Table 4. Multivariate analyses for liver metastases (logistic regression analysis)

	Hazard ratio (95% confidence interval)	P
Vascular invasion positive (vs negative)	3.122 (0.892-10.928)	0.0748
AR; positive (vs negative)	3.204 (1.185-8.659)	0.0217

as breast, prostate, cervix, and liver cancer cells (22, 23). Interference with AR production by specific antisense small interfering RNAs or neutralizing antibodies reduced cell proliferation (24) and reversed many of the neoplastic phenotypic traits of cancer cells *in vitro*, although the expressions of other ligands of the EGFR were preserved in these cells (21, 25, 26). In ~50% of human primary colon carcinomas, AR was overexpressed (27). These reports suggest that AR is an important ligand for EGFR in colon cancer cell transformation.

Zvibel et al. (28) showed that site-specific metastasis was determined by the extracellular matrix of the colonized organ, whereas AR at the secondary colonization site was induced by typical liver-matrix components and stimulated cancer cell proliferation. Under certain conditions, hepatocyte-derived extracellular matrix stimulated the proliferation of colon cancer cells via the induction of AR. Thus, we supposed that AR-positive cells had a strong affinity with the liver, explaining why AR expression was related to liver metastasis and why AR-positive cancer cells were more frequently observed in metastatic lesion of the liver than in the primary lesion. We also indicated that disease-free survival and hepatic metastasis-free survival were related to both venous invasion and AR expression in the primary lesion (Fig. 3). These results might depend on the malignant behavior of AR, as mentioned above.

Previous reports showed that the coexpression of EGFR and c-erbB-2 protein may be related to the distant metastasis of colon cancer (29-32). In the present study, a relationship between malignant behavior and the coexpression of EGFR, HER2, and/or AR in colorectal cancer could not be shown. The low immunoreactivity for EGFR (12.3%) and HER2 (4.7%) in this study might explain the above result. Generally, immunoreactivity depends on the fixation time or the storage time of the archived tissue sections, especially when testing colorectal adenocarcinomas for EGFR expression using the DakoCytomation EGFRpharmDX or breast cancer using the Herceptest. The evaluation of EGFR expression is also dependent on the storage time of archived tissue sections, especially with colorectal adenocarcinomas. The tissue sections should be tested within 9 months to avoid false-negative results (1, 33, 34).

This study is the first report revealing that AR expression in primary lesions of colorectal cancer is significantly correlated with liver metastasis. We conclude that AR expression in colorectal cancer is an important predictive marker for liver metastases.

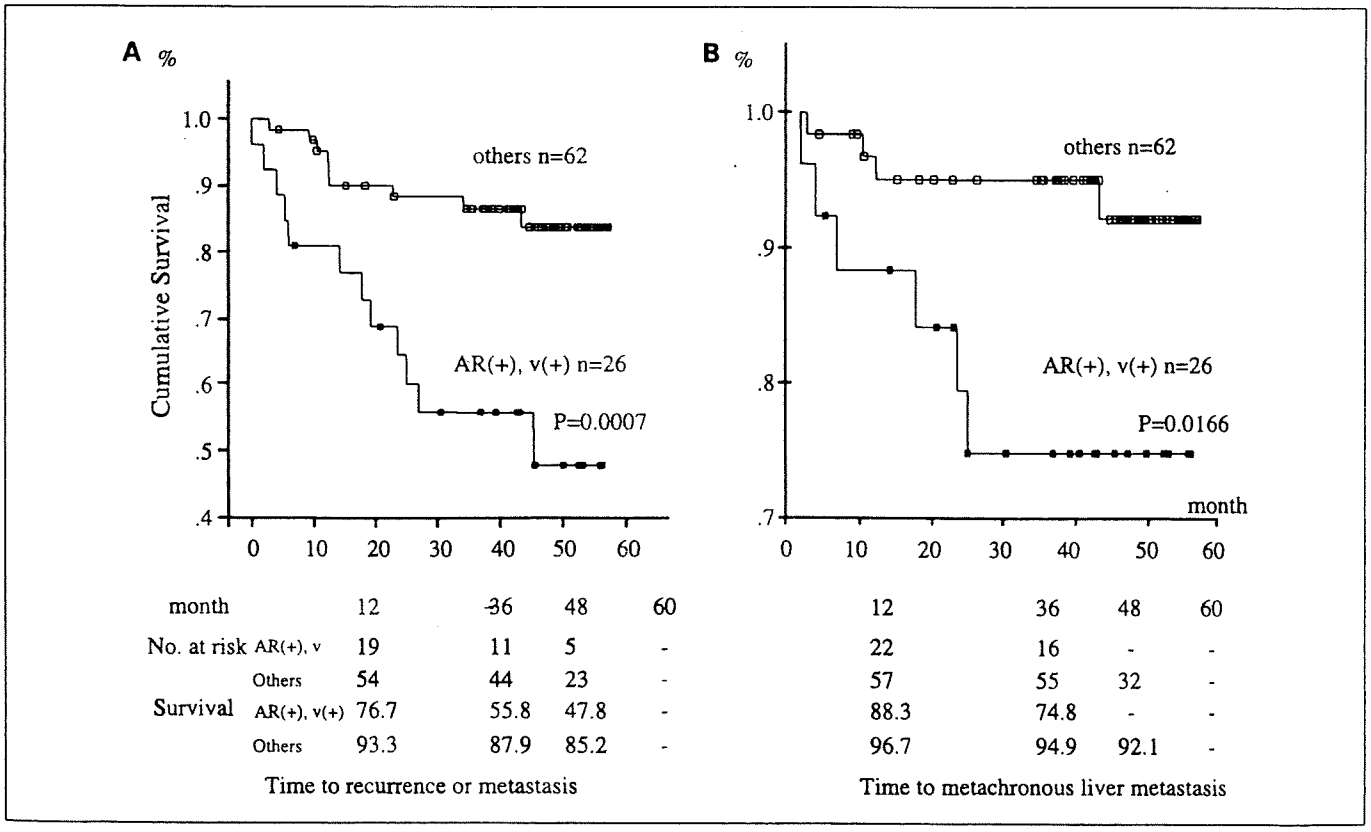

Fig. 3. Disease-free survival (*A*) and hepatic metastasis-free survival (*B*) after curative colectomy for colorectal cancer without synchronous metastases (n = 88)

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Doubling Time of Carcinoembryonic Antigen Is a Significant Prognostic Factor after the Surgical Resection of Locally Recurrent Rectal Cancer

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Key Words
Local recurrence · Rectal cancer · Carcinoembryonic antigen · Doubling time

Abstract
Background: Patients undergoing a curative rectal cancer resection have a risk of developing locoregional recurrence. A curative resection for local recurrence is the option of improvement in prognosis. However, a curative resection is sometimes too invasive and should be considered in selected patients. ***Methods:*** A total of 43 patients with locally recurrent rectal cancer who had been treated by operation between 1989 and 2007 were retrospectively reviewed and the factors, including doubling time of carcinoembryonic antigen (CEA-dt), were analyzed. ***Results:*** The 5-year overall survival rate after the operation for local recurrence was 50.8%. Gender, presence of distant metastasis, tumor size, CEA-dt and curability were found to be significant prognostic factors. A multivariate analysis demonstrated the presence of distant metastasis, CEA-dt and tumor size to be significant prognostic factors for overall survival. The 5-year overall survival rates of patients with a CEA-dt ≥150 days and a tumor size <5 cm were 76.9%. ***Conclusions:*** The tumor size and CEA-dt were useful prognostic factors that were recognizable before surgery. Patients with locally recurrent rectal cancer with a CEA-dt ≥150 days and a recurrent tumor size <5 cm are considered to be good candidates for surgery.

Introduction

Patients undergoing a potentially curative rectal cancer resection have a risk of up to 35% of developing a locoregional recurrence, with 30–50% of these occurring in the absence of distant metastasis [1–7]. Locally recurrent rectal cancer is associated with a poor prognosis. Without treatment, patients with recurrent rectal cancer have a short life expectancy, a median survival of 3.5–11 months [1, 8, 9], and tend to experience unpleasant symptoms such as pain and bleeding. Considerable variations have been reported in the effect of treatment for local recurrence. The 5-year survival rates vary between 0 and 81% for patients treated with a curative approach [10–13]. Radiotherapy, either alone or in combination with chemotherapy, allows symptomatic improvement in most patients, but the 5-year survival is usually less than 5% [14].

