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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Proposed Definition for Oligometastatic Recurrence in Biliary Tract Cancer Based on Results of Locoregional Treatment: A Propensity-Score-Stratified Analysis

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ABSTRACT

Background. Oligometastatic recurrence involves relapsed tumors for which locoregional treatment (LT) may yield a survival benefit. However, there are no clear criteria for selecting patients for LT or determining the effects of LT in recurrent biliary tract cancer (BTC). The aim of this retrospective study is to assess the effects of LT on survival outcomes and to identify potential criteria for selecting LT in recurrent BTC.

Patients and Methods. In the present work, 232 consecutive patients with recurrent BTC who initially underwent curative surgery between 1996 and 2015 were evaluated. The primary outcome was length of survival after recurrence (SAR). Propensity score stratification with various tumor-related factors was used to identify patients who would likely benefit from LT.

Results. Among the cohort, 60 (25.9%) patients underwent LT, whereas 172 (74.1%) patients did not. The multivariate Cox model identified carbohydrate antigen 19-9 levels of > 50 U/mL, multiorgan recurrence, tumor number > 3, tumor size > 30 mm, and early recurrence (≤ 1 year) as independent predictors of poor SAR ($P < 0.001$ for each factor). In the propensity-score-stratified analysis, LT was associated with survival benefits for patients representing single-organ recurrence with at most three tumors and late-onset recurrence (> 1 year) (median SAR: 48.6 vs. 14.2 months, $n = 33$ vs. $n = 34$, hazard ratio: 0.10, 95% confidence interval: 0.04–0.20, $P < 0.001$).

Conclusions. Patients with recurrent BTC may benefit from LT if they have single-organ recurrence with at most three tumors and late-onset recurrence. We propose that these patients may have clinically relevant "oligometastatic recurrence" of BTC.

Keywords Oligometastasis · Oligorecurrence · Biliary tract cancer · Locoregional treatment

Biliary tract cancer (BTC) is a lethal malignancy that is becoming increasingly common worldwide. The types of BTC are intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and gallbladder cancer (GBC). Surgical resection is generally considered the only curative treatment for each BTC subtype, although the dismal prognosis (5-year survival rate of approximately 30%)[1] highlights the need for other effective treatment strategies. To meet this need, a very recent randomized controlled study (the BILCAP trial) demonstrated that adjuvant chemotherapy may play a promising role after surgical resection of BTC.[2] Furthermore, there is increasing recognition of the importance of postrecurrence treatment in improving long-term outcomes.[3] Locoregional

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therapy (LT), such as repeat surgical resection or radiotherapy, as postrecurrence treatment for recurrent BTC might be associated with a survival benefit.[4–15] Therefore, LT might play a key role in achieving long-term survival for patients with recurrent BTC.

The concepts of "oligometastasis" and "oligometastatic recurrence" (i.e., oligorecurrence) are emerging topics in oncology research.[16–24] The concept of oligometastasis was first proposed by Hellman in 1995 based on breast cancer research.[25] Oligometastasis and oligorecurrence have been proposed to be scenarios involving metastatic tumors in which LT might provide long-term survival. Thus, LT has been utilized in the postrecurrence treatment of various malignancies, although LT has not been investigated in recurrent BTC. The aim of the present study is to retrospectively identify patients who benefited most from LT for recurrent BTC. The hypothesis is that these findings might help generate a clinically relevant definition of "oligorecurrence" in BTC.

PATIENTS AND METHODS

Patients

The protocol of this single-center retrospective study was approved by the ethics committee of the Graduate School of Medicine (Kyoto University Graduate School, R1865); the requirement for written informed consent was waived. We retrospectively retrieved prospectively collected data from patients who underwent curative surgery (R0 or R1 resection) for BTC at Kyoto University Hospital between 1996 and 2015. Patients who developed recurrence during the follow-up period were also retrospectively identified and divided into two groups, according to whether they had or had not undergone LT. The LT group included all patients who had undergone LT for recurrent lesions at least once during their follow-up. Follow-up data were most recently updated in January 2019.

Criteria for LT

Treatments for recurrence were comprehensively determined by a cancer board based on the recurrence pattern, tumor diameter, tumor number, tumor location, time to recurrence, availability of other treatments, and patient performance status. The main treatment strategy for recurrent BTC was gemcitabine-based chemotherapy, starting in 2006, which is when gemcitabine was approved for BTC in Japan.[26,27] There was no standard systemic therapy treatment approach for recurrent BTC before 2006. When the tumor appeared localized, LT was considered in order to achieve local control. Repeat surgery was considered for localized and technically resectable tumors. Radiotherapy, radiofrequency ablation, and transcatheter arterial embolization were also considered for select patients with unresectable but localized tumors or patients who could not tolerate surgery.

