surgery is recommended to prevent unfavorable outcomes when a pathologic diagnosis has demonstrated T1 CRC after ER. Nevertheless, approximately 90% of T1 CRC patients do not have LNM; thus, subsequent surgery may amount to overtreatment. To identify high-risk patients for the prevention of unfavorable outcomes and to decrease the incidence of unnecessary surgeries, there have been various studies regarding surgical indication criteria, which have reported that submucosal invasion depth,[4,6–10] lymphatic or venous invasion, poor differentiation,[3–9] or tumor budding[8] are risk factors for LNM. Although these topics have been a matter of debate for 20 years, the treatment strategy remains controversial. In addition, although risk factors for LNM were derived from previous cross-sectional studies with surgically resected specimens, there is not enough evidence with regard to long-term prognosis and outcomes after ER.[8,9,11–17] Therefore, more evidence derived from long-term surveillance is required.

The present study aimed to investigate the long-term efficacy of subsequent surgery after ER and to establish a more efficient treatment strategy for T1 CRC. To address these goals, we conducted a retrospective cohort study with 389 T1 CRC patients treated by ER and then compared outcomes between 2 groups comprising 205 patients who underwent subsequent surgery (ER + SURG group) and 184 patients who did not (ER only group). In addition, we identified a specific subgroup in which the efficacy of subsequent surgery would be optimal. Because this study was a nonrandomized comparison, there were several selection and indication biases within the background characteristics between the ER only and ER + SURG groups. To minimize the effects of such biases, we adjusted significant baseline differences according to the propensity score (ProS) and evaluated the prognosis after ER because of few events and many variables.

Methods

Patients and Study Design

From January 1989–December 2008, 467 patients with histologically confirmed T1 CRC who underwent ER at the Keiyukai Sapporo Hospital (Sapporo, Japan) were retrospectively included in the present study. This study was approved by the Ethics Committee of Keiyukai Sapporo Hospital. T1 CRC was defined as carcinoma that invaded only the submucosa, corresponding to a T1 lesion under the American Joint Committee on Cancer classification guidelines.[18] Patients with synchronous CRC or known cancers of other origins (23 cases), those lost to follow-up (34 cases), and those with uncertain pathologic examinations (21 cases) were excluded. Of the 389 patients included in the study, there were no missing data in any measurement. A total of 205 patients underwent subsequent surgery after ER (ER + SURG group), and 184 did not undergo surgery and were clinically and endoscopically followed (ER only group). We then compared the primary outcomes of time to recurrence and secondary outcomes of time to local recurrence, time to distant metastasis, and disease-specific survival between the ER + SURG and ER only groups.

Clinical and Histologic Information

Clinical outcomes were obtained by reviewing patient medical records and interviewing referring physicians or patients/patients' relatives by phone whenever possible. Baseline comorbidity was measured by using the Charlson Comorbidity Index,[19] measured before ER. All cases of recurrence and metastasis were documented pathologically and/or by radiological imaging. We assessed the histopathologic findings according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines.[20] A submucosal invasion depth of <1000 μm was classified as superficial invasion, whereas a depth of ≥ 1000 μm was classified as deep submucosal invasion.[4,21,22] The histologic type was determined according to the World Health Organization classification scheme.[21] Budding was graded under the microscopic field at $\times 200$ magnification and classified as either low-grade (0–4 buds) or high-grade (≥ 5 buds) budding.[8] All pathologic slides of the tumors were examined by an experienced pathologist (M.F.) who was blinded to the clinical outcomes. More clinical and histologic details are included in the Supplementary Material.

Treatments and Surgical Indication

Endoscopically resectable tumors were determined by endoscopists on the basis of endoscopic features. Lesions with features strongly suggestive of carcinoma invasion near the muscularis propria were excluded, and surgical management was suggested. All the patients underwent ER by applying snare polypectomy techniques or endoscopic mucosal resection.[10] Piecemeal resection was performed for large lesions that could not be resected en bloc. In the 2010 JSCCR guidelines,[20] the following risk factors were proposed as indication criteria for subsequent surgery: vertical tumor margin (positive), deep submucosal invasion, lymphatic or venous invasion, poor differentiation (poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous carcinoma), or high-grade budding. The pathologic identification of any of these risk factors was considered a surgical indication. Subsequent surgery was defined as radical resection such as bowel resection and regional lymph node dissection, which was performed without delay after the decision of subsequent surgery.

