Ontology Representation for Cholangiocarcinoma

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Abstract

Introduction: Cholangiocarcinoma is a critical public health problem in Thailand. Several research projects have been conducted and data related to CCA have been collected to solve this problem. Data about CCA are found in varied sources such as research-based databases and electronic health records that have been collected and stored using different methods and standards. The objective of this study is to develop the Cholangiocarcinoma Ontology (CCAO) to describe findings related to cholangiocarcinoma in a structured and standardized way in order to integrate and analyze data from these diverse sources.

Methods: CCAO has been developed based on data collection forms (CCA forms) of the Cholangiocarcinoma Screening and Care Program (CASCAP). The forms contain data elements about demographics, ultrasound findings, confirmatory diagnoses, final staging diagnoses, and post-operative and follow-up outcomes. These data elements were used to search the Ontobee web browser for matching ontology classes in existing ontologies. Ontology classes from various sources were extracted using a ROBOT tool and imported to CCAO, and new CCAO classes for unmatched classes were added to CCAO manually. CCAO is an application ontology beneath the Basic Formal Ontology (BFO) along with the Ontology of General Medical Science (OGMS), the Information Artifact Ontology (IAO), and the Ontology for Biomedical Investigations (OBI).

Results: Based on the CCA forms we developed 210 novel CCAO classes and created 108 CCAO classes based on NCI Thesaurus classes. We reused classes from various domain ontologies including the Phenotype And Trait Ontology (PATO), the Ontology of Biological Attributes (OBA), the Cell Ontology (CL), the Ontology of Medically Related Social Entities (OMRSE), and Drug Ontology (DRON). Imported classes in CCAO were reorganized under the top-level classes such as OGMS:'clinical finding', OGMS:'disorder', and OBI:'conclusion based on data'. Moreover, we generated logical definitions for many CCAO classes.

Conclusion: CCAO is reusable, interoperable, and easily integrated with related datasets, as well as being human and machine readable. It is compatible with future expansion to represent relevant evidence and knowledge that is not be part of this initial version. CCAO is publicly available on Github (https://github.com/Buffalo-Ontology-Group/CCA-Ontology).

Keywords 1

cholangiocarcinoma, biomedical ontology, basic formal ontology

1. Introduction

Cholangiocarcinoma (CCA) is a major problem in Southeast Asia (SEA). The prevalence of CCA in SEA is much higher than other areas in the world. Culture and traditions of eating raw, fermented, pickled, and undercooked cyprinid fish are the key factors for liver fluke, *Opisthorchis viverrini (O. viverrini)*, infections. *O. viverrini* infections produce hepatic bile ducts and portal connective tissue inflammation. Chronic infections and inflammation have been indicated to be risk factors for the development of multiple stages of carcinogenesis [1, 2].

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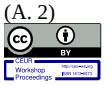

In Thailand, CCA is a common malignancy. Several policies have been deployed over the last 40 years to prevent CCA, but the survival rates of CCA patients are still poor [3]. The Cholangiocarcinoma Screening and Care Program (CASCAP), established by Khon Kaen University, Thailand in 2015, aims to eliminate *O. viverrini* infections and CCA [4].

CASCAP is a prospective cohort study including screening and patient cohorts. Data is collected based on six separate data collection forms: CCA-01, "Demographic Information Enrollment," CCA-02, "Ultrasound," CCA-02.1, "Confirmatory Diagnosis," which is used to confirm suspected CCA participants from ultrasound screenings in CCA-02 based on CT scan, MRI, or other procedures, CCA-03, "Diagnosis and Treatment," CCA-04, "Final Staging Diagnosis," and CCA-05, "Post Operation Follow-up" [4, 5]. Moreover, electronic health records (EHR) from general and community hospitals in Thailand also contain data and information of patients with, or suspected of suffering from CCA including symptoms, clinical findings, treatments, and diagnoses [6].

These databases represent data elements in different ways. EHR uses International Statistical Classification of Disease and Related Health Problems, 10th revision, Thai Modification (ICD-10-TM), which is being used as the Thai standard for morbidity and mortality coding in health services statistics, as well as for billing and payment [7, 8], while the CASCAP study represents data and information as research-based data elements that capture details about CCA more specific than those in ICD-10-TM. Thus, it is a challenge to work with data from different sources and standards.

