ORIGINAL ARTICLE

Radiomics-based Deep Learning Approach to Predict Recurrence in Cholangiocarcinoma Patients after Curative Resection: A Pilot Study

Prin Twinprai, MD[1,2], Piyakarn Watcharenwong, MD[2,3], Warunporn Siriboonpipattana, MD[2,3], Attapol Titapun, MD,PhD[2,4], Vasin Thanasukarn, MD[2,4], Nattaphon Twinprai, MD[5], Prinya Chindaprasirt, PhD[6], Puripong Suthisopapan, PhD[6], Jarin Chindaprasirt, MD[2,3]

[1] Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[2] Cholangiocacinoma Research Institute, Khon Kaen, Thailand
[3] Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[4] Division of Hepatobiliary Surgery, Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[5] Department of Orthopedics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[6] Faculty of Engineering, Khon Kaen University, Khon Kaen, Thailand

Objective: The purpose of the present study was to develop a preoperative CT-radiomics model for predicting recurrence for patients with cholangiocarcinoma (CCA) after curative resection.

Materials and Methods: Preoperative contrast-enhanced CT scans from a randomized phase 3 CCA trial were included (n=56). Segmentation was performed using 3DSlicer program and radiomics-based features were extracted using PyRadiomics. Feature selection was performed by using XGBoost and SHAP values to identify the most important features which consequently were used to train a classification neural network in MATLAB for predicting recurrence.

Results: With a median follow-up time of 55 months, 29 patients had disease recurrence. The 1-yr, 2-yr, and 5-yr recurrence-free survival time rates were 76.8%, 60.7%, and 41.4%, respectively. The ten most important features predicting recurrence were selected and the radiomics-based model was trained for 1,000 epochs and augmented three times, achieving a sensitivity and specificity of 1.0 and accuracy of 1.0.

Conclusion: Radiomics-based deep learning could serve as a valuable tool for predicting the recurrence of cholangiocarcinoma patients in a preoperative setting.

Keywords: Cholangiocarcinoma; Radiomics; Recurrence; Deep learning; XGBoost

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Cholangiocarcinoma is a malignant liver cancer that arises from the bile duct, accounting for 10 to 15% of all liver cancers[1,2]. The highest reported incidence is in Southeast Asia, especially in northeast Thailand (85 per 100,000 people)[3]. The prognosis of cholangiocarcinoma is quite poor, even after curative resection, with a low median overall survival of 12 to 18 months and a 5-year survival rate of about 10 to 20%[4].

Outcomes of bile duct cancer surgery are poor, especially those with early recurrence harbor a worse prognosis. Thus, it is crucial to identify patients with cholangiocarcinoma who are at risk of recurrence so that more aggressive surgical intervention can be implemented and tailor optimal treatment including adjuvant chemotherapy and radiotherapy, which would improve patient survival[5,6].

Several prognostic factors have been identified including tumor size, nodal involvement, imaging-biomarker, pathological surgical margin, and nutritional status[7-9]. However, predicting the outcome of cholangiocarcinoma treatment remains challenging, even among patients at the equal disease stage. There is significant heterogeneity in survival outcomes among patients with the same stage of

Correspondence to:

Chindaprasirt J.

Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

Phone: +66-43-363664, **Fax:** +66-43-202491

Email: jarich@kku.ac.th

ORCID: 0000-0002-0401-9812

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the disease, indicating the complexity and variability of cholangiocarcinoma[4,10]. In clinical practice, preoperative radiological studies including CT scan and MRI demonstrate anatomical involvement of the tumor, nodal involvement, and metastatic disease, guiding the resectability of the cancer. However, the prognostic values of the imaging are still limited.

