Original article

Relationship between period of survival and clinicopathological characteristics in patients with colorectal liver metastasis

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Running title: Period of survival in liver metastasis

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Abstract

Aim: Cancer death in the early period after hepatectomy still remains in patients with colorectal liver metastasis (CLM). We examined the relationship between clinicopathological parameters and survival periods in 130 CLM patients who underwent hepatectomy.

Patients/methods: Patients were divided into four groups: Group 1 (5-year survivors without tumor relapse), Group 2 (survivors at 2–5 years), Group 3 (cancer death at 2–5 years), and Group 4 (cancer death within 2 years).

Results: A short surgical margin was frequent in Group 4 compared to Group 1 (31 vs 78%, $p < 0.05$). Primary node-positive status, absence of fibrous pseudo-capsular formation, higher Clinical Risk Score, and tumor recurrence within 12 months were frequent in Group 4 ($p < 0.05$). Multivariate analysis revealed a short surgical margin (HR; 3.5) and early tumor relapse (HR; 5.9) as independently significant related parameters ($p < 0.05$).

Conclusions: A sufficient surgical margin, or careful follow-up for early tumor relapse may be important to improve outcomes after surgery in CLM patients.

Introduction

Liver resection has become accepted as the standard treatment modality for patients with colorectal liver metastasis (CLM).[1] Previous studies report improving survival after hepatectomy; however, tumor relapse soon after hepatectomy remains common,[2] and may reduce patient survival rates.[3] The overall 5-year survival rate in CLM patients who underwent hepatectomy is favorable, ranging between 33 and 44% according to recent reports.[3-5] Therefore, survival beyond 5 years can be achieved in many patients who undergo hepatectomy. The current goal for this treatment is 5-year survival without tumor relapse.

Although previous studies report the predictors or related features with respect to post-operative survival, [3, 6, 7] a definite consensus is yet to be reached, and various predictive grading systems for survival remain controversial. Regarding predictors, clinicopathologic parameters and biological or genetic parameters have been nominated as prognostic factors. [8, 9]

In the present series, we compared the length of the survival period with these parameters in long-term follow-up of 130 Japanese CLM patients who underwent hepatic resection although the subject was not a large series. Our goal is to clarify the characteristics and prognosis between shorter and longer survival in patients with CLM who underwent hepatectomy at the Japanese single cancer unit.

Patients and Methods

Patients

In this retrospective study, we collected data of 130 CLM patients who underwent surgery at the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS), Japan, and associated cancer institutes between January 1990 and December 2006. Patients with tumor residues after hepatectomy were excluded from the study. Majority of candidates for surgery were limited to Child's A patients. All patients were medically fit for major laparotomy, showed no signs of preoperative dissemination or distant metastases except to the liver, with primary lesions and tumors confined anatomically within the liver. Each patient underwent routine preoperative imaging studies including whole abdomen and chest computed tomography (CT). Ultrasonography was used in each patient during surgery to find additional tumors and determine the incision line. Patients were followed-up at our outpatient clinic, and the clinical course was provided by the attending physicians. Follow-up included measurement of serum carcinoembryonic antigen (CEA) every 3 months and abdominal CT and chest X-ray every 3 to 6 months. When recurrence was detected, patients received re-operation or chemotherapy (intravenous or intra-arterial infusion of anticancer drugs such as 5-fluorouracil (5FU; Kyowa Hakko Chemical Co., Tokyo, Japan) and irinotecan (CPT-11; Yakult Pharmaceutical Inc. Co., Tokyo, Japan)). No defined protocols of adjuvant chemotherapy were applied before or after hepatectomy for prevention of tumor recurrence.

The volume of liver to be resected was estimated according to the indocyanine green retention rate at 15 min (ICG R15) using the formula of Takasaki *et al.*[10] The expected liver volume for resection, excluding the tumor (cm^3), was measured by CT volumetry.[11] Transection of hepatic parenchyma was routinely used a Kelly-clamp crushing technique and ultrasonic dissector was used only around the large Glissonian pedicle. Radical hepatectomy was performed to remove the hepatic tumor without leaving any residual tumor. The study was approved by the Ethics Review Board of our department at NUGSBS. Mortality and morbidity data were collected from the NUGSBS database and provided by collaborating associated hospitals.

