrence-free survival.

Conclusions: Patients with SDM might still be suitable to undergo salvage surgery and achieve favourable overall survival. Distant metastasectomy should be performed first, followed by a sufficient interval to avoid unnecessary LRRC resection in uncurable patients. An HDMR should not be taken into consideration when making surgical plans. Surgical indication of second LRRC should be strict, especially in referred patients.

1. Introduction

Even in the era of total mesorectal excision (TME) and preoperative chemoradiation (CRT), local recurrence after curative rectal resection remains a major problem with reported 5-year local relapse rate of 5.6–17.6% [1–4]. When locally recurrent rectal cancer (LRRC) was treated without salvage surgery, the 5-year overall survival (OS) was quite dismal at 4% [5]. Therefore, salvage surgery for LRRC is still the only possible curative option; however, this operation often requires multivisceral resection, leading to impaired postoperative quality of life (QOL), including bowel, urinary, and/or sexual dysfunction. Additionally, repeat surgery needs a high level of skill in fields with strong adhesions and fibrosis in a narrow pelvis; therefore, aggressive surgical treatment for LRRC has mainly been attempted in specialized centres [6–12]. The R0 resection rate, which is accepted to be an established prognostic factor after LRRC resection, and the subsequent 5-year OS have been reported to be 59–77% and 38.6–47.0%, respectively [8–12]. While such favourable results were reported by a single centre, non-randomized, and retrospective study, another study showed contradictory results that salvage surgery for LRRC could not improve survival [13]. Because of the heterogeneity of LRRC, including previous treatments, the extent of disease, and tumour aggressiveness, the surgical indications might be a crucial issue affecting the outcome.

It is well known that LRRC is caused not only by an aggressive tumour nature, but also by technical failure in primary surgery. So-called surgeon-related factor, which has been reported mainly in

Abbreviations: LRRC, locally recurrent rectal cancer; SDM, synchronous distant metastasis; HDMR, history of distant metastasis resection; NAC, neoadjuvant chemotherapy.

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https://doi.org/10.1016/j.suronc.2020.09.001
Received 16 June 2020; Received in revised form 17 August 2020; Accepted 6 September 2020
Available online 11 September 2020

Western countries, is an important cause of local recurrence [14–16]. However, it is extremely difficult to determine whether the main cause is a surgeon-related factor or aggressive tumour nature, especially in referred patients, because the details of the initial surgery are unclear. On the other hand, distant metastasis is a simple indicator reflecting the tumour's malignant behaviour. It has been widely accepted that distant metastasectomy could improve survival in patients with resectable hepatic or pulmonary metastases from colorectal cancer, although postoperative relapse often occurs. The recurrence-free survival (RFS) rate has been reported to be 28.1–35.4% after hepatectomy [17,18] and 34–40% after pulmonary resection [19,20].

However, it remains controversial whether salvage surgery is indicated for LRRC with resectable synchronous distant metastasis (SDM). Moreover, the impacts of a history of distant metastasis resection (HDMR) and re-resection for a second LRRC on the outcome have rarely been evaluated. This study aimed to clarify the outcomes of patients who underwent resection for both LRRC and resectable SDM with curative intent and to discuss their surgical indication. Additionally, the impacts of HDMR and re-resection of a second LRRC on the outcome were also evaluated.

2. Patients and methods

2.1. Patient population

Seventy consecutive patients (18 females; median age, 64 years) with LRRC who underwent surgical resection with curative intent between August 2006 and August 2018 were identified from the Nagoya University Hospital prospective database and analysed retrospectively. During this study period, 2 patients abandoned curative resection because peritoneal dissemination was found during the operation and were excluded from this study. Four patients with isolated and noninvasive lateral lymph node metastases, which were successfully treated only by lateral lymph node dissection, were also excluded. This study was approved by the Nagoya University Hospital Institutional Review Board (#2019-0197).

