TABLE 3. *Univariate predictors of positive resection margin*

Variable	Microscopic resection margin Negative	Positive	P
Gender			
Female	5	3	1.0
Male	19	14	
Age, years			
< 60	19	10	.18
≥60	5	7	
Primary cancer stage			
I/II/III	23	12	.066
IV	1	5	
Initial surgery			
Local excision, anterior resection	13	8	.76
Abdominoperineal resection	11	9	
Lymphadenectomy at initial surgery			
Conventional	20	13	.70
Extended	4	4	
Local-disease-free interval (month)			
≤12	7	9	.20
> 12	17	8	
Preoperative CEA level (ng/ml)			
≤10	16	6	.062
> 10	8	11	
Extent of preoperative pain			
None, perineum	21	9	.029
Buttock, thigh, leg	3	8	
Tumor extent			
Solitary pelvic tumor	17	7	.11
Pelvic metastasis, distant metastasis	7	10	
Largest tumor diameter (cm)			
≤5	15	9	.75
> 5	9	8	
Sacral involvement			
Adhesion	14	11	.75
Periosteum, marrow	10	6	
Pathological grade			
Well, moderate, mucinous, adenosquamous	21	16	.63
Poor, signet-ring cell	3	1	
Macroscopic growth pattern			
Solitary expanding	12	2	.018
Multiple expanding, infiltrating	12	15	
Preoperative radiation			
Yes	8	3	.31
No	16	14	

CEA, carcinoembryonic antigen.

went palliative-intent resection as a result of gross residual lung metastases were excluded from this study. Univariate analysis revealed that the incidences of microscopic positive margins were significantly higher in patients with multiple expanding or diffuse infiltrating growth (56% vs. 14%; P = .018) and in patients with pain extending to the buttock or further (72% vs. 30%; P = .029; Table 3). On multivariate analysis of the 14 dichotomized variables, excluding resection margin, multiple expanding or diffuse infiltrating growth was independently associated with positive margin (hazard ratio, 7.5 [95% confidence interval, 1.4–40]; P = .019).

TABLE 4. *Sites of first recurrence after abdominal sacral resection in 37 patients undergoing macroscopic curative resection*

Site	No. Patients (%)
Local	
Local alone	6 (24)
Local, lung	3 (12)
Local, adrenal gland	1 (4)
Local, lung, liver	1 (4)
Local, lung, pancreas	1 (4)
Local, liver, para-aortic lymph node	1 (4)
Lung	
Lung alone	5 (20)
Lung, para-aortic lymph node	2 (8)
Liver, lymph node	1 (4)
Para-aortic lymph node	1 (4)
Peritoneum	1 (4)
Brain	1 (4)
Unknown	1 (4)

Recurrence Patterns

Of the 37 patients who underwent macroscopic curative resection, 25 (68%) experienced further recurrence. Sites of their first recurrence after ASR are listed in Table 4. Of them, 13 patients (52%) had local failure, 7 (28%) had lung metastasis, and 14 (56%) had failures confined locally or to the lung. Sites of local failure were the cut end of the sacrum in five, the sacral cut end and buttock in one, and the pelvic side wall or ischium in 3. None of the 25 patients with recurrence was treatable by surgery, so these patients were given chemotherapy, radiotherapy, and/or best supportive care.

Of the 13 patients who developed local failure, 9 had positive margins, and 4 had negative margins on histological analysis. Of the 24 patients without local failure, 20 had microscopic negative margins, and 4 had microscopic positive margins. The rate for local failure was significantly higher in patients with microscopic positive margins than in those with microscopic negative margins (69% [9 of 13] vs. 17% [4 of 20]; P = .003). When the accuracy of the microscopic status of surgical margins in prediction of local failure was evaluated, the sensitivity was 69% (9 of 13), the specificity was 83% (20 of 24), the positive predictive value was 69% (9 of 13), the negative predictive value was 83% (20 of 24), and the overall accuracy rate was 78% (29 of 37). Of the 13 patients with microscopic positive margins, 9 developed local recurrence that corresponded well to histological findings, 1 experienced local failure at a different site with a positive margin, and 3 had no obvious local failure at the last follow-up.

DISCUSSION

The most effective treatment for PPR of rectal carcinoma is a curative resection, that is, complete resection with microscopic negative margins.[13,15,17–19,22] Because the tumor involves contiguous organs, including the sacrum, retained rectum, internal iliac vessels, and genitourinary organs, by either invasion or dense adhesion, combined resection of these organs—that is, ASR—is mandatory for clear surgical margins and possible cure. The overall 5-year survival rate after ASR is reported to be 25% to 31% in the largest series[13,14] and was 34% in this study. Such results have never been achieved with other therapeutic modalities, including chemotherapy and radiotherapy.[4–9]

However, morbidity and mortality after ASR are reported to be 26% to 82%[13,15–18,21,22] and 0% to 9%,[13–22] respectively. In our series, they were 61% and 2%, and 23% of our patients experienced major complications resulting in reoperation or death, and their mean hospital stay was 135 days. In addition, most patients lose genitourinary functions and must endure permanent stomas. These costs are very high and sometimes even catastrophic for those who nevertheless do not obtain long-term survival. Therefore, appropriate patient selection based on survival benefit determined on the basis of prognostic factors is necessary. Also, efforts toward seeking effective adjuvant therapy aiming at the most common sites of recurrence are mandatory. Thus, we analyzed prognostic factors and recurrence patterns after ASR in this study.

Several factors that can be estimated before surgery have been reported to be significantly associated with prognosis on either univariate or multivariate analysis. These include residual tumor extent,[13,15,17–19,22] distant metastasis,[14] initial operation,[13] disease-free interval,[14] preoperative CEA level,[13,14] preoperative CEA doubling time,[14] and proliferating cell nuclear antigen labeling index.[24] In addition, whether significant or not, there are factors definitely indicative of a poor prognosis. Wanebo et al.[13,25] reported that patients with positive margins, bone marrow involvement, or pelvic lymph node involvement had a median survival of only 10 months. Strong suspicion of such factors thus contraindicates ASR. However, the number of patients so far studied is still not sufficiently large to allow definitive patient selection criteria to be established.

We tested 15 factors in multivariate analysis because previous studies indicated their potential relationship to survival after ASR.[13–15,17–19,22,24,25] Of these, microscopic positive margins, LDFI < 1 year, and preoperative pain exceeding the buttock showed a significant independent association with a poor prognosis. Microscopic margin status is the most significant, as reported so far.[13,15,17–19,22] Of our patients with microscopic positive margins, 69% developed local recurrence, and this caused persistent pain and a poor prognosis. Although some previous studies claimed a benefit of palliative resection for both survival and pain,[26] it usually leads to a very poor prognosis and fails to relieve pain, as previously reported.[25,27] Therefore, palliative resection leaving a gross residual tumor should not be attempted. In addition to conventional imaging,[28,29] recent advances in radiological imaging, including thin-section magnetic resonance imaging[30] and multidetector row CT,[31] allow us to accurately evaluate tumor extent so that cautious interpretation can preclude such unnecessary surgery.

The extent of preoperative pain corresponds well with tumor extent and invasiveness and therefore predicts survival.[17] In this study, the survival of the patients with buttock pain was significantly worse than that of patients without pain or with perineal pain and was significantly better than that of patients with thigh or leg pain. Thigh or leg pain, caused by involvement of the first or second sacral nerves, indicates lateral and/or cephalad extension of the tumor, which usually renders curative resection impossible. Indeed, in our series, the affected patients died within 1.2 years. In contrast, if the pain remains within the buttock, there is the possibility of curative resection.

The factors relating to tumor growth rate can predict prognosis only if patients have residual tumors after ASR. Maetani et al.[14] and Onodera et al.[24] reported a significant association of disease-free interval[14] and preoperative CEA doubling time[14] with survival. These parameters reflect not only the growth rate of locally recurrent tumors, but also that of distant metastases. The proliferating cell nuclear antigen labeling index[24] can reflect a growth rate specific to local recurrence, so it may predict prognosis more accurately. Although LDFI has not been studied so far, it is easier to measure than the labeling index, and it is also specific to local recurrence. As this study showed, patients with an LDFI of > 12 months and clear surgical margins are the best candidates for ASR, and a 5-year survival of 67% can be expected. Conversely, if the LDFI is < 12 months, thus indicating rapid tumor growth, and resection is palliative, a 2-year survival of only 11% is expected. In such cases, ASR should not be attempted. Palliative resection is indicated only for patients with an LDFI of > 12 months and preferably > 18 months.[11]

Primary cancer stage, preoperative CEA level, and macroscopic growth pattern were prognostically significant only in univariate analysis in this study. Thus, they are related to any of the previously described independent factors, but they are worth considering to a certain degree when decisions are made. Macroscopic growth pattern, which has not been investigated so far, especially influences the surgical margin status and is important when deciding the extent of resection.

As our logistic regression model showed, multiple expanding or diffuse infiltrating growth is independently associated with positive resection margins. The curative resection of the tumors with multiple expanding or infiltrating growth (44%) is clearly more difficult than with solitary expanding growth (86%). Therefore, cautious evaluation of both growth pattern and tumor extent by magnetic resonance imaging or CT is needed to determine a correct line of resection.

Although tumor extent (distant and pelvic metastases)[14,25] and initial operation type[13,25] have been reported to be significant prognostic factors, this was not confirmed here, presumably at least partly because of differences in patient backgrounds and selection criteria. As described previously,[11] the presence of pulmonary, multiple liver, peritoneal, and extrapelvic lymph node metastases leads to a very poor prognosis, with a median survival of only 1.6 years in our cases, so these patients should not undergo ASR. However, solitary liver metastasis may be an exception. Indeed, in our series, two patients with solitary liver metastases survived disease free for 7.6 and 2.7 years after ASR and liver resection. In such cases, aggressive surgery seems justified.

Because adjuvant external beam radiotherapy has been reported to be beneficial for local control and prolongation of survival in primary rectal carcinoma,[32,33] many surgeons have recommended its application for ASR.[13,15–18,20] In this multivariate study, however, a prognostic benefit of preoperative radiotherapy could not be detected. This may be at least partly caused by the small number of patients, so further investigation is necessary. Marijnen et al.[34] reported that preoperative radiotherapy for primary rectal cancer has a beneficial effect in patients with more than 1-mm resection margins but that it cannot compensate for microscopically nonradical resection resulting in positive margins. Therefore, preoperative radiation should be given only to patients for whom surgical margins are expected to be attained but insufficient.