In order to integrate data from different sources, the Cholangiocarcinoma Ontology (CCAO) is being built as an application ontology under the Basic Formal Ontology (BFO) and the BFO-compatible ontologies including the Ontology of General Medical Science (OGMS), the Information Artifact Ontology (IAO), and the Ontology for Biomedical Investigations (OBI) [9-12]. CCAO relies upon BFO to provide an upper-level framework to structure the ontology.

Ontologies have long been used to designate all entities within an area of reality and all relationships between those entities in a way that make them interpretable by both humans and computers [13], and the application of ontologies in medical and scientific research is a response to need to reuse the voluminous and complex information [14]. The objective of this study is to create an application ontology, CCAO to describe in a structured and standardized way various types of information and findings related to CCA.

2. Methods

CCAO is being developed based on data items of the CASCAP forms which are used to collect data about demographics, ultrasound findings, diagnoses and treatments, and post-operative follow-up outcomes from targeted populations in area of Thailand where OV and CCA are endemic [4, 5]. All variables names and data elements from the CASCAP forms were used to search on the Ontobee web browser for ontology classes [15] for matching with existing ontologies.

2.1. Development of CCAO

We have developed CCAO based on the CASCAP forms 1, 2, 2.1, 3, 4, and 5. The CCA forms were translated from Thai to English. We evaluated the English versions of the CASCAP forms to ensure the correct translation. After the English language forms were prepared, we mapped all data items to classes and classes in existing ontologies using Ontobee [15] and then evaluated the quality of the mapped data items with existing ontology classes.

We have imported classes into CCAO from various different sources including the Uberon multi-species anatomy ontology (Uberon), the Phenotype And Trait Ontology (PATO), the Ontology of Biological Attributes (OBA), the Cell Ontology (CL), the Ontology of Medically Related Social Entities (OMRSE) [16] and Drug Ontology (DRON) [16-21]. We used ROBOT to extract classes from external ontologies and generate import files (.owl) [22], and applied the Syntactic Locality Module Extractor (SLME) method to extract classes using the BOT (The BOT, or BOTTOM) algorithm. The resulting ontology module contains mainly the classes in the seed, plus all their super-classes and the inter-relations between them. All import files along with the upper-level ontologies including BFO, OGMS, IAO, and OBI, were imported directly to Protégé for creating CCAO [9, 11, 12].

The National Cancer Institute Thesaurus (NCIT) [23] provides comprehensive information related to CCA. However, we chose not to import classes from NCIT directly, because of the

difficulty in merging the NCIT classes into the BFO-OGMS hierarchy. As a result, we based many classes in CCAO on similar NCIT classes and have included references to those classes in CCAO. We took advantage of the information content in NCIT class definitions in building CCAO as an OBO Foundry compliant ontology. For example, in CCAO, the 'cholangiocarcinoma' class is defined as a "A adenocarcinoma that arises from a bile duct.". The class is assigned to a CCAO_ID and references the original 'NCIT: Cholangiocarcinoma' class URI using the skos:closeMatch annotation property of the Simple Knowledge Organization System in order to indicate the similarity in meaning to the external class [24].

We found many data items in the CCA forms that did not map to existing ontology classes, so we created new classes for these data elements. We did a literature review for each new ontology class to define its meaning based on principles of best practice in classes, definition, and classification with desiderata for controlled medical vocabularies to improve face value of ontology classes [9, 25].

For instance, we created a new class, 'intrahepatic bile duct mass-forming cholangiocarcinoma', which is defined as "An intrahepatic cholangiocarcinoma of the intrahepatic bile duct that has a mass-forming tumor morphology, consisting of a single solid and lobulated mass with no connection macroscopically discernible with a bile duct and characterized by irregular but well-defined and not encapsulated borders," to represent the intrahepatic bile duct mass-forming data item on CCA-04 form. We also asserted its parent to be 'intrahepatic cholangiocarcinoma' and created a logical definition as follows: 'intrahepatic cholangiocarcinoma' and (hasQuality some 'mass-forming tumor morphology').

