

Factors Influencing the Five-Year Recurrence of Liver Carcinoma after Surgery

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Background: Liver carcinoma is a leading cause of death. Most liver cancers (90%) are hepatocellular carcinoma (HCC), and 10% are cholangiocarcinoma (CCA). Although hepatectomy is the treatment of choice for early stage cancer, the 5-year recurrence rates for HCC and CCA have been reported as 73.4% and 82%, respectively.

Objective: To identify risk factors for 5-year tumor recurrence and the correlation after resection of liver carcinoma.

Materials and Methods: The frequency of recurrence and corresponding risk factors were investigated in patients with HCC and CCA. Data were analyzed using Fisher's exact test and Cox proportion-hazards model.

Results: The present study included 33 HCC and 43 CCA patients (22:11 and 25:18 male:female, 58.0±12.8 and 56.8±8.0 years, respectively). The tumor recurrence rate was 17 (51.5%) and 24 (55.8%) in HCC and CCA patients, respectively.

Conclusion: Vascular invasion was a substantial risk factor for tumor recurrence after complete resection in patients with HCC, whereas serum CA19-9 and vascular invasion were the meaningful risk factors of CCA.

Keywords: Hepatocellular carcinoma, Cholangiocarcinoma, Recurrence

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Liver cancer is the fifth most common cause of death in men and the ninth in women⁽¹⁾. In Thailand, liver cancer is the first and third most common cause of death in male and female patients, respectively⁽²⁾. The main form of liver cancer is hepatocellular carcinoma (HCC) at 90% followed by cholangiocarcinoma (CCA) at 10%⁽³⁾. Treatment for liver cancer includes screening, surgery, thermal destruction of tumor tissue, transarterial chemoembolization (TACE), chemotherapy, use of specific drugs affecting cancer cells, palliative care and methods regarding stage of cancer^(4,5).

The 1-, 3-, and 5-year recurrence rates of HCC and CCA after surgery are 38%, 68% and 73.4% and 32%, 68% and 82%, respectively^(6,7). Recurrence after tumor resection is one of the most important factors affecting patients' physical and psychological conditions, but it also

may be a concerning financial burden, particularly for poor families. These inevitable sequelae also affect the overall survival rate⁽⁶⁾. Parameters affecting survival rate are non-anatomical resection, negative margin in biopsy, function test using Indocyanine Green, microscopic vascular invasion and/or multiple tumors, lymph node metastasis, complications, tumor staging/classification, Child class B or C, poor tissue differentiation, hyperbilirubinemia, serum alpha-fetoprotein and albumin level, hepatitis, cirrhosis and preoperative treatment, such as TACE and radiofrequency ablation (RFA)^(6,9).

The objective of the present study was to identify risk factors for 5-year tumor recurrence and the correlation after resection of liver carcinoma.

Materials and Methods

The retrospective study was approved by the Human Research Ethics Committee, Chulabhorn Research Institute No. 010/2559 and registered at ClinicalTrials.gov (NCT02941861). Data were retrieved from the Hospital Informatics system. Patients with early HCC and CCA who were undergoing hepatectomy and with complete patient information, such as surgical report and pathological results, were included in the present study.

A total of 33 and 43 patients with HCC and CCA underwent liver resection between February 2010 and January 2014, respectively. All patients underwent staging according to the tumor-node metastasis (TNM) system and appraised

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by the hospital tumor board conference. After surgery, an attending physician followed-up with patients by tumor marker evaluation and x-ray imaging. In cases of tumor recurrence, standard treatments were applied until the end of life. Survival time was defined as the number of days between operation and patient death.

Data for statistical analyses included tumor diagnosis, staging, presence of organ metastasis, microscopic vascular invasion and multiple tumors, cirrhosis, hepatitis, level of bilirubin, albumin, alpha-fetoprotein, and CA19-9, surgical technique, negative biopsy margin and tumor differentiation. Disease-free survival (DFS) and overall survival (OS) were verified for content validity index (CVI=1) by three physicians with at least 10 years experience in liver cancer.

Definitions⁽¹⁰⁾

DFS was defined as the length of time that patients survived without any signs or symptoms, after primary

treatment was completed.

OS was defined as DFS plus the time between diagnosis and treatment.

Cancer recurrence (CR) was defined as the return of cancer after completed treatment, independent of whether the recurrence occurred at the same site or at another anatomical site.

