have predictive value for sensitivity against EGFR inhibition, a newly developed CRC molecular target [51–54]. As neutralizing EGFR antibody is effective even against far-advanced CRC without K-*ras* mutation, the development of new treatments, including adjuvant chemotherapy, is eagerly anticipated. On the other hand, CRC with K-*ras* mutation proved ineffective by EGFR inhibition [53]. About 75% CRC cases with K-ras mutation had co-mutated PI3K [49] and, in such cases, downstream inhibition of both B-raf and PI3K may efficiently regulate CRC cells.

None of the rectal patients in the current study underwent radiotherapy either pre- or post-operatively, which may not represent the standard of care of rectal cancer worldwide, and perhaps would effect the outcome of the analysis. In rectal cancer, we would thus examine the K-ras mutation status and prognosis in such patients who undertake the standard therapy in the near future. Actually, we recently adopted neoadjuvant chemoradiotherapy for localized advanced rectal cancer before surgery [55,56]. Even if molecular target therapy such as anti-EGFR MoAb is used, CRC at stage IV has a dismal prognosis [51,52,57] and almost all patients will die of disease progression. That is why improving the prognosis of CRC depends upon improving treatment for curable cases, which includes adjuvant chemotherapy. The most promising treatment strategy for CRC is therefore to develop tailor-made adjuvant chemotherapy using novel indicators on the basis of oncogenic mutational profiles as in the present study.

REFERENCES

1. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al.: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659–1672.
2. Romond EH, Perez EA, Bryant J, et al.: Trastuzumab plus adjuvant chemotherapy for operable HER-2 positive breast cancer. N Engl J Med 2005;353:1673–1684.
3. Denetru GD, von Mehren M, Blanke CD, et al.: Efficiency and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472–480.
4. Heinrich MC, Corless CL, Demetri GD, et al.: Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342–4349.
5. Paez JG, Janne PS, Lee JC, et al.: EGFR mutations in lung cancer: Correlation with clinical response to gefinitib therapy. Science 2004;304:1497–1500.
6. Lynch TJ, Bell DW, Sordella R, et al.: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350:2129–2139.
7. Slamon DJ, Godolphin W, Jones LA, et al.: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989;244:707–712.
8. Pterson MC, Dietrich KD, Danyluk J, et al.: Correlation between c-erb-B2 amplification and risk of recurrent disease in node-negative breast cancer. Cancer Res 1991;51:556–567.
9. Taniguchi M, Nishida T, Hirota S, et al.: Effect of c-kit mutation on prognosis of gastrointestinal stromal tumors. Cancer Res 1999;59:4297–4300.
10. Singer S, Rubin BP, Lux ML, et al.: Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastro-intestinal stromal tumors. J Clin Oncol 2002;20:3898–3905.
11. Schubbert S, Shannou K, G B: Hyperactive Ras in developmental disorders and cancer. Nat Rev Cancer 2007;7:295–308.
12. Shirasawa S, Furuse M, Yokoyama N, et al.: Altered growth of human colon cancer cell lines disrupted at activated K-ras. Science 1993;260:85–88.
13. Okada F, Rak JW, Croix BS: Impact of oncogenes in tumor angiogenesis: Mutant K-ras up-regulation of vascular endothelial growth factor/vascular permeability factor is necessary, but not sufficient for tumorigenicity of human colorectal carcinoma cell. Proc Natl Acad Sci USA 1998;95:3609–3614.
14. Vogelstein B, Fearon ER, Hamilton SR, et al.: Genetic alterations during colorectal-tumor development. N Engl J Med 1988;2:532–535.
15. Benhattar J, Losi L, Chaubert P, et al.: Prognostic significance of K-ras mutations in colorectal carcinoma. Gastroenterology 1993;104:1044–1048.
16. Tanaka M, Omura K, Watanabe Y, et al.: Prognostic factors of colorectal cancer: K-ras mutation, overexpression of the p53 protein, and cell proliferative activity. J Surg Oncol 1994;57:57–64.
17. Span M, Moerkerk PT, De Goeij AF, et al.: A detailed analysis of K-ras point mutations in relation to tumor progression and survival in colorectal cancer patients. Int J Cancer 1996;69:241–245.
18. Cerottini JP, Caplin S, Saraga E, et al.: The type of K-ras mutation determines prognosis in colorectal cancer. Am J Surg 1998; 175:198–202.
19. Pajkos G, Kiss I, Sandor J, et al.: The prognostic value of the presence of mutations at the codon 12, 13, 61 of K-ras oncogene in colorectal cancer. Anticancer Res 2000;20:1695–1701.
20. Andersen SN, Lovig T, Breivik J, et al.: K-ras mutations and prognosis in large-bowel carcinomas. Scand J Gastroenterol 1997; 32:62–69.
21. Hardingham JE, Butler WJ, Roder D, et al.: Somatic mutations, acetylator status, and prognosis in colorectal cancer. Gut 1998; 42:669–672.
22. Tortola S, Marcuello E, Gonzalez I, et al.: p53 and K-ras gene mutations correlate with tumor aggressiveness but are not of routine prognostic value in colorectal cancer. J Clin Oncol 1999; 17:1375–1381.
23. Bouzourence H, Gervaz P, Cerottini JP, et al.: p53 and K-ras as prognostic factors for Dukes' stage B colorectal cancer. Eur J Cancer 2000;36:1008–1015.
24. Esteller M, Gonzalez S, Risques RA, et al.: K-ras and p16 aberrations confer poor prognosis in human colorectal cancer. J Clin Oncol 2001;19:299–304.
25. Pan ZZ, Wan DS, Chen G, et al.: Co-mutation of p53, K-ras genes and accumulation of p53 protein and its correlation to clinicopathological features in rectal cancer. World J Gastroenterol 2004; 10:3688–3690.
26. Hsieh JS, Lin SR, Chang MY, et al.: APC, K-ras, and p53 gene mutations in colorectal cancer patients: correlation to clinicopathologic features and postoperative surveillance. Am Surg 2005; 71:336–343.
27. Locker GY, Hammilton S, Harris J, et al.: ASCO 2006 update of recommendation for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 2006;24:5313–5327.
28. Allegra CJ, Jessup JM, Somerfield MR, et al.: American Society of Clinical Oncology provisional clinical opinion: Testing for K-RAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol 2009;27: 2091–2096.
29. Yamashita K, Tatebayashi T, Shinoda H: Simplified rapid non-radioactive PCR-SSCP method applied to K-ras mutation analysis. Pathol Int 1996;46:801–804.
30. Yamashita K, Kuba T, Shinoda H, et al.: Detection of K-ras point mutations in the supernatants of peritoneal and pleural effusions for diagnosis complementary to cytologic examination. Am J Clin Pathol 1998;109:704–711.
31. Yamashita K, Kida Y, Shinoda H, et al.: K-ras point mutations in the supernatants of pancreatic juice and bile are reliable for diagnosis of pancreas and biliary tract carcinomas complementary to cytologic examination. Jpn J Cancer Res 1999;90:240–248.
32. Yamashita K, Yoshida T, Shinoda H: Novel method for simultaneous analysis of p53 and k-ras mutations and p53 protein expression in single histologic sections. Arch Pathol Lab Med 2001;125:347–352.
33. Yasui W, Yokozaki H, Shimamoto F, et al.: Molecular-pathological diagnosis of gastrointestinal tissues and its contribution to cancer histopathology. Pathol Int 1999;49:763–774.

34. Araujo SE, Bernardo WM, Habr-Gama A: DNA ploidy status and prognosis in colorectal cancer: A meta-analysis of published data. Dis Colon Rectum 2007;50:1800–1810.
35. Zhou W, Goodman SN, Galizia G: Counting alleles to predict recurrence of early-stage colorectal cancers. Lancet 2002;359: 219–225.
36. Ribic CM, Sargent DJ, Moore MJ: Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy. N Engl J Med 2003;349: 247–257.
37. Andre T, Boni C, Mounedji-Boudiaf L: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–2351.
38. Kuebler JP, Wieand HS, O'Connell MJ: Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage 2 and 3 colon cancer: Results from NSABP C-07. J Clin Oncol 2007;25:2198–2204.
39. Andreyev HJ, Norman AR, Cunningham D: Kirsten ras mutations in patients with colorectal cancer: The multicenter "RASCAL" study. J Natl Cancer Inst 1998;90:675–684.
40. Andreyev HJNA, Cunningham D, Oates J, et al.: Kirsten ras mutations in patients with colorectal cancer: The 'RASCAL2' study. Br J Cancer 2001;85:692–696.
41. Goel A, Nagasaka T, Arnold CN, et al.: The CpG island methylator phenotype and chromosomal instability are inversely correlated in sporadic colorectal cancer. Gastroenterology 2007; 32:127–138.
42. Young J, Simms LA, Biden KG, et al.: Features of colorectal canecrs with high-level microsatellite instability occurring in familial and sporadic settings: Parallel pathways of tumorigenesis. Am J Pathol 2001;159:2107–2116.
43. Liu B, Farrington SM, Petersen GM, et al.: Genetic instability occurs in the majority of young patients with colorectal cancer. Nat Med 1995;1:348–352.
44. Whitehall VL, Walsh MD, Young J, et al.: Methylation of O6-methylguanine DNA methyltransferase characterizes a subset of colorectal cancer with low-level DNA microsattelite instability. Cancer Res 2001;61:827–830.
45. Halling KC, French AJ, McDonnell SK: Microsatellite instability and 8p allelic imbalance in stage B2 and C colorectal cancer. J Natl Cancer Inst 1999;91:1295–1303.
46. Lengauer C, Kinzler KW, B V: Genetic instability in colorectal cancers. Nature 1997;386:623–627.
47. Samowitz WS, Sweeney C, Herrick J: Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancer. Cancer Res 2005;65:6063–6069.
48. Barber TD, Vogelstein B, Kinzler KW, et al.: Somatic mutations of EGFR in colorectal cancers and glioblastomas. N Engl J Med 2004;351:2883.
49. Samuels Y, Wang Z, Bardelli A, et al.: High frequency of mutations of the PIK3CA gene in human cancers. Science 2004; 304:554.
50. Rajagopalan H, Bardelli A, Lengauer C, et al.: Tumorigenesis: RAF/RAS oncogenes and mismatch-repair status. Nature 2002;418:934.
51. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, et al.: Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res 2007;67: 2643–2648.
52. Khambata-Ford SGC, Meropol NJ, Basik M, et al.: Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in matastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230–3237.
53. Helena L, Issa JD, Dimitra K, et al.: Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: A systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. Lancet oncol 2008;9:962–972.
54. Zlobec I, Bihl MP, Schwarb H, et al.: Clinico-pathological and protein characterization of BRAF and K-RAS mutated colorectal cancer and implications for prognosis. Int J Cancer 2009; 11.
55. Sato T, Kokuba Y, Koizumi W, et al.: Phase I trial of neoadjuvant preoperative chemotherapy with S-1 and irinotecan plus radiation in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2007;69:1442–1447.
56. Sato T, Kokuba Y, Koizumi W, et al.: Irinotecan and S-1 neoadjuvant chemoradiation therapy in patients with advanced rectal cancer. Hepatogastroenterology 2007;54:1391–1393.
57. Winder T, Mundlein A, Rhomberg S, et al.: Different type of K-Ras mutations are conversely associated with overall survival in patients with colorectal cancer. Oncol Rep 2009;21:1283–1287.