The classes unique to CCAO were assigned CCAO identifier numbers (CCAO_ID). Each new class was added manually using Protégé with a unique IRI in the form of an OBO Foundry persistent URL (PURL) [26]; for instance, a periductal fibrosis class is assigned to http://purl.obolibrary.org/obo/CCAO_00141.

These IRIs do not currently resolve, but we intend to apply for admission to the OBO Foundry in the near term and have thus chosen to use a compatible IRI format.

After importing the external ontology classes, there were a number of irrelevant classes included in CCAO. We removed irrelevant classes and retained only classes related to CCA in order to keep CCAO small and precise. All imported classes were placed under upper-level ontology classes from BFO, OGMS, IAO, and OBI.

3. Results

3.1. Summary of ontology classes

CCAO includes upper-level ontology classes from BFO, OGMS, OBI, and IAO. We developed 210 new CCAO classes based on data items in the CCA forms. We created 117 CCAO classes based on NCIT classes as well as one class based on a Mammalian Phenotype Ontology (MP) class. [27]. Finally, we reused classes from various domain ontologies (Table 1) including 13 classes from PATO such as 'abnormal', 'calcified', 'edematous', 'mucoid', and 'morphology'; 8 classes from OBA such as 'hepatic vein morphology', 'hepatic portal vein morphology', and 'lymph node morphology'; 2 classes from CL, 'neoplastic cell' and 'malignant cell'; 2 classes from OMRSE, 'admission process' and 'patient discharge'; and 1 class from DRON, 'praziquantel oral tablet'.

Table 1
Summary of classes in CCAO

Ontologies	Number
CCAO classes based on CCA forms	210
CCAO based on NCIT classes	108
CCAO based on MP class	1
Uberon	23
PATO	13
OBA	8
CL	2
OMRSE	2
DRON	1

3.2. Mapping of NCIT classes

We used 108 NCIT classes as the basis of new CCAO classes. These classes are needed to represent data elements on the CCA02-CCA05 forms and are classified under the top level ontology classes including: OGMS:'clinical finding' such as 'Bismuth-Corlette perihilar cholangiocarcinoma classification', 'cancer TNM finding', 'intrahepatic bile duct cancer TNM finding v8', and related classes; OGMS:'disorder' such as 'fibrosis', 'cirrhosis', 'ascites', 'neoplasm', and related classes; OGMS:

'diagnostic process' such as 'biopsy', 'computed tomography', 'diagnostic ultrasound', and related classes; OGMS:'therapeutic procedure' such as 'cancer therapeutic procedure', 'percutaneous trans-hepatic biliary drainage', 'bypass', 'surgical procedure', 'biliary stenting', and related classes; and BFO:'process' such as 'activity', 'referral,' and 'withdraw'. We used one MP class 'dilated bile duct' as the basis of a CCAO class, and placed it under OGMS:disorder, in order to represent this as a disorder rather than a phenotype.

3.3. Creation of new CCAO classes

A number of variables and data elements in the CCA forms do not match to existing ontology classes. We created 210 new CCAO classes along with new definitions based on data dictionary of the CCA forms and scientific literature. The participants' self-reported variables and data elements in the CCA-01 form were used as the basis of new CCAO classes modeled as subtypes OBI:'conclusion based on data', for instance, 'conclusion about participant report about history of fecal examination for liver fluke egg', 'conclusion about participant report about consumption of raw fresh-water fish or raw fermented fish', 'conclusion about participant report about history of treatment with antiparasitic drug', and 'conclusion about participant report about having relatives with cholangiocarcinoma'.

The CCA-02 form variables and data elements are about ultrasound screening. We created new CCAO classes and developed new definitions along with appropriate parent classes as needed. There classes were classified under top ontologies classes including: OGMS:'clinical finding' such as 'suspected cholangiocarcinoma', 'finding of thickening of wall of gallbladder', and 'finding about kidney parenchyma with atypical abnormal function'; OGMS:'image finding' such as 'hepatic mass ultrasound echo finding', left lobe hepatic mass high echo finding', 'left lobe hepatic mass low echo finding', and 'left lobe hepatic mass mixed echo finding'; and OGMS:'disorder' such as 'periductal fibrosis' and subtypes, and 'hepatic calcification'; and OGMS:'diagnostic process' including 'liver diagnostic ultrasound', and 'hepatic parenchymal ECHO'.