Data analysis

Data were analyzed using Stata SE12 and are expressed as percentage, mean and standard deviation. The t and exact probability tests were used to compare groups. Study size estimated 10 cases per predictor subsequently the proportion of variables to sample size = 1:10⁽¹¹⁾. Survival curve was calculated by the Kaplan-Meier method and compared with log-rank tests (Mantel-Cox) together with Cox proportional hazard models for adjusted ratios. Wald test methods were used to generate the p-value. A p-value less than 0.05 was considered significant with

Table 1. Demographic characteristics of patients with hepatocellular carcinoma (n=33)

| Variables | Total | Recurrent, n (%) | | p-value |
|------------------------|-------------|----------------------------|-----------------------------|---------|
| | | Yes (n=17) | No (n=16) | |
| Age (mean ± SD) | 54.73±13.13 | 58.0±12.8 | 51.3±19.9 | 0.142 |
| Gender | | | | |
| F:M | 11:22 | 6 (35.3):11 (64.7) | 5 (31.3):13 (68.7) | 1.000 |
| Cirrhosis | | | | |
| N:Y | 20:13 | 11 (64.7):6 (35.3) | 9 (56.3):7 (43.7) | 0.728 |
| Hepatitis | | | | |
| N:Y | 2:31 | 1 (5.9):16 (94.1) | 1 (6.3):15 (93.7) | 1.000 |
| Pre-surg treat | | | | |
| N:Y | 24:9 | 11 (64.7):6 (35.3) | 13 (81.3):3 (18.7) | 0.438 |
| Vas invasion | | | | |
| N:Y | 20:13 | 7 (41.2):10 (58.8) | 13 (81.3):3 (18.7) | 0.032* |
| Stage | | | | |
| I:II:III-IV | 15:13:5 | 5 (29.4):9 (52.9):3 (17.7) | 10 (62.5):4 (25.0):2 (12.5) | 0.164 |
| Margin | | | | |
| F:Nf | 33:0 | 17 (100.0):0 (0) | 16 (100.0):0 (0) | N/A |
| Multitumor | | | | |
| 1:>1 | 23:10 | 10 (58.8):7 (41.2) | 13 (81.3):3 (18.7) | 0.259 |
| Different ^a | | | | |
| W:M:P | 15:15:3 | 7 (41.2):8 (47.1):2 (11.7) | 8 (50.0):7 (43.7):1 (6.3) | 1.000 |
| AFP | | | | |
| <7:≥7 | 18:15 | 9 (56.3):7 (43.7) | 9 (52.9):8 (47.1) | 1.000 |
| Alb | | | | |
| ≥3.5:<3.5 | 29:4 | 14 (82.3):3 (17.7) | 15 (93.7):1 (6.3) | 0.601 |

* p<0.05

F:M=female:male; N:Y=no:yes; F:Nf=free:not free; W:M:P=well:moderate:poor; AFP=Alpha-fetoprotein; Alb=Albumin

95% confidence interval.

Results

The 33 patients with HCC in the present study included 11 female and 22 male patients. Among the total 33 patients, 17 (51.5%) patients showed CR. All 33 patients had free tissue margins from surgical biopsy. Nine were treated preoperatively with TACE and/or RFA but showed no signs of relapse. The risk factors for cancer recurrence in HCC patients were cirrhosis (6, 35.3%), hepatitis (16, 94.1%), pre-surgical treatment (6, 35.3%), vascular invasion (10, 58.8%), tumor stage III-IV (3, 17.7%), multi-tumors (7, 41.2%), poor-differentiated tumor tissue (2, 11.7%), alpha-fetoprotein (AFP) ≥ 7 ng/ml (7, 43.7%) and serum albumin (Alb) <3.5 gm% (3, 17.7%).

Univariate Cox proportion-hazards model showed that only vascular invasion was a significant risk factor for tumor recurrence in HCC patients (HR=4.06; 95% (1.51 to 10.90); $p=0.005$) (Table 1 and 2).

The CCA group included 18 female and 25 male patients; among the total 43 patients, 24 (55.8%) showed cancer recurrence (Table 4). The risk factors were CEA (14, 58.3%) and CA19-9 abnormality (10, 41.7%), Alb level <3.5 gm% (4, 16.7%), vascular invasion (20, 83.3%), no free tissue margin in the surgical biopsy (1, 4.2%), poor differentiation of tumor cells (1, 4.2%) and tumor stage IV (6, 25.0%).

Univariate Cox proportion-hazards model revealed that that CEA (HR=2.93; 95% (1.29 to 6.68); $p=0.010$), CA19-9 (HR=3.39; 95% (1.48 to 7.75); $p=0.004$), albumin (HR=3.52; 95% (1.19 to 10.47); $p=0.023$), vascular invasion (HR=3.68; 95% (1.25 to 10.79); $p=0.018$), stage III (HR=4.90; 95% (1.58 to 15.19); $p=0.006$) and stage IV (HR=4.01; 95% (1.22 to 13.20); $p=0.022$) were predictors for tumor recurrence in CCA patients.