2.2. Clinical assessment

Continuous data are expressed as the median (range) unless specified otherwise. To assess resectability, enhanced chest and abdominopelvic multidetector-row computed tomography (CT) with a 1 mm or thinner slice thickness, pelvic magnetic resonance imaging (MRI) with a 4 mm slice thickness, and 18F-fluorodeoxyglucose positron emission tomography-CT were routinely performed. In patients with liver metastases, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced abdominal MRI and indocyanine green retention rate were also performed to evaluate resectability.

The interval from the initial surgery was calculated as the period between the date of initial surgery and diagnosis of LRRC. The initial surgeries were divided into sphincter-preserving and non-sphincter-preserving surgeries. Nonfunctional sphincter-preserving surgeries, such as Hartmann's procedure, were included in the sphincter-preserving surgery group. SDM was defined as distant metastasis that existed when local recurrence was diagnosed. Any previous surgical resections except for primary resection and resection for LRRC were included as an HDMR.

2.3. Preoperative treatment

In principle, preoperative CRT was not given if complete resection was fully expected based on the preoperative imaging findings during this study period. In this series, neoadjuvant chemotherapy (NAC) was favour due to the low completion rates of adjuvant chemotherapy after extended pelvic surgery.

2.4. Surgical indications

All patients were selected as candidates for surgical resection at the pretreatment multidisciplinary conferences. The surgical indications and technical details of LRRC have been previously reported [10,21] but have gradually changed year by year. Enduring absolute contraindication included tumors extend to the sacral promontory resulting in impracticality of the S1 nerve preservation, grown into the sciatic nerve, with leg edema secondary to lymphatic or venous obstruction, and with invasion of the external iliac artery. Concomitant a few liver metastases that were amenable to R0 resection were the original indications for resection with curative intent. In recent years, even for patients with not only liver but also lung metastases or other distant metastases, surgical resection was indicated if the tumors were technically resectable. For patients with SDM, simultaneous resection was the original choice if it was considered to be sufficiently tolerated, taking into account the patient's physical condition and the invasiveness of the surgery. Recently, staged resection, in which distant metastasectomy was principally performed first, followed by LRRC resection has been chosen.

The contraindication for LRRC resection included the following: tumour extension into the sacral promontory indicating the impracticality of S1 nerve preservation, growth into the sciatic notch, leg edema secondary to lymphatic or venous obstruction, and invasion into the external iliac artery.

2.5. Follow-up

The curability was evaluated as the status of the microscopic resection margin: R0, surgical margin not involved; or R1, surgical margin involved. Major complications were defined as those classified as grade III or higher according to the Clavien–Dindo classification [22].

Recurrence was diagnosed based on imaging studies, mainly chest and abdominopelvic CT, which were routinely performed every 6 months for 10 years after LRRC resection. In patients who underwent distant metastasectomy, CT was performed every 3 months for the first 5 years and then every 6 months up to 10 years. Regarding the patients who returned to the local hospital, prognostic information was collected by interviewing their local hospital physicians.

2.6. Statistical analysis

The possible clinical characteristics, and surgical and pathological results were compared in terms of the presence of SDM. Variables were compared by the chi-squared test or the Mann–Whitney *U* test, where appropriate. OS was calculated from the date of LRRC resection until death from any cause or the last follow-up, and RFS was defined as the time until any recurrence or the last follow-up. Survival curves were traced using the Kaplan–Meier method and differences between curves were tested using the log-rank test. The prognostic significance of selected factors for OS and RFS was evaluated using the Cox proportional hazards regression model. A p value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 25.0 (IBM Japan Ltd., Tokyo, Japan).

3. Results

3.1. Patients' background and operative results

The baseline characteristics and surgical results of 70 patients are listed in Table 1 according to the presence of SDM. Most of the patients (84.3%) underwent initial surgery at the referring hospital. In 8 patients (11.4%) with primary stage IV disease, the primary tumour and SDM were successfully removed. Pathological lateral lymph node metastases at initial surgery were found in 6.7% of the patients without SMD but none in patients without SMD. Seven patients (10%) underwent prior resection for LRRC and had a second LRRC. Seventeen patients (24.3%)

Table 1
Baseline characteristic and surgical results of 70 patients according to the presence of SMD.