The situation with intraoperative radiotherapy may be different.[13,15–17] Hahnloser et al.[17] reported that the overall 5-year survival rate of patients undergoing palliative resection and intraoperative radiotherapy with or without external beam radiotherapy was 21%. Survival rates for their patients with no fixation, one fixation, two fixations, and three or more fixations were 43%, 24%, 20%, and 0%, respectively. Although candidates for ASR usually have two or more fixations and the expected survival of those with positive margins is not good, intraoperative radiotherapy may benefit those undergoing ASR despite a positive margin.

As to recurrence patterns after ASR, this study showed that, in 56% of our patients, recurrence was confined locally or to the lung. Wanebo et al.[13] reported this to be the case for 68% of their series, in line with other previous studies.[35,36] Thus, in addition to precise resection based on precise evaluation of tumor extent with thin-section magnetic resonance imaging or multidetector row CT, adjuvant therapies aiming at local and lung recurrences may be necessary. For local control, preoperative and intraoperative radiotherapy may be helpful. For lung metastases, systemic adjuvant chemotherapy using 5-fluorouracil–based chemotherapy or newly developed drugs (or their combination) may be effective.[5,6]

Although this retrospective exploratory study featured only a relatively small number of patients, we conclude that ASR is beneficial for a selected subset of patients in terms of survival prolongation and even cure. To select appropriate patients, evaluation of resection margin, LDFI, pain extent, and growth pattern is important. To improve survival, adjuvant treatment should be aimed at local and lung recurrences.

ACKNOWLEDGMENTS

Supported by a Grant-in-Aid for Clinical Research for Evidence Based Medicine and a Grant-in-Aid for Cancer Research from the Ministry of Health Labour and Welfare and a grant from the Foundation for Promotion of Cancer Research in Japan.

REFERENCES

1. Stearns MWJ. Diagnosis and management of recurrent pelvic malignancy following combined abdominoperineal resection. *Dis Colon Rectum* 1980; 23:359–61.
2. Wanebo HJ, Whitehill R, Gaker D, Wang GJ, Morgan R, Constable W. Composite pelvic resection, an approach to advanced pelvic cancer. *Arch Surg* 1987; 122:1401–6.

3. Wanebo HJ, Koness RJ, Turk PS, Cohen SI. Composite resection of posterior pelvic malignancy. *Ann Surg* 1992; 215:685–95.
4. Pearlman NW, Stiegmann GV, Donohue RE. Extended resection of fixed rectal cancer. *Cancer* 1989; 63:2438–41.
5. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. *BMJ* 2000; 321:531–5.
6. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005; 352:476–87.
7. Hoffman JP, Riley L, Carp NZ, Litwin S. Isolated locally recurrent rectal cancer: a review of incidence, presentation, and management. *Semin Oncol* 1993; 20:506–19.
8. Lingareddy V, Ahmad NR, Mohiuddin M. Palliative reirradiation for recurrent rectal cancer. *Int J Radiat Oncol Biol Phys* 1997; 38:785–90.
9. Wong CS, Cummings BJ, Brierley JD, et al. Treatment of locally recurrent rectal carcinoma: results and prognostic factors. *Int J Radiat Oncol Biol Phys* 1998; 40:427–35.
10. Cohen AM, Minsky BD. Aggressive surgical management of locally advanced primary and recurrent rectal cancer. *Dis Colon Rectum* 1990; 33:432–8.
11. Wanebo HJ, Marcove RC. Abdominal sacral resection of locally recurrent rectal cancer. *Ann Surg* 1981; 194:458–71.
12. Brunschwig A, Barber HR. Pelvic exenteration combined with resection of segments of bony pelvis. *Surgery* 1969; 65:417–20.
13. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: technical considerations and outcomes. *Dis Colon Rectum* 1999; 42:1438–48.
14. Maetani S, Onodera H, Nishikawa T, et al. Significance of local recurrence of rectal cancer as a local or disseminated disease. *Br J Surg* 1998; 85:521–13.
15. Mannaerts GH, Rutten HJ, Martijn H, Groen GJ, Hanssens PE, Wiggers T. Abdominosacral resection for primary irresectable and locally recurrent rectal cancer. *Dis Colon Rectum* 2001; 44:806–14.
16. Magrini S, Nelson H, Gunderson LL, Sim FH. Sacropelvic resection and intraoperative electron irradiation in the management of recurrent anorectal cancer. *Dis Colon Rectum* 1996; 39:1–9.
17. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. *Ann Surg* 2003; 237:502–8.
18. Pearlman NW, Stiegmann GV, Donohue RE. Extended resection of fixed rectal cancer. *Cancer* 1989; 63:2438–41.
19. Schiessel R, Wunderlich M, Herbst F. Local recurrence of colorectal cancer: effect of early detection and aggressive surgery. *Br J Surg* 1986; 73:342–4.
20. Temple WJ, Ketcham AS. Sacral resection for control of pelvic tumors. *Am J Surg* 1992; 163:370–4.
21. Takagi H, Morimoto T, Hara S, Suzuki R, Horio S. Seven cases of pelvic exenteration combined with sacral resection for locally recurrent rectal cancer. *J Surg Oncol* 1986; 32:184–8.
22. Yamada K, Ishizawa T, Niwa K, Chuman Y, Aikou T. Pelvic exenteration and sacral resection for locally advanced primary and recurrent rectal cancer. *Dis Colon Rectum* 2002; 45:1078–84.
23. 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; 47:2047–53.
24. Onodera H, Maetani S, Kawamoto K, Kan S, Kondo S, Imamura M. Pathologic significance of tumor progression in locally recurrent rectal cancer: different nature from primary cancer. *Dis Colon Rectum* 2000; 43:775–81.
25. Wanebo HJ, Koness RJ, Vezeridis MP, Cohen SI, Wrobleski DE. Pelvic resection of recurrent rectal cancer. *Ann Surg* 1994; 220:586–95.
26. Deckers PJ, Olsson C, Williams LA, Mozden PJ. Pelvic exenteration as palliation of malignant disease. *Am J Surg* 1976; 131:509–15.
27. Cunningham JD, Enker W, Cohen A. Salvage therapy for pelvic recurrence following curative rectal cancer resection. *Dis Colon Rectum* 1997; 40:393–400.
28. de Lange EE, Fechner RE, Wanebo HJ. Suspected recurrent rectosigmoid carcinoma after abdominoperineal resection: MR imaging and histopathologic findings. *Radiology* 1989; 170:323–8.
29. Farouk R, Nelson H, Radice E, Mercill S, Gunderson L. Accuracy of computed tomography in determining resectability for locally advanced primary or recurrent colorectal cancers. *Am J Surg* 1998; 175:283–7.
30. Brown G, Richards CJ, Newcombe RG, et al. Rectal carcinoma: thin-section MR imaging for staging in 28 patients. *Radiology* 1999; 211:215–22.
31. Fletcher JG, Johnson CD, Krueger WR, et al. Contrast-enhanced CT colonography in recurrent colorectal carcinoma: feasibility of simultaneous evaluation for metastatic disease, local recurrence, and metachronous neoplasia in colorectal carcinoma. *AJR Am J Roentgenol* 2002; 178:283–90.
32. Gastrointestinal Tumor Study Group Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 1985; 312:1465–72.
33. Påhlman L. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997; 336:980–7.
34. Marijnen CA, Nagtegaal ID, Kapiteijn E, et al. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* 2003; 55:1311–20.
35. Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. *Dis Colon Rectum* 2002; 45:585–92.
36. Maetani S, Nishikawa T, Iijima Y, et al. Extensive en bloc resection of regionally recurrent carcinoma of the rectum. *Cancer* 1992; 69:2876–83.

Original Paper

Digestive Surgery

Dig Surg 2007;24:375–381
DOI: 10.1159/000107779

Received: October 4, 2006
Accepted: April 4, 2007
Published online: August 31, 2007

Impact of Upward Lymph Node Dissection on Survival Rates in Advanced Lower Rectal Carcinoma

Keisuke Uehara Seiichiro Yamamoto Shin Fujita Takayuki Akasu Yoshihiro Moriya

Division of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan

Key Words

Lymph node dissection · Upward lymph node dissection · Lower rectal carcinoma

Abstract

Background/Aims: This study investigated appropriate level of upward lymph node (LN) dissection in advanced lower rectal carcinoma. ***Methods:*** A total of 285 consecutive patients with stage II/III lower rectal carcinoma were analyzed. LN dissection was classified as follows: division of the root of the superior rectal artery (UD2), division of the root of the inferior mesenteric artery (UD3) and UD3 with para-aortic LN dissection (UD4). ***Results:*** LN metastases at the root of the inferior mesenteric artery were found in 4 patients. Their prognoses were worse than those of the other stage III patients ($p = 0.011$). On the other hand, LN metastases along the superior rectal artery were discovered in 14 patients, whose 5-year overall survival rate was 61.2%. By removing the LNs either UD2 or UD3/4, a similar survival rate was achieved in stage III patients with LN metastases along the superior rectal artery. ***Conclusion:*** Survival of a minority with metastatic LNs at the root of the inferior mesenteric artery was poor. Additionally, survival is no worse in patients with positive LN along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. Low ligation is adequate for advanced lower rectal carcinoma.

Introduction

It is well known that lower rectal carcinoma has two routes of lymphatic spread, i.e. upward and lateral spread. There have been many reports that discuss the significance of lateral pelvic lymph node dissection for advanced lower rectal carcinoma [1–4]. However, there have not been any definitive conclusions and various opinions have been expressed around the world. On the other hand, the impact of upward lymph node dissection for sigmoid colon or upper rectal carcinoma has been discussed in several reports [5–7], and yet few studies have focused on this issue in advanced lower rectal carcinoma. Although Pezim et al. [8] reported that high ligation of the inferior mesenteric artery had no survival advantage for rectal carcinoma patients, no counterarguments have been published and it remains difficult to generalize about the impact of upward lymph node dissection. The appropriate extent of upward lymph node dissection for advanced lower rectal carcinoma remains an unsolved issue and guidelines need to be established.