Statistical Analyses

Continuous variables were compared by using the t test, and categorical variables were compared by using

Table 1. Demographic and Clinical Characteristics of Patients

Factors	Total (N = 389), n (%)	ER only (n = 184), n (%)	ER + SURG (n = 205), n (%)	*P* value
Observation				
Median (range)	53 (2–238)	40 (2–238)	66 (3–224)	<.001
Age (*y*)				
Mean (SD)	63.9 (10.5)	66.4 (10.9)	61.8 (9.6)	<.001
Age categorized				
≤64 y	197 (50.8)	71 (38.6)	126 (61.8)	
≥65 y	191 (49.2)	113 (61.4)	78 (38.2)	<.001
Gender				
Male	239 (61.4)	113 (61.4)	126 (61.5)	
Female	150 (38.6)	71 (38.6)	79 (38.5)	1.000
Body mass index (kg/m^2)				
≤18.4	28 (7.2)	16 (8.7)	12 (5.9)	
18.5–24.9	238 (61.2)	112 (60.9)	126 (61.5)	
≥25	123 (31.6)	56 (30.4)	67 (32.7)	.538
Performance status				
0	273 (70.4)	105 (57.1)	168 (82.4)	
1	88 (22.7)	56 (30.4)	32 (15.7)	
≥2	27 (7.0)	23 (12.5)	4 (2.0)	<.001
Comorbidity (Charlson Comorbidity Index)				
0	223 (57.3)	99 (53.8)	124 (60.5)	
1	88 (22.6)	39 (21.2)	49 (23.9)	
≥2	78 (20.1)	46 (25.0)	32 (15.6)	.073
Location				
Right colon	97 (24.9)	55 (29.9)	42 (20.5)	
Left colon	237 (60.9)	96 (52.2)	141 (68.8)	
Rectum	55 (14.1)	33 (17.9)	22 (10.7)	.003
Configuration[a]				
Pedunculated	113 (29.0)	54 (29.3)	59 (28.8)	
Sessile	173 (44.5)	71 (38.6)	102 (49.8)	
Flat elevated	75 (19.3)	49 (26.6)	26 (12.7)	
Depressed	28 (7.2)	10 (5.4)	18 (8.8)	.003
Tumor size (*mm*)				
>20	269 (69.2)	124 (67.4)	145 (70.7)	
≤20	120 (30.8)	60 (32.6)	60 (29.3)	.510
Resection method				
En bloc	312 (80.2)	152 (82.6)	160 (78.0)	
Piecemeal	77 (19.8)	32 (17.4)	45 (22.0)	.308
Vertical margin				
–	338 (86.9)	168 (91.3)	170 (82.9)	
+	51 (13.1)	16 (8.7)	35 (17.1)	.016
Submucosal invasion				
Superficial	131 (33.7)	97 (52.7)	34 (16.6)	
Deep	258 (66.3)	87 (47.3)	171 (83.4)	<.001
Lymphatic invasion				
–	366 (94.3)	179 (97.3)	187 (91.7)	
+	22 (5.7)	5 (2.7)	17 (8.3)	.016
Venous invasion				
–	363 (93.3)	178 (96.7)	185 (90.2)	
+	26 (6.7)	6 (3.3)	20 (9.8)	.014
Histologic type				
well, mod	357 (91.8)	175 (95.1)	182 (88.8)	
por, sig, muc	32 (8.2)	9 (4.9)	23 (11.2)	.027
Tumor budding				
Low grade	362 (93.1)	173 (94.0)	189 (92.2)	
High grade	27 (6.9)	11 (6.0)	16 (7.8)	.552
Surgical indication (JSCCR, 2010)				
No	113 (29.0)	88 (47.8)	25 (12.2)	
Yes	276 (71.0)	96 (52.2)	180 (87.8)	<.001
ProS[b]				
Mean (SD), %	52.7 (27.6)	36.6 (24.3)	67.1 (22.0)	<.001

mod, moderately differentiated adenocarcinoma; muc, mucinous carcinoma; por, poorly differentiated adenocarcinoma; SD, standard deviation; sig, signet-ring cell carcinoma; well, well-differentiated adenocarcinoma.

[a]Classified according to Paris classification (Protruded, 0-Ip; Sessile, 0-Is; Flat elevated, 0-IIa; Depressed, 0-IIc, 0-IIa + IIc).

[b]Calculated as probability of receiving subsequent surgery with listed variables by using logistic regression models.

the Fisher exact test. To minimize selection bias, we used the ProS stratification method with variables associated with subsequent surgery because of few events and many variables.[23] The variables used to calculate ProS were age, sex, body mass index, Eastern Cooperative Oncology Group performance status, baseline Charlson Comorbidity Index, location, configuration, resection method, vertical margin, submucosal invasion depth, lymphatic or venous invasion, histologic type, and tumor budding, which were included in a logistic regression model to determine the propensity of undergoing subsequent surgery. To compare time to recurrence and disease-specific survival between groups, we constructed Cox regression models and Kaplan–Meier curves and performed post hoc log-rank test analysis. The cumulative risk of recurrence (CRR) and mortality were estimated by using the Kaplan–Meier method with confidence intervals (CIs) based on Greenwood's formula and the binomial exact method. Two-tailed P values $<.05$ were considered statistically significant. All statistical analyses were performed by using SPSS software version 20 (IBM SPSS Inc, Chicago, IL).