Variables	Total	With SDM	Without SDM	p value
	n = 70	n = 10	n = 60	
Age, year, median (range)	64 (33–78)	64 (57–71)	64 (33–78)	0.801
Gender, n (%)				0.435
Male	52 (74.3)	9 (90.0)	43 (71.7)	
Female	18 (25.7)	1 (10.0)	17 (28.3)	
Stage of primary tumor, n (%)				0.362
I	10 (14.3)	1 (10.0)	9 (15.0)	
II	22 (31.4)	1 (10.0)	21 (35.0)	
III	29 (41.4)	7 (70.0)	22 (36.7)	
IV	8 (11.4)	1 (10.0)	7 (11.7)	
Unknown	1 (1.4)	0	1 (1.7)	
Initial surgery				0.344
At our hospital	11 (15.7)	0	11 (18.3)	
At referring hospital	59 (84.3)	10 (100)	49 (81.7)	
Primary location				0.308
Upper or middle rectum	30 (42.9)	6 (60.0)	24 (40.0)	
Low rectum	40 (57.1)	4 (40.0)	36 (60.0)	
Primary procudure				0.084
Sphincter-preserving	45 (64.3)	9 (90.0)	36 (60.0)	
Non-sphincter-preserving	25 (35.7)	1 (10.0)	24 (40.0)	
Primary approach				0.361
Open	56 (80.0)	9 (90.0)	47 (78.3)	
	14 (20.0)	1 (10.0)	13 (21.7)	
Primary lateral node metastases				1.000
Absent	66 (94.3)	10 (100)	56 (93.3)	
Present	4 (5.7)	0	4 (6.7)	
Interval from initial surgery, n (%)				0.713
<24 months	20 (28.6)	2 (20.0)	18 (30.0)	
>24 months	50 (71.4)	8 (80.0)	42 (70.0)	
Median (range)	33.6 (5.9–182.2)	32.5 (18.6–78.8)	33.6 (5.9–182.2)	0.675
Previous radiotherapy, n (%)				1.000
For primary tumor	2 (2.9)	0	2 (3.3)	
For other disease	1 (1.4)	0	1 (1.7)	
No	67 (95.7)	10 (100)	57 (95.0)	
HDMR, n (%)				0.242
Yes (overlapping)	17 (24.3)	4 (40.0)	13 (21.7)	
Liver	9	2	7	
Lung	7	1	6	
Others	4	1	3	
No	53 (75.7)	6 (60.0)	47 (78.3)	
Second local relapse, n (%)				1.000
Yes	7 (10.0)	1 (10.0)	6 (10.0)	
No	63 (90.0)	9 (90.0)	54 (90.0)	
SDM, n (%)				–
Yes	10 (14.3)	10 (100)	–	
Liver	6	6	–	
Lung	3	3	–	
Para-aortic lymph node	1	1	–	
No	60 (85.7)	–	60 (100)	
Preoperative treatment, n (%)				1.000
Yes (overlapping)	52 (74.3)	8 (80.0)	44 (73.3)	
Chemoradiotherpy	8	1	7	
Systemic chemotherapy	49	8	41	
No	18 (25.7)	2 (20.0)	16 (26.7)	
Operative procedure, n (%)				0.157
Pelvic exenteration	52 (74.3)	7 (70.0)	45 (75.0)	
Abdominoperineal resection	2 (2.9)	0	2 (3.3)	
Anterior resection	8 (11.4)	3 (30.0)	5 (8.3)	
Tumor resection	8 (11.4)	0	8 (11.4)	
Operative approach				0.112
Open	61 (87.1)	7 (70.0)	54 (90.0)	
Laparoscopic	9 (12.9)	3 (30.0)	6 (10.0)	
Bony pelvic resection, n (%)				0.731
Yes	41 (58.6)	5 (50.0)	36 (60.0)	
No	29 (41.4)	5 (50.0)	24 (40.0)	
Operative time, min, median (range)	863 (37–1552)	881 (432–1234)	852 (37–1552)	0.880
Blood loss, ml, median (range)	2041 (5–8673)	1965 (810–3719)	2181 (5–8673)	0.491
Curavility				0.480
R0	47 (67.1)	8 (80.0)	39 (65.0)	
R1	23 (32.9)	2 (20.0)	21 (35.0)	
Major complications				0.308
Yes	34 (48.6)	3 (30.0)	31 (51.7)	
No	36 (51.4)	7 (70.0)	29 (48.3)	
Mortality	0	0	0	1.000
Adjuvant chemotherapy, n (%)				1.000
Yes	7 (10.0)	1 (10.0)	6 (10.0)	
No	63 (90.0)	9 (90.0)	54 (90.0)	