This study presents a detailed estimation of how the level of upward lymph node dissection affects survival rates following curative resection in advanced lower rectal carcinoma.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/dsu

Seiichiro Yamamoto
Division of Colorectal Surgery, National Cancer Center Hospital
5-1-1, Tsukiji, Chuo-ku
Tokyo 104-0045 (Japan)
Tel. +81 3 3542 2511, Fax +81 3 3542 3815, E-Mail seyamamo@ncc.go.jp

Patients and Methods

Between 1990 and 2002, a series of 303 consecutive patients at the National Cancer Center Hospital, Tokyo, underwent curative surgery for stage II or III lower rectal carcinoma. Lower rectal carcinoma was defined as a tumor with a distal margin 7 cm or less from the dentate line by digital examination and/or proctoscopy. Five patients with a history of malignancy (sigmoid colon carcinoma in 3 and bladder carcinoma in 2), who previously underwent lymph node dissection along the inferior mesenteric artery or in the lateral pelvis, were excluded, because the routes of lymphatic spread seemed to be changed in these cases. Two patients with synchronous advanced rectosigmoid carcinoma were excluded. Three stage II patients and 8 stage III patients did not undergo lymph node dissection along the inferior mesenteric artery but only in the mesorectum (UD1), because of preoperative underestimation. These 11 patients were also excluded. Consequently, 285 patients were eligible for this study. The mean (SD) distance from the dentate line of the tumor was 2.4 (1.0) (range 0.0–7.0) cm. No patients received preoperative radiotherapy and/or chemotherapy. All patients were evaluated before surgery by total colonoscopy, barium enema and computed tomography. To evaluate comorbid conditions, cardiopulmonary function and renal function tests were performed. In our study, lateral pelvic lymph nodes were regarded as regional lymph nodes according to the Japanese classification of colorectal carcinoma [9], although lateral pelvic lymph node metastases are regarded as distant metastases in the TNM classification system [10]. Clinical stage II or III middle or lower rectal carcinoma, located at or below the peritoneal reflection, is an indication for lateral pelvic lymph node dissection in our hospital [2, 3]. Postoperative adjuvant chemotherapy using oral or intravenous fluoropyrimidines was administered for 6 months to 27 stage III patients. Two stage III patients received postoperative radiotherapy and another underwent concomitant chemoradiotherapy.

The incidence of upward lymph node metastases based on histopathological data from the resected specimen, recurrence sites and survival rate were retrospectively analyzed and the appropriate extent of upward lymph node dissection for advanced lower rectal carcinoma was evaluated.

Classification of the Level of Upward Lymph Node Dissection

Standard surgical procedures at our institution were previously reported in detail [11, 12]. The extent of upward lymph node dissection was classified as follows: UD1 is defined as resection of the mesorectum, UD2 as division of the root of the superior rectal artery with lymph node dissection below that level, UD3 as division of the root of the inferior mesenteric artery with lymph node dissection below that level and UD4 as UD3 with the addition of para-aortic lymph node dissection (fig. 1) [12]. The level of upward lymph node dissection was determined by preoperative and intraoperative findings. When a patient was diagnosed as stage I, UD1 to UD2 lymph node dissection was performed. UD2 to UD4 lymph node dissection was performed for patients with stage II or III tumor. UD4 was performed until the first half of the 1990s, but has not been performed thereafter because of excessive operative time, blood loss and a high incidence of postoperative sexual dysfunction, especially in males [11, 13, 14].

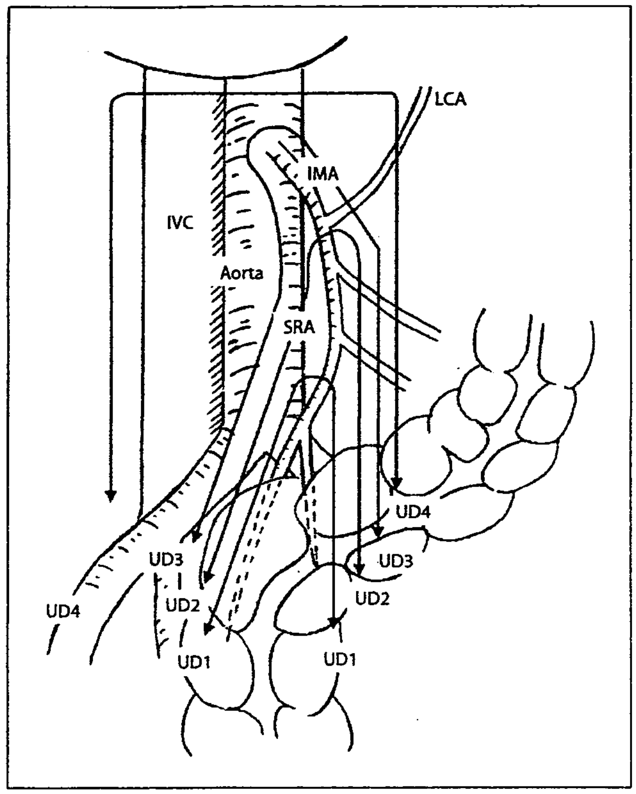

Fig. 1. Classification of the level of upward lymph node dissection. UD1 is defined as resection of the mesorectum; UD2 as division of the root of the superior rectal artery (SRA) and lymph node dissection below this level; UD3 as division of the root of the inferior mesenteric artery (IMA) and lymph node dissection below this level; and UD4 as UD3 with para-aortic lymph node dissection. IVC = Inferior vena cava; LCA = left colic artery.

Statistical Analysis

Survival curves were traced using the Kaplan-Meier method. The differences between curves were tested using the log-rank test. Comparisons between groups were performed using χ^2 test. $p < 0.05$ was considered significant. All statistical calculations were made using SPSS computer software (SPSS 11.0, SPSS Inc., Chicago, Ill., USA).

Results

The characteristics of 285 patients according to the UD classification are shown in table 1. There were 78 (27.4%), 133 (46.7%) and 74 (26.0%) patients who underwent UD2, UD3 and UD4, respectively. All patients were followed up until death or for at least 3 years with a mean follow-up period of 66 months. The rate of sphincter-pre-

Table 1. Patient characteristics according to the UD classification

	Total (n = 285)	UD2 (n = 78)	UD3 (n = 133)	UD4 (n = 74)
Age, years (mean)	58.2	58.1	58.2	58.4
Sex ratio (male:female)	191:94	53:25	90:43	48:26
Follow-up period (mean)	66	59	57	88[a, c]
Surgical procedure				
Sphincter-preserving surgery	143 (50.2)	53 (67.9)	64 (48.1)	26 (35.1)[a, b]
Non-sphincter-preserving surgery	142 (49.8)	25 (23.1)	69 (51.9)	48 (64.9)
Lateral LNs dissection				
No	68 (23.9)	32 (41.0)	31 (23.3)	5 (6.8)[d]
Yes	217 (76.1)	46 (59.0)	102 (76.7)	69 (93.2)
Evaluated LN, n (mean)	42	31	39	57[d]
Metastatic LN, n (mean)	3	2	3	3
TNM classification				
Stage II	94 (33.0)	29 (37.2)	38 (28.6)	27 (36.5)
Stage III	191 (67.0)	49 (62.8)	95 (71.4)	47 (63.5)

Values in parentheses are percentages.
[a] $p < 0.05$ UD2 vs. UD3, [b] $p < 0.05$ UD2 vs. UD4, [c] $p < 0.05$ UD3 vs. UD4, [d] $p < 0.05$ between each UD classification.

serving surgery was higher in UD2 patients than in those who underwent UD3 or UD4. The rate of undergoing lateral lymph node dissection and the number of evaluated lymph nodes increased significantly with the extension of upward lymph node dissection. However, there were no significant differences in the number of metastatic lymph nodes and the ratio of stage II to III among UD classifications.

In each TNM stage, the overall survival curves in relation to the extent of upward lymph node dissection were evaluated and there were no significant differences according to the extent of upward lymph node dissection (fig. 2). Recurrence sites after curative resection are demonstrated in table 2. In both groups with or without lymph node dissection at the root of the inferior mesenteric artery, the lung was the most common site of recurrence followed by the liver. Recurrence sites did not significantly differ between the groups, including para-aortic or mediastinal lymph node metastases.

Table 3 summarizes the characteristics and outcomes of 4 patients with lymph node metastases at the root of the inferior mesenteric artery. They accounted for 1.9% of the 207 patients who underwent UD3 or UD4. Recurrences developed in all cases and their prognoses were significantly worse than those of the other stage III patients who underwent UD3 or UD4 ($p = 0.011$) (fig. 3). None of 4 patients survived for 5 years.

Table 2. Recurrent sites after curative resection

Recurrent site	UD2 (n = 78)	UD3/UD4 (n = 207)	p value
Lung	16 (20.5)	36 (17.4)	0.543
Liver	6 (7.7)	19 (9.2)	0.692
Pelvic cavity	7 (9.0)	15 (7.2)	0.626
Para-aortic or mediastinal LNs	3 (3.8)	4 (1.9)	0.352

Values in parentheses are percentages.

On the other hand, lymph node metastases along the superior rectal artery were discovered in 14 patients, excluding 3 patients with metastatic lymph nodes at the root of the inferior mesenteric artery, and table 4 shows their characteristics. They accounted for 4.9% of all patients. Ten patients developed recurrence and the lung was the most common site (6 patients), followed by the liver (2 patients). The 5-year overall survival rate was 61.2% in this group and there were no significant differences in overall survival among the patients with and without lymph node metastases along the superior rectal artery ($p = 0.338$) (fig. 4a). In addition, there were no significant differences in survival of the patients with lymph node metastases along the superior rectal artery according to the extension of upward lymph node dissection performed (UD2 or UD3/4) ($p = 0.642$) (fig. 4b).

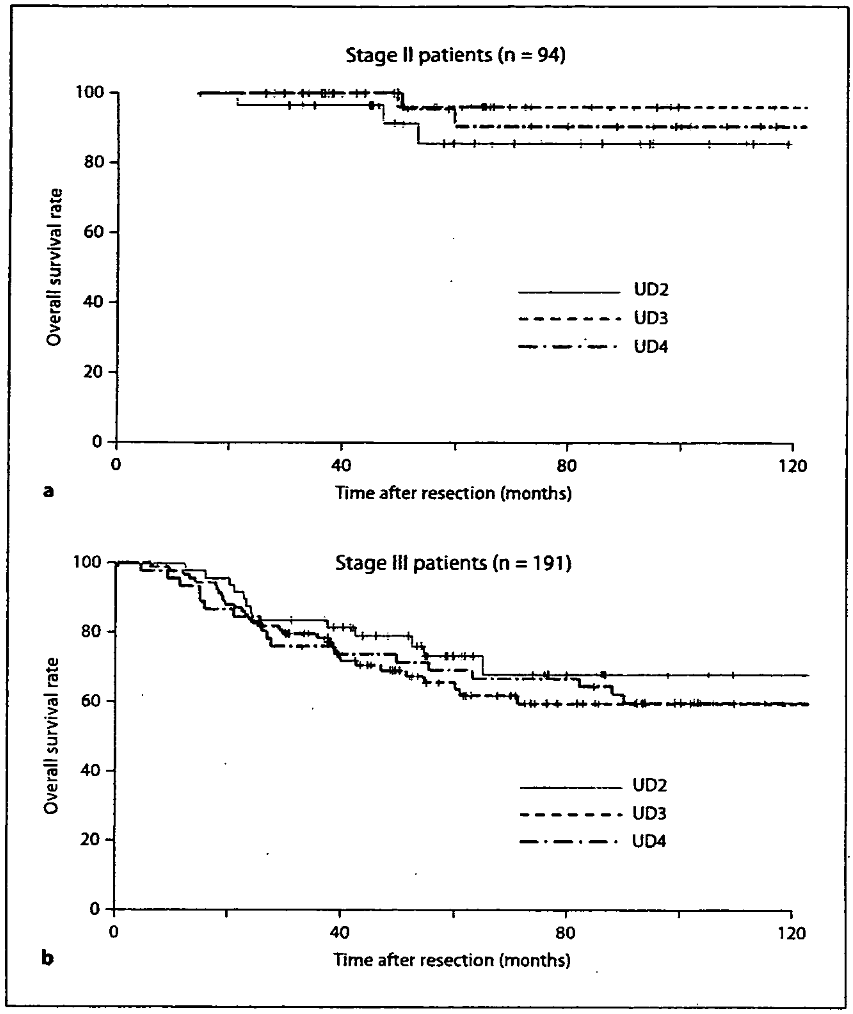

Fig. 2. Overall survival curves in relation to the extent of upward lymph node dissection at each stage: (**a**) stage II and (**b**) stage III. There were no significant differences in each stage.