A surgical resection of recurrent cancer is performed both to avert the morbidity of local tumor growth and

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prolong survival. Generally, a radical resection of the locally recurrent tumor is the only option that offers a significant improvement in prognosis [9, 11, 15, 16]. However, a radical resection, which may involve total pelvic exenteration and/or distal sacrectomy, is sometimes too invasive. The quality of life sometimes dramatically deteriorates due to the postoperative complications and aftereffects such as pain, difficulty in walking, infection and double stoma due to urinary tract diversion. The prognosis of noncurative surgical cases is as poor as that of inoperable cases [3]. Therefore, these invasive procedures should only be considered in carefully selected patients. Although significant prognostic factors influencing the outcome of surgery for local recurrence have been identified, such as postoperative tumor marker levels and pathological curativity of surgical margins [17, 18], recognizable factors after surgery are not useful in determining the indications for surgery. As a result, factors which can be found preoperatively must be identified.

Tumor growth rate plays an important role in the prognosis of patients with cancer. Collins et al. [19] introduced the concept that malignant tumor growth in humans was exponential, and that the rate of growth could be described by the tumor doubling time. Tanaka et al. [20] reported that the tumor doubling time of a liver metastasis from colorectal cancer was the most reliable risk factor for postoperative recurrence in the remnant liver and poor prognosis. Staab et al. [21] stated that doubling time of carcinoembryonic antigen (CEA-dt) was strongly correlated with tumor doubling time. Koga et al. [22] reported that CEA-dt is a prognostic factor after a hepatectomy of liver metastasis from colorectal cancer. However, there have been no reports addressing the prognostic factors including CEA-dt after a surgical resection of locally recurrent rectal cancer.

In this study, patients with locally recurrent rectal cancer were retrospectively reviewed, and the factors associated with their prognosis, including the CEA-dt, were analyzed.

Patients and Methods

A total of 43 patients with locally recurrent rectal cancer were treated by operation in this surgical department in the period between January 1989 and January 2007. Local recurrence was defined as any tumor recurrence in the pelvis or perineum with or without distant metastasis. Distant metastasis was defined as any tumor recurrence outside the pelvis, including multiple metastases to the abdominal cavity, liver, lung, brain or bone.

The CEA-dt was calculated using the following equation: CEA-dt = $\Delta t \log 2/(\log C2 - \log C1)$, where Δt is the CEA measured between 2 voluntary points, C1 is the value of CEA measured the first time and C2 the value measured the second time [22].

Table 1. Characteristics of patients

	n
Primary lesion	
pTNM (stage I/II/III/IV/unknown)	5/11/24/3
Histological differentiation (well/mod./muc./unknown)	17/18/4/4
Adjuvant therapy (done/not done)	30/13
Local recurrence lesion	
Gender (male/female)	23/20
Age (<60/≥60 years)	20/23
Distant metastasis (+/−)	8/35
DFI (<2/≥2 years)	17/26
Size (<5/≥5 cm)	24/19
CEA-dt (<150/≥150 days)	17/21
Curability (curative/noncurative + palliative)	27/16
Preoperative therapy (done/not done)	6/37
Postoperative therapy (done/not done)	32/11

Well = Well-differentiated adenocarcinoma; mod. = moderately differentiated adenocarcinoma; muc. = mucinous adenocarcinoma; DFI = disease-free interval.

The clinicopathological and postoperative follow-up data were also retrospectively collected from the ongoing database in this hospital. Follow-up data were available for all cases. A curative resection was defined as no residual cancer at the local site after surgery even if distant metastasis was found. The overall survival period was defined as the period between surgery for local recurrence and cancer- or surgery-related death. The postoperative overall survival rates were calculated using the Kaplan-Meier method and then compared using the log rank test. A Cox proportional hazards model was used to assess the risk ratio under the simultaneous contribution of several covariates.

The differences in each group were analyzed by the χ^2 or Fisher's exact test. The statistical analysis was performed using the Statview software program (version 5.0; SAS Institute Inc., Cary, N.C., USA). $p < 0.05$ was considered to be statistically significant. This study was approved by the Human Ethics Review Committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases.

Results

Factors Associated with Primary Surgery

The characteristics of the 43 patients are summarized in table 1. The procedures employed for the primary tumor included a sphincter-preserving operation in 21 cases, an abdominoperineal resection in 18 cases and a local excision in 4 cases. All cases were pathologically diag-

nosed to have adenocarcinoma. None of the patients received neoadjuvant therapy. Overall, 30 patients received prior adjuvant chemotherapy consisting of 5-fluorouracil and its derivatives for their primary tumor.

Factors Associated with Surgery for Local Recurrence

There were 23 men and 20 women, and their median age was 58.6 years (range 32–80). The procedures employed for the local recurrences were a pelvic exenteration in 17 cases, an abdominoperineal resection in 8 cases, a wide local resection in 4 cases and a low anterior resection in 6 cases. Of the 43 patients, 8 were found to have evidence of extrapelvic disease during an evaluation just before or at the time of surgery for recurrence (3 liver, 3 lung, 2 peritoneal dissemination). Eight patients underwent surgery with a curative intent and, as a result, 3 patients received a palliative operation (2 bowel bypass, 1 colostomy), while the other 5 patients received either a curative or noncurative operation. The mean interval between surgery for the primary tumor and the diagnosis of the local recurrence (disease-free interval) was 26.3 months (2.7–99.8). Local recurrences were diagnosed within 3 years in 33 patients (76.7%). Of the 43 patients, 27 (62.8%) received a pathologically curative resection, 8 (18.6%) received a noncurative resection because of gross or microscopic residual cancer cells, and 8 (18.6%) received only a palliative operation (2 diagnostic laparotomy, 3 bowel bypass, 2 colostomy, 1 other). No patients died of postoperative complications. Six patients received neoadjuvant therapy for a local recurrence. Thirty-two patients received postoperative chemotherapy and/or radiotherapy for local recurrence. The follow-up was complete for all patients. The median postoperative follow-up period for all patients was 44 months (range 0.9–146).

Outcome after Surgery

The 3- and 5-year overall survival rates after the operation for local recurrence were 54.7 and 50.8%, respectively (fig. 1). Table 2 shows a summary of the prognostic univariate analysis using various tumor-related variables on overall survival after the surgery for the local recurrence. Gender (male vs. female: $p = 0.0079$), recurrence pattern (local recurrence with distant metastasis versus local recurrence without distant metastasis: $p = 0.0041$), tumor size (<5 vs. ≥5 cm: $p < 0.0001$), CEA-dt (<150 vs. ≥150 days: $p = 0.0081$) and curability (curative vs. noncurative and palliative: $p = 0.0025$) were found to be significant prognostic factors. Disease-free interval was not a significant factor. Neoadjuvant and adjuvant therapy did not influence survival. In addition, a multivariate analysis was conducted by using preoperatively recognized factors (gender, presence of distant metastasis, tumor size and CEA-dt). The multivariate analysis demonstrated the presence of distant metastasis, CEA-dt and tumor size to be significant prognostic factors for overall survival (table 3). The 3-year overall survival rates of patients with distant metastasis (n = 8) and patients without distant metastasis (n = 35) were 14.3 and 64.6%, respectively ($p = 0.0041$). There was only 1 patient with distant metastasis surviving more than 3 years. Next, the pa-

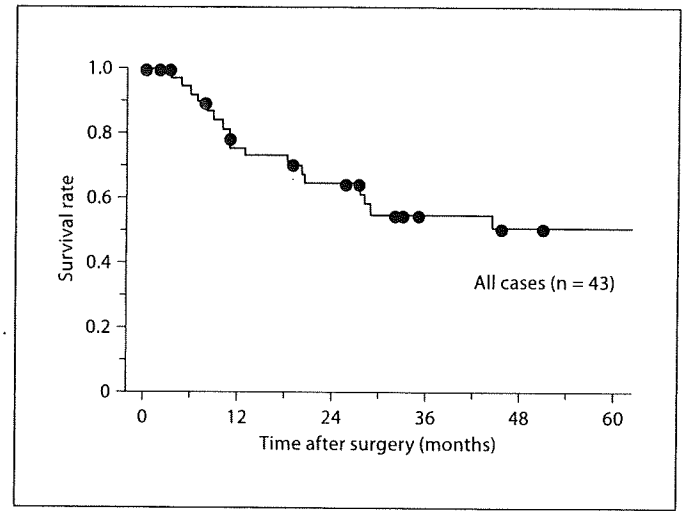

Fig. 1. The overall survival rate of patients with locally recurrent rectal cancer.

Table 2. Univariate analysis of the prognostic factors for overall survival

	p
Gender (male/female)	0.0079
Distant metastasis (+/–)	0.0041
DFI (<2/≥2 years)	0.6454
Size of local recurrence lesion (<5/≥5 cm)	<0.0001
CEA-dt (<150/≥150 days)	0.0081
Curability (curative/noncurative + palliative)	0.0025
Preoperative therapy for local recurrence (done/not done)	0.4579
Postoperative therapy for local recurrence (done/not done)	0.2354

DFI = Disease-free interval.