had an HDMR, including hepatectomy (n = 9), pulmonary resection (n = 7), and distant lymph node resection (n = 2) (overlapping). Ten patients (14.3%) had SDM at a single site. NAC was applied in 79 patients (70%). None of the backgrounds or surgical results significantly differed between the patients with and without SMD.

3.2. Characteristics of patients with SDM

The details of 10 patients with SDM (median age of 64 years) are shown in Table 2. Nine patients (90%) were male and half of the patients had an HDMR. The most dominant site of SDM was the liver (n = 6), followed by the lung (n = 3). NAC was introduced in 8 patients (80%). Four patients underwent simultaneous resection, whereas the other 6 patients experienced staged resection with the distant first approach. In patient 10, ipsilateral repeated pulmonary resection was performed for early recurrent disease, which developed during the interval between the initial pulmonary and LRRC resection. That patient also underwent contralateral pulmonary resection in the last phase because the lung lesion was quite small and was not definitively diagnosed. Seven patients underwent pelvic exenteration, and pathological R0 resection was achieved in 8 patients (80%). Postoperative relapse developed in 9 patients (90%), including local relapse (n = 4) and distant metastasis (n = 6), with median RFS of 11.4 months. Among the 9 recurrence patients, 3 patients underwent re-resection of the recurrent disease (2 liver and 1 local), and 2 patients who underwent liver re-resection achieved long-term survival without cancer (patients 2 and 6).

3.3. Oncological outcomes

The median follow-up duration was 41.1 (6.2–153.7) months. In the entire cohort, postoperative recurrence developed in 45 patients (64.3%) and the most dominant sites were the lung and local in 20 patients (28.6%). The 5-year OS and 3-year RFS rates were 51.4% and 33.3%, respectively. In patients who achieved R0 resection, the 5-year OS rate was 61.7%, which was better than that of patients with R1 resection, but there was no significant difference (30.3%, $p = 0.069$).

Fig. 1 demonstrates the OS and RFS in patients according to SDM, HDMR, or second LRRC. The 5-year OS rate in patients with SDM was 40.5%, which was similar to that in patients without SDM (53.3%, $p =$

Table 2
Details of 10 patients with SDM.

Case	Year	Age	Sex	Primary stage	HDMR	SDM	NAC	Order	Local procedure	Local pR	Recurrence	Re-resection	Outcome	RFS (year)	OS (year)
1	2008	71	M	3	–	Liver	–	Simultaneous	Hartmann	1	Local	–	Died	1.6	4.9
2	2010	58	M	2	–	Liver	+	Simultaneous	TPE + S,P	0	Liver	+	Alive without cancer	0.6	9.6
3	2011	65	M	1	Liver	Liver	–	Liver → Local	Hartmann	1	Local	+	Alive with cancer	1.7	8.4
4	2011	63	M	3	Liver	Liver	+	Simultaneous	TPE + S	0	Liver	–	Died	0.3	1.0
5	2013	66	M	3	Local	Lung	+	Lung → Local	TPE	0	Local	–	Died	1.4	3.1
6	2014	59	M	3	–	Liver	+	Liver → Local	TPE + S	0	Liver	+	Alive without cancer	0.1	5.8
7	2014	66	M	3	–	Liver	+	Liver → Local	ISR + prostatectomy	0	Liver, lung, pelvis LNs	–	Died	0.5	1.8
8	2015	63	M	3	–	Lung	+	Lung → Local	TPE + S	0	Lung	–	Died	0.5	1.8
9	2017	57	F	4	Overy	Para-aortic LNs	+	Simultaneous	TPE + para-aoritic LNs dissection	0	–		Alive without cancer	2.1	2.1
10	2018	68	M	3	Lung x 2	Lung (bilateral)	+	Lung (2) → Local →Lung	TPE + S	0	Lang, local	–	Alive with cancer	1.3	1.3