Prediction of Residual Disease or Distant Metastasis After Resection of Locally Recurrent Rectal Cancer

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PURPOSE: It is important to preoperatively identify patients at high risk of relapse at extrapelvic sites or residual disease after salvage surgery for locally recurrent rectal cancer to maximize the survival benefit by indicating whether a surgical approach might be successful.

METHODS: Data from 101 consecutive patients who underwent exploration with curative intent for local recurrence after radical resection of rectal cancer were retrospectively collected. Preoperative factors were examined in univariate and multivariate analyses for their ability to predict resectability and distant disease-free survival.

RESULTS: The 5-year disease-specific survival rates of R0, R1, and R2 resection were 43.3%, 19.5%, and 10.0%, respectively ($P < .001$). In a logistic regression analysis, upper sacral (above the inferior margin of the second sacrum)/lateral invasive type and high-grade lymphatic invasion of the primary tumor were associated with palliative surgery. A Cox regression analysis revealed that upper sacral/lateral invasive type, extrapelvic disease, hydronephrosis at recurrence, and high-grade lymphatic or venous invasion of the primary tumor were associated with a lower distant disease-free survival rate. Patients with one or more of these risk factors had a 3-year distant disease-free survival rate of 6.2% compared with 54.1% for those with none of these risk factors.

CONCLUSION: It was possible to preoperatively identify patients at high risk of relapse or residual disease. This system might be used on an individual basis to select patients with locally recurrent rectal cancer for chemotherapy or radiotherapy before surgical intervention with curative intent.

KEY WORDS: Rectal cancer; Recurrence; Surgery.

In patients who undergo radical surgery for rectal cancer, 4% to 30% develop locoregional relapse.[1-4] Since the 1990s, several studies have reported 5-year survival rates favorably ranging from 22% to 58% after resection of locally recurrent rectal cancer (LRRC).[5-10] These observations strongly support the view that surgery is the most effective therapy for selected patients with LRRC, because it offers a potential for long-term survival that is not possible with other treatment modalities. However, these advantages are tempered by the high incidence of postoperative complications and the early development of a second distant recurrence.[9,11-13] Without complete resection (R0), these patients have a short life expectancy[7,9,12-18] and tend to experience unpleasant symptoms, especially pain, and their quality of life becomes extremely poor.[19] The patients who present with metastatic disease soon after a curative resection of their local recurrence may experience delays in systemic treatment secondary to complications from surgery. Optimal patient selection and multimodality treatment strategies are desirable but difficult. We conducted a retrospective study of patients with isolated pelvic recurrences who underwent exploration with curative intent to determine predictors of resectability and distant disease-free survival after surgery. It may contribute greatly to the development of methods for the

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TABLE 1. Patterns of pelvic invasion of locally recurrent cancer

Anastomotic site invasive type	Recurrent tumor is localized to the anastomotic site
Visceral/lower sacral invasive type	• Recurrent tumor is localized to adjacent pelvic organs or connective tissue without contact onto or invasion into bone
	• Recurrent tumor invades or abuts the lower sacrum (S3, S4, S5) or coccyx
Upper sacral/lateral invasive type	• Recurrent tumor invades or abuts the structures on the lateral pelvic sidewall, including the greater sciatic foramen, sciatic nerve through to piriformis, gluteal region or cortex above the inferior margin of the second sacrum (S1, S2)

preoperative identification of patients likely to benefit from surgery.

MATERIALS AND METHODS

Patients Included in the Study

Between January 1981 and December 2006, a total of 101 consecutive patients (57 men and 44 women) underwent surgical exploration with curative intent for LRRC at Aichi Cancer Center Hospital. The patients' ages ranged from 36 to 78 (median, 57) years. All of the patients had previously undergone radical resection of the primary rectal adenocarcinoma. Fifty-five patients (54.5%) underwent surgical treatment of their primary tumors elsewhere and were referred to our institution for treatment of their recurrences. Details of the primary tumor and management were obtained from the hospitals in which the patients were originally treated. This included date of surgery, type of operation, tumor (T) stage, node (N) stage, Dukes classification, lymphatic invasion, venous invasion, and histologic grade of the primary tumor. The clinicopathological features were retrospectively reviewed by use of case charts and written pathological reports. The degree of lymphovascular invasion was classified according to the criteria of the "General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus,"[20] in which lymphatic and venous invasions are classified as follows: no invasion (grade 0), minimal invasion (grade 1), moderate invasion (grade 2), and marked invasion (grade 3). This classification was dichotomized, ie, classed as low (grade 0–1) or high (grade 2–3) for analysis. Local recurrence was defined as tumor recurrence in the previous operative field, and was classified according to the pattern of pelvic invasion of the recurrent tumor (Table 1, Fig. 1). The extent of the locally recurrent tumor was classified by the 3 patterns of pelvic invasion on CT or MRI as follows: anastomotic site invasive type, visceral/lower sacral invasive type, and upper sacral/lateral invasive type. This classification was based on modified criteria from the previous reported pelvic invasive pattern of local recurrence (localized, sacral, or lateral), which influenced prognosis after resection.[21] Local recurrence occurred at a median of 17.9 months (range, 2.2–111.6 mo) after the initial operation. Details of the operation for local recurrence, and of perioperative radiotherapy and chemotherapy were recorded.

Before the surgery for locoregional recurrence, 6 patients had undergone liver resection, 3 had pulmonary resection, one had both, one had peritonectomy, and one had inguinal lymphadenectomy for distant metastases. At salvage surgery for LRRC, 4 patients had liver metastases, 2 had lung metastases, 1 had both, 1 had para-aortic nodal metastasis, and 2 had localized peritoneal metastases. Metastatic tumors in 3 of 10 patients with concurrent distant metastases were resected simultaneously. In the remaining 7 patients, the initial plan for staged surgery was abandoned because the disease rapidly progressed to multiple metastases after salvage surgery for the pelvic local disease. These patients were entered into a group of incomplete resections with gross residual disease for the analysis. Including the patients who had evidence of distant metastatic disease before or at the time of resection of their local recurrence, a total of 22 patients included in the study were defined as having extrapelvic disease. The entire cohort of 101 patients was followed up completely, with a median follow-up time for live patients of 53.7 months (range, 3.2–140.0 mo).

Preoperative Evaluation

All patients underwent clinical assessment and preoperative imaging to determine tumor resectability, to exclude metastatic disease outside the pelvis, and to assess the general fitness of the patient and ability to withstand major surgery. Each patient underwent CT of the thorax and abdomen to exclude distant metastases and to assess involvement of the bony pelvis. The presence of extensive abdominal or thoracic metastases was considered to be a contraindication to resection of the pelvic recurrence. Patients also underwent MRI of the pelvis to assess the location of the tumor, its direction of invasion, and involvement of local viscera and the pelvic sidewall structures. Contraindications to locally curative surgery as determined by imaging included extensive pelvic sidewall involvement or adherence, tumor encasement of the iliac vessels, extension of the tumor into the sciatic notch, and proximal sacral invasion above the level of the S1–S2 junction. Patients who had had surgery since 2000 in the study underwent whole-body positron emission tomography (PET) or PET-CT scans as part of their preoperative evaluation. Although PET-CT scans are now a standard component of preoperative assessment through improved diagnostic accuracy, still, a 10% of false-positive rates in the detection of
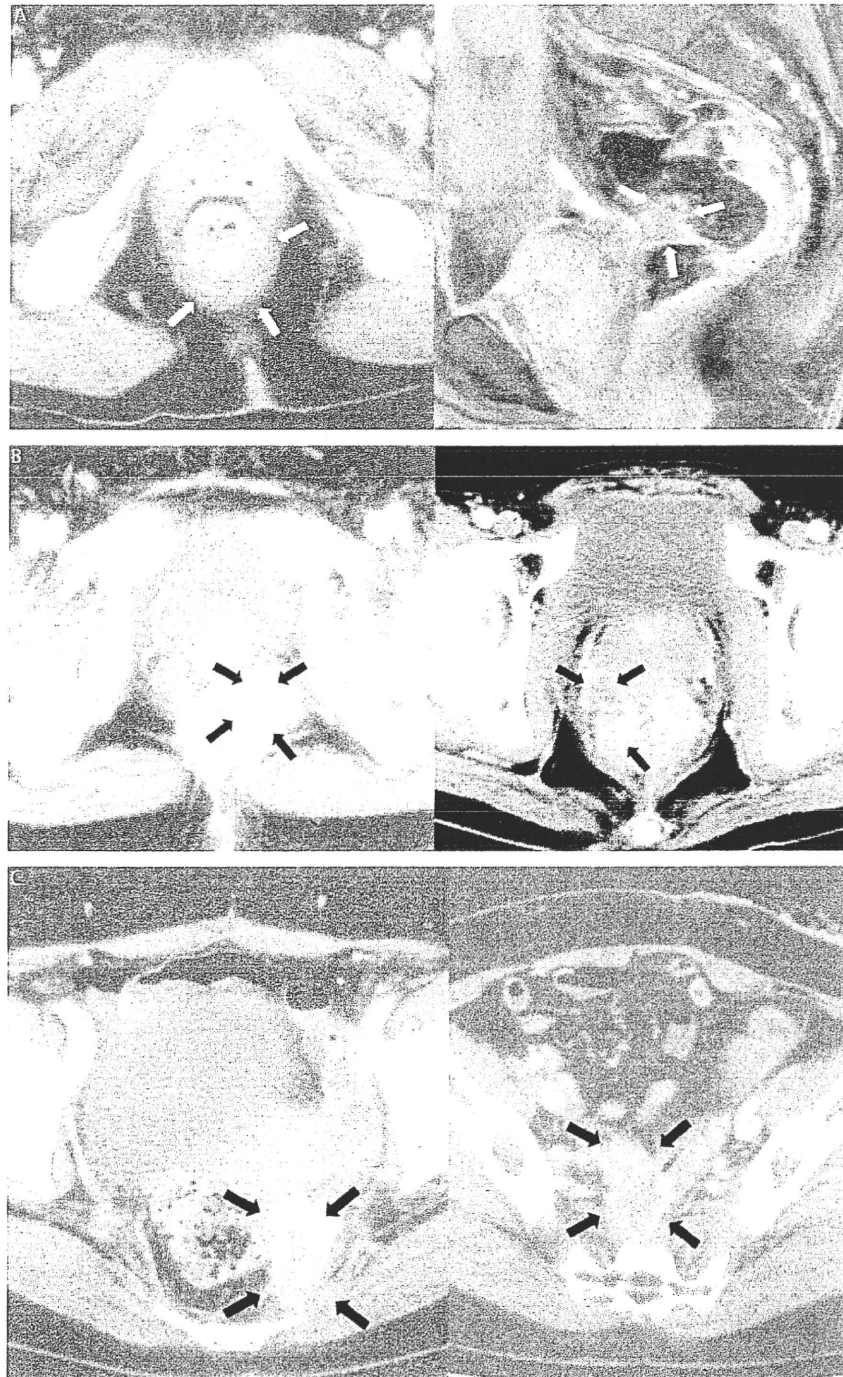
FIGURE 1. A, Anastomotic site invasive type. B, Visceral/lower sacral invasive type. C, Upper sacral/lateral invasive type. Arrows reveal a recurrent tumor.

pelvic recurrence in patients with colorectal cancer has been reported.[22] Therefore, histologic confirmation of malignancy by CT-directed fine-needle aspiration or biopsy per rectum was obtained for all patients before surgical intervention. Serum CEA concentration was measured in most patients as part of their preoperative workup.