Clinicopathological parameters, surgical records, tumor grading, and subgroups of postoperative survival

We recorded the following clinical parameters: patient demographics, preoperative CEA level (normal value: < 5 ng/mL), time to liver metastasis following surgery for the primary colorectal carcinoma, regional lymph node metastasis of the primary tumor, number of tumors, tumor size, tumor distribution, surgical resection margin, tumor relapse within 12 months, vascular involvement, histological differentiation, fibrous pseudo-capsular formation, pattern of tumor infiltration, and postoperative adjuvant chemotherapy. The histological findings were guided by *the General Rules for Clinical and Pathologic studies on Cancer of the Colon, Rectum and Anus*.[12] We applied the clinical risk score (CRS) of the Memorial Sloan-Kettering Cancer Center (MSKCC)[13] for grading of CLM. Based on our previous reports, postoperative survivals in CLM patients with surgical margin less than 5mm was significantly different from that in

patients with surgical margin beyond 5mm and a report by Kokudo et al. was referred. [14]

Therefore, 5mm of surgical margin was used as a cut-off level in the present study.

With respect to patient survival, subjects were divided into four subgroups as follows: Group 1, 5-year survivors without tumor relapse; Group 2, survivors between 2 and 5 years with or without tumor relapse; Group 3, patients with cancer death between 2 and 5 years; and Group 4, patients with cancer death within 2 years.

Statistical analysis

Continuous data are expressed as mean ± SD. Data of different groups were compared using one-way analysis of variance (ANOVA) followed by Student's *t*-test or Dunnet's multiple comparison test. In univariate analysis, categorical data were analyzed by the chi-square test or Fisher's exact test. In multivariate analysis, logistic multivariate regression analysis was applied. A two-tailed *p* value of < 0.05 was considered significant. Statistical analyses were performed using SAS software (Statistical Analysis System Inc., Cary, NC, USA).

Results

Patient Demographics and Follow-Up

The study group included 85 males (66%) and 45 females; the median age of the 130 patients at the time of surgery was 63 years (range, 24–85 years); 43 patients (33%) were more than 70 years old. According to the Child–Pugh classification, 126 patients were classified as A (98%) and 4 (2%) as B. Partial resection was performed in 94 patients (72%) and hemihepatectomy or extended hemihepatectomy in 36 (28%). Hepatic tumor was resected simultaneously with the primary tumor in 59 patients (44%) with synchronous liver metastasis. Partial resection was performed three times in four patients and five times in one.

The median and minimum follow-up periods for survivors were 56 and 24 months, respectively. Fifty-three patients (41%) had died by the time of the last follow-up and the median time to death from hepatectomy was 22 months (range, 3–130 months). The numbers of patients in each of the subgroups were as follows: Group 1, n = 16; Group 2, n = 62; Group 3, n = 12; and Group 4, n = 40.

Primary and Metastatic Tumors

For primary tumors, colonic carcinoma was identified in 70 patients (54%) and rectal carcinoma in 60. Regional lymph node metastases from the primary tumor were detected in 92 patients (71%). CLM was detected synchronously with the primary tumor in 59 patients (46%) and within 12 months of detection of the primary tumor in 44 (34%). The median number of CLM was 2 (range, 1 to 11 tumors), while a solitary tumor was identified in 61 (47%) patients. The median size of the CLM was 2.9 cm

(range, 1–20 cm) and tumor size ≥ 5 cm was observed in 31 (25%) patients. The CRS score was 0 in 8 patients, 1 in 25, 2 in 53, 3 in 37, and 4 in 7 patients.

Tumor Recurrence and Patient Survival

Of 92 patients (71%) who had tumor recurrence after hepatectomy (in liver [n = 88], bone [n = 2], lung [n = 22], and lymph nodes [n = 2]), 26 underwent another hepatectomy, 5 underwent pulmonary resection, 3 received microwave coagulation therapy, 76 received chemotherapy (intravenous infusion in 58 and arterial pump infusion in 18), and 8 received no therapy for tumor relapse. Actuarial overall survival was 84% at 1 year after hepatectomy, 54% at 3 years, and 41% at 5 and 10 years; the median survival period was 67 months. The disease-free survival rate was 47% at 1 year after hepatectomy, 21% at 3 years, and 15% at 5 and 10 years; the median survival period was 31 months.