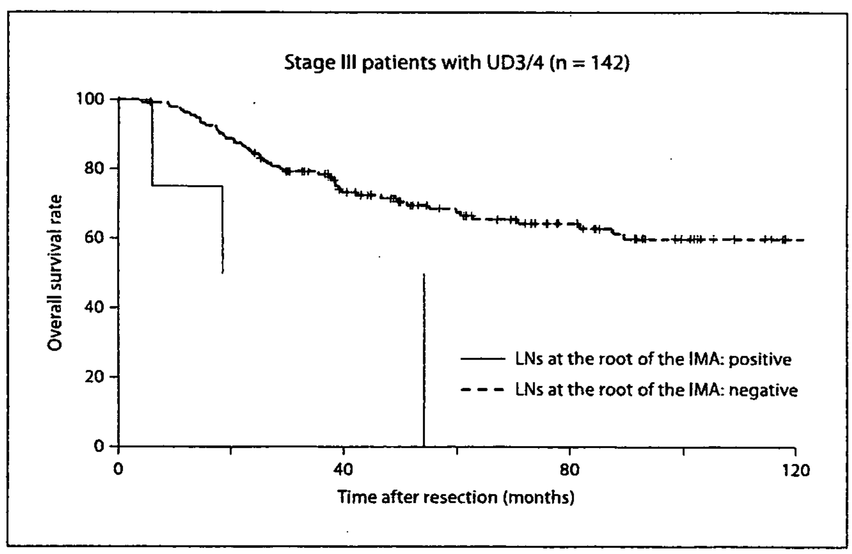

Fig. 3. Overall survival curves for the stage III patients with or without metastatic lymph nodes at the root of the inferior mesenteric artery (IMA). The former was significantly worse than the latter (p = 0.011).

Table 3. Characteristics of the patients with metastatic LNs at the root of the inferior mesenteric artery

Age	Sex	UD	Histology	pT	Metastatic LNs, n	Recurrent site	Disease-free time, months	Outcome months
33	F	3	well-differentiated adenocarcinoma	pT3	3	lung, bone	25	died (54)
64	F	3	moderately differentiated adenocarcinoma	pT3	4	lung	22	alive with recurrent tumor (39)
51	M	3	poorly differentiated adenocarcinoma	pT3	25	pelvic cavity	11	died (19)
57	M	3	poorly differentiated adenocarcinoma	pT3	16	pelvic cavity, peritonium	4	died (6)

Discussion

Surgical decisions regarding upward lymph node dissection for advanced lower rectal carcinoma remain controversial. In our study, patients with metastatic lymph nodes at the root of the inferior mesenteric artery comprised a small minority (4 patients, 1.9%) and their prognoses were very poor. Their prognoses seemed to be almost equal to those of patients who underwent UD4 dissection and were pathologically proven to have metastatic para-aortic lymph node, although such patients are classified as stage IV in TNM classification and were excluded from this study. Furthermore, we could not demonstrate an effect of prophylactic lymph node dissection at the root of the inferior mesenteric artery in patients with any stage of disease. Moreover, lymph node dissection without the root of the inferior mesenteric artery did not result in increased para-aortic or mediastinal lymph node metastases, which we had thought might be caused by failing to perform lymph node dissection. We conclude that lymph node dissection at the root of the inferior mesenteric artery does not provide any survival advantage for patients with advanced lower rectal carcinoma and metastatic lymph nodes at this level have systematic disease.

Likewise, there were also a small number of patients with metastatic lymph nodes along the superior rectal artery (14 patients, 4.9%) and the positive rate was far below the rate of lateral lymph nodes (55 of 217 patients who underwent lateral lymph node dissection, 25.3%) in this series. However, the 5-year overall survival rate in this group was 61.2% and there were no significant differences among stage III patients with and without lymph node metastases along the superior rectal artery. In addition, survival is no worse in patients with positive lymph node along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. We conclude that UD2 lymph node dissection is adequate even for stage III patients with lymph node metastases along the superior rectal artery.

Table 4. Characteristics of the patients with metastatic LNs along the SRA (exception for three with metastatic LNs at the root of the IMA)

Patients		14
Age, years (mean)		58.8
Sex ratio (male:female)		12:2
Upward LNs dissection	UD2	4
	UD3	6
	UD4	4
Lateral LNs dissection	no	5
	unilateral pelvic	2
	bilateral pelvic	7
pT category in TNM classification	pT1	2
	pT2	2
	pT3	7
	pT4	3
pN category in TNM classification	pN1	7
	pN2	7
Recurrence	yes	10
	no	4

SRA = Superior rectal artery; IMA = inferior mesenteric artery.

There are some problems with the existing classifications of rectal carcinoma. TNM classification considers lymph nodes at the root of the inferior mesenteric artery as regional lymph nodes for colorectal carcinoma without regard to the location of the tumors, as well as lymph nodes along the superior rectal artery [10]. Under this classification, patients with metastatic regional lymph nodes are regarded as stage III and are subcategorized into three groups by the depth of tumor invasion and number of metastatic lymph nodes, not by the location of metastatic lymph nodes. The problem with this classification is that we cannot distinguish whether stage III patients have lymph node metastases at the root of the inferior mesenteric artery.

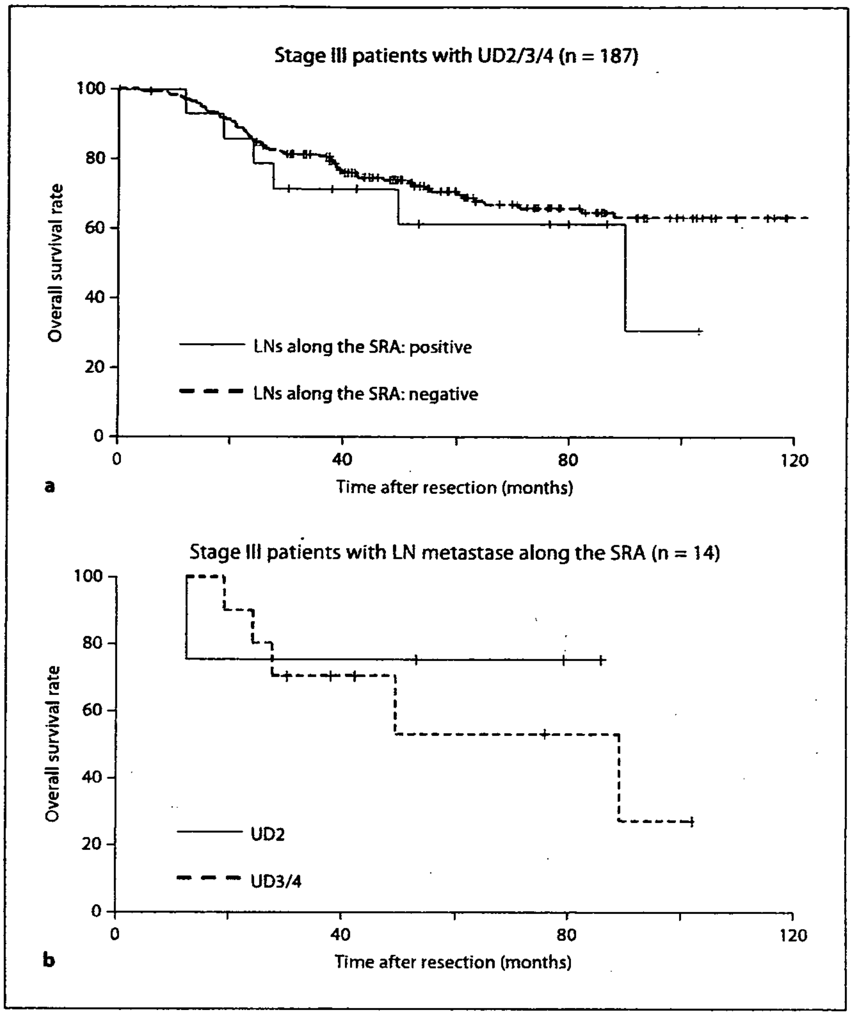

Fig. 4. **a** Overall survival curves for stage III patients with or without metastatic lymph nodes along the superior rectal artery, excluding 4 patients with lymph node metastases at the root of the inferior mesenteric artery. There were no significant differences in overall survival between both groups (p = 0.338). **b** Overall survival curves in relation to the extent of upward lymph node dissection for stage III patients with metastatic lymph nodes along the superior rectal artery, excluding 3 patients with lymph node metastases at the root of the inferior mesenteric artery. There were no significant differences in survival of the patients with lymph node metastases along the superior rectal artery according to the extension of upward lymph node dissection performed (UD2 or UD3/4) (p = 0.642).

In comparison, the Japanese classification of colorectal carcinoma [9] treats regional lymph nodes in rectal carcinoma as follows: pararectal lymph nodes are defined as group 1, lymph nodes along the superior rectal artery as intermediate lymph nodes (group 2) and lymph nodes at the root of the inferior mesenteric artery as the main lymph nodes (group 3). However, this classification defines patients with metastatic lymph nodes in group 2 and/or group 3 as same stage (stage IIIb). Based on the results of this study, these criteria should be reevaluated.