Data Collection and Follow-Up

The patients' clinicopathological characteristics included age, sex, cancer type, tumor stage, lymph node status at the primary surgery (based on the International Union Against Cancer classification, seventh edition),[28] carcinoembryonic antigen (CEA) levels, carbohydrate antigen 19-9 (CA19-9) levels, affected organs, multiorgan recurrence, maximum tumor diameter, tumor number, time to recurrence, adjuvant chemotherapy, systemic chemotherapy, and time period (1996–2005 or 2006–2015 to account for the approval of gemcitabine treatment). Tumor number and diameter were determined based on imaging at the diagnosis of recurrence. In patients who could not be evaluated, such as patients with peritoneal carcinomatosis and ascites, the tumor number and diameter were classified as "not identified." The maximum number of tumors was capped at 10 for analytical purposes.

Patients underwent computed tomography, ultrasonography, and/or magnetic resonance imaging at 3-month intervals after surgery, unless there was a confirmed relapse. CEA and CA19-9 levels were also monitored every 3 months until there was a confirmed relapse.

Statistical Analyses

We used propensity score stratification, rather than conventional subgroup analysis, in order to minimize the effects of confounding and selection bias. The propensity score was estimated to predict the probability of LT being used in a given case, and explanatory variables were selected based on the factors that predicted survival outcomes.[29,30] Therefore, when the patients had similar propensity scores, the distributions of prognostic variables were comparable between the patients with and without LT use.[31] Using a three-step approach, we identified the stratum of patients who would be expected to benefit most from LT based on their tumor-related characteristics. First, we identified tumor-related factors that were associated with survival outcomes. Second, we performed propensity

scoring using these prognostic factors. Third, we analyzed the propensity scores to identify the subgroup of patients who would benefit the most from LT.

Continuous variables are expressed as median (range) and were compared using the Mann–Whitney *U* test. Categorical variables were compared using the Chi square test or Fisher's exact test. The main outcome was defined as survival after recurrence (SAR), which was calculated from date of relapse until death from any cause. The SAR outcomes were determined based on the most recent date of confirmed survival for patients who continued to survive or who were lost to follow-up. The SAR outcomes were compared using the Kaplan–Meier method and log-rank test. Cut-off values for continuous variables were identified using the minimum *P* value approach. Cut-off values were then used to convert the continuous variables into categorical variables. Factors that predicted survival were identified using a multivariate Cox proportional hazards model with stepwise selection and the minimum Bayesian information criterion method. The multivariate selection used variables that were significant in the univariate analyses, and LT was excluded from the later analysis of the relationship with those variables. A propensity score was estimated using logistic regression to predict the probability of LT use, and the *c*-statistic was calculated to determine the model's ability to discriminate between patients with or without LT use. The patients were subsequently separated into subsets based on their estimated propensity scores using intervals of 0.1. All tests were two-tailed, and differences were considered significant if *P*-values were < 0.05. All statistical analyses were performed using JMP software (version 14.0, SAS Institute, Inc.; Cary, NC) or R software with the "design" and "survival" packages (version 3.5.1, R Foundation for Statistical Computing; http://www.r-project.org) and in consultation with a statistician.

RESULTS

Figure 1 shows the study flowchart. We identified 439 consecutive patients who underwent surgical resection of BTC; of these, 207 were excluded due to absence of recurrence ($n = 147$), surgery-related death ($n = 31$), R2 surgery ($n = 17$), or loss to follow-up ($n = 12$). Thus, the present study included 232 patients with median follow-up time of 12.6 months (1.2–186 months) and median SAR of 12.7 months (3-year SAR: 15.5%, 5-year SAR: 8.9%).

Patient Characteristics and Survival Outcomes

Among the 232 eligible patients, 60 patients (25.9%) underwent LT and 172 patients did not (non-LT group). The LT modalities consisted of radiotherapy (including chemoradiotherapy: $n = 34$, 56.7%), repeat surgery ($n = 23$, 38.3%), radiofrequency ablation ($n = 7$, 11.7%), transcatheter arterial embolization ($n = 3$, 5.0%), microwave coagulation therapy ($n = 3$, 5.0%), and percutaneous ethanol injection ($n = 1$, 1.7%). The patients' clinical characteristics are presented in Table 1. The LT group had significantly fewer adverse tumor factors [e.g., high tumor stage ($P = 0.023$) and lymph node metastasis ($P = 0.022$) at primary surgery, high CA19-9 levels at recurrence