Results

Patient Demographics and Clinical Characteristics

Table 1 shows demographic and clinical characteristics in the ER only and ER + SURG groups. Notably, after ER, 25 of the 113 patients (22.1%) who did not meet the current JSCCR surgical criteria underwent subsequent surgery according to the very strict previous indication

Table 2. Associations Between Conventional Clinicopathologic Risk Factors and Recurrence

	ER only			ER + SURG		
	Recurrence			Recurrence		
Factors	No	Yes	HR[a] (95% CI)	No	Yes	HR[a] (95% CI)
Location						
Right colon	53	2	0.2 (0.4–1)	42	0	N/A
Left colon	90	6	0.3 (0.1–1.2)	138	3	0.2 (0.4–1.4)
Rectum	27	6	Reference	20	2	Reference
Configuration						
Pedunculated	53	1	Reference	58	1	Reference
Sessile	64	7	6.2 (0.8–50.2)	99	3	1.7 (0.2–16.8)
Flat elevated	44	5	6.5 (0.8–55.8)	26	0	N/A
Depressed	9	1	7.2 (0.5–116.1)	17	1	3.0 (0.2–48.2)
Resection method						
En bloc	145	7	Reference	155	5	Reference
Piecemeal	25	7	5.3 (1.9–15.2)	45	0	N/A
Vertical margin						
–	161	7	Reference	167	3	Reference
+	9	7	16 (5.5–46.6)	33	2	3.3 (0.5–19.6)
Submucosal invasion						
Superficial	94	3	Reference	34	0	Reference
Deep	76	11	4.3 (1.2–15.3)	166	5	N/A
Lymphatic invasion						
–	167	12	Reference	183	4	Reference
+	3	2	7.3 (1.6–33.2)	16	1	2.2 (0.2–20)
Venous invasion						
–	166	12	Reference	181	4	Reference
+	4	2	6.1 (1.3–27.8)	19	1	2.5 (0.3–22)
Histologic type						
well, mod	164	11	Reference	179	3	Reference
por, sig, muc	6	3	5.7 (1.6–20.6)	21	2	5.3 (0.9–31.5)
Tumor budding						
Low grade	161	12	Reference	185	4	Reference
High grade	9	2	3.8 (0.9–17.3)	15	1	3 (0.3–26.6)
Surgical indication (JSCCR, 2010)						
No	87	1	Reference	25	0	Reference
Yes	83	13	12.9 (1.7–98.5)	175	5	N/A
Total	170	14		200	5	

mod, moderately differentiated adenocarcinoma; muc, mucinous carcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; well, well-differentiated adenocarcinoma.

Right colon, cecum-transverse colon; left colon, descending-sigmoid colon.

[a]HR for time to recurrence compared with Reference categories in each factor stratified by the treatment.

criteria formerly used in Japan (submucosal invasion deeper than very shallow invasion exceeding approximately 200–300 μm).[9,24] Of the 276 patients indicated for surgery, 180 (65.2%) underwent subsequent surgery, whereas 96 did not because of either patient refusal or medical reasons.

Conventional Known Risk Factors and the Need for Surgery

The association between known conventional risk factors (ie, location,[3,25] configuration,[4,26–29] resection method,[29,30] and risk factors included in the JSCCR guidelines) and the incidence of recurrence was assessed (Table 2). In the ER only group, there were significant associations between a higher incidence of recurrence and the risk factors included in the resection method and in the JSCCR guidelines except budding, whereas in the ER + SURG group, these tendencies were not obvious. Notably, most incidences of recurrence (18 of 19) occurred in patients indicated for surgery.

We then assessed the differences in CRR between patients who did and those who did not undergo subsequent surgery. Because the frequency of recurrence highly differed between patients with and those without surgical indication, we performed stratification analysis by using the status of the surgical indicator. In patients not indicated for surgery, there was no incidence of recurrence in the ER + SURG group, and CRR was only 2.3% in the ER only group (Figure 1*A*). In contrast, in