Table 3. Multivariate analysis of the prognostic factors for overall survival

	OR	95% CI	p
Gender (female/male)	0.282	0.078–1.121	0.0735
Distant metastasis (+/–)	4.242	1.305–13.790	0.0163
CEA-dt (≥150/<150 days)	0.268	0.084–0.861	0.0270
Size of local recurrence lesion (≥5/<5 cm)	9.850	2.504–38.742	0.0011

OR = Odds ratio; 95% CI = 95% confidence interval.

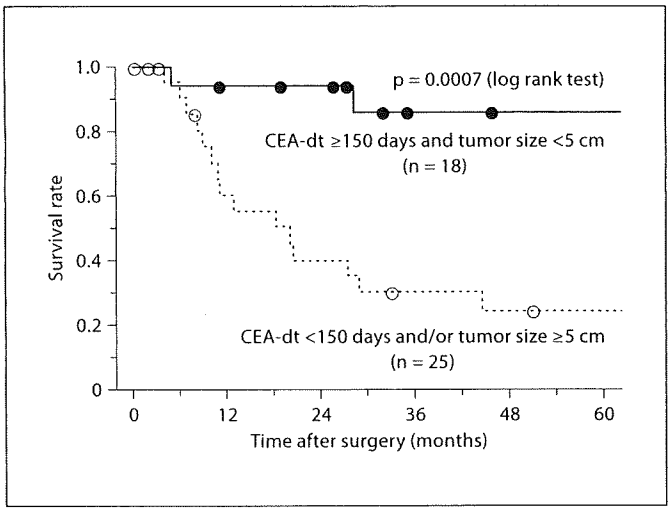

Fig. 2. The overall survival rate of patients with a CEA-dt of ≥150 days and tumor size of <5 cm (solid line) in comparison to that of patients with a CEA-dt of <150 days and/or tumor size of ≥5 cm (dotted line).

tients were divided into 2 groups based on the CEA-dt and tumor size. When the CEA-dt was ≥150 days and recurrent tumor size was <5 cm (n = 18), the 3- and 5-year overall survival rates of patients after the resection were both 86.3% (fig. 2). On the contrary, when the CEA-dt was <150 days and/or the recurrent tumor was ≥5 cm in diameter (n = 25), the 3- and 5-year overall survival rates of patients after the resection were 30.3 and 24.2%, respectively (p = 0.0007).

There were 6 cases of distant metastasis alone and 8 cases of local recurrence with or without distant metastasis even after a curative operation for local recurrence. In addition, there were 13 cases (48.1%) without recurrence.

Discussion

A number of prognostic factors affecting survival after a surgical resection of a local recurrence of rectal cancer have been reported by many investigators, including maximum tumor size [17], interval between the primary surgery and surgery for recurrence [23], curability of the surgery for recurrence [24, 25], procedure of primary surgery [26, 27], absence of severe symptoms [28], fixity of the recurrent tumor [28], gender [29] and the preoperative serum CEA level [11, 27, 30]. However, the survival in relation to the prognostic factors varied among the institutions, and the factors which are the best indicators for a surgical resection remain unclear.

The tumor doubling time was initially reported as a way to estimate when pulmonary metastasis from colorectal cancer might become apparent, with a short tumor doubling time thus indicating a rapid tumor growth [19]. Thereafter, serum CEA-dt level was also reported to strongly correlate with the survival of patients with recurrent colorectal cancer [21]. Onodera et al. [31] reported that CEA-dt reflects the rate of growth and is the most powerful determinant, while it also correlates with survival, more closely than the CEA level. In this study, a CEA-dt cutoff point of 150 days was used because the median value of CEA-dt was 158 days (mean 343 days; range 28.8–2,453). The CEA-dt was selected as an independent prognostic factor, presumably because a short CEA-dt may reflect adverse tumor characteristics including a high potential for spread.

The tumor size as a prognostic factor still remains controversial. Cunningham et al. [32] demonstrated that tumor size is not statistically related to survival. Gagliardi et al. [17] reported that the recurrent tumor diameter (5 cm) was the only independent prognostic factor. In this study, the mean of tumor diameter was 4.6 cm and we used 5 cm as the cutoff line. A tumor diameter <5 cm was determined to be an independent prognostic factor, and

the tumor diameter may thus reflect the curability of a resection.

The presence of distant metastases at the time of surgery for local recurrence remains an unresolved problem. Most reports consider distant metastases to be a criterion for excluding the resectability of recurrent tumors. However, Hashiguchi et al. [33] analyzed the presence of distant metastases at the time of resection of a local recurrence and did not find any statistical significance, suggesting that not even the intraoperative discovery of a liver metastasis should be considered a contraindication to surgery for a local recurrence. Gagliardi et al. [17] showed that resection of metastases at the time of the recurrence excision is an independent prognostic factor. Based on this result, no surgical limitation is presented by the presence of distant metastases. The current study revealed distant metastasis to be an independent prognostic factor according to a multivariate analysis. However, 1 patient with distant metastasis whose CEA-dt was 523 days received an operation for distant metastasis and local recurrence at the same time and is presently alive without recurrence for 75 months. This may be due to a slow rate of tumor progression. The prognosis of patients with distant metastasis is not always poor, and surgery for those patients may be considered when the distant metastasis can be controlled and the CEA-dt is long.

Considering the results of this study, patients with locally recurrent rectal cancer should therefore receive a surgical resection when the CEA-dt is ≥150 days and recurrent tumor is <5 cm in diameter. In contrast, patients with locally recurrent rectal cancer with either distant metastasis or with a CEA-dt of <150 days and/or recurrent tumor measuring ≥5 cm in diameter may undergo neoadjuvant and/or adjuvant therapy, because surgery alone does not result in a good prognosis. Even after a curative operation, 8 of 27 cases developed local recurrences. This result suggests that local control for local recurrence is difficult. A true curative surgical approach can be obtained only when the microscopic margins are negative. A pathologically true negative margin can be achieved in about 45% of cases, ranging from 10 to 67% [34]. In the current study, 27 of 43 patients (62.8%) received a pathologically curative resection. The involvement of the pelvic side wall and/or adjacent organs makes a curative resection a very ambitious target. Preoperative chemoradiation and intraoperative radiation may improve local control and survival in patients with locally recurrent disease with acceptable morbidity. Vermaas et al. [35] reported that preoperative radiotherapy for recurrent rectal cancer results in a higher number of complete resections and improved local control in comparison to patients treated without radiotherapy. High-dose rate interstitial brachytherapy delivers high-dose, highly controlled and focused radiation to specific sites of disease, thereby minimizing the degree of injury to normal tissues. It was reported that high-dose rate interstitial brachytherapy was useful for increased local control, better palliation and increased salvage of patients [36, 37]. Recently, carbon ion radiotherapy was reported to be effective in terms of improved local control and less risk of normal tissue damage in comparison to traditional radiotherapy. Tsujii et al. [38] reported that the 3- and 5-year overall survival rates of patients with locally recurrent rectal cancer treated by carbon ion radiotherapy were 65% and 55%, respectively. The patients with unresectable local recurrence may receive high-dose rate interstitial brachytherapy or carbon ion radiotherapy. In our study, there was no survival benefit with either neoadjuvant or adjuvant therapy. However, the regimen of chemotherapy and the quality of radiation in this study were different from the modalities we use today, and we also could not deny the benefit of either neoadjuvant or adjuvant therapy. However, due to the small number of patients investigated in these studies and the short follow-up, no definitive conclusions could be made.

Based on the findings of this study, the presence of distant metastasis, tumor size and CEA-dt were all identified to be useful prognostic factors before surgery. Patients with locally recurrent rectal cancer with a CEA-dt ≥150 days and a recurrent tumor measuring <5 cm in diameter are therefore considered to be good candidates for surgery.