Machine learning radiomics is the high-throughput extraction of texture features from any imaging modality[11]. It relies on the quantitative analysis of the texture and features of a segmented region of interest through semi-automatic or automatic software. The radiomics-based features of several tumors, based on patterns of pixel and voxels, have demonstrated a strong association with the pathology data and prognosis that generates mineable databases that can be used to build predictive models[12,13]. In primary liver tumor, radiomics is mainly used as a non-invasive tool for predicting pathological results and survival outcomes in cholangiocarcinoma and hepatocellular carcinoma[12,14,15].

Hence, the present study aimed to extract important radiomics-based features predicting recurrence in cholangiocarcinoma patients after curative resection and to develop a deep-learning radiomics model.

Materials and Methods

Patients and clinicopathological data

The present study included cholangiocarcinoma patients underwent curative surgery and enrolled in the GeCiCCA (A randomized controlled trial of Gemcitabine alone versus Gemcitabine plus Cisplatin as adjuvant chemotherapy after curative intent resection of cholangiocarcinoma: TCTR20161101003) study from January 2016 to December 2020 in Srinagarind Hospital, Khon Kaen University, Thailand. The main inclusion criteria were: 1) Pathological diagnosis of cholangiocarcinoma after curative surgery, 2) No distant metastasis, and 3) Adequate organ functions. Patients were excluded if: 1) lack of pre-operative CT data in DICOM format, 2) loss to follow-up. A total of 56 patients were included in the present study (Figure 1). All patients received adjuvant gemcitabine-based chemotherapy.

Clinicopathological and radiographic data

Baseline clinical data including age, sex, ECOG performance status, and laboratory data were all collected before surgery. Tumors were staged according to the TNM tumor staging (8th edition).

Patients were followed-up postoperatively per the GeCiCCA study protocol. Clinical and laboratory assessment was performed every 3 months during the first year and at 6 months afterward. CT imaging was performed every 6 months in the first three years. Recurrence was defined as either local recurrence or distant metastasis. Recurrence-free survival was defined as the duration between the surgery date and the date of tumor recurrence or death.

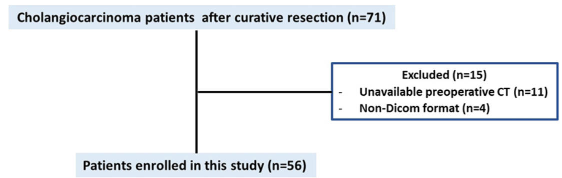

Figure 1. Flowchart of the enrolled study patients.

Image selection, segmentation, and feature extraction

Areas of interest including the parenchymal tumor, bile duct lesion, and regional pathological lymph nodes were delineated and segmented by two experienced oncologists using 3D Slicer (Version 5.2.2) as shown in Figure 2. All segmented areas were re-reviewed by a sub-board-certified advanced body imaging radiologist to ensure the completeness of the input data.

Feature selection and radiomics model construction

Radiomics-based features were extracted using PyRadiomics, a tool that converts imaging data of lesions into numerical features. A total of 100 unique features were extracted for each patient. The authors employed XGboost with SHAP analysis to identify the 10 most important features associated with the outcome prediction. To prevent overfitting, stochastic feature augmentation was applied only to the training set. Subsequently, a classification AI model was built using MATLAB. To address the need for a complex and sophisticated model capable of addressing the research question, the authors developed a deep neural network with four hidden layers, (Figure 3).

The dataset was divided into a training and a test set (70: 30 ratio). To ensure the class balance, patients were randomly assigned to each set while maintaining the original proportions of recurrence and non-recurrence cases. This resulted in a training set of 40 patients (20 recurrent and 20 non-recurrent patients) and a test set of 16 patients (7 recurrent and 9 non-recurrent patients).