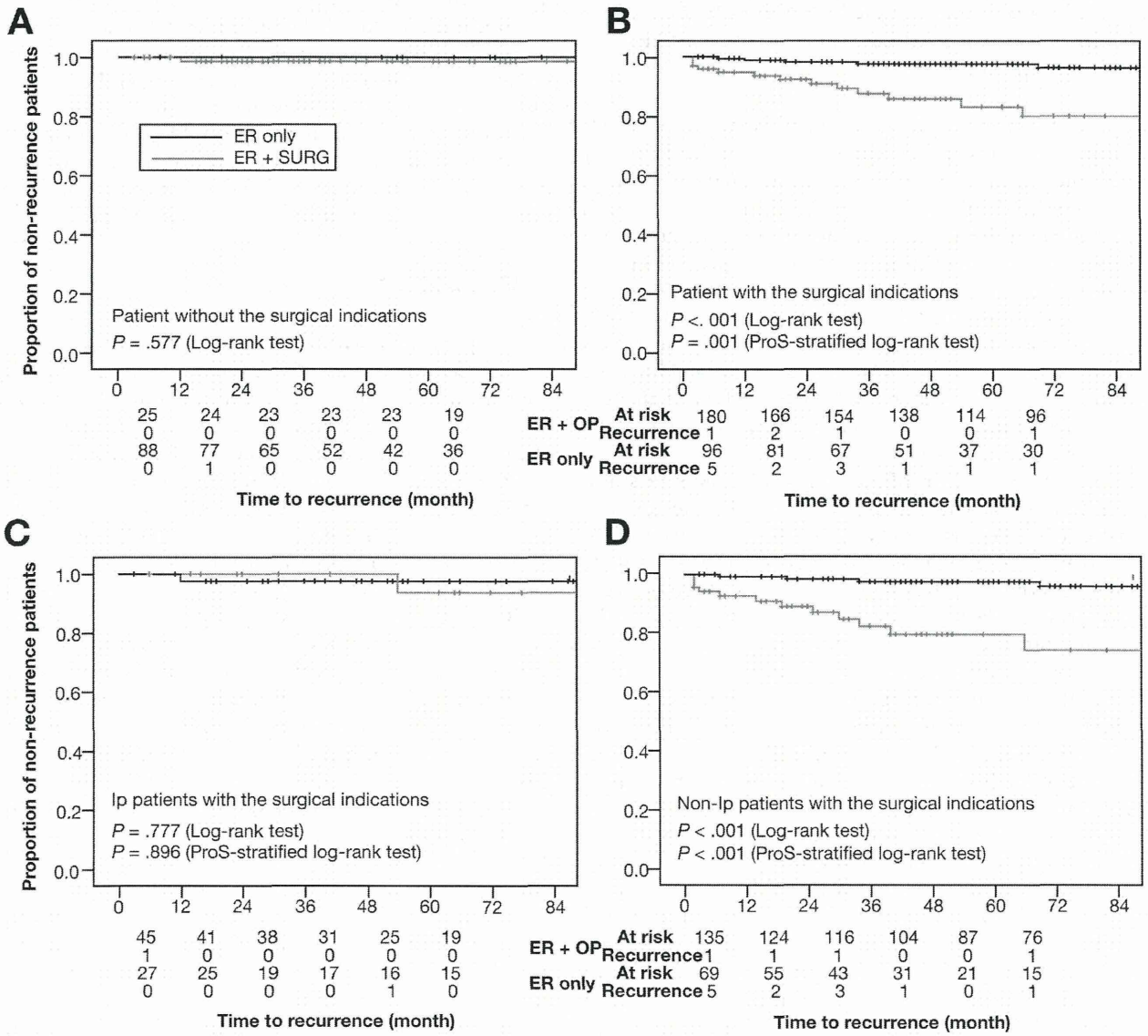

Figure 1. Kaplan–Meier curves for recurrence with a post hoc log-rank test stratified by status of conventional risk factors. CRR in patients without surgical indication (*A*), those with surgical indication (*B*), Ip-type patients with surgical indication (*C*), and non–Ip-type patients with surgical indication (*D*). OP, operation.

patients indicated for surgery, the ER only group showed a significantly higher incidence of recurrence than the ER + SURG group. CRR was 20.1% in the ER only group and 3.7% in the ER + SURG group (Figure 1*B*).

We then performed stratification analyses by pedunculated type (Ip) in patients with surgical indications because better prognoses were reported in patients with type Ip lesions.[4,8,13–16,27,28] As shown in Figure 1*C*, a very low incidence of recurrence was observed in Ip patients, and the need for surgery seemed to be limited. In contrast, in non-Ip patients (sessile, flat elevated, or depressed), CRR was 25.6% in the ER only group and 4.0% in the ER + SURG group (Figure 1*D*).

Further Stratified Analysis on the Basis of the Status of Other Surgical Indications, Except Submucosal Invasion, Among Patients With Surgical Indication

As shown in Table 1, the most common reason to necessitate subsequent surgery was a finding of deep submucosal invasion, which was indicated in 83.4% of the cases in the ER + SURG group. We found that 57.8% of patients (104 of 180) in the ER + SURG group underwent subsequent surgery without the presence of any risk factor except deep submucosal invasion. Therefore, we divided the surgically indicated patients into 2 subgroups, namely low-risk patients with only deep submucosal invasion (n = 164) as a risk factor and high-risk patients with 1 or more risk factors other than deep submucosal invasion (n = 112), to explore a more efficient surgical indication.