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【治　療】

大腸癌の肝・肺同時転移/再発の外科的治療方針

Treatment of Simultaneous Liver and Lung Metastasis from Colorectal Cancer

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Summary

大腸癌の肝・肺同時転移/再発例は外科的切除の対象となることは少なく，大部分が化学療法もしくは対症療法の適応となっている。また，再発時期や無再発生存期間が予後規定因子であるという報告もあるが，一定の見解は得られていない。今回のわれわれの検討では，原発巣切除後の5年生存率と肝および肺切除後の3年生存率はそれぞれ，肝・肺同時転移/再発例(N=7)では，33.3%，33.3%，肝，肺異時転移/再発例(N=21)では，90.5%，75.9%と，肝・肺同時転移/再発例で予後不良であった。したがって，肝・肺同時転移/再発例に対する外科的切除は，より慎重に選択すべきである。しかしながら，単一施設の症例数では十分な解析は困難であり，今後，多施設で肝・肺同時転移/再発の臨床病理学的因子を検討する必要がある。

● 大腸癌　● 肝転移　● 肺転移
● 同時性　● 手　術

Key words

はじめに

肝転移，肺転移は，大腸癌の転移頻度が高く，また予後規定因子でもあり，これらに対する治療戦略は重要な課題である。

Weissらのカスケード理論によると[1]，転移は段階的に生じ，肝転移，肺転移のそれぞれが単独であれば同時性(Stage Ⅳ)でも異時性(再発)でも，「転移巣が切除可能であれば切除を考慮する」と，ガイドラインにも一定した治療方針が示されている[2]。しかしながら，肝，肺のように2臓器に転移が存在していれば，よりsystemic diseaseに近いきわめて進行した病態であると考えられる。ガイドラインにも，Stage Ⅳ大腸癌の治療方針には，「複数部位への遠隔転移を伴う場合：原発巣と肝・肺転移巣の切除が安全かつ容易であれば，切除も考慮される」とあるが，再発大腸癌の治療方針には，「再発臓器が2臓器以上の場合，それぞれが切除可能であれば切除を考慮してもよいが，統一見解は得られていない」と記載されており，このような病態で

は外科的切除が考慮されるものの，より明らかな方針は明示されていない。

本稿では，われわれが経験した肝・肺同時転移 再発例を紹介し，若干の文献的検討を加えた。なお，大腸癌の肝，肺への転移 再発は，原発巣との併存の有無や転移 再発の出現時期により，実際にはさまざまなパターンが存在する。したがって，本稿では表1のようにこれらの病態を分類することにした。

症例報告(表2，症例7)

症　例：70歳代の男性。

現病歴：便柱狭小化の精査の結果，S状結腸癌を指摘。画像上は遠隔転移なしと診断。

治療経過：1993年4月，S状結腸切除術(D3)を施行したが，術中肝S4に径3mmほどの単発転移を認めたため，部分切除を行うとともに動注リザーバーを留置した。原発巣は3型の中分化型腺癌，pSS，pN2(7/42)，ly1，v1，Cur B手術であった。術後補助化学療法として，肝動注(ADM，MMC)と経口抗がん剤(5'DFUR)を1年間施行。経過観察していたが，1996年10月，肝再発(単発，S4，φ15mm)を認めたため肝S4部分切除術を施行。1999年12月には，肝再発(単発，S5，φ38mm)と肺再発(単発，左上区域，φ18mm)を同時に指摘され(図1)，肝S5部分切除術と左肺上区域切除術を施行。肝切除，肺切除はいずれも組織学的に治癒切除であった。その後も経過観察しているが，初回手術から113ヵ月，最終の転移巣切除術から33ヵ月経過した現在，無再発生存中である。

本症例は，初回の同時性肝転移の手術からの無再発生存期間が36ヵ月で，以降，肝に2回，肺に1回再発をきたしたが，いずれも単発であり，当施設における肝・肺同時転移/再発症例の中で最も長期生存中である。

治療成績

表1に示すように，当施設の大腸癌の肝および肺転移/再発例の中で，28例が外科的に治癒切除されていた。内訳は，肝転移と肺転移が同時に診断された肝・肺同時転移/再発例が7例で，肝転移と肺転移がそれぞれ異時に診断された肝，肺異時転移/再発が21例であった。原発巣切除後の5年生存率

表1　肝および肺転移/再発時期による分類

	同時性 synchronous (原発巣あり)	異時性 metachronous (原発巣なし)
肝・肺同時転移/再発(7例) simultaneous 同時性肝・肺転移 異時性肝・肺転移	肝・肺	肝・肺
肝，肺異時転移/再発(21例) sequential	肝 → 肺 肺 → 肝	肝 → 肺 肺 → 肝

表2　肝・肺同時転移/再発(7例)

症 例	肝・肺転移時期	年齢性別	原発部位	pT	pN	原発stage	DFI (m)	肝転移 個数	肝転移 最大径(mm)	肺転移 個数	肺転移 最大径(mm)	肝肺切除後再発	観察期間(m)	転 帰
1	同時性	60代M	結 腸	SE	N0	Ⅳ	0	2	30	1	40	肝，肺	26.7	原病死
2	同時性	50代M	直 腸	A	N3	Ⅳ	0	2	16	2	6	骨	18.6	原病死
3	同時性	50代M	結 腸	SS	N1	Ⅳ	0	1	15	3	18	肺→脳	47.2	原病死
4	同時性	70代M	結 腸	SS	N1	Ⅳ	0	1	16	1	11	肺→肝→副腎	31.9	原病死
5	同時性	40代F	直 腸	A	N2	Ⅳ	0	1	14	2	32	脳	15.1	担癌生存
6	異時性	60代M	結 腸	SS	N2	Ⅲb	33.1	2	44	1	15	肺→肝	71.0	原病死
7	異時性	70代M	結 腸	SS	N2	Ⅲb	36.1	1	38	1	18	な し	112.9	生 存

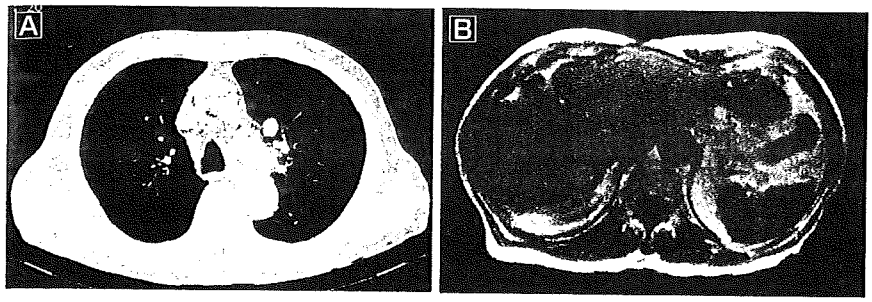

図1　肝・肺転移のCT・MRI所見(症例7)
A：胸部CT。左肺S3に大きさ18mmの単発の転移巣を認める。縦郭リンパ節腫大は認めず。B：腹部MRI(T1強調)。肝S5に大きさ38mmの単発の転移巣を認める。

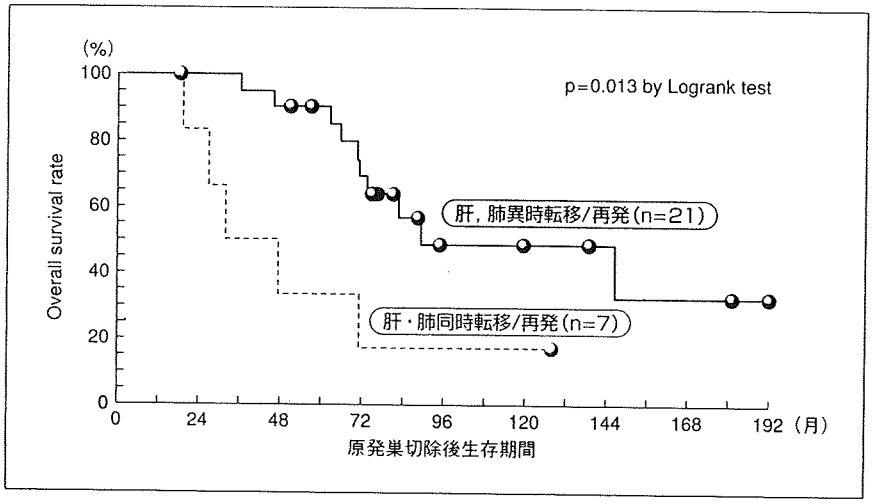

図2　原発巣切除後の全生存期間の比較
●，○は打ち切り症例。肝・肺同時転移/再発症例は破線，異時転移/再発症例は実線で表示。

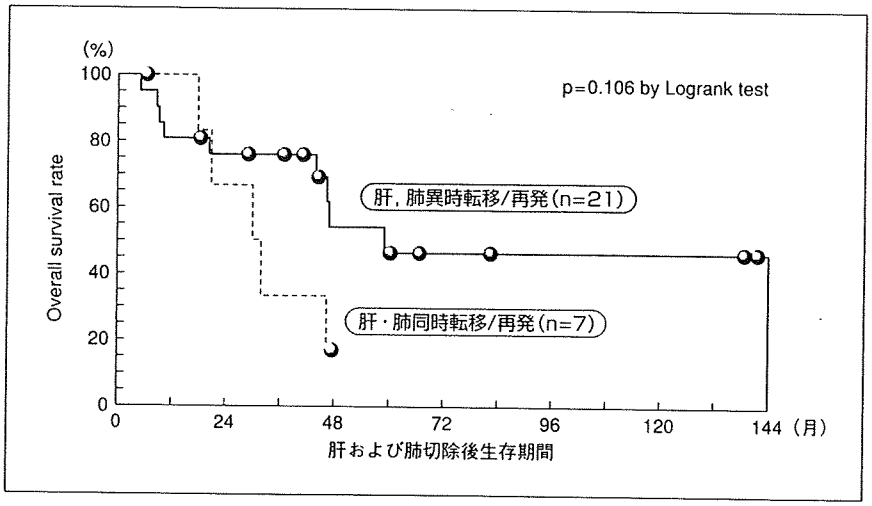

図3　転移巣切除後の全生存期間の比較
●，○は打ち切り症例。肝・肺同時転移/再発症例は破線，異時転移/再発症例は実線で表示。

(図2)と肝および肺切除後の3年生存率(図3)はそれぞれ，肝・肺同時転移/再発群(n=7)では，33.3%，33.3%，肝，肺異時転移/再発群(n=21)では，90.5%，75.9%であり，原発巣切除後の生存率では有意差(p=0.013)があったが，肝および肺切除後の生存率では差は認められなかった。