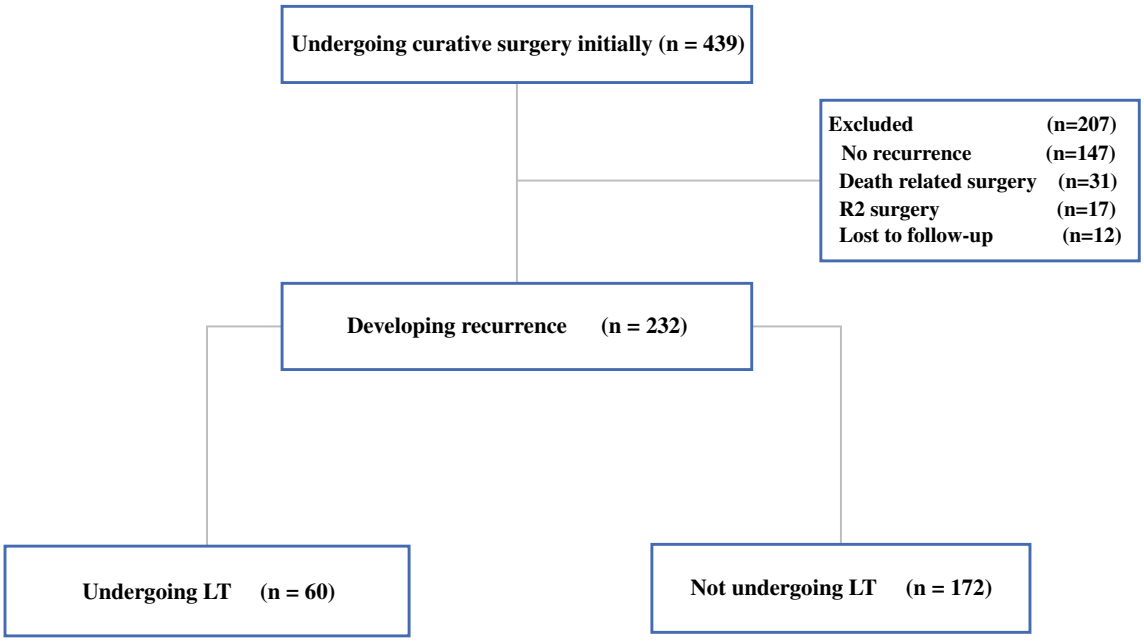

FIG. 1 Study flowchart

TABLE 1 Patient and clinicopathological characteristics

Variable	LT (n = 60)	Non-LT (n = 172)	P value
Age (years)	65 (43–83)	67 (26–88)	0.233
Sex (male:female)	35:25	91:81	0.466
Cancer			
ECC	16 (26.7%)	93 (54.1%)	< 0.001
ICC	40 (66.7%)	43 (25.0%)	
GBC	4 (6.7%)	36 (20.9%)	
Subtype of ECC			
Hilar	11 (68.8%)	50 (53.8%)	0.291
Distal	5 (31.2%)	43 (46.2%)	
Findings at primary surgery			
Tumor stage			
< 4	47 (78.3%)	108 (62.8%)	0.023
4	13 (21.7%)	64 (37.2%)	
Node status			
Negative	32 (53.3%)	76 (44.2%)	0.022
Positive	25 (41.7%)	95 (55.2%)	
Unknown	3 (5.0%)	1 (0.6%)	
R1 surgery	16 (26.7%)	48 (27.9%)	0.852
CA19-9 (U/mL)	55.9 (1–1788)	76.8 (0.8–87,382)	0.255
CEA (ng/mL)	1.9 (0.4–168)	2.6 (0.6–116)	0.024
Findings at recurrence			
CA19-9 (U/mL)	33.3 (1–962)	80.5 (0.6–28,226)	< 0.001
CEA (ng/mL)	2.4 (0.5–310)	3.4 (0.7–161)	0.003
Location			
Liver	24 (40%)	84 (48.8%)	0.235
Lymph node	18 (30%)	64 (34.3%)	0.540
Local	4 (6.7%)	33 (19.2%)	0.024
Lung	8 (13.3%)	23 (12.8%)	0.914
Bone	10 (16.7%)	4 (2.3%)	< 0.001
Peritoneum	5 (8.3%)	36 (20.9%)	0.030
Tumor size			
Not identified	1 (1.7%)	13 (8.4%)	0.118
Diameter	18 (5–75)	20 (3–150)	0.336
Tumor number			
Not identified	0	8 (4.9%)	0.113
Number	1 (1–10)	3 (1–10)	< 0.001
Multiorgan recurrence	8 (13.3%)	65 (37.8%)	< 0.001
Single-organ recurrence	52 (86.7%)	107 (62.2%)	
Tumors for multiorgan recurrence	3 (2–10)	4 (2–10)	0.318
Tumors for single-organ recurrence	1 (1–7)	1 (1–10)	0.009
Adjuvant chemotherapy	25 (41.7%)	73 (42.4%)	0.916
Time to recurrence (months)	15.7 (1.7–120.6)	9.3 (0.4–101.8)	0.012
Systemic chemotherapy	46 (76.7%)	137 (81.1%)	0.470
First period (1996–2005)	29 (48.3%)	63 (36.6%)	0.112
Second period (2006–2015)	31 (51.7%)	109 (63.7%)	