In recent years, sphincter-preserving surgery has been increasingly adopted in patients with lower rectal carcinoma [15, 16]. The most important postoperative complication in this procedure is anastomotic leakage. To avoid this complication, all colorectal surgeons pay attention to blood flow in the remnant colon, together with the tension of the anastomosis. Therefore, Western surgeons perform mobilization of the splenic flexure for most patients [17], but the position of the splenic flexure in Japanese is usually very deep in the left upper subphrenic area and it is sometimes rather difficult to mobilize the left side colon. However, Japanese patients usually have a long sigmoid colon, and if the surgeon preserves 1 or 2 arcades of marginal vessels of the sigmoid colon by dividing the sigmoid artery between the superior rectal artery and these marginal vessels, mobilization of the splenic flexure becomes unnecessary. In this situation, arterial blood flow is not being compensated. Preservation of the blood flow of the left colic artery is one solution to this problem, because the appropriate extent of upward lymph node dissection for lower rectal carcinoma is considered to be UD2. When the length of the vascular pedicle for lower anastomosis is short, we can cut the periphery of the left colic artery. Some surgeons choose left colic artery-preserving lymph node dissection at the root of the inferior mesenteric artery, but this increases the risk of damaging the lumbar splanchnic nerve.

Another problem encountered with lymph node dissection for lower rectal surgery is lateral lymph node dissection. Some reports mainly from Japan have supported the effectiveness of lateral pelvic lymph node dissection, and it is well established as the standard procedure in leading hospitals in Japan. However, in Western countries, the survival benefits of lateral pelvic lymph node dissection are regarded as doubtful. Instead, preoperative chemoradiotherapy is widely performed [18, 19]. To resolve this disparity, a multicentric randomized clinical trial that compares lateral pelvic lymph node dissection with autonomic nerve preservation to total mesenteric excision (JCOG-0212) is underway in Japan and data regarding this issue will become available in the near future [20].

In conclusion, survival of a minority with metastatic lymph nodes at the root of the inferior mesenteric artery was very poor. In addition, survival is no worse in patients with positive lymph node along the superior rectal artery as long as these positive nodes are resected by either UD2 or UD3/4. Surgeons should take these data into consideration and recognize that low ligation is adequate for advanced lower rectal carcinoma.

References

▶1 Moriya Y, Sugihara K, Akasu T, Fujita S: Nerve-sparing surgery with lateral node dissection for advanced lower rectal cancer. Eur J Cancer 1995;31A:1229–1232.

▶2 Moriya Y, Sugihara K, Akasu T, Fujita S: Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. World J Surg 1997;21: 728–732.

▶3 Fujita S, Yamamoto S, Akasu T, Moriya Y: Lateral pelvic lymph node dissection for advanced lower rectal cancer. Br J Surg 2003; 90:1580–1585.

▶4 Ueno M, Oya M, Azekura K, Yamaguchi T, Muto T: Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. Br J Surg 2005;92:756–763.

▶5 Shida H, Ban K, Matsumoto M, Masuda K, Imanari T, Machida T, Yamamoto T: Prognostic significance of location of lymph node metastases in colorectal cancer. Dis Colon Rectum 1992;35:1046–1050.

▶6 Surtees P, Ritchie JK, Phillips RK: High versus low ligation of the inferior mesenteric artery in rectal cancer. Br J Surg 1990;77:618–621.

▶7 Slanetz CA Jr, Grimson R: Effect of high and intermediate ligation on survival and recurrence rates following curative resection of colorectal cancer. Dis Colon Rectum 1997; 40:1205–1218.

▶8 Pezim ME, Nicholls RJ: Survival after high or low ligation of the inferior mesenteric artery during curative surgery for rectal cancer. Ann Surg 1984;200:729–733.

9 Japanese Society for Cancer of the Colon and Rectum: Japanese Classification of Colorectal Carcinoma, ed 1. Tokyo, Kanehara, 1997.

10 International Union against Cancer: TNM classification of malignant tumours, ed 6. New York, Wiley-Liss, 2002.

11 Moriya Y: Pelvic node dissection with autonomic nerve sparing for invasive lower rectal cancer: Japanese experience; in Wanebo HJ (ed): Colorectal Cancer. St. Louis, Mosby, 1993, pp 274–289.

12 Akasu T, Moriya Y: Abdominopelvic lymphadenectomy with autonomic nerve preservation for carcinoma of the rectum: Japanese experience; in Wanebo HJ (ed): Surgery for Gastrointestinal Cancer: A Multidisciplinary Approach. Philadelphia, Lippincott-Raven, 1997, pp 667–680.

▶13 Maas CP, Moriya Y, Steup WH, Kiebert GM, Kranenbarg WM, van de Velde CJ: Radical and nerve-preserving surgery for rectal cancer in The Netherlands: a prospective study on morbidity and functional outcome. Br J Surg 1998;85:92–97.

▶14 Sugihara K, Moriya Y, Akasu T, Fujita S: Pelvic autonomic nerve preservation for patients with rectal carcinoma: oncologic and functional outcome. Cancer 1996;78:1871–1880.

▶15 Schiessel R, Novi G, Holzer B, Rosen HR, Renner K, Holbling N, Feil W, Urban M: Technique and long-term results of intersphincteric resection for low rectal cancer. Dis Colon Rectum 2005;48:1858–1867.

▶16 Rullier E, Laurent C, Bretagnol F, Rullier A, Vendrely V, Zerbib F: Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. Ann Surg 2005;241: 465–469.

17 Milson JW, Stolfi VM: Low rectal and midrectal cancers; in Wanebo HJ (ed): Colorectal Cancer. St. Louis, Mosby, 1993, pp 214–241.

▶18 Rullier E, Goffre B, Bonnel C, Zerbib F, Caudry M, Saric J: Preoperative radiochemotherapy and sphincter-saving resection for T3 carcinomas of the lower third of the rectum. Ann Surg 2001;234:633–640.

▶19 Schaffer M, Thoma M, Wilkowski R, Schaffer P, Duhmke E: Radio-chemotherapy as a preoperative treatment for advanced rectal cancer: evaluation of down-staging and morbidity. Onkologie 2002;25:352–356.

20 http://clinicaltrials.gov/ct/gui/show/NCT00190541 [ClinicalTrials.gov web site]. Accessed October 4, 2006.

Available online at www.sciencedirect.com
ScienceDirect
EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO 33 (2007) 741–745
www.ejso.com

Outcomes of hepatic artery infusion therapy for hepatic metastases from colorectal carcinoma after radiological placement of infusion catheters

S. Sameshima [a,*], H. Horikoshi [b], K. Motegi [c], S. Tomozawa [a], I. Hirayama [a], T. Saito [a], T. Sawada [a]

[a] Department of Surgery, Gunma Prefectural Cancer Center, 617-1 Takabayashi-nishi, Ota, Gunma 373-8550, Japan
[b] Department of Diagnostic Radiology, Gunma Prefectural Cancer Center, 617-1 Takabayashi-nishi, Ota, Gunma 373-8550, Japan
[c] Department of Gastroenterology, Gunma Prefectural Cancer Center, 617-1 Takabayashi-nishi, Ota, Gunma 373-8550, Japan

Accepted 12 February 2007
Available online 30 March 2007

Abstract

Aim: The aim of this study is to evaluate the safety and efficacy of hepatic artery infusion (HAI) of 5-fluorouracil (5FU) for patients with liver metastases from colorectal carcinoma after radiological placement of infusion catheters.
Methods: Forty-two patients with liver metastases from colorectal carcinoma received radiological placement of infusion catheters using the distal fixation method. They received continuous HAI of 5FU 1000–1500 mg for 5 h weekly or biweekly. Tumor status was assessed by chest-abdominal computed tomography (CT) scan after every 10 infusions. Hepatic perfusion was checked by CT arteriography via the infusion port after every 10 infusions.
Results: Radiological placements of catheters were performed successfully in all cases. Each patient received an average of 36 treatments (range: 10–98). Catheter failure was found in 3 patients (7.1%). Nine incidents of grade 1 toxicity were observed in 8 patients (19.0%). There was a complete response in 6 patients, partial remission in 18, stable disease in 9, and progression of disease in 9 (response rate: 57.1%). Overall median survival time was 29.1 months. Using Cox's proportional hazard model, lymph node metastases in primary colorectal carcinoma and pre-treatment serum CEA affected overall survival ($P = 0.011$, $P = 0.005$).
Conclusions: HAI after radiological placement of infusion catheters is a safe and effective treatment particularly for patients with no lymph node metastasis in primary carcinoma or with a low pre-treatment serum CEA level.

Keywords: Median survival time; Response rate; Toxicity; CEA; Lymph node metastases; Arteriography; Infusion port; Distal fixation method

Introduction

Hepatic metastasis is one of the serious events that determine the prognosis of patients with advanced colorectal carcinoma. Surgical resection alone can result in significant prolongation of survival in patients with favorable prognostic factors. The 5-year survival rate of patients who underwent resection of hepatic metastases was reported to be 30% to 40%.[1,2] Chemotherapy is used to treat hepatic metastases in colorectal carcinoma patients when surgical resection cannot be performed. A number of phase 3 clinical trials have reported median survival times of nearly 20 months using combination chemotherapy with 5-fluoruracil (5FU), leucovorin (LV), oxaliplatin or irinotecan for metastatic colorectal carcinomas.[3–5] However, these systemic chemotherapy regimens cause a higher incidence of clinically significant toxicities and make it difficult for patients to continue with treatment.

Randomized trials evaluating hepatic artery infusion (HAI) therapy for the treatment of unresectable hepatic metastases have demonstrated higher response rates (31%–50%) than those achieved with systemic chemotherapy (8%–20%), but no survival benefit was reported.[6,7] HAI offers a means for achieving high drug concentrations in liver metastases and low concentrations systemically.[8] HAI results in a high response rate for local control and is associated with a very low incidence of toxicities.[9] In

* Corresponding author. Tel.: +81 276 380 771; fax: +81 276 388 386.
E-mail address: shinsame@gunma-cc.jp (S. Sameshima).

0748-7983/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejso.2007.02.012

order to obtain a sufficient therapeutic effect, HAI should be continued successfully without catheter failure. In most HAI studies, catheter placements were performed surgically. When placed surgically, catheter problems can result, which is one of the reasons why HAI was previously unsuccessful for improving survival. In 1992, a new radiological technique was developed in which a side-hole catheter is placed in the hepatic artery with the tip fixed in the gastroduodenal artery.[10] With this technique, the risk of catheter failure and toxicity is reduced. It has also been reported that computed tomography (CT) arteriography via the infusion port is useful for detecting hepatic perfusion abnormalities during HAI.[11]

Although hepatic metastases respond well to HAI treatment, extra-hepatic metastases or recurrence often appear and are important factors for defining the prognosis of HAI-treated patients. Since peripheral venous concentrations of 5FU are lower and plasma clearance rates are higher following HAI compared with a similar dose administered by intravenous infusion, HAI is less effective for controlling extra-hepatic metastases.[12] To maximize the therapeutic efficacy of HAI, patients who can benefit more from HAI than from systemic chemotherapy should be selected. However, prior studies of HAI have not identified the patient types for which HAI is indicated.