文献的報告

われわれが，PubMedで検索しえた範囲では，肝・肺同時転移に対する外科的切除の報告は比較的少なく[3-9]，切除された症例数も少ない(表3)。これら切除例では，5年生存率は0~23%，Medianは14~42ヵ月と，その成績は芳しいものではない。しかしながら，非切除例に比べると予後は良好であると報告されている[6]。また一方で，Shahらは5年生存率74%，Medianで87ヵ月と非常に良好な成績を報告している[8]。予後因子としては，転移時期(同時性・異時性)，無再発生存期間，転移個数(単発・多発)，肺転移の局在(片肺・両肺)，腫瘍マーカー(CEA)，年齢などが報告されているが，今のところ一定の見解は得られていない。

おわりに

従来の肝転移[10]や肺転移[11]の単独臓器転移を伴うStage Ⅳ大腸癌の手術成績は約50~60%と良好である。しかしながら，今回のテーマである肝・肺同時転移/再発の成績はこれらの肝，肺単独臓器転移に比べて不良である。今後，非切除で化学療法を選択した場合と比較して外科的切除のbenefitは何

表3　代表的な文献的報告

Author	肝・肺同時転移/再発(simultaneous)		肝, 肺異時転移/再発 (sequential)	予後因子	肝・肺同時転移/再発 (simultaneous)の治療成績
	同時性肝・肺転移 (synchronous)	異時性肝・肺再発 (metachronous)			
Ambiru ら[3]	1	0	5	CEA 単発再発	6m 無再発生存
Murata ら[4]	1	11	18	肺転移局在 肝肺転移時期	Median：24m 5y-OS：22.2%
Kobayashi ら[5]	7	14	26	肺転移個数 肝肺転移時期	Median：24m 5y-OS：22%
Robinson ら[6]	2	0	23	年 齢 肝転移個数 肝肺転移時期	Median：14m 5y-OS：0%
Nagakura ら[7]	4	3	20	肝肺転移時期	Median：23m 5y-OS：0%
Shah ら[8]	11		28	治癒切除	Median：87m 5y-OS：74%
Miller ら[9]	12	20	99	年齢 肝転移個数 肝肺転移時期	Median：42m 5y-OS：23%

なのか，予後規定因子は何なのか，などの検討が必要である。

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Original Paper

Intraoperative Thermal Ablation Therapy for Small Colorectal Metastases to the Liver

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KEY WORDS:
MCT; RFA; Liver metastasis; Colorectal cancer; Hepatic resection; Intrahepatic recurrence

ABBREVIATIONS:
Thermal Ablation (TA); Microwave Coagulation Necrosis Therapy (MCT); Radiofrequency Interstitial Thermal Ablation (RFA); Computed Tomography (CT); Magnetic Resonance Imaging (MRI); Ultrasound (US); Carcinoembryonic Antigen (CEA)

ABSTRACT

Background/Aims: Thermal ablation (TA) therapies such as microwave coagulation therapy (MCT) and radiofrequency interstitial thermal ablation (RFA) for colorectal metastasis to the liver cannot always achieve a complete tumor cell death, and the multiple insertions of the TA probe may lead to intrahepatic dissemination and/or distant metastasis.

Methodology: The achieved local control rate, any recurrence in the residual liver, and any extrahepatic recurrence has been evaluated in 105 patients who underwent hepatectomy and/or intraoperative TA between 1994 and 2004.

Results: A total of 102 unresectable liver metastatic lesions (mean size 21mm) were selectively treated with TA either as initial treatment (32 patients) and/or as re-treatment (18 patients) for recurrence in the residual liver, in combination with hepatectomy. Overall, TA achieved a high local tumor control rate of 95%. Multivariate analysis revealed that initial-TA therapy was not a significant predictive factor of hepatic recurrence or any recurrence.

Conclusion: TA therapies in combination with hepatectomy may offer increased resectability without increased risk of intrahepatic dissemination or extrahepatic recurrence for certain patients who would otherwise be deemed inoperable, when relatively small tumors are indicated for TA.

INTRODUCTION

The incidence of hepatic surgery for colorectal metastasis has increased, with a reported 5-year-survival rate of 20-51%, if all the metastatic tumors can be totally resected (1,2). On the other hand, when unresectable hepatic metastases are involved, the outcome can be quite poor. Unfortunately, only approximately one third of patients with liver metastases are candidates for surgery because of a variety of factors including the anatomical distribution of the metastases, proximity to major vascular structures, and extrahepatic disease (3). Thermal ablation (TA) therapies such as microwave coagulation therapy (MCT) and radiofrequency interstitial thermal ablation (RFA) are new techniques to increase the number of patients eligible for curative treatment. Recently, TA has been used in association with hepatectomy in patients that would not otherwise be indicated for surgery (4-6). There is a group of patients with multiple metastases who are deemed unresectable due to only 1 or 2 of the metastases being anatomically difficult to reach, situated either in the proposed hepatic remnant or alongside a large vein. Localized wedge resection of such tumors is not always technically feasible, particularly if they are deep within the hepatic parenchyma. If such lesions can be treated by TA, then the tumor and remaining metastases may be curatively resected. Repeat hepatic resection for recurrent liver metastases after a first hepatic resection has also been reported in selected patients as beneficial in terms of mortality, morbidity, and survival (7,8). However, the indication for a repeat hepatic resection is much reduced compared with that for a first hepatectomy because of the severity of the factors mentioned above. TA therapy may increase the overall number of patients surgically-treated curatively, even in treatment for recurrent tumors in the residual liver. Strategies designed to increase the proportion of patients who are candidates for complete surgical treatment of liver metastases are now emerging.

We have employed intraoperative TA therapy either with or without hepatic resection for totally unresectable and relatively small colorectal metastases to the liver to improve curability and survival, and/or even for resectable metastases to reduce surgical invasiveness since 1994. However, MCT and RFA cannot always achieve a complete tumor cell killing, resulting in recurrence at the site of ablated lesion (9). Moreover, the multiple insertions of the TA probe into a large metastatic tumor may lead to intrahepatic dissemination and/or in distant metastasis. Thus, it is important to know the capability of TA to achieve local control and its influence to intrahepatic or extrahepatic recurrence, and survival, in order to apply TA adequately to colorectal metastases to the liver. In the present study, to clarify the ability of local control and the influence on intrahepatic

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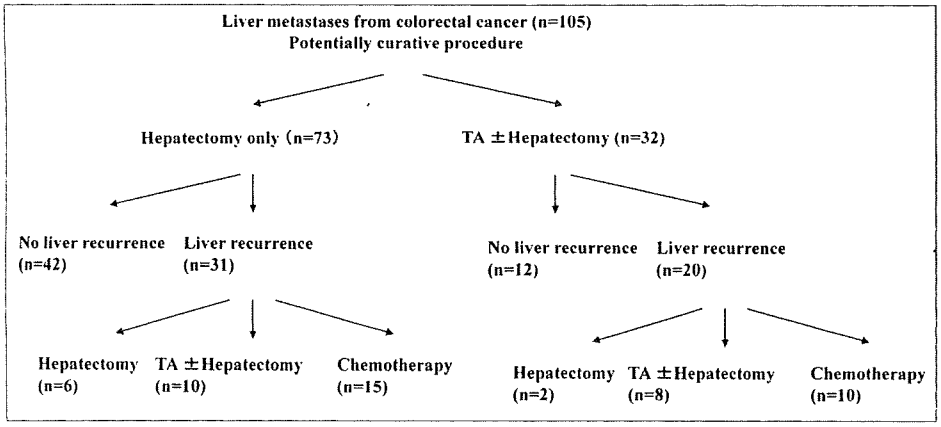

FIGURE 1 Distribution of patient groups studied. The TA therapy was performed as an initial treatment in 23 patients with hepatectomy and in 9 patients without hepatectomy, and as secondary treatment against recurrent liver metastases during follow-up after first treatment in 11 patients without hepatectomy and in another 7 patients with hepatectomy.

recurrence and distant metastasis of the intraoperative TA therapy for relatively small metastases, the data of patients who underwent intraoperative TA therapy for colorectal metastases to the liver has been reviewed.

