TNM-O an Ontology for the Tumor-Node-Metastasis Classification of Malignant Tumors: a Study on Colorectal Cancer

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ABSTRACT

Objectives: To (1) present an ontological framework for the TNM classification system, (2) implement a TNM ontology for colon and rectum tumors based on this framework, and (3) evaluate this ontology with a classifier for pathology data.

Methods: The TNM ontology uses the Foundational Model of Anatomy for anatomical entities and BioTopLite 2 as a domain top-level ontology. General rules for the TNM system and the specific TNM classification for colorectal tumors were formulated. Additional information was collected from tumor documentation practice in an academic Comprehensive Cancer Center. Based on the ontology, an automatic classifier for pathology data was developed.

Results: TNM was represented as an information artefact which consists of single representational units. Corresponding to every representational unit, tumors and tumor aggregates were defined. Tumor aggregates consist of the primary tumor and (if existent) of infiltrated regional lymph nodes and distant metastases. TNM codes depend on the location and certain qualities of the primary tumor (T), the infiltrated regional lymph nodes (N) and the existence of distant metastases (M). Tumor data from clinical and pathological documentation were successfully classified with the ontology.

Conclusion: A first version of the TNM Ontology represents the TNM system for the description of the anatomical extent of malignant tumors. The presented work is already sufficient to show its representational correctness and completeness as well as its applicability for classification of instance data.

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide and accounts for 9 % of all cancer incidence (Marmot *et al.*, 2007; Haggar and Boushey, 2009). In 2002, it affected more than one million humans. Treatment of cancer patients and research on causes of cancer are main goals of worldwide cancer control programs[1].

The premise for an evidence-based cancer treatment is a correct and unambiguous cancer diagnosis. Interdisciplinary expert groups, e.g. from clinical medicine, imaging and pathology, work closely together to establish precise tumor diagnoses (DeVita *et al.*, 2011). One of the most challenging tasks in clinical oncology is to correctly classify and code clinical findings, using a multitude of available coding systems.

Clinical and pathological staging of malignant tumors is one of the most important procedures in the diagnosis of cancer to assess prognosis and to plan the treatment necessary. The staging procedure compiles several clinical and pathological parameters: the location and the size of the *primary* tumor, the location and the number of the infiltrated *regional* lymph nodes, and the existence of distant metastases.

By far, the most important coding system for staging information is the Tumor-Node-Metastasis (TNM) classification (Sobin *et al.*, 2009) for malignant tumors, published by the Union for International Cancer Control (UICC)[2]. Despite its importance and formal precision, no logic-based representation of TNM is available so far. Such a formal representation would have several advantages over its current natural language release. An initial attempt to represent staging of lung tumors and glioma tumors was not continued (Dameron *et al.*, 2006; Marquet *et al.*, 2007).

One advantage would be the enhanced support for the TNM development and refinement. With a taxonomic backbone and axiomatic descriptions the existing complex natural language descriptions would be made explicit. This would help decompose the descriptions into all their defining criteria. This could help to detect errors, inconsistencies and ambiguities in definitions (Ceusters *et al.*, 2004; Cornet and Abu-Hanna, 2005). Many combinations of tumor findings are difficult to code due to ambiguos or overlapping criteria (non-disjoint definitions) or non-exhaustive definitions, which often results in cases where no TNM code or more than one TNM code is applicable to a given tumor state.

Additionally, logical inconsistencies and coding problems due to complexity could be detected earlier by automated reasoning. Description logics (DL) would here be the method of choice. Such a TNM DL ontology could be further used for automatic classification of instance data from clinical databases on a sound logical basis. Advanced retrieval and querying tools would be additional benefits. For these use cases, a formalized TNM version could constitute a unified source from which a variety of clinical documentation and analysis tools could be derived.

With this work we propose to close the gap of a missing formal representation by outlining and prototyping a TNM ontology (TNM-O).

Following up initial attempts in the breast cancer domain (Boeker *et al.*, 2014) the objectives of this work are (1) to present an ontological

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[1] http://www.who.int/cancer/modules/en/

[2] http://www.uicc.org

framework for the TNM classification system, (2) to implement a TNM ontology describing colon and rectum tumors based on this framework, and (3) to evaluate this ontology with a classifier for pathology data.