Clinicopathological Parameters and Patient Survival

Table I shows the relationship of survival to patient demographics, tumor markers, and surgical records. Demographics and CEA level did not differ significantly among groups. A short surgical margin was significantly more common in Group 4 compared with Group 1 (78% vs. 31%). Table II shows the relationship of survival to tumor-related factors and post-operative chemotherapy. Regional lymph node metastasis in primary carcinoma (85% vs. 38%), absence of fibrous pseudo-capsular formation (90% vs. 10%), higher CRS (3-4) (48% vs. 31%), and postoperative tumor recurrence within 12 months (93% vs. 44%) were significantly more frequent in

Group 4 compared with Group 1. Significant predictive parameters for early tumor recurrence ($p<0.05$) were multiple number of the tumor (83% vs. 59% compared to single tumor), tumor distribution in both lobes of the liver (90% vs. 64% compared to tumors in the hemi-lobe) and a short surgical margin of less than 5 mm (81% vs. 62% compared to surgical margin ≥5mm). Six of 7 survivors with early tumor relapse in Group 1 underwent repeat hepatectomy and one was completely cured by the arterial infusion therapy using 5FU and CPT-11. In the group 2, repeat hepatectomy was undergone in 10 patients, heat ablation therapy was undergone 5 and chemotherapy was undergone 22. In group 3, 2 patients underwent hepatectomy and 5 underwent chemotherapy. In group 4, no patients underwent repeat hepatectomy and 18 underwent chemotherapy.

Multivariate analysis of shorter survival after hepatectomy

Univariate analysis revealed that a shorter surgical margin, regional lymph node metastasis from the primary carcinoma, absence of fibrous pseudo-capsule formation, higher CRS, and early tumor relapse after hepatectomy were parameters significantly associated with Group 4 in comparison with other groups, especially Group 1. Logistic multivariate regression analysis (Table III) revealed that a short surgical margin of less than 5 mm and tumor relapse within 12 months after hepatectomy were independently significant related parameters.

Discussion

Background of the study

Patient survival following tumor recurrence after hepatectomy has improved over time, [15, 16] with advanced adjuvant chemotherapy, radiofrequency ablation, and repeat hepatectomy contributing to improved prognosis; even so, there is poor 2-year survival in those patients with immediate tumor recurrence after hepatectomy. With this in mind, we examined patient characteristics for subgroups of survival periods with and without tumor relapse in our series. Some problems of background in the present study were considered. The first problem of the present study was that the subject was not a large series because of a single cancer unit at districted area in Japan. Furthermore, during 16 years of this study, imaging and treatment modalities have dramatically changed, which might influence the treatment indication or patient outcomes.[17] In our series, the multidetector computed tomography was applied since 2004 and, subsequently, enhanced magnetic resonance analysis was applied since 2005. However, improvement of these technologies has not been significantly contributed and the most powerful imaging might be intraoperative ultrasonography (data not shown at present). Systemic chemotherapy has been recently advanced worldwide and, however, preoperative or adjuvant systemic chemotherapy was not routinely or aggressively performed in our series. There were few 5-year survivors with tumor relapse and cancer deaths over 5 years after hepatectomy; these subjects were excluded from the present study. In the present small series at a single cancer center, the prevalence of major hepatectomy was lower compared to those in the previous Western reports.[1, 7, 18] However, the recent report showed that anatomical

resection of the liver was not necessary and limited resections are enough to obtain treatment curability. [19] Basically, we have had a surgical strategy to perform limited hepatic resections for CLM except a large tumor to preserve parenchyma of the remnant liver.

Predictive parameters of patient survival

Over the 5-year period post-hepatectomy, many investigators report predictive factors associated with patient survival for those who underwent hepatectomy. [3–7, 15,16] Time of tumor recurrence after hepatectomy might be associated with overall survivals. Malik et al. reported the impact of early tumor recurrence after hepatectomy upon survival is an important finding.[20] Only Tanaka *et al*. reported prognostic analysis of patients with subgroups of 5-year survivors and patients who died before 5 years.[15] In the present study, we subdivided the subjects to clarify the characteristics in detail. In patient-related parameters, only advanced age differed among the groups. [6, 21] Today, selected patients over 80 years old in good physical condition can survive for long periods. Preoperative CEA level was a candidate as a predictor of survival;[7] this factor did not differ among groups. In factors related to surgery, a short surgical margin (< 5 mm) was significantly more frequent in Group 4 compared with Group 1, and was found to be a predictor of tumor relapse and poor prognosis, in agreement with the findings of the present study and previous reports. [5, 6, 22] The prevalence of a short surgical margin in Groups 2 and 3 was intermediate between that in Groups 1 and 4. Macroscopically, a 10-mm-margin has been recommended, and we also intended to obtain a margin greater than 10 mm; a border of 5 mm was revealed by the

histological findings. It is important to maintain a surgical margin of more than 5 mm histologically. Recently, however, De Haas indicated the new concept of hepatectomy in CML that operative results in R1 resection with narrow surgical margin up to 1mm was equivalent to that in R0 resection in the modern era of powerful systemic chemotherapy [23]. This concept would be reasonable at the present stage.