Continuous variables reported as median (range) and compared using Mann–Whitney U-test or median test. Categorical variables compared using Chi square test or Fisher's exact test

LT locoregional treatment, *ECC* extrahepatic cholangiocarcinoma, *ICC* intrahepatic cholangiocarcinoma, *GBC* gallbladder cancer, *Vater* carcinoma of the ampulla of Vater, *CEA* carcinoembryonic antigen, *CA* carbohydrate antigen

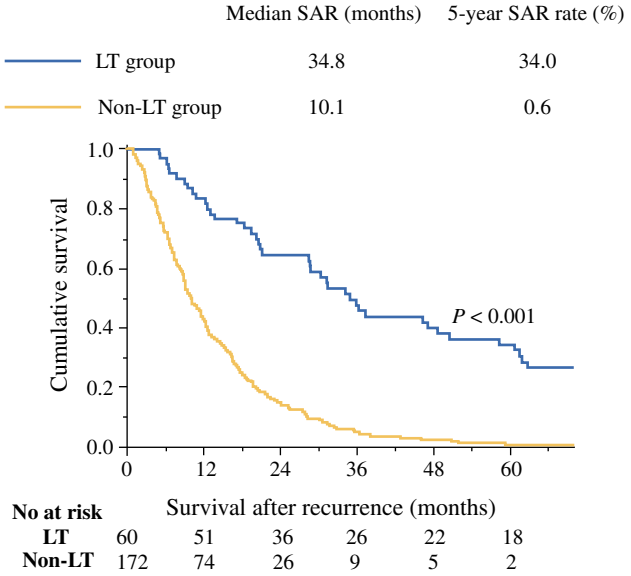

FIG. 2 Kaplan–Meier estimates of survival after recurrence among the entire cohort with and without LT (log-rank $P < 0.001$);*LT* locoregional treatment, *SAR* survival after recurrence, *No.* number

($P < 0.001$), multiorgan recurrence ($P < 0.001$), high tumor number ($P < 0.001$), and time to recurrence ($P = 0.012$)] compared with the non-LT group. No significant differences were observed regarding treatment time period ($P = 0.112$) or chemotherapy use ($P = 0.470$).

During the follow-up period, 46 (76.7%) and 170 (98.8%) patients from the LT and non-LT groups, respectively, died. The LT group had significantly longer median SAR [Fig. 2; 34.8 vs. 10.1 months, hazard ratio (HR) 0.23, 95% confidence interval (CI) 0.15–0.32, $P < 0.001$] and higher SAR rates at 3 years (47.5% vs. 4.7%) and 5 years (34.2% vs. 0.6%) than the non-LT group.

Prognostic Factors for Survival After Recurrence

The results of the univariate and multivariate SAR analyses are presented in Table 2. Based on the minimum *P*-value approach, the optimal cut-off values were determined to be 5 ng/mL for CEA, 50 U/mL for CA19-9, 30 mm for tumor size, three for the number of tumors in single-organ recurrence, and 1 year for time to recurrence (Supplementary Table 1).

On univariate analyses, the significant prognostic factors were cancer type (ECC, ICC, or GBC), CEA level > 5 ng/mL, CA19-9 level > 50 U/mL, recurrence location (liver, local, and peritoneum), multiorgan recurrence, tumor number > 3 in single-organ recurrence, tumor size > 30 mm, and time to recurrence of ≤ 1 year. Since multiorgan recurrence and the number of tumors in single-organ recurrence are mutually exclusive factors, we combined these variables for the multivariate analyses as "single-organ recurrence with at most three tumors" and "multiorgan recurrence or tumor number of > 3". The multivariate analysis revealed that poor SAR was associated with multiorgan recurrence or tumor number > 3 (HR: 2.34, 95% CI: 1.67–3.28, $P < 0.001$), CA19-9 level > 50 U/mL (HR: 2.18, 95% CI: 1.58–3.01, $P < 0.001$), time to recurrence ≤ 1 year (HR: 2.07, 95% CI: 1.50–2.85, $P < 0.001$), and tumor size > 30 mm (HR: 1.85, 95% CI: 1.29–2.65, $P < 0.001$).