The TNM classification

The UICC published the first edition of the TNM coding system based on the anatomic extent of disease (EOD) in 1968. Since then, the system has undergone several revisions and arrived in 2009 at the 7th edition. The objectives of the TNM classification are six-fold. It supports treatment planning, prediction of outcomes (prognosis), evaluation of treatment results, exchange of information between different participants in the treatment process, continuing research in malignant diseases, and cancer control (Sobin *et al.*, 2009; Webber *et al.*, 2014).

The TNM coding procedure requires a high degree of both domain knowledge and experience in tumor documentation. Even documentation experts frequently engage in discussions about how a given case should be coded correctly. This is mainly due to the development of the TNM classification as an evolutionary process (Webber *et al.*, 2014), which has to account for the huge amount of new scientific insights in tumor prognosis and the dependency of therapeutic effects on tumor stage. Controlled by medical experts, TNM's underlying structure has become more and more complex over the years. Experts in different fields of oncology require for a change in TNM maintenance representing the increasing complexity, the separation from clinical practice and the resources needed for documentation (Quirke *et al.*, 2010, 2007).

Dependent on the location of the primary tumor, the three parts of the code (T, N, and M) represent different aspects of a tumor. *T* describes size and sometimes infiltrative level of the *primary* tumor, *N* describes infiltrated regional lymph nodes, and *M* distant metastases. T and N usually provide three to four levels with increasing severity, *viz.* T0–T3 and N0–N3, respectively. For distant metastases, there is only a binary classification into M1 (evidence) an M0 (no evidence).

The results from the *clinical* assessment have to be accurately discerned from the *pathological* assessment due to their different meanings and evidence levels. This distinction is symbolized by a prefix *c* (clinical) and *p* (pathological) for most primary tumor locations.

Many users of the TNM struggle with the correct coding as well as with the interpretation of TNM codes. This is one of the reasons for the need in improvement of tumor documentation and coding in primary documentation, clinical studies and cancer registries (Abernethy *et al.*, 2009; Aumann *et al.*, 2012; Nagtegaal *et al.*, 2000).The classification of the different primary tumor locations differs to the same extent as the underlying diseases. As a consequence, even expert coders resp. physicians in one organ system might encounter difficulties in the correct application or interpretation of TNM to a different organ system.

Besides the complex semantics of the main numeral TNM codes, a series of additional symbols exists, which might have largely different meanings in the different tumor locations. Prefixes, suffixes, and certainty factors increase the confusion, e.g. for *carcinoma in situ* the suffix "is" has to be used (Tis). With the possibility to always use a code of "X" if the underlying clinical or pathological situation provides incomplete information, inaccurate and incomplete code assignments become widespread (MX for "no statement on metastases possible").

Type	ICO-O 3 morphology
adenocarcinoma	8140/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3
Small cell carcinoma	8041/3
Squamous cell carcinoma	8070/3
Adenosquamous carcinoma	8560/3
Medullary carcinoma	8510/3
Undifferentiated carcinoma	8020/3

Table 1. ICD-O 3 morphology codes for tumors of the colon and the rectum

METHODS

The TNM ontology uses the Foundational Model of Anatomy (Rosse and Mejino Jr., 2003) for anatomical entities and BioTopLite 2 as a domain top-level ontology (Beißwanger *et al.*, 2008; Schulz and Boeker, 2013). Tailored for the biomedical domain and based on description logics (Baader *et al.*, 2007), BioTopLite 2 (BTL2) provides upper-level types both for general categories like *Material object*, *Process*, *Information object*, *Quality* etc., as well as constraints on all of them, using a set of sixteen canonical relations, partly derived from the OBO Relation Ontology (RO) (Smith *et al.*, 2005). They constrain each category by means of a set of general class axioms. It also contains other axioms such as relationship chains, existential and value restrictions. Thus, the building of domain ontologies under BTL2 heavily constrains the freedom of the ontology engineer, which is fully intended as this guarantees a higher predictability of the domain ontologies produced under BTL2.

The general rules for the TNM system and the specific TNM for tumors of the colon and the rectum (ICD-O topography chapters C18-C21, for ICD-O morphology codes see Table 1) were represented as described in Sobin et al. (2009) and Hamilton et al. (2000).

A classifier for individuals (instances) derived from pathology reports was developed employing the OWL API (version 4.0.1)[3] and the HermIT DL reasoner (version 1.3.8)[4]. It classifies breast tumor and colorectal tumor data based on the corresponding TNM ontologies. The classifier reads either tabular input data from files or can process data from manual entry via a graphical user interface.