We placed infusion catheters for HAI radiologically in patients with liver metastases from colorectal carcinomas using the distal fixation method. Hepatic perfusion was checked by CT arteriography via the infusion port periodically. We administered 5FU by HAI as first-line therapy and examined the clinical safety and efficacy of HAI treatment. We also examined the status of liver metastases and the clinicohistological features of the primary colorectal carcinomas of HAI-treated patients in order to identify candidates most likely to benefit from HAI therapy.

Patients and methods

Patients

We included patients with liver metastases from colorectal carcinomas which were confirmed histologically. Their primary colorectal carcinomas were resected surgically between January 1998 and September 2005. Patients with extra-hepatic metastases, defined as pulmonary metastases or local recurrence, were excluded. Forty-two patients met the criteria and were enrolled in the study. Informed consent was obtained from all patients. HAI was started between November 1999 and October 2005. Response and survival rates were monitored for all patients.

Procedure of catheter placement

Catheter placements in the hepatic artery were done radiologically by interventional radiologists. The side-hole catheters were placed using the distal fixation method.[10] The gastroduodenal artery and right gastric artery were embolized radiologically with coils before the catheter fixation. The tip of the catheter was fixed into the gastroduodenal artery and the side hole was placed in the common hepatic artery. The catheter was inserted via the right femoral artery and connected to the infusion port (Infuse-a-Port, Strato Medical Corp., Beverly, MA, USA). The port was implanted in the subcutaneous space.

Procedure of HAI

HAI treatment was performed weekly or biweekly at an outpatient chemotherapy room. 5FU (1000–1500 mg) was dissolved in 200 ml of physiological saline and packed into a portable infusion pump (INTERMATE LV 50 ml/h; Baxter Healthcare Corp., Deerfield, IL, USA). Before every injection, the catheter and the port were flushed with 5 ml saline. HAI was performed continuously for 5 h. The catheter and the port were filled with 5000 units of heparin after each infusion. Hepatic perfusion was assessed by CT arteriography via the infusion port after every 10 infusions. The treatments were discontinued when the therapeutic response was judged as progressing disease (PD) or catheter failure. National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 was used to assess toxicity.[13]

Clinical response evaluation

Patients scheduled for HAI received a chest-abdominal CT scan before the start of treatment. Tumor status was assessed by chest-abdominal CT scan after every 10 infusions. The therapeutic response was evaluated according to RECEIST guideline.[14] Serum carcinoembryonic antigen (CEA) levels were also measured before treatment and after every 10 infusions.

Survival and statistical analysis

Actuarial survival curves were computed by the Kaplan–Meier method. The survival rate results among the subgroups were analyzed by log-rank analysis. Cox's proportional hazard model was used to analyze differences in risk factors for survival using SPSS software version 14.0.

Results

Patients and treatments

Forty-two patients with liver metastases from colorectal carcinomas were enrolled for HAI treatment. The characteristics of the patients are shown in Table 1. Catheter placements in the hepatic artery and HAI treatments were performed successfully in all cases.

Each patient received an average of 36 treatments (range: 10–98). CT arteriography via the infusion port showed hepatic artery occlusion after 18 or 29 infusions

Table 1
Patients characteristic

Characteristic	No. of patients	Characteristic	No. of patients
Sex		pTNM of primary colorectal carcinoma	
Male	27	pT	
Female	15	pT1	0
Age (average)	65.8	pT2	0
Onset of liver metastases		pT3	39
Synchronous	26	pT4	3
Metachronous	16	pN	
Previous hepatectomy		pN0	12
Yes	3	pN1	16
No	39	pN2	14
No. of liver metastases		pM	
≤4	27	pM0	16
5≤ ≤9	7	pM1	26
≥10	8	Histology of primary colorectal carcinoma	
Serum CEA level		Well	13
≤50	23	Moderate	26
50< ≤300	8	Poorly	2
>300	11	Mucinous	1

in 2 patients, and displacement of the catheter from the hepatic artery in 1 patient. These 3 patients (7.1%) discontinued the treatment. Collateral circulation from the right inferior phrenic artery to the liver was detected in 3 patients. They were embolized by coils radiologically in order to correct the intra-hepatic perfusion of 5FU and the treatments were restarted.

Toxicity

Nine incidents of grade 1 toxicity were observed in 8 patients. No grade 2–4 toxicity was observed. The rate of chemotherapy-related toxicity due to HAI was 19.0% (8/42).

Therapeutic response rate to HAI

We evaluated the therapeutic response to HAI by CT scanning according to RECEIST guidelines. Complete response (CR) in 6 patients, partial remission (PR) in 18 patients, stable disease (SD) in 9 patients, and PD in 9 patients were observed. The overall response rate was 57.1%. Extra-hepatic metastases appeared in 22 patients and in these cases HAI was switched to systemic chemotherapy.

In relation to lymph node involvement in primary colorectal carcinoma, the response rate was 66.7% in pN0, 50.0% in pN1, and 57.1% in pN2. The differences between groups were not statistically significant. No significant differences in the response rate were observed in relation to the histology of primary carcinomas or pre-treatment serum CEA levels. Thirty-three of 42 patients showed elevated (>5.0 ng/ml) serum CEA levels prior to treatment. A CEA decline of 50% or more in patients who had increased baseline CEA levels was observed in 26 patients (78.8%).

Survival of patients treated by HAI

The overall median survival time (MST) was 29.1 months. We examined survival rates in relation to lymph node involvement in primary colorectal carcinoma. MST was 50.1 months in pN0 and 23.2 months in pN1-2. The survival rate in patients with pN0 was significantly higher than in patients with pN1 or pN2 ($P = 0.011$) (Fig. 1). The survival curves did not differ significantly in relation to the number of hepatic metastases prior to treatment ($P = 0.60$). We also examined MST in relation to pre-treatment serum CEA levels. MST was 36.3 months in patients with serum CEA ≤50 ng/ml and 24.1 months in patients with serum CEA >50 ng/ml ($P = 0.01$). No significant difference was observed between the subgroups of patients with synchronous and metachronous liver metastases ($P = 0.33$). Furthermore, the histological features of the primary carcinoma did not differ significantly between the subgroups. Multivariate analysis showed lymph node metastases of primary colorectal carcinoma (pN) and pre-treatment serum CEA to be significant risk factors ($P = 0.017$ and $P = 0.004$, respectively) (Table 2).

Discussion

HAI and systemic chemotherapy for liver metastases from colorectal carcinomas

We administered 5FU by HAI in patients with liver metastases from colorectal carcinoma after radiological placement of infusion catheters using the distal fixation method. The overall response rate and MST were better than those of the systemic chemotherapy reported. Prior studies of systemic chemotherapy included patients who had extra-hepatic

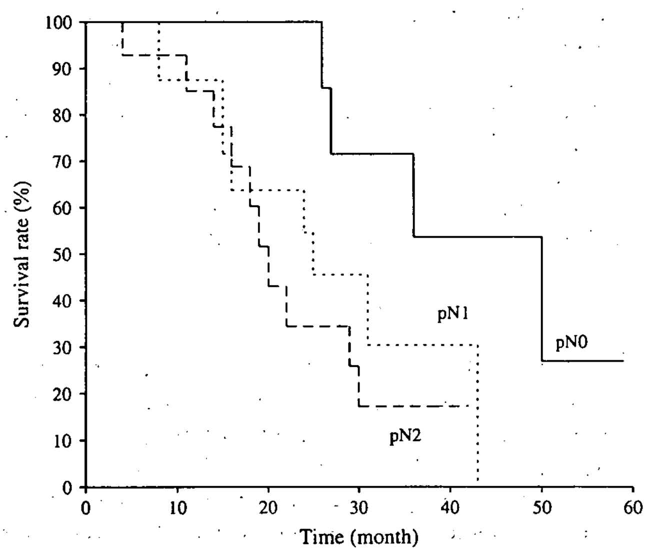

Figure 1. Survival curves according to pN stage of primary colorectal carcinoma. Significant differences were seen between pN0 and pN1 ($P < 0.001$) and between pN0 and pN2 ($P < 0.001$).

Table 2
Multivariate analysis of risk factors for overall survival

Risk factor	Hazard ratio	95% CI	*P* value
pN0 vs. pN1–2	4.50	1.31–15.47	0.017
Serum CEA ≤50 vs. >50	3.67	1.42–9.49	0.004

metastases or recurrences, and these patients had a worse prognosis than patients with hepatic metastases only. It is difficult to compare these results with our study, which did not include cases with extra-hepatic metastases. Kerr and associates reported a multicenter, randomized trial of HAI versus intravenous 5FU and LV for colorectal carcinoma liver metastases.[15] There was no significant difference in MST or progression-free survival. However the HAI group received a median of only 2 cycles, because of catheter failure, compared with 8.5 cycles for the intravenous group. Recently, Kemeny and associates reported the results of a randomized trial comparison between HAI using floxuridine and systemic chemotherapy using 5FU and LV.[16] Overall survival was significantly longer for HAI versus systemic treatment (median, 24.4 v 20 months). The median number of cycles received was 3 and 4 for the HAI and systemic arms, respectively. In cases where catheters are placed accurately and maintained without failure, the therapeutic response to HAI was deemed to be preferable for the treatment of liver metastases.

Successful HAI with new techniques

In order to continue HAI successfully without catheter failure, it is essential for interventional radiologists to be highly skilled in performing the procedure. When inserting the catheter, the branch vessels of the hepatic artery should be embolized accurately.[17] Otherwise, 5FU can flow into the stomach or pancreas and cause toxicity, such as nausea and vomiting, which can lead the physician to discontinue treatment. CT arteriography via the infusion port is useful for detecting abnormal perfusion during HAI. Collateral circulation from extra-hepatic vessels to the liver during HAI should be also embolized radiologically in order to correct for variations in intra-hepatic perfusion of 5FU.[18] The radiological placement of the catheter and careful follow-up using CT arteriography are essential for maintaining safe HAI.