In CCA-02.1 form "Confirmatory Diagnosis," we developed new CCAO classes for CCA tumor morphology including 'mass-forming', 'periductal infiltrating', 'intraductal intrahepatic tumor', and 'mixed type tumor morphology'. Additionally, we developed new CCAO classes for other CCA tumor morphologies such as 'cholangiocarcinoma-encased hepatic artery', and 'cholangiocarcinoma-positive lymph node along hepatoduodenal ligament'.

In CCA-03 form "Diagnosis and Treatment," most variables and data elements about diagnostic process, treatment, and complications in this form could be mapped to NCIT classes. We generated new CCAO classes based on these NCIT classes for supporting the CCA-03 form, such as 'extended right hepatectomy', 'surgical resection of hilar cholangiocarcinoma', 'exploratory laparotomy of liver including biopsy,' and 'palliative percutaneous transhepatic biliary drainage'.

The CCA-04 form is used to collect data about the results of pathological diagnoses, which are final staging diagnoses. We developed new CCAO classes and definitions to classify types of CCA based on this form and review of the literature. In Figure 1, CCA was categorized by a tumor site in bile duct including intrahepatic, perihilar, and distal CCA along with mass-forming, intraductal, and periductal infiltrating tumor morphology. The CCA types were also classified by the histology and mucinous type.

- **intrahepatic cholangiocarcinoma**

  =def. - A cholangiocarcinoma found in any site of the intrahepatic biliary tree that arises from the intrahepatic bile duct epithelium

  Logical definition - *cholangiocarcinoma and (overlaps some 'intrahepatic bile duct').*

- **perihilar cholangiocarcinoma**

  =def. - A cholangiocarcinoma found in the common hepatic duct between the second-order biliary ducts (the left and right hepatic ducts) and the cystic duct insertion.

  Logical definition - *cholangiocarcinoma and (overlaps some 'common hepatic duct').*

- **distal cholangiocarcinoma**

  =def. - A cholangiocarcinoma found in the common bile duct between the cystic duct and the ampulla of Vater (except Klatskin tumors and ampulla of Vater cancer), which includes mid common bile duct tumors (between the junction with the cystic duct and the junction with the pancreas) and distal (intrapancreatic) bile duct tumors.

  Logical definition - *cholangiocarcinoma and (overlaps some 'common bile duct').*

Figure 1: Cholangiocarcinoma hierarchy in CCAO

We also created an extension of cancer TNM staging (T: primary tumor, N: regional lymph nodes, and M: distant metastasis) including new classes such as 'intrahepatic bile duct cancer pt4a TNM finding v8', 'intrahepatic bile duct cancer pt4b TNM finding v8,' 'perihilar bile duct cancer pt3a TNM finding v8', and 'perihilar bile duct cancer pt3b TNM finding v8'. Moreover, new CCAO classes were created to represent the metastatic malignant neoplasm in lung, diaphragm, and lung or pleura. On the other hand, we did not create any new class for the CCA-05 form "Post Operation and Follow Up," because we were able to reuse existing ontologies to represent variables and data elements.

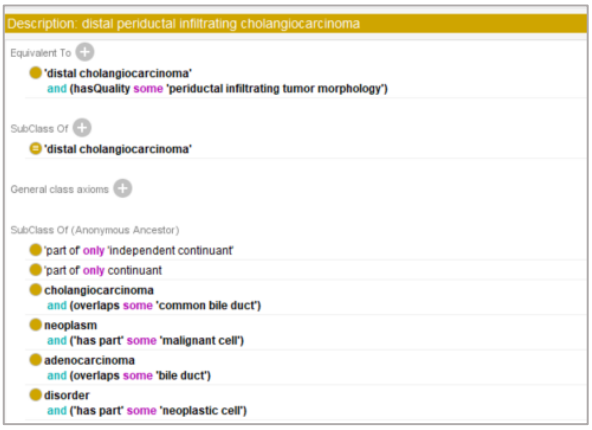

Figure 2: Logical definition of distal periductal infiltrating cholangiocarcinoma in Protégé