RESULTS

TNM-O is designed as a modular system of independent ontologies. For every organ or organ system based module of the TNM classification system, TNM-O provides a specific set of ontologies. The TNM connecting ontology serves as a hub to import BioTopLite2 as well as the organ and organ system specific TNM ontologies (see Table 2). The modular architecture allows for inclusion of only those modules which are actually needed by an application.

[3] http://owlapi.sourceforge.net/

[4] http://hermit-reasoner.com/

Without inclusion of BioTopLite2, the TNM hub ontology has the description logic expressivity of ALC. It consists of 79 axioms, 38 logical axioms, and 39 classes. It includes 35 subClassOf and 1 EquivalentTo axioms. Most of the classes are proxy classes to BioTopLite2. Inclusion of BioTopLite2 changes the DL expressivity to SRI.

The TNM ontology for colorectal tumors has the description logic expressivity of ALC. For TNM version 7.0 (version 6.0 in brackets), it consists of 386 (357) axioms, 291 (199) logical axioms, and 158 (149) classes. It includes 177 (160) subClassOf, 21 (18) EquivalentTo and 18 (18) DisjointClasses axioms.

Representational units in the TNM-Ontology

The representation of the TNM system is decomposed in representational units T, N and M and the location of the primary tumor. Thus, for every existing code Tn, Nn and Mn in combination with a specific organ there exists one *TNM-O:RepresentationalUnit* which is an *btl2:InformationObject*. E.g. every TNM code for colorectal cancer is represented by a separate class. These classes are connected with their patho-anatomical relata of type *PrimaryTumor* or *TumorAggregate* by the relation **btl2:isRepresentedBy**. In the remaining text, the namespace of the TNM ontology is suppressed for clarity:

TumorOfColonAndRectumWith7OrMoreMetastaticRegionalLymphNodes
subClassOf
TumorAggregate and
btl2:isRepresentedBy some
(*ColonRectumTNM_pN2b* or *ColonRectumTNM_N2b*) and
btl2:isRepresentedBy only
(*ColonRectumTNM_pN2b* or *ColonRectumTNM_N2b*)

Representation of the primary tumor

The primary tumor is represented as *PrimaryTumor*, a subclass of *MalignantAnatomicalStructure*. The characteristics relevant for the representational unit *T* of the TNM classification system are represented as location and qualities of *PrimaryTumor*. For colorectal tumors the exact localization of the tumor in the gut wall, the quality of the tumor confinement with respect to neighboring organs (confined or invasive), the quality of the assessment (no assessment, no evidence or carcinoma in situ), are important. *PrimaryTumor* is directly related to the corresponding representational unit:

InvasiveTumorOfSubmocosaOfColonAndRectum EquivalentTo
ColonAndRectumTumor and
(**btl2:isBearerOf** some (*Confinement* and
(**btl2:projectsOnto** some *Invasive*))) and
(**btl2:isIncludedIn** some
SubmocosaOfLargeIntestine)

InvasiveTumorOfSubmocosaOfColonAndRectum subClassOf
btl2:isRepresentedBy some
(*ColonRectumTNM_T1* or
ColonRectumTNM_pT1) and
btl2:isRepresentedBy only
(*ColonRectumTNM_T1* or
ColonRectumTNM_pT1)

Name	Description
BioTopLite2	Upper domain level ontology
TNM-O	TNM-O central connecting ontology
TNM-O_breast_7	TNM-O for breast cancer (TNM version 7) in: Boeker et al. (2014)
TNM-O_colorectal_6	TNM-O for colorectal cancer (TNM version 6)
TNM-O_colorectal_7	TNM-O for colorectal cancer (TNM version 7)

Table 2. Modular structure of TNM-O. Codes in clinical documentation and cancer registries are versioned by TNM versions. The meaning of codes and stages changes between versions. The modular structure is designed to include versions for every available TNM encoded entity (tumor location) so that the intended meaning is preserved according to the version which was used for coding.