The results of stratified analyses by the risk status are summarized in Figure 2*A* and *B*. In the low-risk patients, CRR was very low in both groups. In contrast, in the high-risk patients, there was a significant difference in the incidence of recurrence between the groups. CRR was only 5.8% in the ER + SURG group but 58.0% in the ER only group. When we stratified the high-risk group by the Ip type (Figure 2*C* and *D*), subsequent surgery seemed to be highly efficient in the non-Ip high-risk group (CRR: 73.7% in the ER only group and 6.6% in the ER + SURG group). Stratified analysis by the Ip type in the low-risk group is summarized in Supplementary Figure 1*A* and *B*. CRR with 95% CI values and results of Cox regression analysis with ProS adjustment for each risk category are summarized in Table 3. After this, we assessed the incidence of distant metastasis and local recurrence and the disease-specific survival stratified by the risk status. These results are summarized in Figure 2*E* and *F*, Supplementary Figure 1, and Supplementary Table 1. As shown in Figure 2*E* and *F*, in the high-risk group, the cumulative risk of distant metastasis was 6.1% (95% CI, 0%–13.1%) in the ER + SURG group and 37.7% (95% CI, 9.5%–65.9%) in the ER only group, whereas very low incidence was observed in the low-risk group.

In addition, LNM in the low-risk and high-risk groups was 1.9% and 15.8% ($P = .001$), respectively.

An Overview of Patients Experiencing Recurrences

The characteristics of all patients with recurrence after ER are summarized in Table 4. In patients without surgical indication, there was only 1 case (patient 1) of recurrence, namely an intramucosal local recurrence after 12 months that was cured by additional ER. The other 18 cases were patients with surgical indications. However, there were only 4 cases (patients 2, 3, 15, and 16) with deep submucosal invasion only (low risk) because all the other cases had risk factors other than deep submucosal invasion. Although we performed additional therapy on local recurrence, 4 cases developed distant metastases (patients 6, 9, 14, and 15) and had other risk factors (eg, mucinous carcinoma or venous invasion) but not vertical margin positivity. Of the 11 patient deaths, 9 were due to primary cancers, and 2 were due to other causes. The final recurrence event during the observation period occurred at 69 months (5.8 years).

Discussion

The present study reports the factors associated with risk for CRC recurrence after ER of T1 tumors with ProS adjustment. To reduce biases attributed to retrospective nonrandomized comparison causing overestimation and/or underestimation of the need for surgery, we adjusted for ProS because of few events and many variables.[23] In our study, patients without surgical indications recommended by the 2010 JSCCR guidelines showed almost no risk of recurrence, which is in accordance with the findings reported in a recent Japanese multicenter study.[16] Moreover, the patients with only deep submucosal invasion as a risk factor for surgical indication (low risk) showed low recurrence risks and mortality, regardless of subsequent surgery. Subsequent surgery is therefore not justified in low-risk patients. In contrast, subsequent surgery was recommended for T1 CRC cases with 1 or more indicators other than deep submucosal invasion (high risk) because recurrence risk was particularly high, and surgery sufficiently decreased the incidence of recurrence. In addition, after ProS adjustment, there was no significant difference in time to distant metastasis and disease-specific survival between the ER only and ER + SURG groups, possibly because of effective secondary therapies after recurrence, including salvage procedures and chemotherapy.

In several studies, the most frequent indication for subsequent surgery was deep submucosal invasion,[4,7] whereas our results suggested that many T1 CRC patients treated by ER can be followed up without