HDMR = history of distant metastases resection; SDM = synchronous distant metastases; NAC = neoadjuvant chemotherapy; OS = overall survival; RFS = recurrence-free survival; TPE = total pelvic exenteration; S = sacrectomy; P = pubic resection; ISR = intersphincteric resection; LN = lymph node.

0.519). Similarly, the 5-year OS rates in patients with and without HDMR did not differ significantly (37.9% and 55.7%, respectively, $p = 0.476$). However, the 5-year OS rate in patients with a second LRRC was 16.7%, which was significantly worse than that in patients with their first LRRC (55.8%, $p = 0.023$).

The patients with an HDMR had a similar 3-year RFS rate compared to those without an HDMR (31.8% vs. 33.7%, $p = 0.604$). On the other hand, the 3-year RFS rate in patients with SDM was significantly worse than that in patients without SDM (10.0% vs. 37.5%, $p = 0.031$).

3.4. Risk factor analysis for OS and RFS

Table 3 reveals the results of the univariate and multivariate risk factor analysis for OS using the Cox regression model. Multivariate analysis showed that primary non-sphincter-preserving surgery, second LRRC, and R1 resection were independent risk factors for poor OS. Similarly, multivariate risk factor analysis for RFS demonstrated that primary non-sphincter-preserving surgery, second LRRC, presence of SDM, and R1 resection were independent risk factors for poor RFS (Table 4).

4. Discussion

Tumour within the pelvis and expected R0 resection are absolute indications for salvage surgery. On the other hand, the surgical indications for LRRC with SDM remain controversial. In this study, 70 consecutive patients who underwent curative LRRC resection at a single institution over 12 years were analysed, and SDM was found to be an independent risk factor for RFS but not for OS. In addition, a second LRRC could predict poor OS and RFS. On the other hand, an HDMR had no impact on either OS or RFS.

A retrospective study of 200 LRRC patients, among whom 24 patients (13.3%) had SDM, reported that SDM was not an independent risk factor for OS and RFS, suggesting that SDM itself never restricts the surgical indications [9]. On the other hand, Rahabari et al. showed that SDM, which coexisted in 19 of 92 LRRC patients (20.6%), was an independent risk factor for poor disease-free survival (hazard ratio: 2.86), although salvage surgery was justified in well-selected patients [11]. Bird et al. reported that SDM or HDMR was a predictor not only of RFS (hazard ratio: 3.23) but also of OS in 98 patients with LRRC [12]. The major difference between the above three studies was the R0 resection rates, which were 74.4%, 66%, and 58.7% among the entire cohort respectively. A higher R0 resection rate might lower the requirement for surgical indications in patients with SDM. In this study, the R0 resection rate in the entire cohort of 67.1% was not satisfactory. Moreover, SDM itself predicted poor RFS (hazard ratio: 3.14), with a median RFS of 11.4 months. Therefore, efforts to improve the R0 resection rate in addition to efforts to suppress distant metastasis are essential.

Whether better simultaneous resection or staged resection, and whether local or distant metastasis resection should be performed first in staged resection, is a controversial issue [6]. Recently, staged resection with distant metastasis resection first followed by a 2-month interval has been preferred in our institution. The main purpose is to confirm the curability of the distant metastasis, avoiding unnecessary LRRC resection in uncurable patients. Nevertheless, the distant recurrence rate within one year after LRRC surgery was still high at 50%, leading to recommendation for a longer interval, probably at least 4–6 months. Although the experience only included two cases, aggressive surgical re-resection for liver recurrence led to subsequent long-term survival without cancer. Repeated hepatectomy or pulmonary resection for liver-only or lung-only recurrence should be encouraged [23].