Propensity Score Stratification

Next, a logistic regression model to predict the probability of LT using the four predictive factors for SAR was developed. As presented in Supplementary Table 2, single-organ recurrence with at most three tumors [odds ratio (OR): 6.89, 95% CI : 2.79–17.0, $P < 0.001$], CA19-9 level ≤ 50 U/mL (OR: 4.65, 95% CI : 2.16–9.97, $P < 0.001$), and late-onset recurrence (> 1 year) (OR: 2.44, 95% CI : 1.15–5.16, $P = 0.018$) showed significant associations with implementation of LT. On the basis of this result, propensity scores were generated using the following equation:

$$\text{Propensity score} = \frac{1}{1 + \exp(1.427 - 0.913X_1 - 0.786X_2 - 0.416X_3)}$$

where X_1 is single-organ recurrence with at most three tumors, X_2 is CA19-9 level ≤ 50 U/mL, and X_3 is late-onset recurrence (> 1 year).

The *c*-statistic was 0.809, which suggests that the propensity score exhibited high ability to predict use of LT. The propensity score stratification for predicting implementation of LT is shown in Fig. 3. The patients who achieved significantly better SAR from LT followed two strata: the 0.6–0.7 propensity score stratum (X_1+, X_2+, X_3+, HR 0.10, 95% CI 0.03–0.28, $P < 0.001$) and the 0.3–0.4 propensity score stratum (X_1+, X_2-, X_3+, HR 0.10, 95% CI 0.03–0.30, $P < 0.001$). These two strata satisfying X_1+ and X_3+, namely patients with recurrent BTC representing single-organ recurrence with at most three tumors (X_1+) and late-onset recurrence (X_3+), might benefit most from LT.

Survival Outcomes of the Identified Group

Sixty-seven patients (LT group $n = 33$, non-LT group $n = 34$) showed single-organ recurrence with three or fewer tumors and late-onset recurrence. Clinical characteristics of these patients according to the treatment are presented in Table 3. There were more instances of ICC (60.6% vs. 14.7%) and fewer instances of ECC (33.3% vs. 79.4%) in the LT group relative to the non-LT group

TABLE 2 Factors associated with survival after recurrence using the minimum Bayesian information criterion method in univariate and multivariate Cox proportional hazard analyses

Variable	*N*	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
ECC					
No	123	Ref		–	
Yes	109	1.42 (1.08–1.86)	0.010		
ICC					
No	149	Ref		–	
Yes	83	0.54 (0.40–0.73)	< 0.001		
GBC					
No	192	Ref		–	
Yes	40	1.46 (1.03–2.07)	0.029		
CEA					
≤ 5 ng/mL	147	Ref		–	
> 5 ng/mL	60	1.67 (1.21–2.29)	0.001		
CA19-9					
≤ 50 U/mL	99	Ref		Ref	
> 50 U/mL	110	2.13 (1.58−2.86)	< 0.001	2.18 (1.58–3.01)	< 0.001
Recurrence					
Liver					
Absent	124	Ref		–	
Present	108	1.35 (1.03–1.77)	0.028		
Local recurrence					
Absent	195	Ref		–	
Present	37	1.47 (1.03–2.11)	0.032		
Peritoneum					
Absent	191	Ref		–	
Present	41	1.42 (1.01–2.00)	0.043		
Single-organ recurrence	159	Ref			
Multiorgan recurrence	73	2.00 (1.50–2.68)	< 0.001		
Tumors in single-organ recurrence					
≤ 3	121	Ref			
> 3	32	3.42 (2.24–5.22)	< 0.001		
Single-organ recurrence and ≤ 3 tumors	121	Ref		Ref	
Multiorgan recurrence or > 3 tumors	105	2.70 (2.03–3.59)	< 0.001	2.34 (1.67–3.28)	< 0.001
Tumor size					
≤ 30 mm	153	Ref		Ref	
> 30 mm	59	1.80 (1.27–2.53)	< 0.001	1.85 (1.29–2.65)	< 0.001
Time to recurrence					
> 1 year	106	Ref		Ref	
≤ 1 year	126	1.95 (1.48–2.56)	< 0.001	2.07 (1.50–2.85)	< 0.001