Multivariate Cox proportion-hazards model revealed that CA19-9 (HR=2.80; 95% (1.21 to 6.49); $p=0.016$) and vascular invasion (HR=3.10; 95% (1.04 to 9.24); $p=0.042$) were predictors for tumor recurrence in CCA patients (Table 3 and 4). However, the DFS and OS of patients with HCC and CCA were comparable (Table 5).

Kaplan-Meier survival curves showed that the median DFS time for CCA and HCC groups was 24 and 48 months, respectively. Examination of the DFS time between CCA and HCC groups using Wilcoxon (Breslow) test for equality of survivor functions revealed no significant difference between the groups ($p=0.696$). The median survival time of HCC and CCA was 24 months (Figure 1).

The overall survival of the HCC and CCA groups was not significantly different ($p=0.065$). The median survival time of the CCA group was 44 months, with an OS of 50% (Figure 2).

Discussion

The authors found that vascular invasion was a substantial risk factor for tumor recurrence after complete resection in patients with HCC, whereas serum CA19-9

Table 2. Cox proportion-hazards model in patients with hepatocellular carcinoma (n=33)

| Variables | Univariate | |
|-------------------------|---------------------------|---------|
| | HR (95%) | p-value |
| Age | 1.02 (0.98 to 1.06) | 0.295 |
| Gender | | |
| F/M | 1.00/0.90 (0.33 to 2.43) | 0.832 |
| Cirrhosis | | |
| N/Y | 1.00/0.64 (0.24 to 1.73) | 0.381 |
| Hepatitis | | |
| N/Y | 1.00/1.21 (0.16 to 9.16) | 0.852 |
| Pre_surg | | |
| N/Y | 1.00/1.41 (0.52 to 3.82) | 0.500 |
| Margin | | |
| F/NF | N/A | N/A |
| AFP | | |
| $<7/\geq 7$ ng/ml | 1.00/1.25 (0.48 to 3.25) | 0.645 |
| Alb | | |
| $\geq 3.5/\leq 3.5$ gm% | 1.00/1.45 (0.41 to 5.05) | 0.564 |
| Vascular invasion | | |
| N/Y | 1.00/4.06 (1.51 to 10.90) | 0.005* |
| Stage | | |
| I | 1.00 | |
| II | 2.89 (0.96 to 8.68) | 0.059 |
| III-IV | 2.87 (0.68 to 12.07) | 0.150 |
| Differentiation | | |
| Well | 1.00 | |
| Moderate | 1.70 (0.54 to 5.35) | 0.368 |
| Poor | 4.32 (0.83 to 22.48) | 0.082 |

* $p<0.05$

F:M=female:male; N:Y=no:yes; F:NF=free: not free; W:M:P=well: moderate:poor; AFP=Alpha-fetoprotein; Alb=Albumin

and vascular invasion were the meaningful risk factors for patients with CCA. Vascular spreading in HCC is a frequent histological finding; its appearance suggests the development of early metastasis^(4,5,7,12).

Preoperative TACE and RFA were effective treatments for liver cancer patients in the present study because the nine treated patients with HCC showed no signs of relapse. Preoperative TACE under bridging reduces the tumor size by vascular occlusion, which is consistent with the findings of Chapman and Ogata^(8,13). TACE is well accepted as a useful technique for preoperative treatment of high-risk or inoperable tumors. However, the patient outcome after TACE seems to be debatable. Hanazaki et al reported that TACE increased the recurrence rate after hepatic resection⁽⁷⁾. Additionally, Xia, et al emphasized the technical

Table 3. Demographic characteristics of patients with cholangiocarcinoma (n=43)