Stage and Treatment of Primary Tumors

The initial tumor stage according to Dukes classification was A in 18 patients (17.8%), B in 21 patients (20.8%), C in 52 patients (51.5%), D in 5 patients (5.0%), and unknown in 5 patients (5.0%). All the metastatic tumors in patients with Dukes stage D were resected simultaneously or

TABLE 2. Clinical and pathological characteristics of patients who underwent resection of locally recurrent rectal cancer

	n	%
Age (y)[a]	57 (36–78) (58)	
Sex		
Female	44	43.6
Male	57	56.4
Interval to recurrence (mo)[a]	17.9 (2.2–111.6) (24.2)	
Recurrent disease		
Pelvic invasive pattern		
Anastomotic invasive type	18	17.8
Visceral/lower sacral invasive type	41	40.6
Upper sacral/lateral invasive type	27	26.7
Unknown	15	14.9
CEA		
Normal	42	41.6
Elevated	54	53.5
Unknown	5	4.9
Extrapelvic disease		
Yes	22	21.8
No	79	78.2
Hydronephrosis		
Yes	5	4.9
No	83	82.2
Unknown	13	12.9
Primary disease		
Dukes stage		
A	18	17.8
B	21	20.8
C	52	51.5
D	5	5.0
Unknown	5	5.0
Histology		
Well	21	20.8
Moderately	72	71.3
Mucinous or poorly	7	6.9
Unknown	1	1.0
Lymphatic invasion		
Grade 0–1	54	53.5
Grade 2–3	33	33.7
Unknown	14	12.8
Venous invasion		
Grade 0–1	70	69.3
Grade 2–3	17	17.9
Unknown	14	12.8
Surgical procedure		
Local resection	4	4.0
HAR	15	14.9
LAR	46	45.5
APR	32	31.7
Hartmann procedure	4	4.0

HAR = high anterior resection; LAR = low anterior resection; APR = abdominoperineal resection.

[a]Values are median (range) (mean).

metachronously. Primary cancers had been surgically treated by transanal or transsacral resection (n = 4, 4.0%), high anterior resection (n = 15, 14.9%), low anterior resection (n = 46, 45.5%), abdominoperineal resection (APR) (n = 32, 31.7%), or Hartmann procedure (n = 4, 4.0%) (Table 2). Adjuvant chemotherapy, using 5-fluorouracil plus leucovorin or 5-fluorouracil prodrugs (ura-

TABLE 3. Surgical procedure and additional therapy performed for recurrent disease

Procedure	Total	With sacrectomy	%
Operation			
Local resection	10	0	9.9
APR	22	9	21.8
Hartmann procedure	8	0	7.9
LAR	12	0	11.9
TPE	36	16	35.6
Posterior pelvic exenteration	13	6	12.9
Margins at recurrent resection			
R0	62		61.4
R1	20		19.8
R2	19		18.8
Ratiotherapy for recurrence			
Yes	43		42.6
External-beam radiation	43		42.6
IORT	18		17.8
No	57		56.4
Unknown	1		0.9
Chemotherapy for recurrence			
Yes	41		40.6
No	59		58.4
Unknown	1		1.0

APR = abdominoperineal resection; LAR = low anterior resection; TPE = total pelvic exenteration; IORT = intraoperative radiotherapy.

cil and tegafur) was administered to 33 patients and radiotherapy was given to 3 patients with tumors deemed to be at high risk for metastasis.

Clinical Presentation of Recurrent Disease

Fifty-one patients (50.5%) exhibited symptoms caused by their local recurrences, such as pelvic pain, rectal bleeding, or changes in bowel habits. CEA levels on presentation were available for 96 patients: 54 had elevated levels and 42 had normal levels (Table 2). The median CEA level on presentation for the salvage surgery was 6.6 ng/mL (normal level, <5 ng/mL).

TABLE 4. Description of surgery for recurrent disease

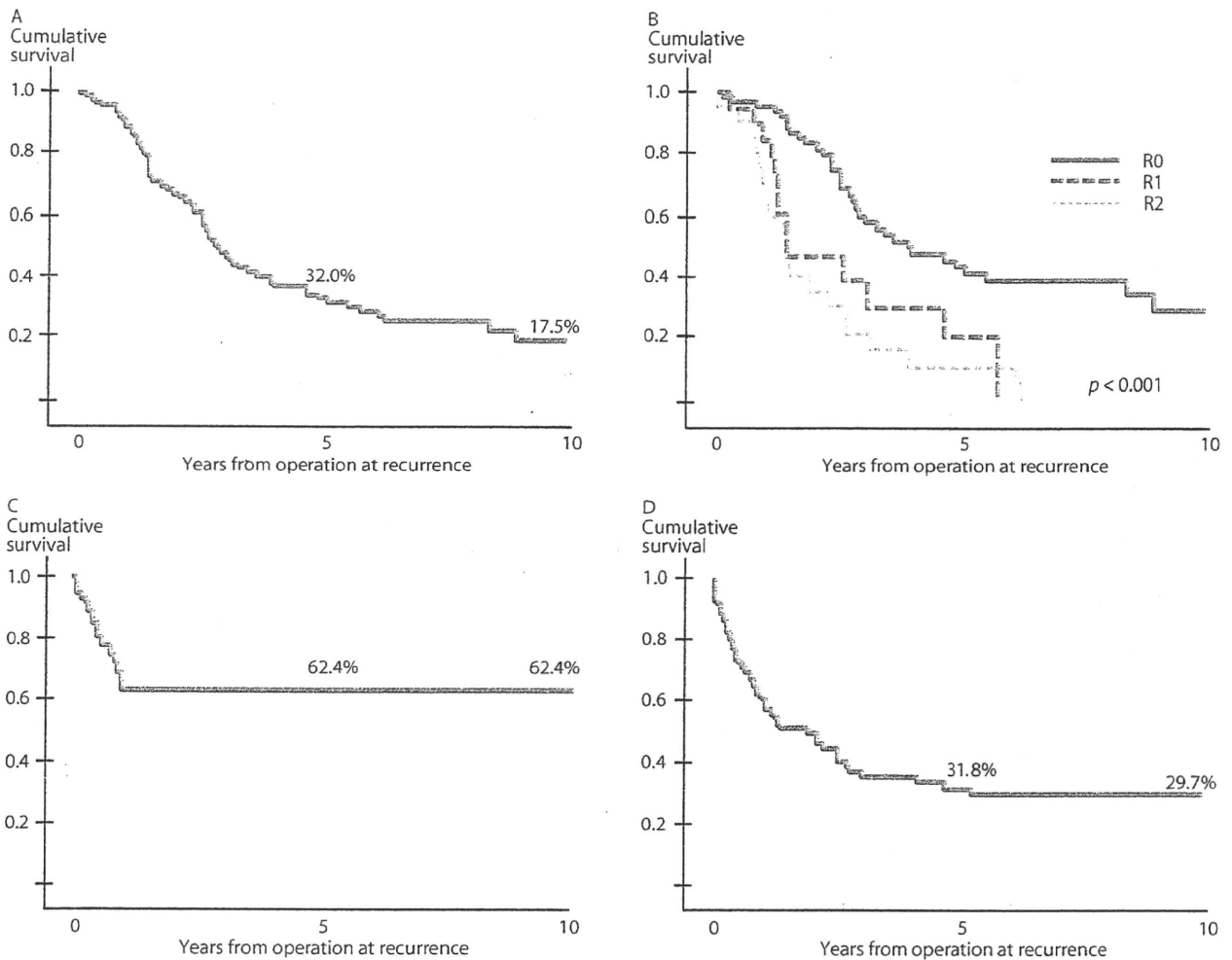|	n	% of 101 patients
Operative time (min)[a]	495 (32–1101) (509)	
Blood loss (mL)[a]	2500 (0–24300) (4005)	
Hospital stay (d)[a]	62 (6–466) (79)	
In-hospital mortality	5	5.0
Morbidity	82	81.2
Pelvic abscess	38	37.6
Fistula	24	23.8
Bowel obstruction	21	20.8
Leakage of ileal conduit	10	9.9
Wound infection	8	7.9
Leakage of intestines	3	2.9
Septicemia	2	2.0

[a]Values are median (range) (mean).

FIGURE 2. Kaplan-Meier estimates. A, Disease-specific survival after resection in the entire cohort (n = 101). B, Disease-specific survival after resection by margin status of resected specimen. C, Local disease-free survival after resection in the entire cohort (n = 101). D, Distant disease-free survival after resection in the entire cohort (n = 101). R0 = negative for disease; R1 = microscopically positive for disease; R2 = gross residual disease.