METHODOLOGY

This study reviews the data from 105 patients with colorectal metastases to the liver who underwent open laparotomy with hepatectomy and/or TA, between 1994 and 2004 at Kurume University Hospital. The patients consisted of 72 males and 33 females, and the mean age of all patients was 61.5 years, with an age range from 30-83 years. A total of 42 patients were treated with MCT and/or RFA as an initial treatment (32 patients) intraoperatively with hepatectomy (23 patients) or without hepatectomy (9 patients) for liver metastases, and as re-treatment for recurrent tumors in the residual liver (18 patients) with or without hepatectomy **(Figure 1)**. A total of 102 metastases were treated with 52 sessions of TA. The mortality and morbidity rates in those receiving TA therapy, the rate of local recurrence at the treatment site, the disease-free survival rate, the liver-disease-free survival rate, and the overall survival rate were evaluated.

All 105 patients had pathologic confirmation of colorectal liver metastasis. Preoperative imaging included chest radiograph or computed tomography (CT) when indicated, as well as abdominopelvic imaging with CT or magnetic resonance imaging (MRI) in all patients. All patients underwent a baseline evaluation, including a history and physical examination; serum laboratory tests consisting of a complete blood count, platelets, coagulation profile, renal panel, liver functions, and carcinoembryonic antigen (CEA). At 1 week after TA any complete ablation was confirmed by dynamic CT. Follow-up ultrasound (US), CT or MRI of the abdomen, chest radiography, and CEA measurement were performed at 1 month and then at every 3 months up to 2 years, and then at every 6 months during the following years after surgery.

All clinical and pathological data, including sex, age, laterality and number of hepatic metastases, the diameter of the hepatic metastases, type of hepatic resection, involvement of any extra-hepatic metastases, interval after initial treatment of the primary colorectal lesion, TA therapy and the histopathological findings of the primary colorectal tumor were reviewed with regard to hepatic recurrence. The median follow-up time after the initial hepatic treatment for all patients was 47 months (range: 2-134 months).

MCT was performed using a microwave tissue coagulator OT-110M (Nihon Shouji, Osaka, Japan) for a total duration of 2-20 minutes at an output of 90 Watts for near-surface metastasis and of 60 Watts for deeper metastasis. The needle electrode was inserted several times into each target lesion under the guide of ultrasonography, using a 5-MHz US probe (Toshiba, Tokyo, Japan) directly on the surface of the liver to monitor the coagulation of the lesion, until the echogenecity of the tumor and its surrounding area became high, which occurred due to water vapor generated by local heat. The tumors were treated one-by-one until all the target lesions in the liver showed coagulation.

RFA was performed using an RF 2000 generator system (Boston Scientific-Japan, Tokyo, Japan) using a 2-phase algorism. The RF 2000 system consists of a generator that supplies up to 100 Watts of power, a LeVeen monopolar array needle electrode, and indifferent dispersive electrode pads applied to the patient's skin. The LeVeen needle electrode contains multi-individual hook-shaped electrode arms that are deployed *in situ* after ultrasound-guided placement of the needle electrode into the liver tumor. The initial power was set at 50 Watts, and was then increased in 10-Watt increments at 1-minute intervals. The power and tissue impedance were monitored continuously from the RF generator until power 'roll-off' occurred as a result of coagulative necrosis of the tissue in the treatment field. After a 20-second pause, the power was reapplied at 75% of the maximum power achieved until power roll-off again occurred. When a lesion was larger than 25mm, then multiple insertions were performed to achieve a complete ablation of the lesion including at least a 1cm margin zone of the surrounding liver

TABLE 1 Background of the Patients at the Initial Treatment for Liver Metastases

Treatment	Age (years)	Sex (M/F)	Liver metastases: Number *	Size** (mm)	Distribution* (uni/bilateral)	Synchronous+ /metachronous	Extrahepatic Disease (%)
Hepatectomy-alone (n=73)	63±11	52 / 21	2.2±1.8	39±25	56 / 17	37/36	11(15%)
Thermal ablation with or without hepatectomy (n=32)	59±11	20 / 12	4.0±2.5	28±11	10 / 22	24/8	7(22%)

Data represent mean±SD for age, and number and maximum size of tumors.
*: $p<0.001$; **: $p=0.016$; +: $p=0.031$

parenchyma wherever possible.

Any statistically significant difference in clinicopathological characteristics between groups was assessed using the chi-square test, Fisher's exact test, and Student's *t* test. The survival rates were calculated by the Kaplan-Meier method. Any difference in the survival rate between groups was evaluated using the Log-rank test. The prognostic influence of each variable on hepatic recurrence was analyzed using Cox's proportional hazards model for multivariate analysis.

RESULTS

Background of the Patients and Ablated Tumors

The background of the patients in the Hepatectomy-alone Group (n=73) and in the TA Group (n=32) at the initial treatment for liver metastases are shown in **Table 1**. The reasons for applying TA were anatomically unresectable metastases in 11 patients (in order to increase resectability), metastases located too deep within the hepatic parenchyma in 8 patients (to reduce surgical invasiveness), high general risk for hepatectomy in 2 patients (to reduce surgical invasiveness), concomitant resection of the primary lesion in 1 patient (to reduce surgical invasiveness), extrahepatic disease which needed to be resected in 2 patients (to allow low surgical invasiveness as a priority over curability), patient's choice in 2 patients, and combination of the above in the other 6 patients. **Figure 2** shows the preoperative CT in a patient presenting several reasons for the application of the TA therapy. The number of liver metastases was 4.0±2.5 in the Initial-TA Group, which was significantly higher ($p<0.001$) than 2.2±1.8 in the Hepatectomy-alone Group. Also, the incidence of bilateral metastases was significantly higher ($p=0.001$) in the Initial-TA Group than in the Hepatectomy-alone Group. However, the maximum size of metastases in the Initial-TA Group (28±11mm) was significantly smaller ($p=0.016$) than that in the Hepatectomy-alone Group (39±25mm). The rate of synchronous liver metastasis in the TA Group was significantly ($p=0.031$) higher than that in the Hepatectomy-alone Group.

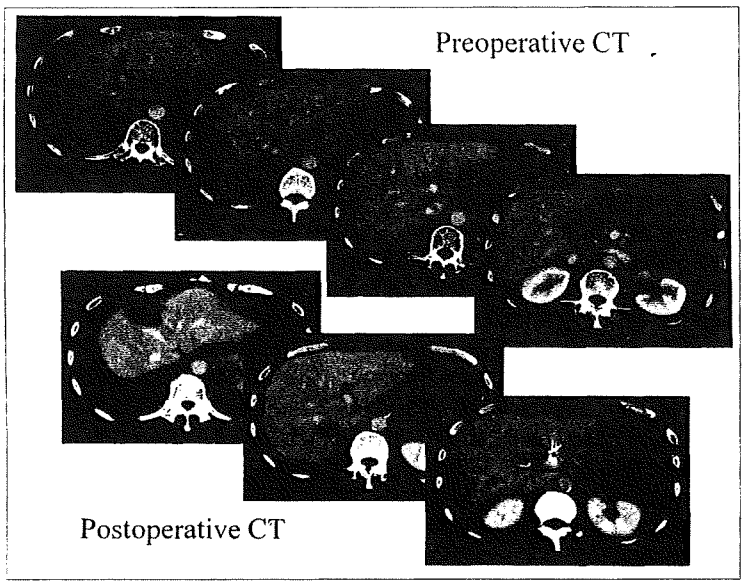

FIGURE 2 Pre- and post-operative CT scans. A 51-years old man presented rectal cancer associated with 5 synchronous liver metastases in the bilateral lobes. Low anterior resection and hepatic wedge resection of S1, S3 and S4-8 were performed, and the other 2 liver lesions in S6 and S7 were treated with RFA (arrow). Total resection of the metastatic lesions was thought to be too invasive because of the bilateral distribution, the deep location within the hepatic parenchyma, and the concomitant resection of the primary lesion.

The initial-TA was MCT for 39 metastatic lesions in 18 patients, and RFA for 27 lesions in 16 patients (both RFA and MCT were performed in 2 patients). Follow-up TA as a repeat or re-repeat treatment for recurrent liver metastases, was MCT for 20 metastatic lesions in 11 patients, and RFA for 16 lesions in 9 patients (both RFA and MCT were performed in 2 patients). The overall mean size of the ablated lesions was 21±10mm with a range from 12-40mm. Only 3 tumors were larger than 30mm in size.

Mortality and Morbidity of Ablation Therapies

In all 42 patients there was no mortality involving 52 sessions of TA, including repeat and re-repeat TA for recurrent liver metastases. Also no hepatic insufficiency, no renal insufficiency, and no coagulopathy developed in any patient after TA. Liver abscess developed in 2 patients of those involving 59 metastatic lesions treated with MCT, and in no patients of those involving 43 lesions treated with RFA. One of the 2 patients with a liver abscess was associated with biliary fistula. All these complications were successfully treated conservatively. There was no massive hemorrhage in any of the patients treated with TA.