HR hazard ratio, *CI* confidence interval, *ECC* extrahepatic cholangiocarcinoma, *ICC* intrahepatic cholangiocarcinoma, *GBC* gallbladder cancer, *Vater* carcinoma of the ampulla of Vater, *CEA* carcinoembryonic antigen, *CA* carbohydrate antigen

($P < 0.001$). No significant differences were observed in the prognostic factors between the two groups [e.g., CA19-9 level > 50 U/mL ($P = 0.110$), tumor size > 30 mm ($P = 0.374$), time to recurrence ($P = 0.331$), multiorgan recurrence ($P = 1.000$), and tumor number ($P = 0.252$)]. Relative to the non-LT group, the LT group showed significantly longer median SAR (Fig. 4; 48.6 months vs. 14.2 months, HR: 0.10, 95% CI: 0.04–0.20, $P < 0.001$)

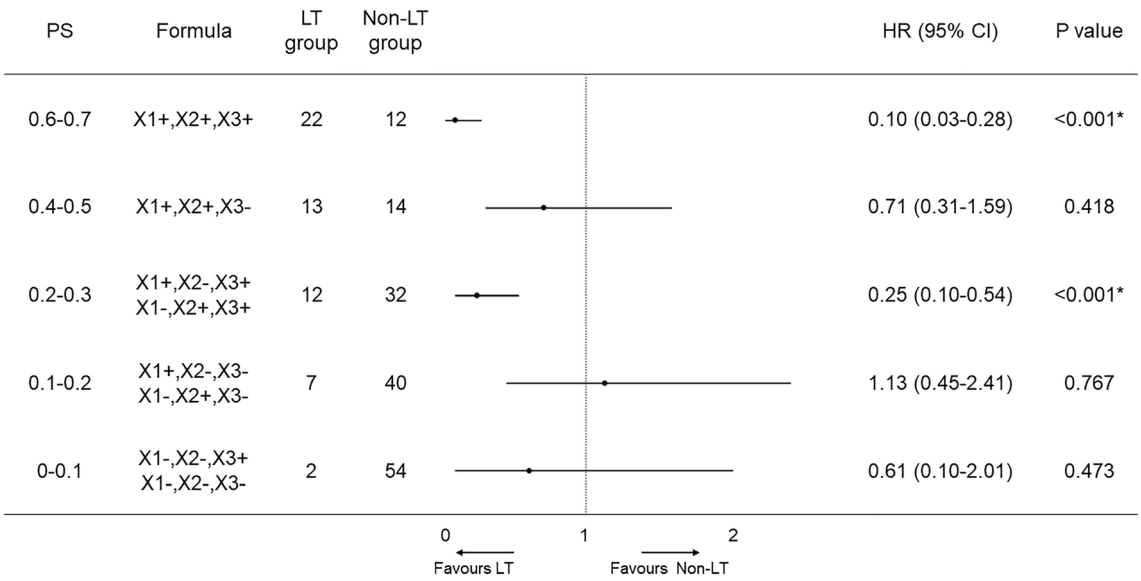

FIG. 3 Hazard ratios for the effects of LT on survival after recurrence according to the propensity score; *significant, *LT* locoregional treatment, *PS* propensity score, *HR* hazard ratio, *CI* confidence interval, *No*. number, *X1* single-organ recurrence with at most three tumors, *X2* CA19-9 level ≤ 50 U/mL, *X3* late-onset recurrence

and higher SAR rates at 3 years (66.7% vs. 3.0%) and 5 years (45.6% vs. 0%).

DISCUSSION

This study identified patients with recurrent BTC who would benefit most from LT, which might be useful in developing a clinically relevant definition of "oligorecurrence" in BTC. Consistent with previously published data, LT use was associated with better SAR in patients with recurrent BTC. In addition, the propensity scores that were generated based on significant prognostic factors exhibited good ability to identify patients who underwent LT. Further propensity score stratification confirmed that LT use was associated with a survival benefit in patients with recurrent BTC that involved single-organ recurrence with at most three tumors and late-onset recurrence. For the bias-adjusted group, LT still contributed to a favorable prognosis.

Metastasis and recurrence of BTC generally develop in the last stage of the patient's life. The standard treatment for these BTC cases is systemic chemotherapy, with the first-line treatment involving gemcitabine plus cisplatin.[26,27] However, the median survival times from two randomized controlled trials were only 11.2–11.7 months, which suggests that this treatment is unsatisfactory. In addition, LT (e.g., repeat surgical resection or radiotherapy) for recurrent BTC is associated with a survival benefit,[4–15] although these outcomes are obviously influenced by selection bias. Thus, we used propensity score stratification to help identify patients who benefitted most from LT for recurrent BTC based on their SAR values (48.6 vs. 14.2 months; Fig. 2B).