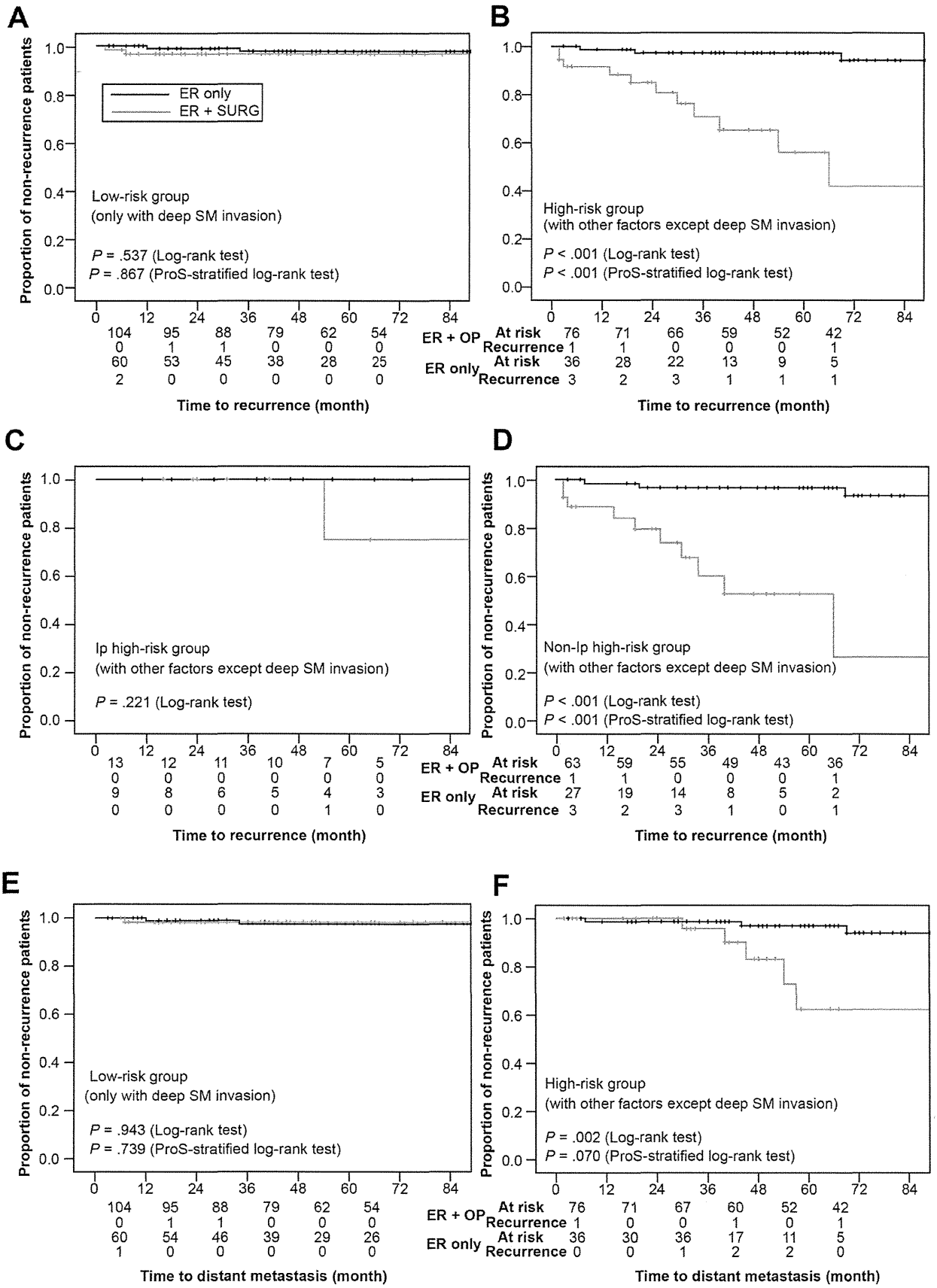
A
B
C
D
E
F
Proportion of non-recurrence patients
ER only
ER + SURG
Low-risk group
(only with deep SM invasion)
P = .537 (Log-rank test)
P = .867 (ProS-stratified log-rank test)
High-risk group
(with other factors except deep SM invasion)
P < .001 (Log-rank test)
P < .001 (ProS-stratified log-rank test)
Ip high-risk group
(with other factors except deep SM invasion)
P = .221 (Log-rank test)
Non-Ip high-risk group
(with other factors except deep SM invasion)
P < .001 (Log-rank test)
P < .001 (ProS-stratified log-rank test)
Low-risk group
(only with deep SM invasion)
P = .943 (Log-rank test)
P = .739 (ProS-stratified log-rank test)
High-risk group
(with other factors except deep SM invasion)
P = .002 (Log-rank test)
P = .070 (ProS-stratified log-rank test)
ER + OP At risk 104 95 88 79 62 54
Recurrence 0 1 1 0 0 0
ER only At risk 60 53 45 38 28 25
Recurrence 2 0 0 0 0 0
ER + OP At risk 76 71 66 59 52 42
Recurrence 1 1 0 0 0 1
ER only At risk 36 28 22 13 9 5
Recurrence 3 2 3 1 1 1
ER + OP At risk 13 12 11 10 7 5
Recurrence 0 0 0 0 0 0
ER only At risk 9 8 6 5 4 3
Recurrence 0 0 0 0 1 0
ER + OP At risk 63 59 55 49 43 36
Recurrence 1 1 0 0 0 1
ER only At risk 27 19 14 8 5 2
Recurrence 3 2 3 1 0 1
ER + OP At risk 104 95 88 79 62 54
Recurrence 0 1 1 0 0 0
ER only At risk 60 54 46 39 29 26
Recurrence 1 0 0 0 0 0
ER + OP At risk 76 71 67 60 52 42
Recurrence 1 0 0 1 0 1
ER only At risk 36 30 36 17 11 5
Recurrence 0 0 1 2 2 0
Time to recurrence (month)
Time to recurrence (month)
Time to recurrence (month)
Time to recurrence (month)
Time to distant metastasis (month)
Time to distant metastasis (month)