Treatment of Recurrence

Two patients received preoperative adjuvant radiation of 50 Gy during 5 weeks because preoperative imaging indicated frank invasion of adherent structures. All 101 patients underwent a potentially curative resection of the local recurrence. This included a local resection in 10 patients, APR in 13, APR with sacral resection in 9, Hartmann procedure in 8, low anterior resection in 12, total pelvic exenteration (TPE) in 20, TPE with sacral resection in 16, posterior pelvic exenteration in 7, and posterior pelvic exenteration with sacral resection in 6 (Table 3). TPE was accompanied by urinary reconstruction by use of an ileal conduit. Levels of sacral transection included S2 to S3 in 9 patients, S3 in 3 patients, S3 to S4 in 10 patients, S4 in 3 patients, and S4 to S5 in 6 patients. The extent of sacral resection was limited to the distal sacrum below S2. Frozen-section analysis was performed of the resected specimen and of the closest margins. On detection of any positive margins, further tissue was resected until negative margins were achieved or until it was not possible to resect further. Sixty-two of the patients underwent curative (R0) resections with negative microscopic margins. Marginal (R1) resections with positive microscopic margins were performed for 20 patients, and incomplete (R2) resections with gross residual disease were performed for 19 patients. Eighteen patients (17.8%) with suspected or confirmed microscopic residual disease in the pelvis received intraoperative radiotherapy (10–20 Gy). When the outcome of frozen sections taken during surgery was positive with macroscopic or gross residual disease, external beam radiotherapy (45–50 Gy) was delivered postoperatively in 41 patients (40.6%). Forty-one patients received perioperative

	Univariate		Multivariate (logistic)	
Variable	OR	P	OR	P
Age				
≥60 vs <60	0.8 (0.4–2.1)	0.770	–	–
Sex				
Male vs female	1.3 (0.5–2.9)	0.577	–	–
Pelvic invasive pattern				
Upper sacral/lateral vs anastomotic invasive type	7.0 (1.8–27.5)	0.005	54.6 (3.2–2.1941.0)	0.005
Visceral/lower sacral vs anastomotic invasive type	1.3 (0.3–4.7)	0.708	3.3 (0.3–38.4)	0.331
CEA				
Normal vs elevated	0.5 (0.2–1.1)	0.079	–	–
Extrapelvic disease				
Yes vs no	3.0 (0.7–2.1)	0.002	3.9 (0.7–20.9)	0.112
Hydronephrosis				
Yes vs no	3.0 (0.5–18.7)	0.251	–	–
Primary disease				
Lymph node metastasis				
Yes vs no	4.8 (1.6–13.8)	0.004	3.6 (0.6–19.8)	0.140
Histology				
Well vs moderately	0.5 (0.2–1.8)	0.311	–	–
Mucinous or poorly vs moderately	1.8 (0.2–14.1)	0.561	–	–
Lymphatic invasion[b]				
Grade 2–3 vs grade 0–1	5.9 (2.2–15.4)	<0.001	11.7 (1.6–85.4)	0.015
Venous invasion[b]				
Grade 2–3 vs grade 0–1	4.5 (1.4–13.8)	0.008	1.5 (0.2–14.1)	0.741

TABLE 5. Factors associated with palliative vs curative resection[a]

OR = odds ratio.
[a]Values in parentheses are 95% confidence intervals.
[b]The degree of invasion was divided into 4 grades according to the Japanese criteria.[20] Grade 0 = no invasion; grade 1 = minimal invasion; grade 2 = moderate invasion; grade 3 = marked invasion.

chemotherapy, usually 5-fluorouracil-based, for the locally recurrent tumor, most frequently concurrent with external beam radiotherapy.

Statistical Analysis

Survival time was calculated from the date of surgery for local recurrence of rectal cancer until the last follow-up visit, or the occurrence of the defined events. Survival rates were estimated using the Kaplan-Meier method. Comparisons of survival rates between groups were made using the log-rank method. Multivariate survival analyses were performed by use of a Cox proportional hazards model. Univariate and multivariate analyses of factors influencing curative (R0) vs palliative (R1 or R2) resections were performed by use of logistic regression. Multivariate models were constructed based on variables known to be predictive of risk of events in univariate models.[23] Among the significant prognostic characteristics, variables measured during preoperative investigations were chosen to establish a prediction model. Missing variables occupying more than 20% of the data set were omitted from the model. For all tests, a P value of 0.05 was considered significant.

RESULTS

Descriptive statistics regarding the surgeries are shown in Table 4. The median operating time was 495 minutes (range, 32–1101 min). Median blood loss was 2500 mL (range, 0–24,300 mL). The median length of hospital stay was 62 days (range, 6–466 d) with an in-hospital mortality rate of 5.0%. The postoperative complication rate was 81.2% with the most common major complications being pelvic abscess (37.6%), enterocutaneous or colovesical fistula (23.8%), and bowel obstruction (20.8%).

The 1-, 3-, 5-, and 10-year disease-specific survival rates for the 101 patients that underwent surgery for LRRC were 87.9%, 47.5%, 32.0%, 17.5%, respectively, whereas the median survival time for these patients was 33.6 months (Fig. 2A). Completeness of resection correlated strongly with survival rates, as shown in Figure 2B. The 5-year disease-specific survival rates of curative (R0), R1, and R2 resection were 43.3%, 19.5%, and 10.0%, respectively (P < .001).

Predictors of Curative Resection

Table 5 compares the characteristics of patients who underwent curative and palliative resection. The pattern of

TABLE 6. Univariate/multivariate regression of factors related to local disease-free survival[a]

Variable	Univariate		Multivariate (Cox)	
	HR	P	HR	P
Age				
≥60 vs <60	0.5 (0.3–1.2)	0.118	–	–
Sex				
Male vs female	0.6 (0.3–1.2)	0.148	–	–
Pelvic invasive pattern				
Anastomotic vs upper sacral/lateral invasive type	0.2 (0.0–0.8)	0.028	0.2 (0.0–0.9)	0.045
Visceral/lower sacral vs upper sacral/lateral invasive type	0.5 (0.2–1.2)	0.124	0.5 (0.2–1.1)	0.083
CEA				
Normal vs elevated	0.6 (0.3–1.2)	0.170	–	–
Extrapelvic disease				
Yes vs no	1.3 (0.6–2.7)	0.542	–	–
Hydronephrosis				
Yes vs no	1.0 (0.2–4.3)	0.991	–	–
Interval to recurrence (mo)				
<12 vs ≥12	1.1 (0.5–2.2)	0.811	–	–
Margins at recurrent resection				
R0 vs R2	0.5 (0.2–1.2)	0.115	–	–
R1 vs R2	0.9 (0.3–2.5)	0.882	–	–
Chemotherapy for recurrent disease				
Yes vs no	1.3 (0.7–2.6)	0.387	–	–
Radiotherapy for recurrent disease				
Yes vs no	2.0 (1.5–3.9)	0.078	–	–
Primary disease				
Lymph node metastasis				
Yes vs no	2.1 (1.1–4.7)	0.046	2.0 (0.8–5.0)	1.110
Histology				
Moderately vs well	2.2 (0.7–6.3)	0.157	–	–
Mucinous or poorly vs well	3.2 (0.3–28.6)	0.306	–	–
Lymphatic invasion[b]				
Grade 2–3 vs grade 0–1	0.9 (0.4–1.9)	0.705	–	–
Venous invasion[b]				
Grade 2–3 vs grade 0–1	0.6 (0.2–1.7)	0.328	–	–

HR = hazard ratio.
[a]Values in parentheses are 95% confidence intervals.
[b]The degree of invasion was divided into 4 grades according to the Japanese criteria.[20] Grade 0 = no invasion; grade 1 = minimal invasion; grade 2 = moderated invasion; grade 3 = marked invasion.

pelvic invasion of the recurrent tumor ($P = .005$) and grade of lymphatic invasion of the primary tumor ($P = .015$) had significant effects on the possibility of curative resection. The proportion of patients undergoing palliative resection was much higher in upper sacral/lateral invasive type (66.7%) than in viscera/lower sacral invasive type (26.8%) or anastomotic site invasive type (22.2%).

Factors Affecting Local Disease-Free Survival After Resection

The 1-, 3-, 5-, and 10-year local disease-free survival rates of the entire cohort were 68.2%, 62.4%, 62.4%, and 62.4%, respectively (Fig. 2C).

Univariate analyses suggested that the pattern of pelvic invasion of the recurrent tumor ($P = .028$) and lymph node metastasis of the primary tumor ($P = .046$) were independently associated with local disease-free survival after salvage surgery. Multivariate analyses of fac-

tors identified as significant by univariate analyses revealed that only the pattern of pelvic invasion of the recurrent tumor ($P = .045$) retained statistical significance (Table 6).

Factors Affecting Distant Disease-Free Survival After Resection

The 1-, 3-, 5-, and 10-year distant disease-free survival rates of the entire cohort were 59.5%, 36.8%, 31.8%, and 29.7%, respectively (Fig. 2D).

Univariate analyses suggested that margins at recurrent resection ($P < .001$), high-grade lymphatic ($P = .004$) or venous ($P = .004$) invasion of the primary tumor, presence of hydronephrosis with recurrent tumor ($P = .031$), presence of extrapelvic disease before or at resection ($P < .001$), and the pattern of pelvic invasion of the recurrent tumor ($P = .001$) were independently associated with distant disease-free survival after salvage surgery. Multivariate analyses of factors identified as significant by univariate

TABLE 7. Univariate/multivariate regression of factors related to distant disease-free survival[a]

Variable	Univariate		Multivariate (Cox)	
	HR	P	HR	P
Age				
≥60 vs <60	1.3 (0.7–2.1)	0.432	–	–
Sex				
Male vs female	1.1 (0.7–2.0)	0.675	–	–
Pelvic invasive pattern				
Anastomotic vs upper sacral/lateral invasive type	0.4 (0.2–0.9)	0.019	0.5 (0.2–1.5)	0.228
Visceral/lower sacral vs upper sacral/lateral invasive type	0.4 (0.2–0.7)	0.001	0.4 (0.2–0.9)	0.040
CEA				
Normal vs elevated	0.7 (0.4–1.3)	0.259	–	–
Extrapelvic disease				
Yes vs no	2.7 (1.5–4.8)	<0.001	2.3 (1.1–5.2)	0.044
Hydronephrosis				
Yes vs no	3.2 (1.1–9.1)	0.031	3.4 (0.9–12.3)	0.063
Interval to recurrence (mo)				
<12 vs ≥12	0.9 (0.5–1.7)	0.971		
Margins at recurrent resection				
R0 vs R2	0.2 (0.1–0.4)	<0.001	0.4 (0.1–0.8)	0.031
R1 vs R2	0.6 (0.3–1.2)	0.150	0.8 (0.3–2.5)	0.761
Chemotherapy for recurrent disease				
Yes vs no	0.9 (0.6–1.6)	0.805	–	–
Radiotherapy for recurrent disease				
Yes vs no	1.4 (0.8–2.3)	0.206	–	–
Primary disease				
Lymph node metastasis				
Yes vs no	1.8 (0.9–3.3)	0.065	–	–
Histology				
Moderately vs well	1.3 (0.7–2.7)	0.433	–	–
Mucinous or poorly vs well	0.7 (0.1–5.4)	0.725	–	–
Lymphatic invasion[b]				
Grade 2–3 vs grade 0–1	2.3 (1.4–3.9)	0.004	3.1 (1.3–7.5)	0.009
Venous invasion[b]				
Grade 2–3 vs grade 0–1	2.6 (1.3–5.1)	0.004	0.7 (0.2–1.8)	0.418

HR = hazard ratio.
[a]Values in parentheses are 95% confidence intervals.
[b]The degree of invasion was divided into 4 grades according to the Japanese criteria.[20] Grade 0 = no invasion; grade 1 = minimal invasion; grade 2 = moderated invasion; grade 3 = marked invasion.

analyses revealed that margins at recurrent resection ($P =$ .031), lymphatic invasion of the primary tumor ($P =$ .009), extrapelvic disease ($P =$ .044), and the pattern of pelvic invasion of the recurrent tumor ($P =$ .040) retained statistical significance. Hydronephrosis showed borderline significance ($P =$ .063) (Table 7).