Representation of regional lymph nodes

The most complex part of the TNM classification of many primary tumor locations is the interpretation of the axis *N*, which describes to which extent the primary tumor has infiltrated regional lymph nodes. The anatomy of lymph nodes draining the colon and rectum was modeled according to clinical anatomical conventions. Metastatic regional lymph nodes can exactly be located by the exact subclass of infiltrated regional lymph node:

MetastaticLymphNodeOfColonAndRectumTumor EquivalentTo
LymphNode and
(**btl2:hasPart** some
MetastasisOfColonAndRectumTumor)

MetastaticRegionalLymphNodeOfColonAndRectumTumor EquivalentTo
MetastaticLymphNodeOfColonAndRectumTumor and
ColonAndRectumRegionalLymphNode

To define regional lymph node metastases of colorectal cancers, the aggregate of primary tumor and infiltrated lymph nodes around the colon and rectum (*TumorAggregate*) has to be considered as one (composite) entity. The representational unit *N* of the TNM classification of colorectal cancers is dependent on the count of metastatic regional lymph nodes and the presence of subserosal tumor deposits without regional lymph node metastases. The count of metastatic lymph nodes is represented by subclasses of *CardinalityValueRegion*:

TumorOfColonAndRectumWith2or3MetastaticRegionalLymphNodes
EquivalentTo
TumorOfColonAndRectumWith1to3MetastaticRegionalLymphNodes and
(**btl2:isBearerOf** some
(*Cardinality* and
(**btl2:projectsOnto** some
Cardinality2or3) and
(**btl2:projectsOnto** only
Cardinality2or3)))

Representation of distant metastases

For the representational unit *M* of the TNM classification system the existence and number of distant metastases is evaluated. The definition of distant metastases excludes *regional* lymph nodes as their localization:

DistantMetastasisOfColonAndRectumTumor EquivalentTo
MetastasisOfColonAndRectumTumor and

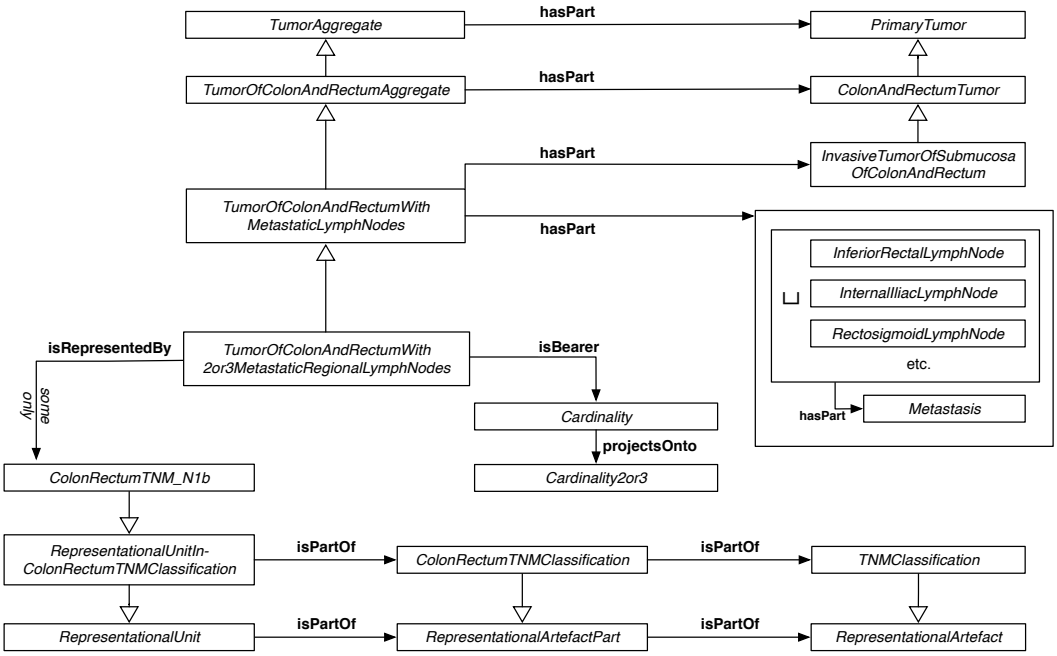

Abbildung 1: Graph of the patho-anatomical structures represented by an N1b representational unit of the TNM-O for colorectal tumors version 7 (TNM-O_colorectal_7.owl). T and M representational units are unspecified.