The present study revealed that LT provided a long-term survival benefit for recurrent BTC in cases with single-organ recurrence, tumor number ≤ 3, and late-onset recurrence (time to recurrence ≥ 1 year). Other researchers have also reported that time to recurrence is an important factor in selecting LT for recurrent BTC.[4–8] In addition, early recurrence is strongly associated with tumor aggressiveness at primary surgery (e.g., lymph node metastasis, poor tumor differentiation, microvascular invasion, and R1 surgery).[32] The present study is the first to demonstrate that LT can be selected for recurrent BTC in part by using simple clinical findings, viz. tumor number ≤ 3 for single-organ metastasis. This factor likely reflects the tumor's biological progression and may determine the opportunity for and nature of effective therapeutic interventions.[16] Therefore, because our model is composed of two parameters that appear to reflect tumor biology in the recurrent period, we suggest that this definition may be clinically useful and valid.

The concept of "oligometastasis" was first proposed in breast cancer[18,19] and has since been expanded to lung cancer,[20] prostate cancer,[21,22] colon cancer,[23] and gastric cancer.[24] In addition, "oligorecurrence" was proposed to be a notion similar to oligometastasis.[17] Although these

TABLE 3 Patient and clinicopathological characteristics of the defined group

Variable	LT (n = 33)	Non-LT (n = 34)	P value
Age (years)	66 (43–77)	69 (47–82)	0.125
Sex (male:female)	19:14	18:16	0.702
Cancer			
ECC	11 (33.3%)	27 (79.4%)	< 0.001
ICC	20 (60.6%)	5 (14.7%)	
GBC	2 (6.1%)	2 (5.9%)	
Subtype of ECC			
Hilar	8 (72.7%)	18 (66.7%)	1.000
Distal	3 (27.3%)	9 (33.3%)	
Findings at primary surgery			
Tumor stage 4	5 (15.2%)	5 (14.7%)	1.000
Lymph node metastasis	13 (39.4%)	10 (29.4%)	0.338
R1 surgery	9 (27.3%)	3 (8.8%)	0.061
Findings at recurrence			
CA19-9 level > 50 U/mL	16 (48.5%)	23 (67.6%)	0.110
CEA level > 5 ng/mL	4 (12.5%)	9 (26.5%)	0.218
Location			
Liver	13 (39.4%)	10 (29.4%)	0.447
Lymph node	9 (27.3%)	7 (20.5%)	0.520
Local	2 (6.1%)	12 (35.3%)	0.005
Lung	4 (12.1%)	1 (2.9%)	0.197
Bone	2 (3.0%)	0	0.238
Peritoneum	2 (6.1%)	3 (8.8%)	1.000
Tumor size > 30 mm	6 (18.8%)	9 (28.1%)	0.374
Tumor number	1 (1–3)	1 (1–3)	0.252
Multiorgan recurrence	0	0	1.000
Adjuvant chemotherapy	16 (48.5%)	11 (32.3%)	0.177
Time to recurrence (months)	19.8 (12.1–120)	25.4 (12.6–101)	0.331
Systemic chemotherapy	26 (78.8%)	27 (79.4%)	1.000
First period (1996–2005)	16 (48.5%)	12 (35.3%)	0.273
Second period (2006–2015)	17 (51.5%)	22 (64.7%)	

Continuous variables reported as median (range) and compared using Mann–Whitney U-test or median test. Categorical variables compared using Chi square test or Fisher's exact test

LT locoregional treatment, *ECC* extrahepatic cholangiocarcinoma, *ICC* intrahepatic cholangiocarcinoma, *GBC* gallbladder cancer, *Vater* carcinoma of the ampulla of Vater, *CEA* carcinoembryonic antigen, *CA* carbohydrate antigen

concepts are still poorly defined, some investigators have attempted to propose various definitions. However, different cancers' varying aggressiveness can influence their clinical course, and it may be necessary to develop definitions of "oligometastasis/recurrence" for each cancer type. Recurrent BTC has a dismal prognosis, although LT can help prolong survival for select patients. Therefore, we aimed to identify patients with recurrent BTC who would benefit the most from LT, as we speculated that their characteristics might be used to develop the definition of "oligorecurrence" in BTC. To the best of the authors' knowledge, this is the first study to propose a definition of "oligorecurrence" in BTC.