Relationship Between Pattern of Recurrence and Curability

The incidence rates of distant and local diseases at 2 years after resection of LRRC were shown according to the curability in Figure 3. Patients with R2 demonstrated an incidence rate of distant diseases higher than that of the patients with R1, and almost twice that of the patients with R0 (R2, 77.0%; R1, 67.1%; R0, 38.7%). However, patients with R1 and R2 had identical 2-year incidence rate of local diseases after resection of LRRC (R2, 45.5%; R1, 47.0%; R0, 30.9%).

Establishment of a Model Predicting Treatment Failure After Surgery

Among the significant prognostic factors by univariate analyses (Table 7), lymphatic or venous invasion of the primary tumor, hydronephrosis with recurrent tumor, extrapelvic disease before or at resection, and the pattern of pelvic invasion of the recurrent tumor were chosen as the factors that could be detected before an operation for LRRC. Multivariate analyses of these factors revealed that lymphatic invasion of the primary tumor ($P <$ .001), hydronephrosis ($P =$ .043), extrapelvic disease ($P =$ .016), and the pattern of pelvic invasion of the recurrent tumor ($P =$ .001) retained statistical significance. Venous invasion of the primary tumor showed borderline significance ($P =$ .079) (Table 8).

We assigned the patients to 2 groups based on the 5 preoperative investigated risk factors identified for systemic failure after treatment: those with no risk factors and
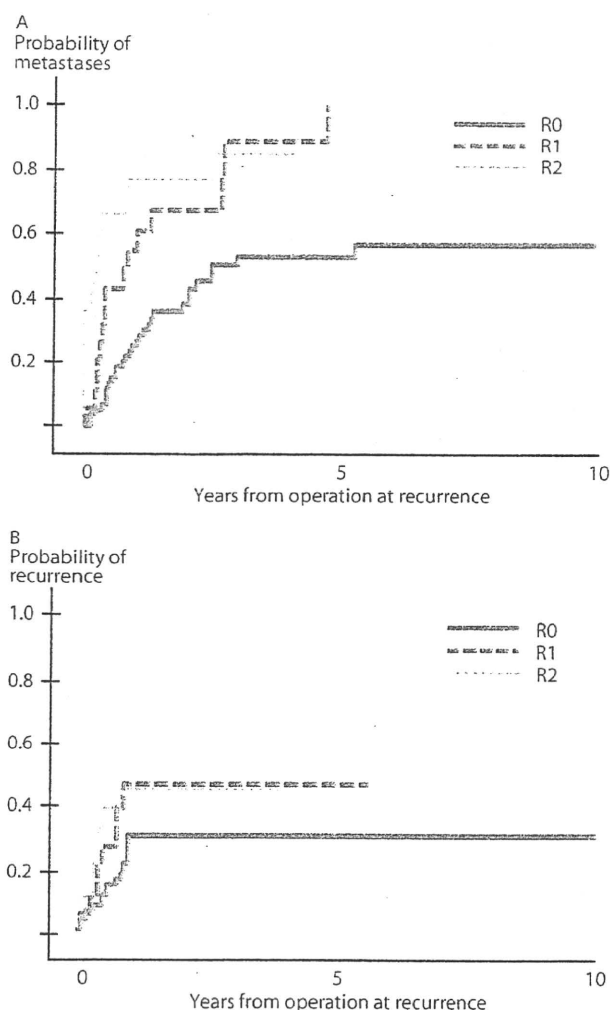
A
Probability of
metastases

B
Probability of
recurrence

FIGURE 3. A, Time to distant metastases by curability. B, Time to local diseases by curability. R0 = negative for disease; R1 = microscopically positive for disease; R2 = gross residual disease.

TABLE 8. Multivariate regression of preoperative investigated factors related to distant disease-free survival

Variable	Multivariate (Cox)	
	HR	P
Pelvic invasive pattern		
Anastomotic vs upper sacral/lateral invasive type	0.4 (0.1–1.1)	0.072
Visceral/lower sacral vs upper sacral/ lateral invasive type	0.2 (0.1–0.6)	0.001
Extrapelvic disease		
Yes vs no	2.9 (1.2–6.8)	0.016
Hydronephrosis		
Yes vs no	3.7 (1.1–14.3)	0.043
Primary disease		
Lymphatic invasion[a]		
Grade 2–3 vs grade 0–1	4.9 (1.9–12.5)	<0.001
Venous invasion[a]		
Grade 2–3 vs grade 0–1	2.1 (0.7–5.9)	0.079

Values in parentheses are 95% confidence intervals.
HR = hazard ratio.
[a]The degree of invasion was divided into 4 grades according to the Japanese criteria.[20] Grade 0 = no invasion; grade 1 = minimal invasion; grade 2 = moderated invasion; grade 3 = marked invasion.

published literature.[24–28] Negative resection margins were achieved in 61% of the patients in our study. The limitations of preoperative diagnosis are reflected by the fact that there were a number of palliative resections in locally recurrent diseases that had been considered resectable. On the other hand, the majority of patients with recurrence after resection for LRRC developed extrapelvic disease before or at the time of resection.[9,12,13] In the present study, which is the first to analyze prognostic predictors of systemic failure after treatment, the distant disease-free survival curve had a steep decline within one year after resection, indicating a high frequency of residual or subclinical

those with at least one risk factor. We found a statistically significant difference in the distant disease-free survival curves for the 2 risk groups ($P < .001$). The 3-year distant disease-free survival rate decreased from 54.1% in patients with no risk factors to 6.2% for those with one or more risk factors (Fig. 4).

DISCUSSION

In studies that have analyzed factors affecting the survival of patients after resection of LRRC, the possibility of performing curative resection has been consistently reported as a significant determinant of survival. The reported 5-year survival rates vary from 22% to 58% after obtaining R0 resection.[5–10] Although the validity of an R0 resection has been established, this can only be achieved in approximately 45% of cases, ranging from 10% to 67% in the
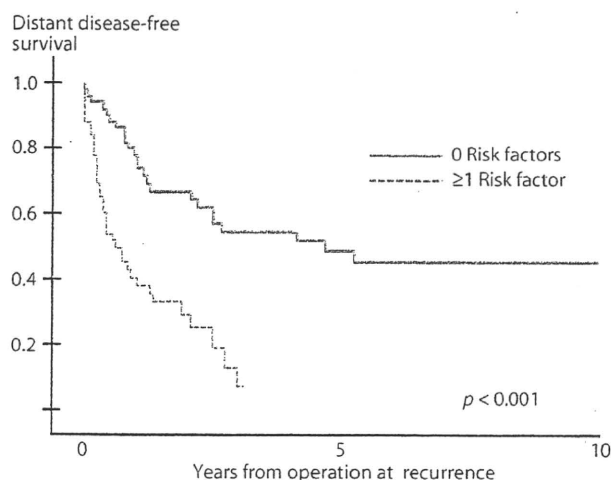
Distant disease-free
survival

FIGURE 4. Distant disease-free survival after resection based on the number of risk factors.

metastatic disease outside the pelvis in patients with isolated LRRC. It is essential to predict failure patterns accurately in patients with treatable LRRC so that appropriate therapy can be selected as an adjunct to extensive surgery for the local recurrence. The incidence of treatment failure could be reduced by specific prophylactic measures including adjuvant radiotherapy and chemotherapy. Multimodality treatment of LRRC is essential. The aim of the present study was to identify predictors of local and systemic failure after surgery.

This study identified several variables that affect curative surgery. In the multivariate analysis, the pattern of pelvic invasion of the recurrent tumor visualized by only preoperative imaging, which needed no histopathological confirmation, had the greatest impact on a curative resection. We obtained the highest probability of curative resection for patients with recurrent disease limited to the anastomosis. This group has been reported previously to represent a small but favorable subset of local recurrences.[5,21,29,30] In contrast, a high frequency of the recurrent tumors of the upper sacral/lateral invasive type were not amenable to curative resection. We found that pelvic recurrences involving or attaching to the lateral pelvic sidewalls were less likely to be curatively resected than those involving axial or anterior lesions, which has led to a higher incidence rate of distant diseases after resection; disseminated spread might be the major reason for not undertaking curative resection. In addition, sacral involvement above the S2 narrows the therapeutic window because of the functional sequelae of higher resections and the small likelihood of obtaining clear margins, making these recurrences difficult to control. The biological aggressiveness of the primary tumor, represented by the lymphatic invasion, was also a significant predictor of curative resection. Although imaging studies provide valuable information, the ability to predict margins preoperatively would be of great value.

Although some reports deal with factors that potentially influence survival after reoperation in cases of LRRC,[7,8,21] high-grade lymphatic or venous invasion of the primary tumor, presence of hydronephrosis with recurrent tumor, presence of extrapelvic disease before or at resection, and the pattern of pelvic invasion of the recurrent tumor were first established as predictors of systemic failure after reoperation. Hydronephrosis does not necessarily preclude a curative resection,[31] but all 5 patients with hydronephrosis (2 in R0, 3 in R1) in this study manifested systemic diseases within 2 years after surgery. Hydronephrosis occurring under circumstances of sidewall involvement or ureteral obstruction at the bladder, requiring more extended resections, may portend a poor outcome. In cases of distant metastasis, we extended the indications to 22 patients with one or 2 metastases. This group achieved a curative resection rate of 41%, a 2-year distant disease-free survival rate of 11%, and a 3-year disease-specific survival rate of 18%. However, none survived 5 years.

The presence of extensive abdominal or thoracic metastases is considered to be a contraindication to resection of the pelvic recurrence. However, our experience has demonstrated that highly selected patients with this traditional adverse factor can experience medium-term survival following reoperation for LRRC. Therefore, we did not delete extrapelvic disease from the analysis.