Table 3. CRR and Cox Regression Analysis for Efficacy of Subsequent Surgery

Surgical indication (JSCCR)	Risk	Period	Treatment	N		CRR	Cox regression				ProS[b] (%)
							Crude		ProS-adjusted		
				At risk	Recurrence	Rate, % (95%CI)[a]	HR[a]	(95%CI)	HR[a]	(95%CI)	
No	Total	Overall	ER only	88	1	2.3 (0–4.8)	N/A		N/A		16.9
			ER+SURG	25	0	0.0 (0–13.7)[c]					40.4
Yes	Total	Overall	ER only	96	13	20.1 (9.3–30.9)	6.1	(2.2–17.2)	6.1	(2–18.7)	51.0
			ER+SURG	180	5	3.7 (0.4–7)	Reference		Reference		72.8
	Ip	Overall	ER only	27	1	6.2 (0–18.2)	1.5	(0.9–23.9)	0.8	(0.4–17.3)	36.0
			ER+SURG	45	1	2.4 (0–7.1)	Reference		Reference		78.4
	Non-Ip	Overall	ER only	69	12	25.6 (11.2–40.1)	8.0	(2.6–25.0)	8.5	(2.4–30.8)	48.0
			ER+SURG	135	4	4.0 (0–8.1)	Reference		Reference		75.5
	Low-risk	Overall	ER only	60	2	3.4 (0–7.9)	1.8	(0.3–13.1)	1.2	(0.2–9.7)	51.4
			ER+SURG	104	2	2.3 (0–5.4)	Reference		Reference		70.4
	High-risk	Overall	ER only	36	11	58.0 (28.3–87.7)	14.4	(3.9–53.5)	12.8	(2.5–65)	44.9
			ER+SURG	76	3	5.8 (0–12.6)	Reference		Reference		78.7
		0–1 y	ER only	36	3	8.4 (0–17.5)					
			ER+SURG	76	1	1.4 (0–4)					
		1–2 y	ER only	28	2	15.1 (2.8–27.4)					
			ER+SURG	71	1	1.4 (0–4)					
		2–3 y	ER only	22	3	29.3 (11.3–47.2)					
			ER+SURG	66	0	2.8 (0–6.7)					
		3–4 y	ER only	13	1	34.7 (15.2–54.2)					
			ER+SURG	59	0	2.8 (0–6.7)					
		4–5 y	ER only	9	1	44.0 (20.2–67.8)					
			ER+SURG	52	0	2.8 (0–6.7)					
	Ip high-risk	Overall	ER only	9	1	25.0 (0–67.5)	N/A		N/A		N/A
			ER+SURG	13	0	0.0 (0–24.7)[c]					
	Non-Ip high-risk	Overall	ER only	27	10	73.7 (35.3–100.0)	17.4	(4.4–69.2)	26.4	(3.1–225)	42.0
			ER+SURG	63	3	6.6 (0–14.2)	Reference		Reference		82.0
		0–1 y	ER only	19	2	11.3 (0–23.2)					
			ER+SURG	59	1	1.7 (0–5.0)					
		1–2 y	ER only	14	2	20.6 (4.3–36.9)					
			ER+SURG	55	1	3.4 (0–8.1)					
		2–3 y	ER only	8	3	39.9 (17.0–62.8)					
			ER+SURG	49	0	3.4 (0–8.1)					
		3–5 y	ER only	5	1	47.4 (23.1–71.7)					
			ER+SURG	43	0	3.4 (0–8.1)					

[a]Calculated by Greenwood's formula.
[b]Calculated as probability of receiving surgery separately in each stratum.
[c]Calculated by the binomial exact method.

subsequent surgery. Although submucosal invasion depth is a highly sensitive factor to identify high-risk patients, it is an inadequate indicator for subsequent surgery. In addition, submucosal invasion depth is not adequate in view of LNM because the majority of patients were negative for LNM. Nakadoi et al[7] reported that the risk of LNM was only 1.2% when conventional factors other than submucosal invasion depth were absent. Consistent with their report, only 1.9% of low-risk patients had LNM, regardless of submucosal invasion depth.

Advances in endoscopic methods such as magnifying chromoendoscopy,[31] image-enhanced endoscopy,[32] and endoscopic ultrasonography[33] have made it possible to diagnose submucosal invasion depth more accurately. However, among the indication criteria for subsequent surgery, only submucosal invasion depth could be diagnosed beforehand. Other indicators such as vascular invasion, poor differentiation, and tumor budding cannot be assessed. Ultimately, the decision of subsequent surgery after ER is dependent on pathologic evaluation other than submucosal invasion depth. Complete en bloc resection is recommended to attain precise pathologic evaluations. Novel methods such as endoscopic submucosal dissection are useful to achieve complete en bloc

Figure 2. Kaplan–Meier curves for recurrence and distant metastasis with a post hoc log-rank test stratified by risk groups for more efficient surgical indication. CRR in the low-risk group with only deep submucosal invasion as a risk factor (*A*), in the high-risk group with risk factors other than deep submucosal invasion (*B*), in the Ip high-risk patients (*C*), and in the non-Ip high-risk patients (*D*). The cumulative risk of distant metastasis after ER in the low-risk (*E*) and high-risk groups (*F*). OP, operation.