The optimal perioperative treatment for patients with SDM is also unresolved. The timing of initiating developed chemotherapy seems to be considerably important. It is indisputable that the completion rate of adjuvant chemotherapy following such highly extended pelvic surgery will be low [24]; therefore, there is a natural reason to shift to

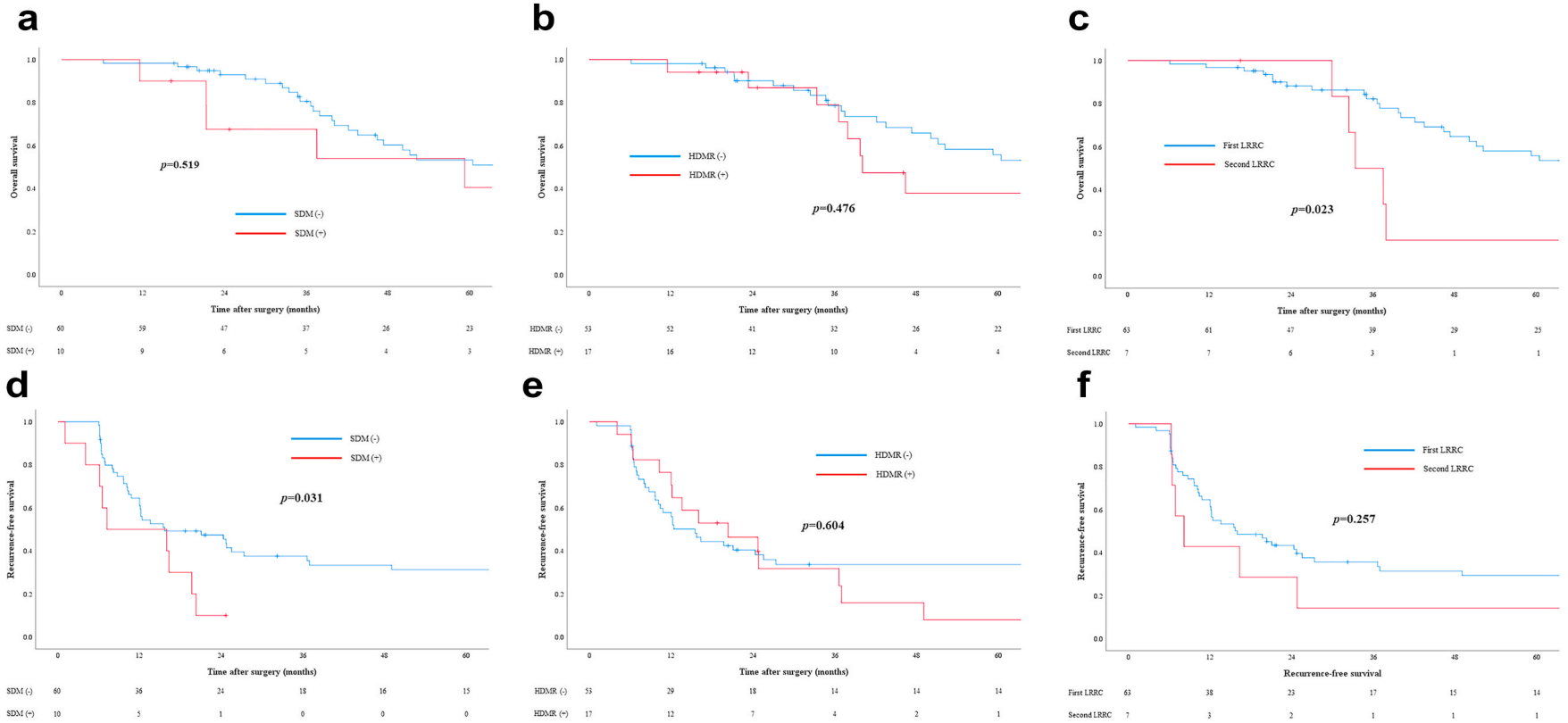

Fig. 1. Overall survival (OS) and recurrent-free survival (RFS) in patients with locally recurrent rectal cancer (LRRC) according to the synchronous distant metastases (SDM), history of distant metastases resection (HDMR), or second LRRC; a: Overall survival of 70 patients by SDM, b: Overall survival of 70 patients by HDMR, c: Overall survival of 70 patients by second LRRC, d: Recurrence-free survival of 70 patients by SDM, e: Recurrence-free survival of 70 patients by HDMR, f: Recurrence-free survival of 70 patients by second LRRC.