Preoperative selection of patients at a high risk for failure after reoperation is particularly important given the high morbidity, as shown in our study, that can be incurred by an aggressive surgical approach to LRRC. The classification system based on variables selected by multivariate analysis assigned patients undergoing resection for LRRC to 2 groups, each with a different probability of developing relapse at extrapelvic sites or residual disease. This system was able to define a group of patients with a 3-year distant disease-free survival rate of only 6.2%. The majority of patients with at least one risk factor developed extrapelvic disease within one year; none of these patients had an operable recurrence. They would not benefit from surgery alone. Multimodality treatment strategies are critical for selecting and supporting these patients perioperatively and over the long term. With the development of new and more effective chemotherapeutic regimens for the treatment of colorectal cancer, strong consideration should be given to preoperative adjuvant treatment for LRRC to maximize the chance of clear margins, and to suppress residual or subclinical metastatic disease outside the pelvis. There is still much room for improvement, in particular, for patients at a high risk for treatment failure after reoperation.[32] Our predictive model may help to delineate patients who will subsequently benefit from addition of chemotherapy or radiotherapy before operating with curative intent for LRRC. This model should be validated in a larger, unselected population.

CONCLUSION

The ability to obtain a negative margin, highly predicted by the pattern of pelvic recurrence on imaging, is critical for avoiding local and systemic failure. Our results suggest that, in addition to preoperative imaging, certain biologically related tumor factors of the patients, ie, high-grade lymphatic or venous invasion of the primary tumor, presence of hydronephrosis with recurrent tumor, and presence of extrapelvic disease, will be important in their selection for pelvic resections. Preoperative treatments for a selected LRRC have the potential to downsize bulky disease, optimize the ability to perform an R0 resection, and optimize long-term patient outcomes. This system might be used on an individual basis to determine when surgery would be most beneficial and to select patients with LRRC for chemotherapy or radiotherapy before surgical intervention with curative intent.

REFERENCES

1. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery-the clue to pelvic recurrence? *Br J Surg.* 1982;69: 613–616.
2. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet.* 1993;341:457–460.
3. Law WL, Chu KW. Resection of local recurrence of rectal cancer: results. *World J Surg.* 2000;24:486–490.
4. Moore E, Heald RJ, Cecil TD, Sharpe GD, Sexton R, Moran BJ. Almost all five year disease free survivors are cured following rectal cancer surgery, but longer term follow-up detects some late local and systemic recurrences. *Colorectal Dis.* 2005;7:403–405.
5. Salo JC, Paty PB, Guillem J, Minsky BD, Harrison LB, Cohen AM. Surgical salvage of recurrent rectal carcinoma after curative resection: a 10-year experience. *Ann Surg Oncol.* 1999;6:171–177.
6. Lindel K, Willett CG, Shellito PC, et al. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. *Radiother Oncol.* 2001;58:83–87.
7. Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. *Dis Colon Rectum.* 2002;45:585–592.
8. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. *Ann Surg.* 2003;237:502–508.
9. Moriya Y, Akasu T, Fujita S, Yamamoto S. Total pelvic exenteration with distal sacrectomy for fixed recurrent rectal cancer in the pelvis. *Dis Colon Rectum.* 2004;47:2047–2053.
10. Bakx R, van Tinteren H, van Lanschot JJ, Zoetmulder FA. Surgical treatment of locally recurrent rectal cancer. *Eur J Surg Oncol.* 2004;30:857–863.
11. Maetani S, Nishikawa T, Iijima Y, et al. Extensive en bloc resection of regionally recurrent carcinoma of the rectum. *Cancer.* 1992;69:2876–2883.
12. Wells BJ, Stotland P, Ko MA, et al. Results of an aggressive approach to resection of locally recurrent rectal cancer. *Ann Surg Oncol.* 2007;14:390–395.
13. Bedrosian I, Giacco G, Pederson L, et al. Outcome after curative resection for locally recurrent rectal cancer. *Dis Colon Rectum.* 2006;49:175–182.
14. Boyle KM, Sagar PM, Chalmers AG, Sebag-Montefiore D, Cairns A, Eardley I. Surgery for locally recurrent rectal cancer. *Dis Colon Rectum.* 2005;48:929–937.
15. Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. *Ann Surg Oncol.* 2007;14:447–454.
16. Henry LR, Sigurdson E, Ross EA, et al. Resection of isolated pelvic recurrences after colorectal surgery: long-term results and predictors of improved clinical outcome. *Ann Surg Oncol.* 2007; 14:1081–1091.
17. Asoglu O, Karanlik H, Muslumanoglu M, et al. Prognostic and predictive factors after surgical treatment for locally recurrent rectal cancer: a single institute experience. *Eur J Surg Oncol.* 2007;33:1199–1206.
18. Heriot AG, Byrne CM, Lee P, et al. Extended radical resection: the choice for locally recurrent rectal cancer. *Dis Colon Rectum.* 2008;51:284–291.
19. Camilleri-Brennan J, Steele RJ. The impact of recurrent rectal cancer on quality of life. *Eur J Surg Oncol.* 2001;27:349–353.
20. Japanese Research Society for Cancer of the Colon and Rectum. *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus.* 7th ed. Tokyo, Japan: Kanahara Shuppan; 2006.
21. Yamada K, Ishizawa T, Niwa K, Chuman Y, Akiba S, Aikou T. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. *Br J Surg.* 2001;88:988–993.
22. Even-Sapir E, Parag Y, Lerman H, et al. Detection of recurrence in patients with rectal cancer: PET/CT after abdominoperineal or anterior resection. *Radiology.* 2004;232:815–822.
23. Cox DR. Regression models and life tables. *J R Stat Soc.* 1972;34: 187–220.
24. Caricato M, Borzomati D, Ausania F, Valeri S, Rosignoli A, Coppola R. Prognostic factors after surgery for locally recurrent rectal cancer: an overview. *Eur J Surg Oncol.* 2006;32:126–132.
25. Huguier M, Houry S. Treatment of local recurrence of rectal cancer. *Am J Surg.* 1998;175:288–292.
26. Garcia-Aguilar J, Cromwell JW, Marra C, Lee SH, Madoff RD, Rothenberger DA. Treatment of locally recurrent rectal cancer. *Dis Colon Rectum.* 2001;44:1743–1748.
27. Cheng C, Rodriguez-Bigas MA, Petrelli N. Is there a role for curative surgery for pelvic recurrence from rectal carcinoma in the presence of hydronephrosis? *Am J Surg.* 2001;182:274–277.
28. Wiggers T, Mannaerts GH, Marinelli AW, Martijn H, Rutten HJ. Surgery for locally recurrent rectal cancer. *Colorectal Dis.* 2003;5:504–507.
29. Pihl E, Hughes ES, McDermott FT, Price AB. Recurrence of carcinoma of the colon and rectum at the anastomotic suture line. *Surg Gynecol Obstet.* 1981;153:495–496.
30. Vassilopoulos PP, Yoon JM, Ledesma EJ, Mittelman A. Treatment of recurrence of adenocarcinoma of the colon and rectum at the anastomotic site. *Surg Gynecol Obstet.* 1981;152:777–780.
31. Henry LR, Sigurdson E, Ross E, Hoffman JP. Hydronephrosis does not preclude curative resection of pelvic recurrences after colorectal surgery. *Ann Surg Oncol.* 2005;12:786–792.
32. Austin KK, Solomon MJ. Pelvic exenteration with en bloc iliac vessel resection for lateral pelvic wall involvement. *Dis Colon Rectum.* 2009;52:1223–1233.

Validation of a Nomogram for Predicting Overall Survival After Resection of Pulmonary Metastases from Colorectal Cancer at a Single Center

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Abstract

Background The goal of this study was to validate a survival nomogram at a single center, originally developed at multiple institutions in Japan, which combines readily available preoperative variables to predict overall survival after resection of pulmonary metastases from colorectal cancer.

Methods An external patient cohort from a prospective pulmonary metastases database at the Aichi Cancer Center in Japan was used to test the validity of the pulmonary metastases from a colorectal cancer nomogram. The cohort included 58 consecutive patients who had surgery between January 1999 and December 2005. Nomogram predictions for 3- and 5-year overall survival were calculated for each patient and compared with actual survival. The concordance index was used as an accuracy measure.

Results Data for all necessary variables were available for all patients. At the last follow-up, 30 patients were alive, with a median follow-up of 39 (range, 5–94) months. The 1-, 2-, 3-, and 5-year overall survival rates were 96.6, 84.5, 70.5, and 48.9%, respectively. The nomogram concordance index was 0.81 with excellent calibration for both 3- and 5-year overall survival rates.

Conclusions The high predictive accuracy of pulmonary metastases from a colorectal cancer nomogram demonstrates that this predictive tool derived at multiple institutions can be applied to a small cohort of patients in a single center.

Introduction

Among patients who undergo curative resection for colorectal cancer, 10–20% will develop pulmonary metastases [1–3]. Surgical resection is an important component in the treatment of pulmonary metastases from colorectal cancer. The majority of institutions depend on easily accessible clinical parameters, such as tumor quantity, size, and location, to evaluate operability. However, criteria for resection of pulmonary metastases are not yet well established and reliable prognostic factors after pulmonary metastasectomy remain to be determined.

The ability to combine multiple clinically available prognostic factors in a scoring system would serve as a useful basis for clinical decision making. A nomogram is a mathematical model that utilizes prognostic variables in an attempt to calculate percentage survival in the short- and long-term. These have been developed and rigorously validated for use in soft tissue sarcomas, prostate cancer, and breast cancer [4–7]. A prognostic nomogram for pulmonary metastases from colorectal cancer was developed from a large cohort of 313 patients treated by high-volume surgeons between 1990 and 1998 at 11 major medical centers throughout Japan (Fig. 1). Performance of this model has been subsequently validated on 357 patients treated by high- and low-volume surgeons between 1990 and 2000 at another 72 hospitals in Japan. Validation of this dataset successfully demonstrated similar performance

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Fig. 1 Preoperative nomogram for patients with pulmonary metastases from colorectal cancer. With permission, *British Journal of Surgery*
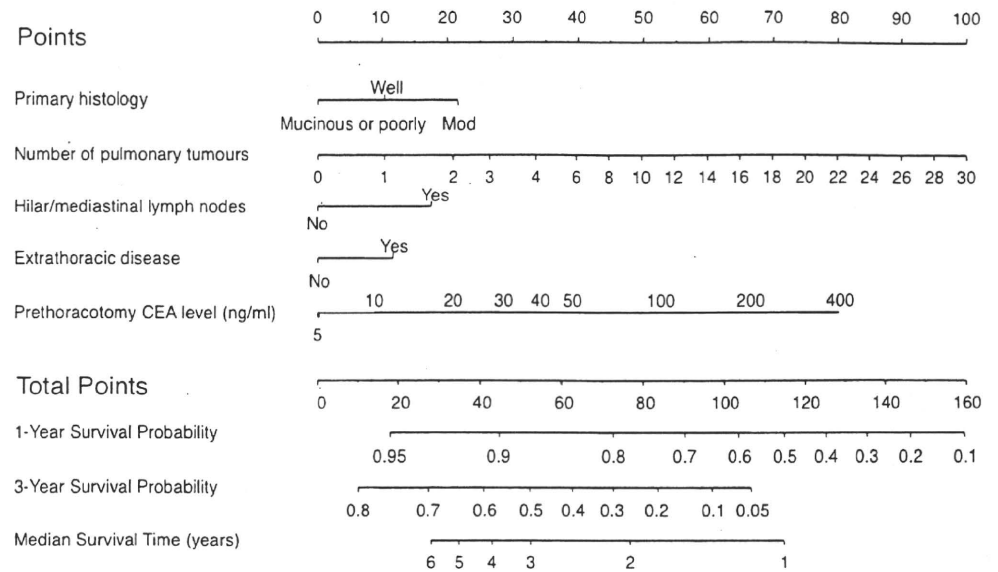
Br J Surg 2004;91:112-120

characteristics that were not significantly different from those initially developed [8].