Statistical analysis

Clinical characteristics were analyzed using descriptive statistics and presented as the median and interquartile range (IQR). The associations between clinicopathological parameters (including tumor size, location, margin, and lymph node involvement) were analyzed using Chi-square or Fisher's exact test as appropriate. The survival analysis was analyzed using the Kaplan-Meier curve and Cox regression tests. Statistical significance was

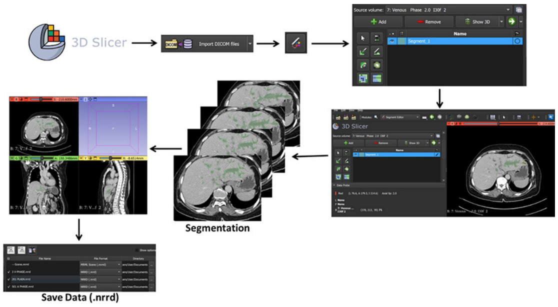

Figure 2. Segmentation with 3D slicer program.

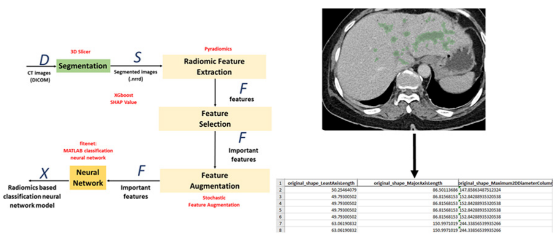

Figure 3. Radiomics workflow.

determined at a p-value less than 0.05. Stata software version 16 (StataCorp LLC) was used to compute model accuracy, sensitivity, specificity, precision, and F1 score. These metrics provided a comprehensive evaluation of the model's performance.

Results

Clinical features

A total of 56 patients were included in the final analysis. During the follow-up period, 29 patients recurred, whereas 27 were free from recurrence. Clinical features of the two patient groups (recurrence and non-recurrence) were summarized in Table 1. The most common anatomical subtype was perihilar CCA (73.2%). The majority of the patients were stage II and III in 35.7% and 30.4% of patients, respectively.

Survival outcomes

The median follow-up time was 55 months (95% CI: 43 to 62 months). The 1-, 2-, and 5-year recurrence-free survival (RFS) for the entire cohort were 76.8%, 60.7%, and 41.4%, respectively, (Figure 4). The median time to recurrence was 18 months (95% CI: 12 to 21 months). The initial recurrence pattern was predominantly local recurrence (65.5%).

Radiomics-based features and model prediction performance

A total of 100 radiologic features were identified to analyze in the model. The ten most important features predicting recurrence were selected (Figure 5) and subjected to cross-validation. The radiomics model was trained for 1,000 epochs and augmented three times, achieving a sensitivity and specificity of 1.0 and an accuracy of 1.0 (Table 2). A neural network model was developed.

Discussion

The present study developed a deep-learning radiomics model to predict the recurrence of cholangiocarcinoma patients after curative resection, which can be used to make personalized treatment decisions based on the recurrent risk of cholangiocarcinoma. Several radiomics studies have been reported on the prognosis of cholangiocarcinoma. Liang et al. developed radiomics models to predict early recurrence in intrahepatic cholangiocarcinoma by using preoperative MRI images[16] and Song et al. used both preoperative MRI and CT images-based radiomics models[17]. The present study used only preoperative CT images because it is more widely available and more accessible.

Song et al. found 15 radiomics-based features and 3 clinical features (CA 19-9 >1,000 u/ml, tumor vascular invasion, and tumor margin) that predict early recurrence in cholangiocarcinoma[17]. However, in the present study, the authors could not identify any clinicopathological factor associated with recurrent outcomes, but found 10 important radiomics-based features that could predict recurrence.

The feature selection process includes various methods, such as LASSO. Song et al. used SHapley Additive exPlanations (SHAP) with the LightGBM model, which outperforms traditional linear models in accuracy but lacks interpretability, often being seen as a black box model[17]. The authors, however, use XGboost program and SHAP value[18]. XGboost program and SHAP value is explainable artificial intelligence, constructing a neural network that encompasses deep machine learning radiomics, which is more complicated and challenging, making it very difficult to create.