| Variables | Total | Recurrent, n (%) | | p-value |
|------------------------|----------|----------------------------|----------------------------|---------|
| | | Yes (n=24) | No (n=19) | |
| Age (mean±SD) | 56.8±8.0 | 56.4±8.8 | 57.3±7.1 | 0.734 |
| Gender | | | | |
| F:M | 18:25 | 9 (37.5):15 (62.5) | 9 (47.4):10 (52.6) | 0.487 |
| CEA | | | | |
| N:AB | 25:18 | 10 (41.7):14 (58.3) | 15 (78.9):4 (21.1) | 0.028* |
| CA19-9 | | | | |
| N:AB | 31:12 | 14 (58.3):10 (41.7) | 17 (89.5):2 (10.5) | 0.039* |
| Alb | | | | |
| ≥3.5:<3.5 gm% | 39:4 | 20 (83.3):4 (16.7) | 19 (100.0):0 (0) | 0.118 |
| Vas invasion | | | | |
| N:Y | 15:28 | 4 (16.7):20 (83.3) | 11 (57.9):8 (42.1) | 0.009* |
| Margin | | | | |
| F:Nf | 42:1 | 23 (95.8):1 (4.2) | 19 (100.0):0 (0) | 1.000 |
| Different ^a | | | | |
| W:M:P | 23:16:4 | 14 (58.3):9 (37.5):1 (4.2) | 9 (47.4):7 (36.8):3 (15.8) | 0.537 |
| Type | | | | 0.129 |
| Intra-hepatic | 29 | 19 (79.1) | 10 (52.7) | |
| Intraductal | 6 | 1 (4.2) | 5 (26.3) | |
| Extra-hepatic | 5 | 3 (12.5) | 2 (10.5) | |
| Other | 3 | 1 (4.2) | 2 (10.5) | |
| Stage | | | | 0.038* |
| I | 16 | 5 (20.8) | 11 (57.9) | |
| II | 9 | 5 (20.8) | 4 (21.0) | |
| III | 9 | 8 (33.3) | 1 (5.3) | |
| IV | 9 | 6 (25.0) | 3 (15.8) | |

* p<0.05

F:M = female:male; CEA = carcinoembryonic antigen; N:AB = normal:abnormal; N:Y = no:yes; F:Nf = free:not free; W:M:P = well:moderate:poor

challenges and problems when applying TACE, such as accurately selecting the hepatic artery and the slow infusion of lipiodol (ethiodized oil). TACE is contraindicated in the presence of dilated bile ducts unless external biliary drainage is performed before injection. In any case, TACE should be performed cautiously with careful postoperative observation, so that potential severe complications, such as spontaneous tumor rupture, perforated duodenum, liver abscess, spasm of the hepatic artery, femoral nerve injury or acute renal failure, can be detected early⁽¹⁴⁾.

CCA showed aggressive periductal and lymphatic dispersion moving directly into the surrounding hepatic parenchyma, portal pedicle and bile duct. Subsequently, intrahepatic metastases developed in almost all cases at a relatively advanced stage^(6,15-17).

The 30-day mortality rate of both HCC and CCA

groups was zero, whereas Hanazaki et al reported a 30-day mortality rate of 4.1%⁽⁷⁾. The 60-month OS of HCC patients, however, was higher than that of patients with CCA. The current study revealed that the median DFS in patients with CCA was 24 months, which is in accordance with the results of Yusoff et al who demonstrated an average DFS of 16 months in these patients⁽¹⁸⁾.

We believe that multidisciplinary preoperative assessment of patients' physical status is crucial for determining the prognosis of the disease. In our hospital, a tumor board including surgeon, radiologists, oncologist and nurses assess patients' preoperative status, which is similar to the strategy emphasized by Wheless et al describing the effect of a multidisciplinary tumor board in managing patients with head and neck cancer⁽¹⁹⁾. Our results showed the success of a 5-year screening project regarding the early detection of

Table 4. Cox proportion-hazards model in patients with cholangiocarcinoma (n=43)

| Variables | Univariate | | Multivariate | |
|-------------------|---------------------------|---------|--------------------------|---------|
| | HR (95%) | p-value | 95% of HR | p-value |
| Age | 0.99 (0.93 to 1.04) | 0.660 | | |
| Gender | | | | |
| F:M | 1.00/1.35 (0.59 to 3.09) | 0.478 | | |
| CEA | | | | |
| N:AB | 1.00/2.93 (1.29 to 6.68) | 0.010* | | |
| CA19-9 | | | | |
| N:AB | 1.00/3.39 (1.48 to 7.75) | 0.004* | 1.00/2.80 (1.21 to 6.49) | 0.016* |
| Alb | | | | |
| ≥3.5:<3.5 gm% | 1.00/3.52 (1.19 to 10.47) | 0.023* | | |
| Vascular invasion | | | | |
| N:Y | 1.00/3.68 (1.25 to 10.79) | 0.018* | 1.00/3.10 (1.04 to 9.24) | 0.042* |
| Margin | | | | |
| F:Nf | N/A | N/A | | |
| Differentiation | | | | |
| Well | 1.00 | | | |
| Moderate | 0.97 (0.42 to 2.24) | 0.946 | | |
| Poor | 0.32 (0.04 to 2.45) | 0.274 | | |
| Type | | | | |
| Intra-hepatic | 1.00 | | | |
| Intraductal | 0.16 (0.02 to 1.18) | 0.072 | | |
| Extra-hepatic | 0.79 (0.23 to 2.69) | 0.712 | | |
| Other | 0.37 (0.05 to 2.77) | 0.33 | | |
| Stage | | | | |
| I | 1.00 | | | |
| II | 1.91 (0.55 to 6.62) | 0.307 | | |
| III | 4.90 (1.58 to 15.19) | 0.006* | | |
| IV | 4.01 (1.22 to 13.20) | 0.022* | | |

* p<0.05

liver cancer.