Despite good performance of the nomogram in a separate dataset, concerns related to the generalizability of the nomogram remained. It is unclear that a prognostic nomogram developed at multiple institutions in Japan by analyzing data on patients in the past few decades pertain to a patient with pulmonary metastases from colorectal cancer whose disease was treated by recent advanced chemotherapy and surgery at a single center. Systems that are underfit may demonstrate reproducibility but not consistent transportability [9]. External validation on several cohorts is essential to ensure the universal applicability of the nomogram [10]. The goal of this study was to validate the accuracy of the colorectal cancer pulmonary metastases nomogram against an independent data series at a single cancer center.

Materials and methods

Patients included in the study

A total of 58 consecutive patients who underwent pulmonary resection for metastatic colorectal cancer at the Aichi Cancer Center between January 1999 and December 2005 were identified prospectively. Data were supplemented by retrospective case chart review. All patients had previous complete resection of primary colorectal cancer. Synchronous identification of pulmonary metastasis from colorectal cancer was found in 11 patients at diagnosis. The primary cancer was resected and these 11 patients restaged

approximately 1 month later; because CT did not reveal irresectable metastatic disease and conditions remained favorable, pulmonary resection was performed. A total of 23 patients had extrathoracic disease, including 18 with hepatic spread in conjunction with the pulmonary metastasis. Of 18 patients with both hepatic and pulmonary metastases, the liver-first approach was applied, in which resection of hepatic metastases precedes resection of the pulmonary metastases. Although patients with extrathoracic disease underwent multiple surgical resections at separate times in this way, no patients developed major complications after pulmonary resection. Principally, limited resection (wedge resection or segmentectomy) was the procedure of the choice, and normal pulmonary parenchyma was preserved as much as possible. Lobectomy was performed for multiple tumors in the same lobe or >3.0 cm in diameter. Video-assisted thoracoscopic surgery (VATS) was indicated since 1998 for metastatic lesions occupying less than one-third of the peripheral lung and with a maximum diameter of 2.0 cm. Hilar or mediastinal lymph node dissection was used to sample lymph nodes of most patients who underwent lobectomy. There were no patients treated with radiofrequency ablation. Although all patients underwent potentially curative resection, 54 of these patients (91.5%) had curative (R0) resections with negative microscopic margins. Nine patients underwent adjuvant chemotherapy (tegafur/uracil/leucovorin or tegafur/uracil) after pulmonary metastasectomy. Adjuvant use reflected the policy of individual physicians.

Criteria for pulmonary resection were: metastatic lesions confined to the lung and technically resectable, no evidence of extrathoracic metastases at the time of thoracotomy,

cardiorespiratory function capable of tolerating complete resection of all pulmonary tumors, and the primary tumor was controlled.

Contrast-enhanced helical computed tomography (chest, 2-mm slice thickness; abdomen, 5-mm slice thickness) was routinely performed to exclude patients with extrapulmonary metastases or irresectable multiple metastases. Some patients who had had surgery since 2000 in the study also underwent whole-body positron emission tomography (PET) or PET-CT scans as part of their preoperative evaluation.

Variables

Variables utilized in the colorectal cancer pulmonary metastases nomogram were primary histology (mucinous/poor, well, or moderate), number of pulmonary metastases, enlarged hilar or mediastinal lymph nodes (yes or no), extrathoracic disease (yes or no), and prethoracotomy carcinoembryonic antigen (CEA) level (ng/ml). All of these variables were routinely measured during preoperative workup. All records of the 58 patients were complete regarding the information needed for calculation of nomogram predictions.

Follow-up

All patients were seen at the outpatient clinic at 3- to 4-month intervals during the first 2 years and every 6 months thereafter for 3 years. Follow-up was complete in all patients until April 2008. Overall, median follow-up was 39 (range, 5–94) months, and median follow-up of the survivors was 51 (range, 29–89) months.

Statistical analysis

Nomogram validation comprised two activities. First, discrimination of the nomogram was quantified with the concordance index (c-index) [11]. The c-index is a modification of the area under the receiver operating characteristic curve (AUC), which was adapted to fit censored data [10]. Its interpretation is similar to that for AUC.

Second, calibration was assessed. Calibration compares the predicted probability of overall survival with the actual survival. This was performed plotting Kaplan–Meier curves for survival, stratified by nomogram prediction. Patients were categorized into quartiles of nomogram-derived risk (e.g., 0–25, 25–50, 50–75, and 75–100%). All analyses were performed using S-Plus® 2000 professional software (Statistical Sciences, Seattle, WA) with the Design and Hmisc libraries added [12].

Results

The 1-, 2-, 3-, and 5-year overall survival rates for the 58 patients were 96.6, 84.5, 70.5, and 48.9%, respectively. Wedge resection or segmentectomy was performed in 43 patients and lobectomy in 15 patients. The 5-year overall survival rates of limited resection and lobectomy were 53.5 and 37.3%, respectively ($p = 0.108$). Metastases or recurrences were identified in 35 of the 58 patients after pulmonary resection (lung, 25; liver, 8; lymph nodes, 5; local, 5; bone, 4; brain, 3; peritoneum, 1). Of these, 7 patients had surgery (lung, 4; liver, 3; local, 2), 23 received chemotherapy, and 9 received chemoradiotherapy. Various chemotherapy regimens were performed for irresectable metastases or recurrences. Basically, a 5-fluorouracil or irinotecan regimen was mainly used between 1999 and 2003. FOLFOX (infusional 5-fluorouracil/folinic acid/oxaliplatin) or FOLFIRI (infusional 5-fluorouracil/folinic acid/irinotecan) after 2004.

Descriptive statistics for two patient populations are presented in Table 1 and comprise that from the original nomogram study and our current cohort. Differences between these two cohorts included a higher rate of extrathoracic disease, a higher number of patients who had moderately differentiated adenocarcinoma, and a lower percentage of patients who had hilar or mediastinal tumor-infiltrated lymph nodes at a computed tomography in the Aichi Cancer Center (ACC) cohort.

The nomogram c-index was 0.81 when the pulmonary metastases from colorectal cancer nomogram was applied to the patients from ACC. Figure 2 illustrates Kaplan–Meier curves for patients, stratified by quartiles of predictions from the nomogram. For each of the four strata in Fig. 2, Kaplan–Meier curves remain within the boundaries of the 3- or 5-year predictions and are clearly separated ($p < 0.0001$). The predictions from the nomogram were divided into four roughly equal groups depending on their points.

Discussion

Surgical resection of pulmonary metastases is currently the treatment of choice in patients with colorectal cancer. For the most part, clinicians have made predictions nonquantitatively, working from a combination of clinical experience and published reports to decide whether to recommend surgery for a particular individual. In several studies, the number of pulmonary metastases [13–15], presence of extrathoracic disease [16], presence of hilar or mediastinal tumor-infiltrated lymph nodes [15, 17], CEA level [13, 14, 16–19], and lymphatic invasion by pulmonary tumor [20, 21] were reported as independent predictors

Table 1 Clinical characteristics of the patients in two independent cohorts

	Nomogram derivation cohort (n = 313)	ACC cohort (n = 58)
Age at thoracotomy (yr)[a]	61 (26–83) (60)	62 (36–84) (62)
Sex ratio (F:M)	130:183	31:27
Primary site		
Colon	126 (40.3)	23 (39.7)
Rectum	187 (59.7)	35 (60.3)
Histology of primary tumor		
Well-differentiated	150 (47.9)	18 (31)
Moderately differentiated	129 (41.2)	38 (65.5)
Mucinous or poorly differentiated	34 (10.9)	2 (3.5)
Metastatic lymph nodes (primary lesion)		
No	124 (39.6)	22 (37.9)
Yes	189 (60.4)	36 (62.1)
Distribution of pulmonary lesions		
Ipsilateral	236 (75.4)	45 (77.6)
Bilateral	77 (24.6)	13 (22.4)
No. of pulmonary tumors[a]	1 (1–29) (2.1)	1 (1–8) (1.8)
Size of largest pulmonary tumor (cm)[a]	2.5 (1–37) (3)	2.0 (1–8) (2.3)
Hilar or mediastinal tumor-infiltrated lymph nodes		
No	274 (87.5)	55 (94.8)
Yes	39 (12.5)	3 (5.2)
Extrathoracic disease		
No	229 (73.2)	35 (60.3)
Yes	84 (26.8)	23 (39.7)
Prethoracotomy CEA level (ng/ml)[a]	6.7 (0.6–555) (19.4)	3.3 (0.5–548) (20.2)
Interval between primary and pulmonary resection (mo)*	30.6 (−4.6 to 111.7) (35.9)	21.3 (1.7 to 117.5) (28)
Adjuvant chemotherapy		
No	228 (72.8)	49 (84.5)
Yes	85 (27.2)	9 (15.5)
Patient status		
Alive	134 (42.8)	30 (51.7)
Died from cause of other than CRC	13 (4.2)	1 (1.7)
Died from unknown cause	21 (6.7)	0 (0)
Died from CRC	141 (45)	27 (46.6)
Died from treatment complications	4 (1.3)	0 (0)
Patient treatment period	Between 1980 and 1998	Between 1999 and 2005

Data in parentheses are percentages unless otherwise indicated

ACC Aichi Cancer Center, *CEA* carcinoembryonic antigen, *CRC* colorectal cancer

[a] Data are median (range) (mean)

of mortality after thoracotomy. Previous studies vary in quality, often with conflicting findings. Unfortunately, patients rarely bear simple prognostic factors; they present with rich and complex arrays of historical, physical, and laboratory findings.