Table 4. Characteristics of 19 Patients With Recurrence After ER

Patient	Therapy after ER	Risk group	Age (*y*)/ gender	Location	Size (*mm*)	Configuration	Resection method	SM depth (μm)	Risk factor (except deep SM)	Recurrence site	Time (*mo*) to recurrence	Therapy for recurrence	Alive/death
1	ER only	Without surgical indication	72/M	S	12	IIa	En bloc	60	—	Local (M)	12	ER	Alive
2	ER only	Low-risk	73/F	R	25	Is	Piecemeal	1000	—	Local (SM)	5	OP	Alive
3	ER only	Low-risk	71/M	S	20	Is	En bloc	2300	—	Liver	7	OP	Cancer death
4	ER only	High-risk	64/M	C	30	Is	Piecemeal	250	VM+	Local (M)	2	ER	Alive
5	ER only	High-risk	65/M	R	20	Is	Piecemeal	1110	VM+	Local (SM)	2	ER	Alive
6	ER only	High-risk	65/M	R	20	Is	Piecemeal	1600	V	Local (SM)→bone	34	ER	Cancer death
7	ER only	High-risk	52/F	R	17	Is	En bloc	1700	VM+	Local (SM)	66	OP	Alive
8	ER only	High-risk	75/M	C	13	IIa	En bloc	2125	VM+, sig	Local (SM)	14	OP	Alive
9	ER only	High-risk	80/F	S	12	Ip	En bloc	2700	Ly	Local (SM)→liver	54	OP	Cancer death
10	ER only	High-risk	83/F	S	16	IIa + IIc	En bloc	3000	Budding	Local (SM)	12	ER	Other death
11	ER only	High-risk	67/M	R	15	Is	En bloc	3125	VM+, v	Local (SM)	25	BSC	Other death
12	ER only	High-risk	59/M	R	20	IIa (LST)	Piecemeal	950	Ly	Liver, LNM	40	CT	Cancer death
13	ER only	High-risk	66/M	R	30	IIa (LST)	Piecemeal	1600	VM+, muc	Local (M)→lung	30	ER	Alive
14	ER only	High-risk	77/F	R	30	IIa (LST)	En bloc	3500	VM+, muc	Local (SM)→ lung, LNM	45	ER	Cancer death
15	ER+SURG	Low-risk	56/M	R	25	Is	En bloc	4000	—	Lung	34	OP	Alive
16	ER+SURG	Low-risk	70/M	S	25	Ip	En bloc	8000	—	Lung	12	OP	Cancer death
17	ER+SURG	High-risk	58/F	R	20	Is	En bloc	3750	v	Local (SM)	20	CRT	Cancer death
18	ER+SURG	High-risk	60/M	S	10	IIa + IIc	En bloc	2000	VM+, ly, por	LNM	69	CT	Cancer death
19	ER+SURG	High-risk	44/F	S	10	Is	En bloc	3000	VM+, por, budding	Lung	7	CT	Cancer death

BSC, best supportive care; C, cecum; CRT, chemoradiotherapy; CT, chemotherapy; Local (M), intramucosal recurrence; Local (SM), submucosal or beyond; LST, lateral spreading tumor, ly, lymphatic invasion; muc, mucinous carcinoma; OP, operation; por, poorly differentiated adenocarcinoma; R, rectum; S, sigmoid colon; sig, signet-ring cell carcinoma; SM, submucosal; v, venous invasion; VM, vertical margin.

resection.[34] Reduction in the rate of unnecessary surgery and local recurrence is expected by the introduction of endoscopic submucosal dissection for T1 CRC cases, offering a negligible risk of adverse outcomes.[35]

There were some limitations to the present study. First, this study was based on a limited number of cases, including those with short follow-up periods at a single institute. Second, although ProS adjustment can compensate for confounding factors by the selection and indication biases, we could not eliminate residual confounding because of unknown factors. Prospective, large, randomized studies can address these issues; however, they are unlikely to be conducted because of ethical implications. In addition, because the incidence of recurrence was very low (19 cases, 4.9%), the statistical power was not sufficient to discern small differences in subgroup analyses of more comprehensive pathologic factors.

Finally, our recommendations for T1 CRC treated by ER are as follows. In patients without surgical indication, surveillance colonoscopy is reasonable for the detection of local recurrence, as seen in in situ colorectal carcinoma, because there is no potential for metastasis. The low-risk patients can be followed up without subsequent surgery and should be followed up for metastatic diseases via computed tomography in addition to colonoscopy. The high-risk patients should be recommended for subsequent surgery because of the high recurrence risk. In particular, surgery is strongly recommended for the treatment of non-Ip high-risk patients. When subsequent surgery is not performed, we should pay close attention to the possibility of recurrence. To detect recurrence, a follow-up examination period of at least 5 years is suggested.

In conclusion, on the basis of a retrospective study of patients who underwent ER for T1 CRC, those with tumors with only submucosal invasion are at low risk for cancer recurrence. However, patients with other high-risk tumor features have greater risks for cancer recurrence and benefit from subsequent surgery.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.08.008.

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Reprint requests
Address requests for reprints to: Shinji Yoshii, MD, Department of Gastroenterology, Nippon Telegraph and Telephone East Corporation, SAPPORO MEDICAL CENTER NTT EC, S1 W15, Chuo-ku, Sapporo 060-0061, Japan. e-mail: shinji-yoshii@umin.ac.jp; fax: +81-11-011-623-7527.

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The authors disclose no conflicts.