Recurrence in the Tumors Treated with Ablation Therapies

CT scans at 1 week after TA revealed no viability in all 102 ablated tumors. The median follow-up period by CT scan for the TA-treated lesions was 33 months. When a new metastatic lesion in the liver developed in continuity with the ablated margin, it was considered to be a recurrence of metastasis at the site of TA. Such recurrence developed at the site of TA in 5 (4.9%) of the 102 treated metastatic lesions, involving 4 (7.7%) of the 52 sessions; 3 of those sessions had used MCT (4/59 lesions, 6.8%), and 1 had used RFA (1/43 lesions, 2.3%).

Disease-free Survival and Liver-disease-free Survival

Hepatic or extrahepatic recurrence after initial treatment for liver metastases developed in 47 patients (64%) in the Hepatectomy-alone Group (n=73), and in 25 patients (78%) in the TA Group (n=32). The disease-free survival rate in the TA Group tended to be lower than that in the Hepatectomy-alone Group, but the difference was not significant (p=0.127). Hepatic recurrence developed in 31 patients (42%) in the Hepatectomy-alone Group and in 20 patients (63%) in the TA Group. However, there was no recurrence along the needle route in the TA Group. The liver-disease-free survival rate in the TA Group was significantly (p=0.027) lower than that in the Hepatectomy-alone Group **(Figure 3)**. The rate of extrahepatic recurrence was 56% in the TA Group and 45% in the Hepatectomy-alone Group, with no significant difference.

Univariate and Multivariate Analysis for Factors Correlated with Hepatic Recurrence

The following were evaluated for their independent contributions to the hepatic recurrence using Cox's proportional hazards model; age, sex, primary tumor location (colon *vs.* rectum), histological tumor grade (G1 *vs.* others), lymph node involvement (- *vs.* +), tumor infiltration (invasion to the adjacent organs + *vs.* -), lymphatic invasion (- *vs.* +) (10), venous invasion (- *vs.* +) (11), laterality (unilateral *vs.* bilateral), solitary metastasis *vs.* multiple metastases, number of liver metastatic lesions (1-4 *vs.* >4), diameter of largest liver metastasis (<50mm *vs.* ≥50mm), type of hepatic resection (anatomical resection or not), extrahepatic disease which were treated with surgery or chemotherapy with curative intent before or at the time of hepatic operation (- *vs.* +), synchronous *vs.* metachronous metastases, and TA as the initial treatment (- *vs.* +). The multiplicity and synchronous metastases in the liver, lymph node involvement by the primary tumor, and the use of TA were found to be significant predictive factors of hepatic recurrence by univariate analysis **(Table 2)**. The multivariate analysis revealed that only synchronous metastases in the liver and lymph node involvement by the primary tumor were found to be independent significant predictive factors of hepatic recurrence, and that initial-TA therapy was no longer a significantly predictive factor of hepatic recurrence **(Table 3)**.

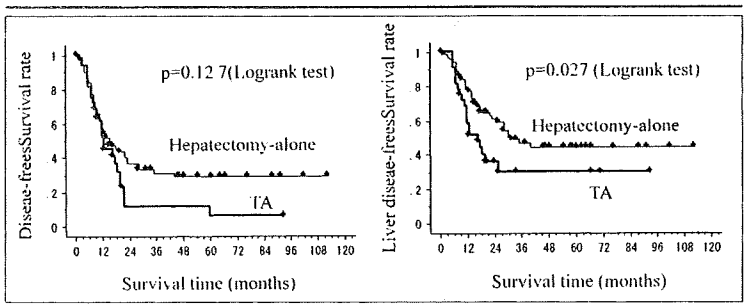

FIGURE 3 Disease-free survival curves and liver disease-free survival curves after initial treatment for liver metastases.The disease-free survival rate (p=0.127) and the liver disease-free survival rate (p=0.027) in the TA Group (n=32) were lower than those in the Hepatectomy-alone Group (n=73).

Overall Survival

The median survival time in the TA Group was 43 months. The 5-year-survival rate was 32% in the TA Group (n=32). Among 51 patients who had recurrence in the liver, repeat hepatectomy-alone was performed in 8 patients, TA-with-simultaneous-hepatectomy in another 7 patients, and TA-alone in the other

TABLE 2 Univariate Analysis for the Factors Correlated to the Hepatic Recurrence Factor

	p-value	Hazard ratio
Lymph node metastasis (+) *	p=0.012	2.151
Synchronous metastasis	p=0.012	2.119
Multiple metastasis	p=0.028	1.859
Thermal ablation (+)	p=0.032	1.845
Lymphatic permeation (+) *	p=0.073	2.551
Bilateral metastasis	p=0.075	1.621
Type of resection (Non-anatomical)	p=0.122	1.525
Postoperative HAI	p=0.182	1.442
Tumor grade (except G1)*	p=0.235	1.387
Number of metastases (>4)	p=0.287	1.433
Venous invasion (+) *	p=0.555	1.323
Tumor size (>50 mm)	p=0.644	1.185
Extrahepatic disease (+)	p=0.673	1.159
Tumor invasion to an adjacent organ *	p=0.885	1.070
Tumor location (rectum) *	p=0.826	1.063
Gender (female)	p=0.974	1.009
Age (<70 years)	p=0.988	1.007

*: findings of primary tumor; HAI: hepatic arterial infusion chemotherapy

TABLE 3 Multivariate Analysis for the Factors Correlated to the Hepatic Recurrence

Variable	*p*-value	95% CI	Hazard ratio
Lymph node metastasis (+)	p=0.032	1.056-3.509	1.923
Synchronous metastasis	p=0.044	1.020-5.382	1.869
Multiple metastases	p=0.229	0.789-2.681	1.456
Thermal ablation (+)	p=0.401	0.670-2.439	1.307

Lymph node metastasis was a finding of the primary tumor.

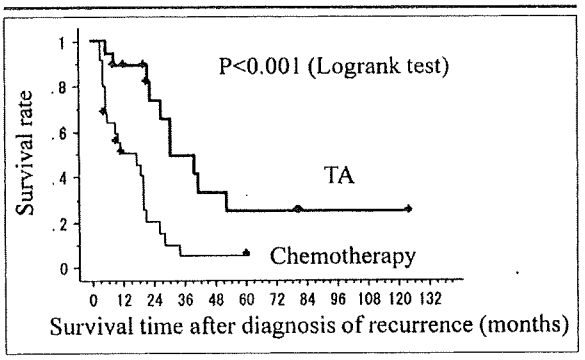

FIGURE 4 Survival curves after diagnosis of recurrent liver metastases. The 3-year-survival rate was 49% and 5-year-survival rates was 24% in the TA (n=18). The survival rate in the TA Group was significantly higher ($p<0.001$) than that in the Chemotherapy Group (n=25).

11 patients. All the other 25 patients, except for 1, received chemotherapy-alone such as hepatic arterial infusion and systemic chemotherapy. Among the 18 patients who were treated with TA for recurrent metastases (2 had received initial-TA-only, 8 initial-TA-with hepatectomy, and 8 initial hepatectomy-alone as initial liver treatment), isolated liver metastases later occurred in 11 patients, and multiple-organ recurrence including the liver occurred in 7 patients. When the survival time in these 18 patients was defined in terms of months after recurrence to the liver, the 3- and 5-year-survival rates were 49% and 24%, respectively. The overall survival rate after the recurrence to the liver in those treated with TA was significantly higher ($p<0.001$) than that in the Chemotherapy-alone Group **(Figure 4)**.

DISCUSSION

The mortality and morbidity rates associated with these combinations of ablation and hepatectomy for curative treatment of liver metastases from colorectal tumors, including both initial and repeat treatments, were acceptable. Also any severe complication was rare and manageable, as the safety of TA therapy has been recognized (12,13).