Unless clinical prediction instruments combine a substantial amount of such information, predictions about individual patients lack power and accuracy. An appropriate treatment policy should include an estimate of the baseline risk, which can be achieved with a risk model that integrates relevant prognostic features. On the basis of findings from a multi-institutional dataset in Japan, a preoperative nomogram that estimates overall survival probabilities for the 3-year period immediately after surgery was developed. Thoracotomy seems warranted for patients with a high probability of survival 3 years after operation. However, the risk of overtreating patients with a predicted life expectancy of less than 3 years after thoracotomy should be avoided because most patients die shortly after. Identifying patients with short life expectancy before treatment by using clinical parameters can prove advantageous when counseling patients and their relatives
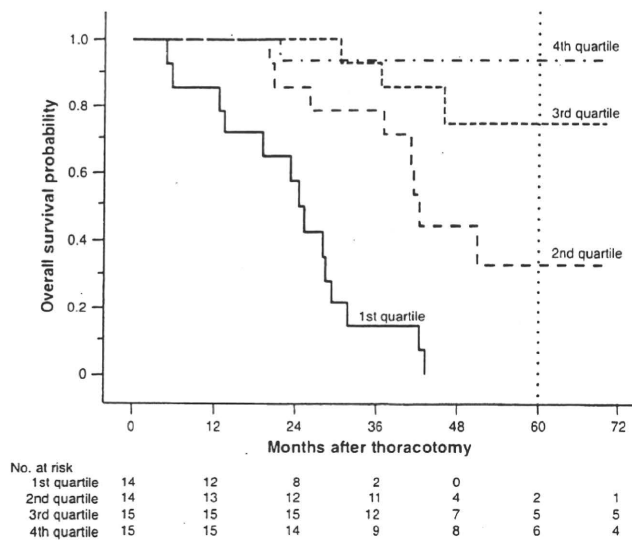
Fig. 2 Patient survival stratified by quartiles of nomogram predictions for 60-month overall survival

regarding potential therapeutic and nontherapeutic interventions. This nomogram performed consistently when applied to patients treated in a large number of institutions by contemporary internal and external validation methods [8]. External validation of published nomograms is useful because it otherwise remains unclear whether the predictive accuracy reported in the original study can be applied more universally.

A prognostic nomogram for pulmonary metastases from colorectal cancer was validated by an external cohort at a single center, at different treatment times, and with different follow-up periods in the present study. A c-index of 0.81 was generated when the multi-institutional colorectal cancer pulmonary metastases nomogram was applied to a cohort of only 58 patients. A c-index of 0.81 implies that, for 81% of randomly selected pairs of patients, the patient predicted to have a worse prognosis will actually die first. Although not perfect, this represents a high level of predictive accuracy [22]. Conversely, because of a high amount of missing data or a shorter follow-up period, the original estimates of the value of this nomogram may have been suboptimal (c-index = 0.72). Compared with the original cohort, patients in this study comprised a higher-risk population. For example, a considerably higher number had moderately differentiated adenocarcinoma as the primary tumor histology and extrathoracic disease. Despite these differences, the 5-year overall survival (48.9%) was better than that of the nomogram derivation dataset (38.3%) [8], possibly reflecting the recent progress in chemotherapy regimens and targeted agents given for metastases or recurrences after thoracotomy. The nomogram maintains accuracy when it is tested in cohorts from

different historical periods, enabling the model to account for the improved prognosis of patients treated more recently.

Recent experience has demonstrated that patients with traditionally adverse factors can experience long-term survival after liver resection. Total number of resectable metastases, whether inside or outside the liver, impacts prognostic value more than the location of the metastases. Consequently, the presence of disease outside the liver should no longer be considered a strict contraindication for liver resection, provided that the disease outside the liver is resectable [23–25]. A similar shift has occurred in the criteria of whether a macroscopically and microscopically complete (R0) resection of the lung can be achieved [21]. Watanabe et al. [21] have reported that previous or concurrent hepatectomy for liver metastases seems warranted when R0 surgery is possible for patients with pulmonary metastases from colorectal cancer. Therefore, the inclusion of extrathoracic disease into the nomogram prediction model allows for a more realistic approximation of whether a patient will be alive for a defined period of time in the ever-evolving field of multimodality treatment for advanced colorectal cancer.

A higher nomogram score was shown to be associated with poor survival. Figure 2 indicates that the quartiles of median survival predictions by the nomogram were associated with different observed period of survival ($p < 0.0001$). Although the calibration graph was difficult to depict given the small sample size, the overall actual survival of patients in the present study was found to be stratified into four risk groups based on predicted survival from the nomogram (Fig. 2). Such stratification helps to identify those who may benefit from therapy before surgery. The ability to preoperatively stratify the prognosis of patients would have the following benefits: (1) it would increase the information available to patients when obtaining their informed consent; (2) it would enable assessment of the need for perioperative chemotherapy; and (3) and it would facilitate comparative studies and clinical trials.

In summary, the nomogram for pulmonary metastases from colorectal cancer is confirmed to be predictive in a dataset independent from those previously published, and it is transportable to a smaller sized population recently treated by high-volume surgeons at a single cancer center. This study demonstrated that the combined information from five commonly used clinical variables could predict outcome in a highly accurate fashion. Patient counseling and adjuvant therapy decision-making will benefit from use of this nomogram.

Conflict of interest None.

References

1. Goya T, Miyazawa N, Kondo H et al (1989) Surgical resection of pulmonary metastases from colorectal cancer: 10-year follow-up. Cancer 64(7):1418–1421
2. Mansel JK, Zinsmeister AR, Pairolero PC et al (1986) Pulmonary resection of metastatic colorectal adenocarcinoma. A ten-year experience. Chest 89(1):109–112
3. McCormack PM, Burt ME, Bains MS et al (1992) Lung resection for colorectal metastases: 10-year results. Arch Surg 127(12): 1403–1406
4. Kattan MW, Leung DH, Brennan MF (2002) Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 20(3):791–796
5. Cripe MH, Beran LC, Liang WC et al (2006) The likelihood of additional nodal disease following a positive sentinel lymph node biopsy in breast cancer patients: validation of a nomogram. Am J Surg 192(4):484–487
6. Lambert LA, Ayers GD, Hwang RF et al (2006) Validation of a breast cancer nomogram for predicting nonsentinel lymph node metastases after a positive sentinel node biopsy. Ann Surg Oncol 13(3):310–320
7. Graefen M, Karakiewicz PI, Cagiannos I et al (2002) Validation study of the accuracy of a postoperative nomogram for recurrence after radical prostatectomy for localized prostate cancer. J Clin Oncol 20(4):951–956
8. Kanemitsu Y, Kato T, Hirai T et al (2004) Preoperative probability model for predicting overall survival after resection of pulmonary metastases from colorectal cancer. Br J Surg 91(1): 112–120
9. Lindsay MR, Ehrenberg AS (1993) The design of replicated studies. Am Stat 47:217–228
10. Justice AC, Covinsky KE, Berlin JA (1999) Assessing the generalizability of prognostic information. Ann Intern Med 130(6): 515–524
11. Harrell FE Jr, Califf RM, Pryor DB et al (1982) Evaluating the yield of medical tests. JAMA 247(18):2543–2546
12. Harrell FE (2001) Regression modeling strategies: with applications to linear models, logistic regression and survival analysis. Springer, New York
13. Zink S, Kayser G, Gabius HJ et al (2001) Survival, disease-free interval, and associated tumor features in patients with colon/ rectal carcinomas and their resected intra-pulmonary metastases. Eur J Cardiothorac Surg 19(6):908–913
14. van Halteren HK, van Geel AN, Hart AA et al (1995) Pulmonary resection for metastases of colorectal origin. Chest 107(6): 1526–1531
15. Welter S, Jacobs J, Krbek T et al (2007) Prognostic impact of lymph node involvement in pulmonary metastases from colorectal cancer. Eur J Cardiothorac Surg 31(2):167–172
16. Sakamoto T, Tsubota N, Iwanaga K et al (2001) Pulmonary resection for metastases from colorectal cancer. Chest 119(4): 1069–1072
17. Saito Y, Omiya H, Kohno K et al (2002) Pulmonary metastasectomy for 165 patients with colorectal carcinoma: a prognostic assessment. J Thorac Cardiovasc Surg 124(5):1007–1013
18. Girard P, Ducreux M, Baldeyrou P et al (1996) Surgery for lung metastases from colorectal cancer: analysis of prognostic factors. J Clin Oncol 14(7):2047–2053
19. Lee WS, Yun SH, Chun HK et al (2007) Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. Int J Colorectal Dis 22(6):699–704
20. Shiono S, Ishii G, Nagai K et al (2005) Histopathologic prognostic factors in resected colorectal lung metastases. Ann Thorac Surg 79(1):278–282
21. Watanabe K, Nagai K, Kobayashi A et al (2009) Factors influencing survival after complete resection of pulmonary metastases from colorectal cancer. Br J Surg 96(9):1058–1065
22. Murphy-Filkins R, Teres D, Lemeshow S et al (1996) Effect of changing patient mix on the performance of an intensive care unit severity-of-illness model: how to distinguish a general from a specialty intensive care unit. Crit Care Med 24(12):1968–1973
23. Minagawa M, Makuuchi M, Torzilli G et al (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 231(4):487–499
24. Elias D, Ouellet JF, Bellon N et al (2003) Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. Br J Surg 90(5):567–574
25. Elias D, Liberale G, Vernerey D et al (2005) Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. Ann Surg Oncol 12(11):900–909

REVIEW

Impact of metastatic lymph node ratio in node-positive colorectal cancer

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Abstract

Colorectal cancer (CRC) is one of the most common malignant diseases in the world. Presently, the most widely used staging system for CRC is the tumor nodes metastasis classification system, which classifies patients into prognostic groups according to the depth of the primary tumor, presence of regional lymph node (LN) metastases, and evidence of distant metastatic spread. The number of LNs with confirmed metastasis is related to the severity of the disease, but this number depends on the number of LNs retrieved, which varies depending on patient age, tumor grade, surgical extent, and tumor site. Numerous studies and a recent structured review have demonstrated associated improvements in the survival of CRC patients with increasing numbers of LNs retrieved for examination. Hence, the impact of lymph node ratio (LNR), defined as the number of metastatic LNs divided by the number of LNs retrieved, has been investigated in various malignancies, including CRC. In this editorial, we review the literature demonstrating the clinicopathological significance of LNR in CRC patients. Some reports have indicated the advantage of considering the LNR compared to the number of LNs retrieved and/or LN status. When the LNR is taken into consideration for survival analysis, the number of LNs retrieved and/or the LN status is not always found to be a prognostic factor. The cut-off points for LNRs were proposed in numerous studies. However, optimal thresholds for LNRs have not yet received consensus. It is still unclear whether the LNR has more prognostic validity than N stage. For all these reasons, the potential advantages of LNRs in the staging system should be investigated in large prospective data sets.

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INTRODUCTION

Colorectal cancer (CRC) is among the most common malignant diseases in the Western world, whereas cancers of the upper gastrointestinal tract (esophagus and stomach) and liver are more predominant in the Eastern world. However, many Asian countries, including Japan, have experienced a