Of the tumor-related factors, four parameters were selected as predictive factors. Time to metastasis from primary colorectal cancer is indicated as a predictor; [3, 7] however, our policy remains to perform simultaneous hepatectomy with primary resection, or hepatectomy immediately after finding liver metastasis following primary resection, but not a "wait and see" policy. [24] We found no significant difference in survival after hepatectomy between synchronous and metachronous liver metastasis. The nodal status of primary colorectal carcinoma or regional lymph node metastasis of the liver is reported as an important predictor of poor prognosis. [6, 16, 25] Our results showed that Group 4 had a higher incidence of node-positive primary carcinoma than Group 1. The prevalence of node-positive in Groups 2 and 3 fell between that in Groups 1 and 4. The number of tumors, tumor size, distribution of tumor, and histological differentiation did not differ among the groups; these factors have been previously reported as predictors of survival. [6, 7, 15] Histologically, there was significantly more fibrous pseudo-capsule formation around the metastatic tumor in Group 1 compared with other groups. This finding is a capsule-like fibrous formation in the non-cancerous region very close to the margin of metastatic liver tumor. [26, 27] This parameter has been recommended as a predictor of better survival in previous reports, including our pilot study. The detailed mechanism of better prognosis has not

yet been clarified; we speculate that this finding is a type of immuno-defence phenomenon that acts to prevent spread of the tumor. By the present result, fibrous pseudo-capsule formation around the metastatic tumor would be a candidate of a marker to decide systemic therapy.

Comprehensive grading system for colorectal liver metastasis

Many investigators have proposed comprehensive grading or staging systems for CLM since the first study by Foster *et al.* in 1978.[14, 27–30] The most commonly used and reliable referral scoring system for prognosis world-wide is the MSKCC-CRS reported by Fong *et al.* and Jarnagin *et al.*,[14, 31] which identifies those high-risk patients most likely to benefit from laparoscopy and preoperative imaging. The CRS > 2 would indicate a poor prognosis [7] in the case of the hepatectomy group in the present study; we divided this group into two groups (CRS 0–2 vs. CRS 3–4). The highest CRS score was found in Group 4. This score would be useful in predicting shorter survival by our recent report. [32] Several recent reports indicate the usefulness of adjuvant chemotherapy in increasing the survival periods in CLM patients undergoing hepatectomy. [3, 6, 15, 16]

Postoperative adjuvant therapy and follow-up

At our institution, we also perform hepatic arterial infusion or systemic chemotherapy for unresectable CLM since 1997; some reactive tumors have become candidates for surgery. At this stage, however, the findings of the present series have not clarified the relationship between adjuvant chemotherapy and patient survival

(data not published yet). In the present series, the definitive and routinely adjuvant chemotherapy for CLM has not been performed and, therefore, influences of chemotherapy would be ignorable. In case of multiple liver metastasis, Previous studies show that distant metastasis and postoperative doubling time of recurrence are significantly associated with poor survival. [6, 16, 21] In the present study, a shorter period until tumor recurrence following hepatectomy (< 12 months) was more frequent in Groups 3 and 4. In cases where poor predictive factors are revealed by comprehensive examinations after hepatectomy, immediate and powerful adjuvant-chemotherapy such as a FOLFOX [33] very careful follow-up (every 1–2 months), and immediate repeat resection would be necessary to improve patient survival. Compared to group 3 and 4, prevalence of repeat hepatectomy (twice or more) for early tumor relapse was more frequent in group 1 and 2 in the present series. The patients undergoing repeat hepatectomy might have a good condition of tumor size or location and of general status. Previous report also showed the survival benefit of repeated hepatectomy for tumor recurrence in the remnant liver [34] and, therefore, surgical resection might be recommended as well as possible in case of tumor recurrence in CLM patients.