Table 3
Univariate and multivariate analysis for overall survival using the Cox regression model.

Variables	n	Univariate analysis		Multivariate alalysis	
		5y-OS	p value	HR (95%Cl)	p value
Age, year, median (range)			0.349		
>65	34	58.3%			
<65	36	45.9%			
Gender, n (%)			0.780		
Male	52	53.3%			
Female	18	41.6%			
Stage of primary tumor, n (%)			0.982		
I-III	61	52.8%			
IV	8	45.7%			
Primary N status, n (%)			0.989*		
N-	35	58.9%			
N+	34	46.1%			
Unknown	1				
Initial surgery, n (%)			0.301		
at our hospital	11	66.7%			
at other hospital	59	48.1%			
Primary procudure, n (%)			0.069	2.497 (1.157–5.387)	0.020
Sphincter-preserving	45	57.2%			
Non-sphincter-preserving	25	41.6%			
Interval from initial surgery, n (%)			0.451		
<24 months	20	55.7%			
>24 months	50	49.6%			
Previous radiotherapy, n (%)			0.097		0.114
Yes	3	52.2%			
No	67	33.3%			
HDMR, n (%)			0.476		0.501
Yes	17	37.9%			
No	53	55.7%			
Second local relapse, n (%)			0.023	5.245 (1.742–15.788)	0.003
Yes	7	16.7%			
No	63	55.8%			
SDM, n (%)			0.519		0.454
Yes	10	40.5%			
No	60	53.3%			
Preoperative treatment, n (%)			0.212		
Yes	52	46.7%			
No	18	64.6%			
Operative procedure, n (%)			0.200		
Pelvic exenteration	52	48.8%			
Others	18	60.2%			
Operative approach, n (%)			0.167		0.239
Open	61	47.9%			
Laparoscopic	9	87.5%			
Bony pelvic resection, n (%)			0.517		
Yes	41	49.0%			
No	29	55.3%			
Curavility, n (%)			0.069	2.123 (1.007–4.476)	0.048
R0	47	61.7%			
R1	23	30.3%			
Major complications, n (%)			0.511		
Yes	34	48.5%			
No	36	54.0%			
Adjuvant chemotherapy, n (%)			0.676		
Yes	7	42.9%			
No	63	53.2%			

* N- vs. N+. HDMR = history of distant metastases resection; SDM = synchronous distant metastases; OS = overall survival; HR = hazard ratio; CI = confidence intervals.

chemotherapy preoperatively. In this study, 80% of the patients with SDM were treated by systemic chemotherapy first, resulting in a relatively favourable OS. On the other hand, although 90% of patients with SMD were radiotherapy naïve, preoperative CRT was given for only one patient, resulting in an R1 resection rate of 20% and a local re-recurrence rate of 40%. The adoption rate of CRT or intraoperative radiation therapy should be increased [25].

The surgical indications for a second LRRC resection are another debatable issue [6]. Salvage surgery remains extremely difficult with a lack of virgin planes to permit a clear dissection. Although the data are extremely scarce, surgical indications for first and second LRRC resection generally seem similar without discrimination. Bird et al. demonstrated that, as a result of an R0 resection rate of 58.7%, a second LRRC-only developed in 26 patients (27%) [12]; however, 11 patients underwent a second resection, resulting in a subsequent 5-year OS of 54.5%. You et al. reported that 48 patients (21%) experienced local-only relapse after LRRC resection and 21 patients (9.2%) underwent second resection; however, the prognostic details were not shown. Both reports showed the results after salvage surgery performed at their own specialized high-volume centre. On the other hand, Harji et al. evaluated 30 surgically treated patients with a second LRRC, among whom 90% underwent previous surgery at a referring hospital [26]. The outcomes were not satisfactory, with an R0 resection rate of 33.3% and a 3-year OS of 27%. Similarly, in this series, 84% of the patients underwent previous surgery at referring hospital and the outcomes were poor with the 5-year OS and 3-year RFS of 16.7% and 14.3%, respectively. In addition, a second LRRC was an independent prognostic factor for poor OS and RFS. The unclear quality of the previous surgery might lead to poor outcomes after second LRRC resection from referring hospitals. Salvage surgery for a second LRRC should be strictly limited, especially in referred patients.