(not (**btl2:isIncludedIn** some
ColonAndRectumRegionalLymphNode)) and
(**btl2:isIncludedIn** some
BodyPart)

TumorOfColonAndRectumWithDistantMetastasis EquivalentTo
TumorOfColonAndRectumAggregate and
(**btl2:hasPart** some
DistantMetastasisOfColonAndRectumTumor)

TumorOfMammaryGlandWithDistantMetastasis subClassOf
(**btl2:isRepresentedBy** only
(*MammaryGlandTNM_M1* or
MammaryGlandTNM_pM1)

The hub TNM Ontology for all tumors can be downloaded from http://purl.org/tnmo/TNM-O.owl. The ontologies for breast tumors and colorectal tumors are named according to Table 2 and can be downloaded from the same site. They need to be loaded in the hub ontology.

Classification of pathology data

We classified data on the state of regional lymph nodes (TNM: N) of 382 specimens of colorectal carcinomas which were documented at the Institute of Surgical Pathology, Medical Center – University of Freiburg. All data were coded as RDF-OWL instance data and classified by an application based on the OWL API using an OWL classifier[5]. Automatic classification was solely based on axioms defined in the colorectal TNM-O version 7 (TNM-O_colon_7.owl). Criteria employed from instance data are shown in table 3.

All instance data could be classified to classes of the ontology. *A-posteriori* comparison of the classification results with the findings from the pathology database by an experienced pathologist showed 100 % correct classification results.

Criterium	btl2 superclass	Value
primary tumor extension	MaterialObject	Epithelium, Submucosa, Lamina propria, Subserosa, Adventitia, VisceralPeritoneum
primary tumor growth pattern	Quality	Infiltrative, Confined
primary tumor epistemology	Quality	NoAssessment NoEvidence
regional LN number	Quality	Cardinality1 Cardinality2or3 Cardinality4to6 Cardinality7orMore
regional LN epistemology	Quality	NoAssessment NoEvidence
distant Mx location	MaterialObject	Peritoneum
distant Mx no. of organs	Quality	Cardinality1 Cardinality2orMore
distant Mx epistemology	Quality	NoEvidence

Table 3. Criteria of TNM version 7 for colorectal cancers. All TNM codes can be inferred from this criteria. The exact wording of the textual definitions of the TNM in version 7 is diverging[6]. Exact count of infiltrated organs in distant metastasis is omitted.

[5] http://owlapi.sourceforge.net/

[6] http://cancerstaging.blogspot.de/2005/02/colon-and-rectum.html

DISCUSSION

TNM is a globally accepted system to describe the anatomical extent of malignant tumors (Sobin *et al.*, 2009; Webber *et al.*, 2014). Although TNM is of high importance for the staging of tumor diseases, to the knowledge of the authors, there exists no formal representation of TNM so far. With this work, the authors provide a first outline of a TNM ontology (TNM-O) and a prototypical implementation of TNM for colorectal cancers. This work also shows also that TNM-O classifies instance data.

Over time, TNM has developed into a coding system which had to accommodate both the pragmatics of coding and representational accuracy. The literature on ambiguities and difficulties of TNM in practice is abundant. The discussion of TNM for breast tumors illustrates the dilemma of its maintainers (Barr and Baum, 1992; Gusterson, 2003; Güth *et al.*, 2007). They had to account for the rapid progression of scientific knowledge on tumors and to keep it usable at the same time: new versions of TNM were already outdated when compared with new scientific insights. On the other hand, it became increasingly complex, with a negative impact on usability by non-expert and expert documentation staff and physicians.

This study is limited as far we provide here a *first version* of the TNM Ontology (TNM-O) which has been developed only for mammary gland (Boeker *et al.*, 2014) and colorectal tumors. As these two tumor entities are the most complex and best represented ones in TNM, the durrent version is already as far complete and stable to be used as a blueprint for TNM-O extensions to other organ systems.

Due to the nature of the domain and the rich top-level ontology employed, the computational resources needed to classify the ontology are considerable. To alleviate performance issues TNM-O will be provided as modules for different organ systems. Thus, the users can import only the modules of interest into their application context.

Future research should evaluate the presented prototype ontology (i) by implementing further tumor locations, and (ii) by systematical application in clinical classification and retrieval scenarios. We will provide the formalization of TNM for other primary tumor locations in a modular way, so that users can select which part of the TNM-O they would like to use. In this way, we hope to reduce the computational resources already needed to a minimum.

Conclusion

We presented a first version of an ontology (TNM-O) that represents the TNM tumor classification system. The presented work is already sufficient to show the representational correctness and completeness of the TNM-O as well as its applicability for classification of instance data. This work provides a foundation for an exhaustive TNM ontology.

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