Prognostic factors of HAI

MST was influenced by lymph node metastases of the primary colorectal carcinomas. Since HAI does not control extra-hepatic metastases, patients with lymph node metastases are not ideal candidates for HAI treatment but can be treated with systemic chemotherapy. Elevated CEA levels are indicative of advanced-stage liver metastases, as suggested by our finding that CEA levels influenced MST. The response rate was not influenced by histological features or lymph node metastases of primary colorectal carcinomas in our study. Also, the response rate was not influenced by the synchronous/metachronous status of liver metastases, the number of hepatic metastases, or pretreatment serum CEA levels. It has been reported that enzymes involved in 5FU metabolism, such as thymidine synthase and dihydropyrimidine dehydrogenase, are important predictors of the therapeutic efficacy of 5FU.[19,20]

Indications for HAI

In this study, we demonstrated that patients with pN0 in primary colorectal carcinoma or a lower serum CEA level before treatment exhibited the longest MSTs. These patients, therefore, are suitable candidates for HAI therapy. Because HAI resulted in a very low toxicity rate, it can be applied as second-line therapy for patients who have discontinued systemic chemotherapies due to toxicity but still have life-threatening liver metastases. In order to maximize the therapeutic effectiveness of HAI, it is important to continue HAI with well-controlled delivery of 5FU without catheter failure or toxicity.

Improvement of HAI

In order to improve the therapeutic efficacy of HAI, new approaches are developing in 2 directions. One of these approaches involves the use of new therapeutic agents.[21] New combinations of 5FU, folinic acid, and interferon-α have been used with HAI and high tumor response rates have been reported.[22] The other approach involves the use of HAI and systemic chemotherapy in combination.[23] Adjunctive systemic chemotherapy can compensate for one of the weakness of HAI; i.e., HAI is completely ineffective for the treatment of extra-hepatic metastases. However it has been reported that combined treatment with HAI and systemic 5FU did not improve survival compared with systemic fluorinated pyrimidine.[24] Further studies are needed to evaluate the effect of HAI and systemic chemotherapies in combination.

References

1. Gayowski TJ, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery* 1994 Oct;**116**(4):703–10 (discussion 10–1).
2. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995 Jan–Feb;**19**(1):59–71.
3. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000 Aug;**18**(16):2938–47.
4. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004 Jan 1;**22**(1):23–30.
5. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal

cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005 Aug 1;**23**(22):4866–75.

6. Martin Jr JK, O'Connell MJ, Wieand HS, et al. Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. A randomized trial. *Arch Surg* 1990 Aug;**125**(8):1022–7.
7. Kelly RJ, Kemeny NE, Leonard GD. Current strategies using hepatic arterial infusion chemotherapy for the treatment of colorectal cancer. *Clin Colorectal Cancer* 2005 Sep;5(3):166–74.
8. Pinedo HM, Peters GF. Fluorouracil: biochemistry and pharmacology. *J Clin Oncol* 1988 Oct;**6**(10):1653–64.
9. Meta-Analysis Group in Cancer. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. *J Natl Cancer Inst* 1996 Mar 6;**88**(5):252–8.
10. Tanaka T, Arai Y, Inaba Y, et al. Radiologic placement of side-hole catheter with tip fixation for hepatic arterial infusion chemotherapy. *J Vasc Interv Radiol* 2003 Jan;**14**(1):63–8.
11. Seki H, Kimura M, Kamura T, Miura T, Yoshimura N, Sakai K. Hepatic perfusion abnormalities during treatment with hepatic arterial infusion chemotherapy: value of CT arteriography using an implantable port system. *J Comput Assist Tomogr* 1996 May–Jun;**20**(3): 343–8.
12. Goldberg JA, Kerr DJ, Watson DG, et al. The pharmacokinetics of 5-fluorouracil administered by arterial infusion in advanced colorectal hepatic metastases. *Br J Cancer* 1990 Jun;**61**(6):913–5.
13. Institute NC. National Cancer Institute Common Toxicity Criteria, version 2.0; 1999.
14. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000 Feb 2;**92**(3):205–16.
15. Kerr DJ, McArdle CS, Ledermann J, et al. Intrahepatic arterial versus intravenous fluorouracil and folinic acid for colorectal cancer liver metastases: a multicentre randomised trial. *Lancet* 2003 Feb 1;**361**(9355): 368–73.
16. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). *J Clin Oncol* 2006 Mar 20;**24**(9): 1395–403.
17. Hohn DC, Stagg RJ, Price DC, Lewis BJ. Avoidance of gastroduodenal toxicity in patients receiving hepatic arterial 5-fluoro-2'-deoxyuridine. *J Clin Oncol* 1985 Sep;**3**(9):1257–60.
18. Sofocleous CT, Schubert J, Kemeny N, et al. Arterial embolization for salvage of hepatic artery infusion pumps. *J Vasc Interv Radiol* 2006 May;**17**(5):801–6.
19. Salonga D, Danenberg KD, Johnson M, et al. Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. *Clin Cancer Res* 2000 Apr;**6**(4):1322–7.
20. Inoue T, Hibi K, Nakayama G, et al. Expression level of thymidylate synthase is a good predictor of chemosensitivity to 5-fluorouracil in colorectal cancer. *J Gastroenterol* 2005 Feb;**40**(2):143–7.
21. Kern W, Beckert B, Lang N, et al. Phase I and pharmacokinetic study of hepatic arterial infusion with oxaliplatin in combination with folinic acid and 5-fluorouracil in patients with hepatic metastases from colorectal cancer. *Ann Oncol* 2001 May;**12**(5):599–603.
22. Pohlen U, Mansmann U, Berger G, et al. Multicenter pilot study of 5-fluorouracil, folinic acid, interferon alpha-2b and degradable starch microspheres via hepatic arterial infusion in patients with nonresectable colorectal liver metastases. *Anticancer Res* 2004 Sep–Oct; **24**(5B):3275–82.
23. Link KH, Leder G, Pillasch J, et al. In vitro concentration response studies and in vitro phase II tests as the experimental basis for regional chemotherapeutic protocols. *Semin Surg Oncol* 1998 Apr–May;**14**(3): 189–201.
24. Allen-Mersh TG, Glover C, Fordy C, Mathur P, Quinn H. Randomized trial of regional plus systemic fluorinated pyrimidine compared with systemic fluorinated pyrimidine in treatment of colorectal liver metastases. *Eur J Surg Oncol* 2000 Aug;**26**(5):468–73.

Jpn J Clin Oncol 2007;37(3)186–192
doi:10.1093/jjco/hym006

Multiple Resections for Hepatic and Pulmonary Metastases of Colorectal Carcinoma

Shinichiro Takahashi[1], Kanji Nagai[2], Norio Saito[3], Masaru Konishi[1], Toshio Nakagohri[1], Naoto Gotohda[1], Mitsuyo Nishimura[2], Junji Yoshida[2] and Taira Kinoshita[1]

[1]Department of Hepato-biliary Pancreatic Surgery, [2]Department of Thoracic Surgery and [3]Department of Colorectal Surgery, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Received May 21, 2006; accepted November 8, 2006

Background: Resections are effective for some patients with both hepatic and pulmonary metastases of colorectal cancer, but the best selection criteria for the resections and effective treatment for recurrence after the resections have not been determined.
Methods: A retrospective analysis was performed for 30 consecutive patients who received aggressive multiple resections for both hepatic and pulmonary metastases of colorectal cancer. Recurrences after resections were surgically treated whenever resectable.
Results: For the 30 patients, 45 hepatectomies and 40 pulmonary resections were performed and 17 patients received three or more resections. No mortality was observed. Overall survival after the first metastasectomy for the second organ (liver or lung) was 58% and nine 5-year survivors were observed. Multivariate analyses revealed that primary colon cancer, stage IV in TNM classification and maximum size of hepatic tumor >3 cm at initial hepatectomy were poor prognostic factors, but several long-term survivors were observed even among patients with those factors.
Conclusions: Multiple resections for hepatic and pulmonary metastases of colorectal cancer are safe and effective. No single factor is considered to be a contraindication for the resections. For recurrence after the resections, surgical resection is also recommended if resectable.

Key words: colorectal cancer – hepatic metastasis – pulmonary metastasis – resection

INTRODUCTION

The liver and lung are the most common sites of distant metastases for colorectal carcinoma (1). Hepatic and pulmonary metastases may be detected sequentially or simultaneously in patients with colorectal carcinoma. Efficacy of resections for these two distant metastases has been reported in several studies (2–14). However, the criteria to select patients for those resections are still obscure.

In addition, although recurrence after those resections is one of the major problems of the strategy, further surgical approaches for recurrence after those resections are controversial.

The purpose of this study was to evaluate the efficacy of aggressive multiple resections for hepatic and pulmonary metastases of colorectal carcinoma and to find prognostic factors that might elucidate who would benefit most from hepatic and pulmonary resections for colorectal metastases.

For reprints and all correspondence: Shinichiro Takahashi, Department of Hepato-biliary Pancreatic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Chiba, Japan. E-mail: shtakaha@east.ncc.go.jp

PATIENTS AND METHODS

Two hundred and sixty-seven patients who had undergone hepatic resection and 98 patients who had undergone pulmonary resection, as the first treatment for colorectal metastasis at the National Cancer Center Hospital East between September 1992 and June 2005 were examined retrospectively. Eight patients had undergone surgical resections for both hepatic and pulmonary metastases as the first treatment for colorectal metastases. Metastases were synchronous with primary colorectal carcinoma in one of the eight patients. In the remaining 259 patients who had undergone hepatic resection as the first treatment for colorectal metastasis, 83 had the second recurrence in the liver, 29 in the lung, 12 in both liver and lung and 52 in the other organs. Sixteen of the 29 patients with pulmonary recurrence and one of the 12 patients with both hepatic and pulmonary recurrences were treated surgically. Two patients had undergone resections for both hepatic and pulmonary recurrences after more than two hepatic metastasectomies. In the remaining 90 patients who had undergone pulmonary resection as the first treatment for colorectal metastasis, three had the second recurrence in the liver, 27 in the lung, four in both liver and lung and 16 in other organs. All three patients with hepatic recurrence were treated surgically. However, all four patients with both hepatic and pulmonary recurrences underwent systemic chemotherapy as the second treatment.

As a result, 30 patients underwent both hepatic and pulmonary resections for colorectal metastasis. The patients consisted of 19 men and 11 women, ranging in age from 24 to 75 years with a mean of 59 years. Two of the patients had received adjuvant chemotherapy (tegafur/uracil and 5-fluorouracil/leucovorin) after primary colorectal resection and one patient had received preoperative chemoradiation for rectal cancer.

The criteria for hepatectomy were as follows: (1) metastatic lesions are confined to the liver and technically resectable, (2) no extrahepatic metastases except resectable pulmonary metastasis are detected, and (3) liver function is equal to complete resection of all hepatic tumors. The criteria for pulmonary resection were as follows: (1) metastatic lesions are confined to the lung and technically resectable, (2) no extrathoracic metastases except resectable hepatic metastasis are detected, and (3) cardiorespiratory function is equal to complete resection of all pulmonary tumors. The timing of the detection of hepatic and pulmonary metastases or the number of prior resections for metastases did not affect these criteria, so the selection criteria for further resections for recurrences after hepatic and pulmonary resections are the same as above.