The model achieved an accuracy, sensitivity, and specificity of 1 indicating superior performance in predicting outcomes correctly compared to other studies from the literature review which reported an accuracy of 0.878 to 0.964, a sensitivity of 0.818 to 0.973, and a specificity of 0.909 to 0.954)[17,19].

This is the first study that develops a radiomics-based model as a tool to preoperatively predict recurrence in cholangiocarcinoma in Thailand. Nevertheless, there were some limitations. First, the study was conducted in a single centre and there was no external validation yet. Therefore, training the present study model with a larger dataset in the future could enhance its predictive efficacy, making it suitable for clinical use.

Table 1. Baseline characteristics and clinicopathological data of cholangiocarcinoma patients

Characteristics	All (n=56)	Recurrence (n=29)	Non-recurrence (n=27)	p-value
Age, median (min-max)	58.5 (26 to 70)	59 (38 to 69)	58 (26 to 70)	0.78
Sex, n (%)				
Male	33 (58.9)	14 (48.3)	19 (70.4)	0.09
Female	23 (41.1)	15 (51.7)	8 (29.6)	
ECOG, n (%)				
0	41 (73.2)	23(79.3)	18 (66.7)	0.29
1	15 (26.8)	6 (20.7)	9 (33.3)	
Location, n (%)				
Intrahepatic	12 (21.4)	4 (13.8)	8 (29.6)	0.33
Perihilar	41 (73.2)	23 (79.3)	18 (66.7)	
Distal CBD	3 (5.4)	2 (6.9)	1 (3.7)	
Tumor morphology, n (%)				
Mass forming	32 (57.1)	16 (55.2)	16 (59.3)	0.76
Periductal infiltrate	30 (53.6)	17 (58.6)	13 (48.1)	0.43
Intraductal growth	25 (44.6)	13 (44.8)	12 (44.4)	0.98
Tumor margin, n (%)				
Positive	21 (37.5)	14 (48.3)	7 (25.9)	0.08
Negative	35 (62.5)	15 (51.7)	20 (74.1)	
Tumor size, median (min-max)	4 (0.5 to 14)	4 (1.5 to 10)	4 (0.5 to 14)	0.69
Lymph node, n (%)				
Positive	18 (32.1)	15 (51.7)	3 (11.1)	0.001*
Negative	38 (67.9)	14 (48.3)	24 (88.9)	
LVI, n (%)				
Positive	29 (51.8)	16 (55.2)	13 (48.2)	0.60
Negative	27 (48.2)	13 (44.8)	14 (51.8)	
PNI, n (%)				
Positive	25 (44.6)	16 (55.2)	9 (33.3)	0.10
Negative	31 (55.4)	13 (44.8)	18 (66.7)	
TNM staging, n (%)				
I	14 (25)	3 (10.3)	11 (40.7)	0.003*
II	20 (35.7)	8 (27.6)	12 (44.4)	
III	17 (30.4)	14 (48.3)	3 (11.1)	
IV	5 (8.9)	4 (13.8)	1 (3.7)	
Preoperative laboratory value, median (IQR)				
CA19-9	51.6 (7.2 to 328)	62 (8.4 to 1,000)	51.2 (7.2 to 126)	0.49
CEA	3.5 (1.9 to 5.3)	4.1 (2.5 to 8.2)	3.2 (1.8 to 4.7)	0.11
Albumin	4.1 (3.6 to 4.4)	4.1 (3.5 to 4.3)	4.1 (3.8 to 4.5)	0.35
Total bilirubin	0.7 (0.4 to 2.4)	1 (0.5 to 2.7)	0.6 (0.4 to 1.9)	0.23
NLR	2.5 (1.7 to 3.6)	2.3 (1.8 to 3.6)	2.6 (1.7 to 4.2)	0.66
Site of recurrence, n (%)				
Local recurrence	-	19 (65.5)	-	-
Distant recurrence	-	15 (51.7)	-	-