This study has three limitations besides its retrospective nature. First, LT included various treatments over a 20-year period, and the treatment-specific effects on survival outcomes or selection bias in the treatment selection or timing were not considered. The heterogeneity of this cohort made it difficult to draw conclusions. While a randomized controlled trial would be needed to clarify the true treatment effects, it is unrealistic to design such a trial for recurrent BTC, as LT is not considered standard practice for recurrent BTC. Furthermore, in the era of multidisciplinary treatment, patients would likely undergo a combination of LT and systemic chemotherapy, which would complicate possible trials. The second limitation is that BTC includes

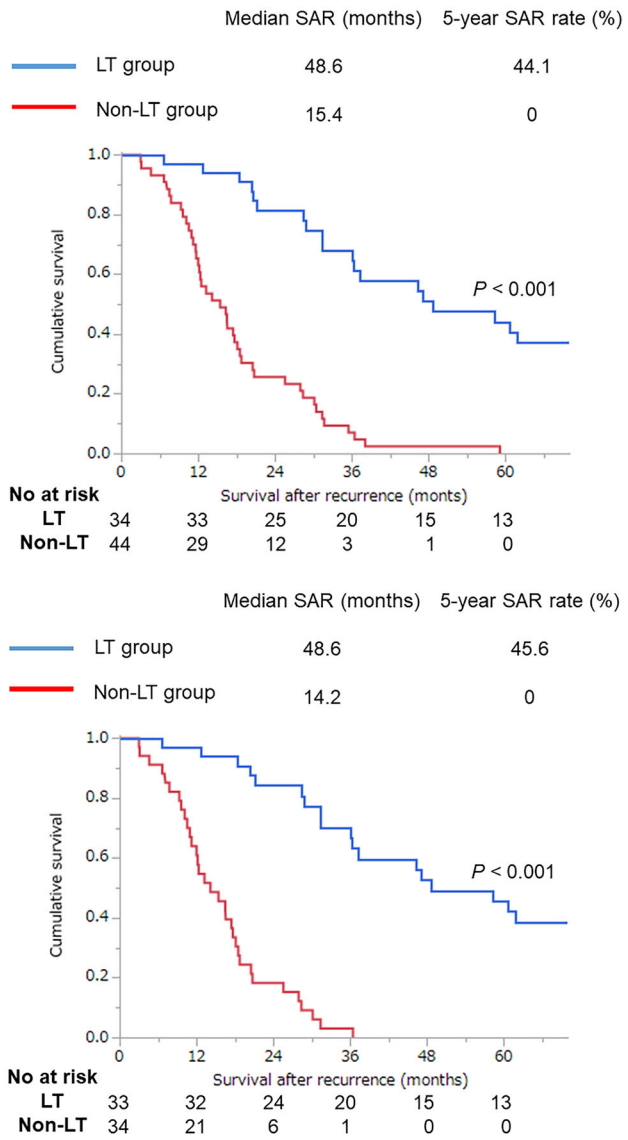

FIG. 4 Kaplan–Meier estimates of survival after recurrence among the adjusted groups with and without LT (log-rank $P < 0.001$); *LT* locoregional treatment, *SAR* survival after recurrence, *No.* number

different cancers (e.g., ECC, ICC, and GBC). Furthermore, in the subgroup identified herein, patients with ICC were more likely to undergo LT than those with ECC, and these tumors do not all have the same biological behavior. However, each cancer type was not a prognostic factor in this analysis, and it has been reported that ECC and ICC have similar prognoses.[33] The third limitation is the uncommon analytical approach and the lack of external validation. Further study will be required to demonstrate our proposal. Nevertheless, we believe that this study's findings could be used to help guide the selection of LT for recurrent BTC.

In conclusion, LT may provide a survival benefit for patients with recurrent BTC who have single-organ recurrence with at most three tumors and late-onset recurrence. These characteristics may also provide insight regarding the concept of "oligorecurrence" in BTC.

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CORRECTION

Correction to: Proposed Definition for Oligometastatic Recurrence in Biliary Tract Cancer Based on Results of Locoregional Treatment: A Propensity-Score-Stratified Analysis

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In the original article, the calculation (Fig. 3 and Supplementary Table 2) and the following formula of propensity score have errors, and "X1−, X2+, X3+" group should be added into the patients who achieved significantly better SAR from LT; however, only one patient received LT in the group and died 3 months after LT. Based on the clinical course, our finding deviates from the concept that the group that can be expected to prolong survival outcome by LT, and this group was excluded from the definition of "oligometastatic recurrence" (Fig. 4a; before exclusion, Fig. 4b; after exclusion).

$$\text{Propensity score} = \frac{1}{1 + \exp(1.427 - 0.913X_1 - 0.786X_2 - 0.416X_3)}$$

Figures 3 and 4, Table 1, and supplementary Table 2 have been corrected in the original article.

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