At hepatectomy, intraoperative ultrasonography was performed to confirm tumor location and size of the lesions in all patients, and all of the resections were ultrasound-guided procedures. Hepatic resection was performed by the forceps fracture method under inflow occlusion (Pringle's maneuver). At pulmonary resection, hilar or mediastinal lymph node dissection was used to sample lymph nodes of most patients who had a lobectomy.

When hepatic and pulmonary metastases were detected simultaneously, hepatic resection was carried out first, followed by pulmonary resection.

No patient received adjuvant chemotherapy after hepatectomy or pulmonary resection.

After hepatic or pulmonary resection, patients were closely followed with diagnostic imaging [chest X-ray and abdominal computed tomography (CT)] and measurement of serum carcinoembryonic antigen (CEA) levels every 3 months; they also underwent an annual colonoscopy to detect any tumor recurrence. The median follow-up of survivors was 53 months.

Morphological Investigations

The resected specimens of colon or rectum, liver and lung were fixed in 10% phosphate-buffered formalin, cut at intervals of 5 mm and embedded in paraffin. Serial sections of 3-μm thickness were stained with hematoxylin and eosin for morphological examination. Each case was histologically classified according to the histological type, tumor size, location, number of metastases, presence of serosal invasion, nodal status and margin status. Histological diagnosis was performed according to the World Health Organization intestinal tumor classification (15).

Statistical Analysis

The student t-test was used to compare data between subgroups by the location of the primary tumor. The Mann–Whitney's U test was used to compare serum CEA levels between subgroups. Analyses of survival rates were performed using the Kaplan–Meier method (16) and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model (17). A P value of less than 0.05 was considered to denote significance.

RESULTS

Clinicopathological Features of Primary and Metastatic Tumors

The primary tumors were staged as I ($n = 1$), II ($n = 10$), III ($n = 15$) and IV ($n = 4$) according to TNM classification (Table 1). All patients at stage IV had hepatic metastasis at resection of the primary tumor.

At the initial hepatectomy, the average number of hepatic tumors was 2.1 (range, 1–12), the average maximum size was 3.2 cm (range, 0.3–9 cm) and the average preoperative CEA level was 19.9 ng/ml (range, 0.8–68.5 ng/ml). In all hepatectomies, the average number of hepatic tumors was 2.8 and the average maximum size was 3.3 cm. Lymph node metastasis at the hepatoduodenal ligament was shown in one patient.

Regarding pulmonary metastases, the average number of pulmonary tumors was 1.8 (range, 1–5), the average maximum size was 2.2 cm (range, 0.7–6.7 cm) and the average prethoracotomy CEA level was 12.4 ng/ml (range, 1.0–66.7 ng/ml) at initial pulmonary resection. In all pulmonary resections, the average number of pulmonary tumors was 2.1 and the average maximum size was 2.5 cm. Hilar lymph node metastasis of the lung was shown in two patients.

Surgical Resections for Hepatic and Pulmonary Metastases

Forty-five hepatectomies (30 partial resections, four subsegmentectomies, seven segmentectomies and four lobectomies

Table 1. Correlation between clinicopathologic factors and overall survival in patients with resected hepatic and pulmonary metastases from colorectal cancer

	No.	Median survival (mo)	*P* value
Primary colorectal lesion			
Location			
rectum	13	52.7	0.03
colon	17	38.6	
TNM classification			
I	1	88.9	0.02*
II	10	48.9	
III	15	38.8	
IV	4	14.6	
Lymph node metastasis			
absent	11	54.8	0.64
present	19	32.8	
Histological type of adenocarcinoma			
well or moderately differentiated	28	38.7	0.77
poorly differentiated and others	2	41.7	
Hepatic metastases			
First hepatectomy			
Number of tumors			
1	18	40.8	0.26
≥2	12	36.8	
Maximum size of the tumor (cm)			
<3	14	40.0	0.03
≥3	16	35.8	
Distribution of metastases			
unilobar	20	40.8	0.36
bilobar	10	36.8	
Lymph node of hepatoduodenal ligament			
negative	29	38.8	0.02
positive	1	13.9	
All hepatectomies			
Total number of tumors			
<3	19	38.6	0.79
≥3	11	38.8	
Maximum size of the tumor (cm)			
<3	13	38.8	0.08
≥3	17	38.6	
Distribution of metastases			
unilobar	17	43.0	0.49
bilobar	13	34.8	

	No.	Median survival (mo)	*P* value
Pulmonary metastases			
First pulmonary resection			
Number of tumors			
1	18	47.9	0.31
≥2	12	27.1	
Maximum size of the tumor (cm)			
<3	21	34.8	0.69
≥3	9	38.8	
Distribution of metastases			
unilobar	24	42.1	0.68
bilobar	6	27.1	
Hilar or mediastinal lymph node			
negative	28	36.7	0.89
positive	2	43.6	
All pulmonary resections			
Number of tumors			
<3	22	38.7	0.92
≥3	8	44.8	
Maximum size of the tumor (cm)			
<3	19	34.8	0.93
≥3	11	38.8	
Distribution of metastases			
unilobar	21	41.1	0.97
bilobar	9	30.8	
CEA level at initial recurrence (ng/ml)			
<50	25	38.7	0.34
≥50	5	33.0	
Disease-free interval from resection of primary tumor			
<1 year	19	38.8	0.23
≥1 year	11	38.6	
Simultaneous detection of hepatic and pulmonary recurrences			
yes	11	34.8	0.35
no	19	38.8	
Initial metastasis in the lung			
yes	3	54.8	0.72
no	27	38.6	
Total number of liver and lung resections			
2	13	33.0	0.50
≥3	17	54.3	

CEA, carcinoembryonic antigen.
*Stage I, II or III versus Stage IV.

according to Couinaud's anatomical classification (18)) and 40 pulmonary resections (32 partial resections, seven lobectomies and one pneumonectomy) were performed on the 30 patients. The average number of operations performed for hepatic or pulmonary metastases per patient was 2.8. Three operations were performed on 11 patients, four operations on four patients each and five operations on two patients each.

There was no perioperative mortality. Five complications were observed: two cases of biliary leak and one case each of portal vein thrombosis after hepatectomy, wound infection and air leak after pulmonary resection.

The location of initial metastasis was lung in three patients, liver in 19, and both liver and lung in eight. Eleven patients experienced hepatic and pulmonary metastases detected simultaneously.

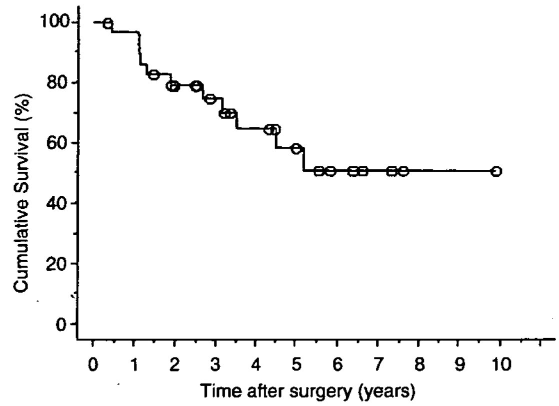

Figure 1. Cumulative survival curves for 30 patients who underwent resections for both hepatic and pulmonary metastases of colorectal cancer.

Recurrence after Surgical Resections for Hepatic and Pulmonary Metastases

Among 30 patients who underwent surgical resections for hepatic and pulmonary metastases, 25 developed recurrences when recurrence was defined as the first recurrent disease after at least one resection each for hepatic and pulmonary metastases. Locations of recurrences were as follows: lung in 11 patients, liver and lymph node in four each, both liver and lung in three, peritoneum, local recurrence and brain in one each. Re-resection could be performed in 15 of the 25 patients. Of the remaining 10 patients, eight received systemic chemotherapy, one each received radiation therapy and best supportive care.

Survival

Survival time was calculated from the date of the first metastasectomy for the second organ metastasized (liver or lung).

Actuarial overall survival was 58% at 5 years with a median survival of 39 months (Fig. 1). Disease-free survival was 56% at 1 year and 8% at 3 years, with a median recurrence-free survival of 13 months. Nine 5-year survivors were observed and eight of the nine patients are still alive without disease. Of the nine 5-year survivors, six had undergone three operations and one had undergone four operations.

When survival time was calculated from the date of the first metastasectomy for the first organ, actuarial overall survival was 70% at 5 years with a median survival of 60 months.

Correlation between Clinicopathologic Factors and Overall Survival

To find prognostic factors for survival after resection of hepatic and pulmonary metastases, clinicopathologic factors and overall survival calculated from the date of the first metastasectomy for the second organ were analyzed in 30 patients (Table 1). Primary colon carcinoma ($P = 0.03$), stage IV in TNM classification ($P = 0.02$), maximum size of hepatic tumor >3 cm at initial hepatectomy ($P = 0.03$), and lymph node metastasis of the hepatoduodenal ligament ($P = 0.02$) were significantly associated with poor overall survival. Whether hepatic and pulmonary metastases were detected simultaneously or sequentially was not correlated with survival ($P = 0.35$). Neither a disease-free interval of less than 1 year from resection of the primary tumor nor initial metastasis in the lung affected survival.

We examined the independent predictive value of the aforementioned factors on overall survival (Table 2). Lymph node metastasis of the hepatoduodenal ligament was excluded from the analysis because only one of the 30 patients had the factor. Primary colon carcinoma (Fig. 2A), stage IV in TNM classification (Fig. 2B), and maximum size of hepatic tumor >3 cm at initial hepatectomy (Fig. 2C) had predictive value for decreased overall survival after resection of hepatic and pulmonary metastases from colorectal cancer.

Comparing clinicopathological factors of patients with primary colon carcinoma and those of patients with primary rectal carcinoma, maximum size of pulmonary tumors (2.6 ± 1.6 cm versus 1.7 ± 0.7 cm) was significantly larger and prethoracotomy CEA level (18.2 ± 23.8 ng/ml versus 5.3 ± 5.4 ng/ml) was significantly higher in patients with primary colon carcinoma. The interval from primary resection to the first pulmonary resection tended to be longer in patients with primary colon carcinoma than in patients with primary rectal carcinoma (25.7 months versus 17.1 months, median).

DISCUSSION

Results of this study indicate that aggressive multiple resections for hepatic and pulmonary metastases of colorectal carcinoma are safe and contribute to long-term survival in some patients.

Hepatic and pulmonary metastases may be detected sequentially or simultaneously in patients with colorectal carcinoma. Although two distant organs are affected by the