The small number of patients in this single centre, retrospective study was our major limitation. Because most of the enrolled patients from were referring hospitals, the quality of the previous surgeries was unclear, and the main causes of relapse were difficult to speculate, thus affecting the surgical indications. Moreover, distant metastases also have heterogeneous nature; therefore, no clear conclusions could be drawn. However, needless to say, the most important goals are to objectively evaluate our own skills to make surgical indications, to use multidisciplinary treatment to improve the R0 resection rate, and to avoid major complications and mortality.

In conclusion, LRRC patients with SDM might be suitable to undergo for salvage surgery and achieve favourable OS. However, the RFS was quite short; therefore, distant metastasectomy should be performed first, followed by a sufficient interval to avoid unnecessary LRRC resection in uncurable patients. During this interval, chemotherapy and/or CRT should be considered. An HDMR should not be taken into consideration when identifying surgical indications. Surgical indication of second LRRC should be strict, especially in referred patients.

CRediT author statement

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Table 4
Univariate and multivariate analysis for recurrence-free survival using the Cox regression model.

Variables	n	Univariate analysis		Multivariate alalysis	
		3y-RFS	p value	HR (95%CI)	p value
Age, year, median (range)			0.097	1.795 (0.970–3.321)	0.062
>65	34	39.5%			
<65	36	27.3%			
Gender, n (%)			0.959		
Male	52	33.0%			
Female	18	37.0%			
Stage of primary tumor, n (%)			0.460		
I-III	61	33.6%			
IV	8	37.5%			
Primary N status, n (%)			0.429		
N-	35	25.8%			
N+	34	41.8%			
Unknown	1				
Initial surgery, n (%)			0.905		
at our hospital	11	43.6%			
at other hospital	59	31.2%			
Primary procudure, n (%)			0.123	2.718 (1.384–5.336)	0.004
Sphincter-preserving	45	39.4%			
Non-sphincter-preserving	25	20.1%			
Interval from initial surgery, n (%)			0.780		
<24 months	20	45.0%			
>24 months	50	28.9%			
Previous radiotherapy, n (%)			0.213		
Yes	3	0.0%			
No	67	34.9%			
HDMR, n (%)			0.604		0.895
Yes	17	31.8%			
No	53	33.7%			
Second local relapse, n (%)			0.257	2.609 (10.33–6.586)	0.042
Yes	7	14.3%			
No	63	35.7%			
SDM, n (%)			0.031	3.140 (1.371–7.191)	0.007
Yes	10	10.0%			
No	60	37.5%			
Preoperative treatment, n (%)			0.448		
Yes	52	32.2%			
No	18	36.4%			
Operative procedure, n (%)			0.617		
Pelvic exenteration	52	33.4%			
Others	18	33.3%			
Operative approach, n (%)			0.593		
Open	61	33.5%			
Laparoscopic	9	33.3%			
Bony pelvic resection, n (%)			0.833		
Yes	41	30.1%			
No	29	39.4%			
Curavility, n (%)			<0.001	3.713 (1.978–6.970)	<0.001
R0	47	47.1%			
R1	23	4.6%			
Major complications, n (%)			0.801		
Yes	34	33.0%			
No	36	33.1%			
Adjuvant chemotherapy, n (%)			0.854		
Yes	7	28.6%			
No	63	34.4%			

* N- vs. N+. HDMR = history of distant metastases resection; SDM = synchronous distant metastases; RFS = recurrence-free survival; HR = hazard ratio; CI = confidence intervals.

Funding support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare no conflict of interest in this work.

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