* Statistical significance

ECOG=Eastern Cooperative Oncology Group; LVI=lymphovascular invasion; PNI=Perineural invasion; IQR=interquartile range; CA19-9=Carbohydrate antigen 19-9; CEA=Carcinogenic embryonic antigen; NLR=Neutrophil-lymphocyte ratio

Conclusion

From the present pilot study, a model was built using XGBoost and SHAP with Radiomics-based Deep Learning which provides ten key important features that could predict recurrence in cholangiocarcinoma patients after curative resection. Further validation in larger cohorts is needed

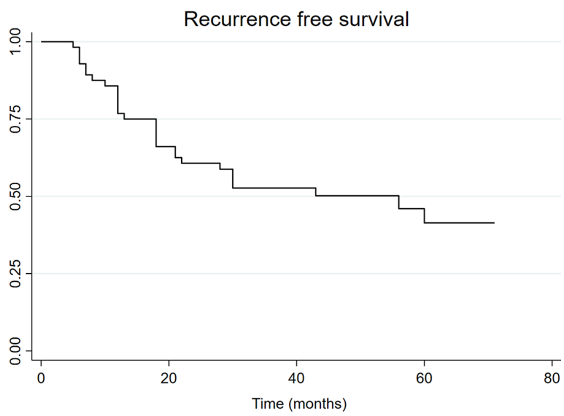

Figure 4. Recurrence-free survival of the entire cohort (n=56).

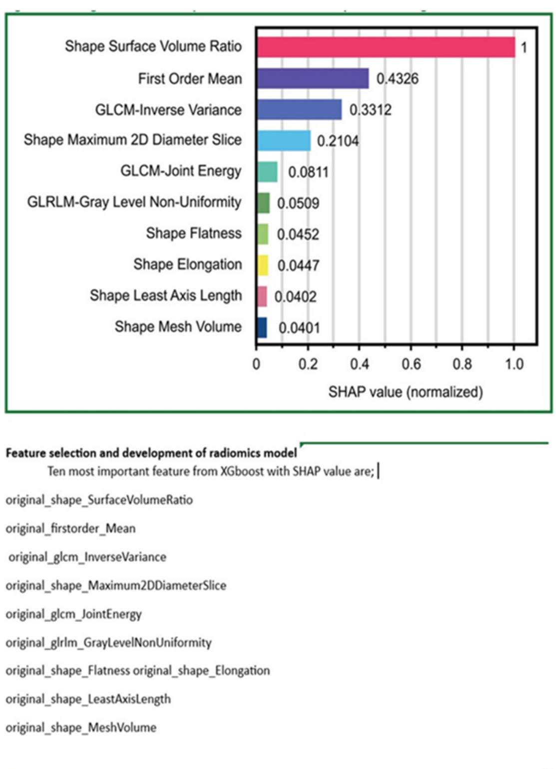

Figure 5. Ten most important features identified by XGBoost using SHAP values.

before clinical application.

Ethics statement

Written informed consents were obtained from all patients. The present study was approved by the Institutional Review Board of the Khon Kaen University Ethics Committee for Human Research based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines (HE591330).

Table 2. The prediction performance of a radiomics-based model

Augment	ACC	REC	PREC	F1	SPEC
Augmentx1	0.88	0.86	0.86	0.86	0.89
Augmentx2	0.94	1	0.86	0.92	1
Augmentx3	1	1	1	1	1

ACC=Accuracy; REC=recall or sensitivity; PREC=precision or positive predictive value; SPEC=specificity

What is already known on this topic?

Cholangiocarcinoma recurrence rate after surgery is high. Currently, there is no preoperative imaging modality or features that can accurately predict recurrence.

What this study adds?

Using deep learning employed to analyze imaging data (CT scans) to identify tumor characteristics can help predict recurrence. The model can assess the tumor imaging and provide insights that may not be captured by traditional methods.

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Conflicts of interest

The authors declare no conflict of interest.

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