Furthermore, we provided 41 new CCAO classes with logical definitions. For example, 'distal periductal infiltrating cholangiocarcinoma' is defined as "A distal cholangiocarcinoma that has a periductal infiltrating tumor morphology in which the tumor spreads along the biliary tree, without mass formation," and has been given the logical definition *'distal cholangiocarcinoma' and (hasQuality some 'mass-forming tumor morphology'))* (illustrated in Figure 2). Similarly, 'distal intraductal cholangiocarcinoma' has the logical definition *'distal cholangiocarcinoma' and (hasQuality some 'intraductal intrahepatic tumor morphology').*

4. Discussion

CCAO is designed to cover all data items in the CCA forms using a BFO-based hierarchy and relying on the principles of OBO Foundry in order to avoid repetition of efforts and to facilitate reuse of and compatibility with domain ontologies [28]. We made attempts to find and reuse existing domain ontology classes related to the CCA forms. We were able to match many data elements with the existing classes, and we created new classes when no existing ontology classes could be found and because some data elements were very specific in the domain of CCA in Thailand, such as the consumption of raw fish dishes (cyprinoid fish).

Schuler and Ceusters [29] reported that building application ontologies appeared to be a challenging job, and described a number of problems they encountered. In line with their work, the main problem we experienced was to find adequate ontologies and adequate classes within them. We found some relevant ontologies to representing items on the CCA forms, such as NCIT, were not BFO-compatible and rarely followed the principles of the OBO Foundry. Although many data elements could be matched with existing ontologies classes in our first attempt at mapping, we then decided not to reuse these classes because they were placed in inconsistent hierarchies or had suble differences in definition that did not match our needs for CCAO.

NCIT is of particular interest in that it is an extraordinary source of cancer knowledge and vocabulary; unfortunately, it is not a BFO-compatible ontology. In our early efforts, we used NCIT as a core domain ontology and extracted relevant classes using ROBOT for inclusion in CCAO. However, the extracted NCIT module contained many classes irrelevant to CCA and the

overall hierarchy was incompatible with BFO and OGMS. NCIT contains top-level concept classes such as 'Conceptual Entity', 'Disease, Disorder, or Finding', and 'Drug, Food, Chemical or Biomedical Material', that proved impossible to classify under the upper level ontologies used in CCAO.

Eventually, we removed NCIT classes and created similar CCAO classes to use in our ontology. This also allowed to use Uberon for all anatomical terms rather than NCIT anatomical classes. During the process of mapping the data elements to Uberon, we found that there was no class 'wall of gallbladder' available in Uberon, although this term exists in the Foundational Model of Anatomy Ontology (FMA). In order to limit the mixing of hierarchies as much as possible, we submitted a request to Uberon editors to add a new class, 'wall of gallbladder', which was added to Uberon and reused in CCAO.

CCAO has 41 logical definitions in this initial version, which we will improve upon in the future. We are working in a parallel fashion to develop a first order logic axiomatization using Common Logic Interchange Format (CLIF) in order to render the CCAO compatible with BFO2020 axiomatization [30] and to allow for more complex reasoning. CLIF can work with time indexing and negation. We will use CLIF to create axiomatization for all classes in CCAO and then generate an owl-compatible version based on this work. This approach will be used to verify the consistency and satisfiability of CCAO.

In upcoming work, CCAO will be used to analyze associated patient datasets from the Kalasin Provincial Public Health, Ministry of Public Health, Thailand that include verbal and ultrasound screening data and EHR-recorded symptoms and diagnoses related to CCA. The criteria for participants include people who live in Kalasin, Thailand and who participated and provided the information in all stages of verbal screening, ultrasound screening, and made hospital visits related to CCA. Ontology-based enrichment analysis and predictive models will be performed in order to understand the complexity of risk factors for CCA.

This project has been approved by University at Buffalo Institutional Review Board (IRBID: STUDY00006059).

5. Conclusions

CCAO has been developed to represent data about CCA using best practices in ontology development. The ontology is publicly available at Github (https://github.com/Buffalo-Ontology-Group/CCA-Ontology) and is compatible with future expansion to represent new evidence and knowledge not be part of this initial version.

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