Conclusion

Vascular invasion and serum CA19-9 were important parameters indicating tumor recurrence after hepatectomy in patients with liver carcinoma. Elective hepatectomy was a safe procedure regarding acute outcome; the 30-day survival rate in our patients was 100%. The 60-month survival for patients with HCC was not significantly different compared with patients with CCA.

Limitation of the study

Limitations of this study include its retrospective study design, with a small sample size, no randomization

and no specific criteria for patient selection. Additionally, we recorded only patients undergoing surgery in a single university hospital.

What is already known on this topic?

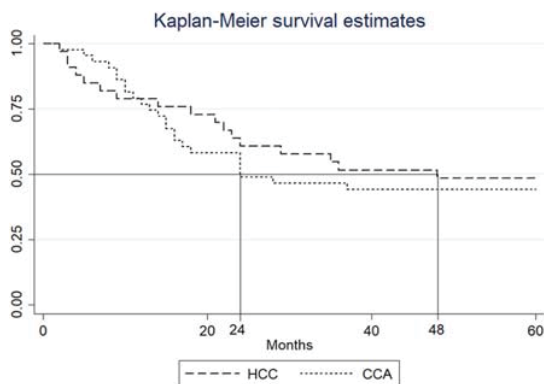
Previous studies showed that the 5-year recurrence rates of HCC and CCA after surgery are 73.4% and 82%, respectively.

What this study adds?

Our study showed that the 5-year recurrence rates of HCC and CCA after surgery were 51.5% and 55.8%, respectively. Both vascular invasion and serum CA19-9 were the risk factors to determine the advancement of disease.

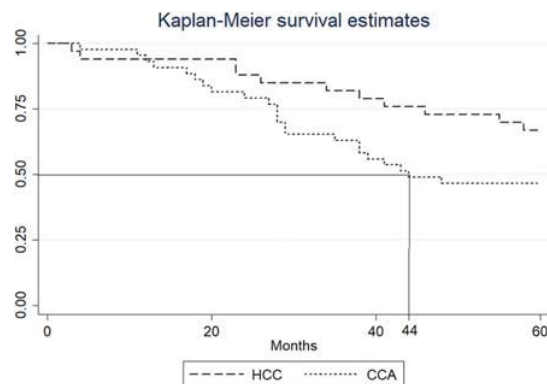
Table 5. Disease-free and overall survival of patients with hepatocellular carcinoma (n=33) and cholangiocarcinoma (n=43) after surgery

| Survival | Time (months) | HCC (95% CI) | CCA (95% CI) |
|--------------|---------------|----------------------|----------------------|
| Disease-free | 12 | 78.8% (60.6 to 89.3) | 76.7% (61.1 to 86.7) |
| | 24 | 60.6% (42.0 to 74.9) | 48.8% (33.3 to 62.7) |
| | 36 | 51.5% (33.5 to 66.9) | 46.5% (31.2 to 60.4) |
| | 48 | 48.5% (30.8 to 64.1) | 44.2% (29.2 to 58.2) |
| | 60 | 48.5% (30.8 to 64.1) | 44.2% (29.2 to 58.2) |
| Overall | 12 | 93.9% (77.9 to 98.4) | 93.0% (79.9 to 97.7) |
| | 24 | 87.9% (70.9 to 95.3) | 79.1% (63.3 to 88.5) |
| | 36 | 81.8% (63.9 to 91.4) | 62.8% (46.6 to 75.3) |
| | 48 | 72.7% (54.1 to 84.8) | 46.5% (31.2 to 60.4) |
| | 60 | 66.7% (47.9 to 80.0) | 46.5% (31.2 to 60.4) |



HCC = hepatocellular carcinoma, CCA = cholangiocarcinoma

Figure 1. Recurrence (disease free) of HCC and CCA in 5 years Wilcoxon (Breslow) test was performed for equality of survivor functions (p=0.696).



HCC = hepatocellular carcinoma, CCA = cholangiocarcinoma

Figure 2. Overall survival of HCC vs. CCA in 5 years Wilcoxon (Breslow) test was performed for equality of survivor functions (p=0.065).

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Potential conflicts of interest

The authors declare no conflicts of interest.

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