The rates of recurrence in the ablated tumors were 6.8% after MCT and 2.3% after RFA. These are reasonable from a local treatment modality with curative intent. This low rate of local recurrence may be due to the limited indication for TA. In other words, TA was performed during open laparotomy in selected tumors smaller than 40mm in diameter (most tumors were smaller than 30mm, average size: 21±10mm). With regard to local control of MCT, Seki *et al.* (14) reported that complete coagulation was achieved in 13 of 15 patients with solitary liver metastasis smaller than 30mm in diameter despite using a percutaneous approach, and that no recurrence occurred during follow-up (9-37 months). With regard to local control by RFA, in an earlier study on RFA for colorectal metastases to the liver, a rate of more than 50% was reported for local recurrence (15,16). However in 1999, Curley *et al.* (12) showed improved local control rate by RFA in 123 patients, including 61 patients who had colorectal metastasis, with a low recurrence rate of only 1.8% (involving only 3 of 169 lesions). They suggested that the reason for the achieved high local control rate was the use of percutaneous RFA for only patients with metastatic lesions smaller than 30mm in size and less than 3 in number, and the use of intraoperative RFA for others. Moreover, they used the pringle-maneuver technique to avoid incomplete tumor cell killing due to a cool-down effect of blood perfusion. Elias *et al.* (17) have reported using intraoperative RFA for 227 metastatic lesions in 88 patients and achieving a local control rate of 5.7%, compared to 7.1% achieved by wedge resection for 99 metastatic lesions in 64 patients. Their data included lesions larger than 30mm, and lesions in direct contact with large vessels, which were correlated with local recurrence. On the other hand, percutaneous RFA continues to show a reported recurrence rate of about 40% within one year (18). However, the poor results from percutaneous RFA have mainly occurred only when the lesions were relatively large: RFA has achieved local control in 78% of tumors 25mm or less, in 47% of tumors 26-40mm, and in only 32% of tumors 40mm or larger in diameter. Amersi *et al.* reported that percutaneous RFA of tumors was found to be a statistical predictor for local recurrence compared to intraoperative RFA (19). Taken together, MCT and RFA have each shown equal efficacy to partial hepatic resection in terms of tumor local control when adequate indication and an optimum approach are chosen.

In hepatocellular carcinoma, rapid intrahepatic dissemination after RFA treatment has previously been reported (20). The RFA needle creates a pathway along its borehole between vascular districts (arterious and venous-portal). It is possible that the seeding along new pathway had facilitated the migration of tumor cells from a high-pressure tumoral arterious district to a low-pressure portal liver district. Although it is not clear whether metastatic colorectal tumor cells reach the portal branch walls and invade to other segments as do hepatocellular carcinoma cells, such pathway to the portal branches may permit intrahepatic dissemination, and the communication with liver veins may allow lung and systemic tumor spread. Thus, in addition to the present evaluation of achieving local control at the ablated site, for application of TA therapy instead of wedge resection, it should be noted whether TA induces intrahepatic dissemination or extrahepatic recurrence or not. It has been recently shown that intraoperative RFA with simultaneous hepatectomy for unresectable colorectal metastases to the liver has resulted in a much higher rate of intrahepatic recurrence compared with hepatectomy-alone, despite the relatively low rate of ablated-site recurrence at 6% and no differences in tumor size and number, patient or primary tumor characteristics except anatomic distribution between the groups (21). These data suggest possible intrahepatic dis-

semination by intraoperative RFA. In this crude data, a higher rate of intrahepatic recurrence and a lower liver-disease-free survival rate were found in the TA Group compared to those in the Hepatectomy-alone Group, despite the low rate of ablated-site recurrence. These data suggest that TA might have induced the intrahepatic recurrence. However, the multivariate analysis revealed that the TA therapy was not a significantly predictive factor for intrahepatic recurrence. Therefore, at this time, we have concluded that the higher rate of intrahepatic recurrence in the TA Group was due to some difference between the patient's backgrounds such as in the number, the distribution, or in the timing of metastases (synchronous or metachronous metastasis). The data also suggested that TA did not induce any distant metastasis.

A randomized study on MCT and hepatic resection for multiple liver metastases which were potentially amenable to hepatic resection revealed similar overall survival rates between the groups (22). Favorable 3-year and 5-year-survival rates of 68% and 40% after RFA were reported by Rossi *et al.* (23). Gillams *et al.* (24) reported that the 3-year and 4-year-survival rates after percutaneous RFA in 69 patients including recurrent cases in the liver were 34% and 22%. In particular they found the 5-year-survival rates in patients in whom more than 95% coagulation of the lesions could be achieved and in patients treated after 1995, whose lesions were less than 4 in number and smaller than 50mm, were favorable at 50% and 80%, respectively. These findings suggested that TA might be equal to surgical resection in effectiveness for liver metastases from colorectal cancer in terms of short-term-survival rate.

It is of interest to surgeons, if TA is similar to wedge resection in local control and survival benefit, that TA of small centrally-situated liver metastases allows complete curative R0 resection, which would otherwise have been unattainable. Two typical scenarios can summarize the benefits of TA. First, the finding of a large number of bi-lobar liver metastases is no longer considered a contraindication to hepatectomy: it is possible to perform anatomical major resection (lobectomy, segmentectomy) of large lesions and/or of lesions close to a large vessel - associated with wedge resection for a peripheral lesion and with ablation for centrally-located small lesions. Secondly, extensive extrahepatic surgery is frequently contraindicated because an unresectable central liver metastasis renders the operation essentially palliative. In these cases, intraoperative TA is able to obtain curative results and in this way permits a considerable increase in the number of patients in whom curative hepatectomy for metastases is possible. At least in half of our 32 patients treated with initial-TA with or without hepatectomy, if the ablation had not been used then palliative chemotherapy would have been performed and the prognosis would likely have been poorer. However, the 5-year-survival rate and the median survival time in these patients were favorable at 32% and 43 months, respectively.

The survival benefit of TA as a retreatment for recurrent liver metastasis was also acceptable. In the 18 patients who underwent TA-alone or TA-with-hepatectomy for recurrent liver tumors, the 3- and 5-year-survival rates were 49% and 24%, respectively, and the median survival time was 31 months. These results were not inferior to those after repeat-hepatectomy reported elsewhere (7,8). The survival rates were significantly higher compared to those in patients treated with chemotherapy-alone, although the backgrounds of the 2 groups were not equivalent. We suspect that the survival benefit after TA for recurrent liver metastases may be greater than that after initial-TA for initial metastasis, because of the low resectability and the extremely poor prognosis in patients with unresectable recurrent liver metastases.

In conclusion, TA such as MCT and RFA in combination with surgical resection is a safe technique and may offer increased resectability without risk for intrahepatic dissemination and extrahepatic recurrence in certain patients who would otherwise be deemed inoperable, when relatively small tumors are indicated for TA. The absence of risk of intrahepatic dissemination and the definitive survival benefit of TA can be expected in future randomized large studies.

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特集 ····再発癌への挑戦—肺・肝転移，手術でどこまで制御できるか····

切除不能両葉多発大腸癌肝転移症例における切除率向上の対策

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Strategies for Improving Resectability in Unresectable, Bi-lobar Colorectal Metastases to the Liver: Ogata Y[*1], Murakami H[*1], Sasatomi T[*1], Uchida S[*1], Murakami N[*1], Isobe T[*1], Akagi Y[*2], Ishibashi N[*2] and Shirouzu K[*2] ([*1]Department of Surgery, Kurume University Medical Center, [*2]Department of Surgery, Kurume University School of Medicine)

We have evaluated the achieved local control rate, any recurrence in the residual liver, and any extrahepatic recurrence after thermal ablation (TA) therapies such as microwave coagulation therapy (MCT) and radiofrequency interstitial thermal ablation (RFA) for colorectal metastasis to the liver in 137 patients who underwent hepatectomy and/or intraoperative TA between 1994 and 2006. A total of 88 unresectable liver metastatic lesions (19 mm in mean size) were selectively treated with TA as initial treatment (42 patients) basically in combination with hepatectomy. Overall, TA achieved a high local tumor control rate of 94%. Multivariate analysis revealed that initial-TA therapy was not a significantly predictive factor of hepatic recurrence or any recurrence. TA therapies in combination with hepatectomy may offer improving resectability without risk to intrahepatic dissemination or to extrahepatic recurrence.

Key words: MCT, RFA, Liver metastasis, Colorectal cancer, Hepatic resection
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はじめに

大腸癌肝転移に対する肝切除の有用性については異論のないところである[1,2]．しかし，肝切除の適応となる症例は限られている[3]．欧米と本邦では基本的な肝切除術式が異なる（欧米：葉切除を基本，本邦：部分切除）ため，本邦における切除率は欧米のそれに比べるとやや高いものの30～40%程度と推測される．

一方，切除不能な肝転移は化学療法の対象となる．最近大腸癌に有効な新薬の開発により大腸癌化学療法は目覚ましい進歩を遂げている．切除不能肝転移に対する治療戦略として化学療法を先行することによる切除率の向上が考えられる．切除可能となった肝転移症例の生存率はそもそも切除可能であった症例に比べやや劣るものの遜色ないことが報告されている[3]．

大腸癌肝転移に対する局所療法として，肝動注化学療法やマイクロ波またはラジオ波を用いた熱凝固療法が行われている．凝固療法は深部の腫瘍に対しても容易に施行可能で，肝切除に比べると低侵襲性であることから，poor risk 症例に対する局所療法として，あるいは切除不能と考えられる両葉多発肝転移例に対して凝固療法を肝切除に

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