Multivariate analysis for cancer death within 2 years (Group 4) revealed that short surgical margin and time to tumor relapse after hepatectomy were independent risk factors. Our results showed that a short surgical margin was also related to tumor relapse and, furthermore, multiple metastases and wide distribution of the metastatic regions were related to early recurrence. Therefore, according to the present results, a sufficiently wide resection with regard to the surgical margin is necessary, a careful follow-up with a short period (every 1-2 months) is necessary in cases of multiple and

widely distributed CLM, or powerful adjuvant chemotherapy would be important to prevent cancer death at the early period after surgery. It may be necessary to obtain various other parameters such as tumor biological factors that would provide additional information relating to poor prognosis. As reported in our preliminary study, in the near future we plan to analyze other candidates as predictive factors, such as microvessel counts and adhesion molecules, [26, 35] using the follow-up data obtained for these parameters in the present series. Furthermore, new imaging technologies such as F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance diffusion imaging appear to enable tumor grade to be defined, and thus could be useful as a prognostic parameters in the near future. [36, 37] In the present series, PET has not been applied to decide the operative indications at all.

Conclusion

In conclusion, we analyzed the clinicopathologic and surgical features in CLM patients who underwent hepatic resection, and compared these data in four subgroups with regard to survival period and tumor relapse. Primary node status, fibrous pseudo-capsule formation, high CRS, a short surgical margin (less than 5 mm), and a shorter time to tumor recurrence after hepatectomy (less than 12 months) were factors significantly associated with cancer death within 2 years in CLM patients; the latter two factors were independent associated factors by multivariate analysis. A sufficient surgical margin, careful follow-up, or powerful adjuvant chemotherapy for early tumor relapse may be important to improve outcomes after surgery in CLM patients.

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Table 1. Relationship between survival periods, and patient demographics, tumor markers and sSurgical records

	Group 1 (n=16)	Group 2 (n=62)	Group 3 (n=12)	Group 4 (n=40)	P value
Gender					
Male / Female	13/3	38/24	9/3	25/15	0.61
Age	64±7	63±13	63±10	62±13	0.56
CEA (ng/ml)	49±86	47±106	10±8	74±226	0.79
Child-Pugh					
A / B	16/0	60/2	11/1	39/1	0.88
Hepatectomy [a]					
Major / minor	5/11	20/42	4/8	7/33	0.39
Surgical margin					
≥5mm / <5mm	11/5	25/37	3/9	9/31	0.009

CEA, carcinoembryonic antigen

[a] major hepatectomy is a hemihepatectomy or more extended hepatectomy

Table 2. Relationship between survival periods, and tumor-related findings and postoperative chemotherapy

	Group 1 (n=16)	Group 2 (n=62)	Group 3 (n=12)	Group 4 (n=40)	P value
Time of metastasis					
Synchronous/metachronous	7/9	26/36	6/6	20/20	0.84
Lymph node metastasis in primary carcinoma					
No/Yes	10/6	15/47	7/5	6/34	0.004
Number of tumor					
Solitary/Multiple	7/9	33/29	6/6	15/25	0.63
Tumor distribution					
Hemi-liver/both liver	13/3	43/19	9/3	25/15	0.46
Tumor size					
<5cm/≥5cm	14/2	46/16	10/2	29/11	0.48
Micro-daughter nodule					
No/Yes	10/6	53/9	8/4	27/13	0.14
Histological differentiation					
Well/moderately/poor	4/12/0	17/43/2	3/8/0	8/26/6	0.25
Glisson's pedicle invasion					
No/Yes	13/3	46/16	9/3	32/8	0.83
Hepatic vein invasion					
No/Yes	16/0	52/10	9/3	32/8	0.25
Fibrous pseudo-capsule formation					
No/Yes	4/12	54/8	8/4	36/4	<0.001
Clinical risk score [a]					
0/1/2/3/4	3/4/4/5/0	2/13/34/12/1	1/3/5/2/1	2/5/10/18/5	0.011
Adjuvant chemotherapy					
No/Yes	2/14	24/38	3/9	14/26	0.42
Post-hepatectomy early recurrence					
No/Yes	9/7	23/39	3/9	3/37	<0.001

Histologic findings were referred by *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus* .[13]

[a] Scoring system proposed by Memorial Sloan-Kettering Cancer Center[14]

Table 3. Multivariate logistic regression analysis of cancer-death within 2 Years.

	HR	95%CI Lowest-highest CI	P value
Lymph node metastasis in primary carcinoma			
Yes vs. No	2.2	0.81-5.90	0.12
Fibrous pseudo-capsule formation			
No vs. Yes	2.7	0.64-8.81	0.19
Clinical risk score#			
3/4 vs. 0/1/2	1.4	0.56-3.59	0.46
Surgical margin			
≥5mm / <5mm	3.5	1.08-11.10	0.037
Post-hepatectomy early recurrence			
Yes vs. No	5.9	2.16-15.88	<0.001

HR: hazard ratio

CI: confidence interval