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Prediction of Bladder Cancer Treatment Side Effects Using an Ontology-Based Reasoning for Enhanced Patient Health Safety

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Abstract: Predicting potential cancer treatment side effects at time of prescription could decrease potential health risks and achieve better patient satisfaction. This paper presents a new approach, founded on evidence-based medical knowledge, using as much information and proof as possible to help a computer program to predict bladder cancer treatment side effects and support the oncologist's decision. This will help in deciding treatment options for patients with bladder malignancies. Bladder cancer knowledge is complex and requires simplification before any attempt to represent it in a formal or computerized manner. In this work we rely on the capabilities of OWL ontologies to seamlessly capture and conceptualize the required knowledge about this type of cancer and the underlying patient treatment process. Our ontology allows case-based reasoning to effectively predict treatment side effects for a given set of contextual information related to a specific medical case. The ontology is enriched with proofs and evidence collected from online biomedical research databases using "web crawlers". We have exclusively designed the crawler algorithm to search for the required knowledge based on a set of specified keywords. Results from the study presented 80.3% of real reported bladder cancer treatment side-effects prediction and were close to really occurring adverse events recorded within the collected test samples when applying the approach. Evidence-based medicine combined with semantic knowledge-based models is prominent in generating predictions related to possible health concerns. The integration of a diversity of knowledge and evidence into one single integrated knowledge-base could dramatically enhance the process of predicting treatment risks and side effects applied to bladder cancer oncotherapy.

Keywords: bladder cancer; healthcare; treatments; side-effects; safety; evidence-based medicine; knowledge representation; health informatics; reasoning

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1. Introduction

Bladder cancer (BC) remains a major concern for urologists worldwide despite considerable advances in the medical field. BC has a standardized overall age-specific mortality rate estimated at 4.7 per 100,000 [1]. It is of a particular importance in the field of urological carcinology in predicting treatment side effects (SEs), due to its frequency, its anatomopathological polymorphism, the difficulty of precise staging and the great prognostic uncertainty. Prediction, early detection, prevention and treatment of the long-term complications of such diseases should help to limit costs, and promote the emergence of new organizations that are more effective and secure than conventional practices and usually offer a better quality of life to patients.

As a multifactorial disease, cancer has become the disease that kills the most. The quantity of data and knowledge contribution to the theories within this discipline plays an important role in the management of many inclusive pathologies. Oncotherapy choices have grown considerably since the deciphering of the human genome and the collection of specific data with the adoption of evidence-based medicine principles [2]. We are now able

to predict with ever-increasing accuracy related health risks for the patient, particularly possible future cancers.

As far as the prescribing of drugs, we are aiming to be able to assess at an early stage the effectiveness of the chosen treatment option by referring to the latest studies in this field. Thus, we can avoid those treatments reported as more problematic and expensive, as well as less effective. Such a proactive approach to prescribing is highly recommended before the onset of the disease to prevent or delay it. This breakthrough belongs to the major evolution in oncology referred to as precision or personalized medicine, which makes it possible to decide on the right treatment for the patient.

Semantic web technologies primarily driven by ontologies could provide a good approach for managing BC knowledge including oncotherapy procedures and their related clinical processes. They are highly used in a wide range of clinical applications in which domain knowledge is modelled and conceptualized, in a formal way, to support computer-based processing and reasoning. These functionalities could help to reason and to generate new knowledge automatically. Particularly, in this paper, this reasoning serves the main goal of our work, which is the development of a decision-making tool to assist oncologists throughout the process of treatment prescribing. An effective decision support system (DSS) in this context should allow the application of scientific findings in the field of BC to medical cases. This includes theoretical and empirical knowledge in the domain along with archived cases of patients previously diagnosed with and treated for this epidemic. The gathering of all this variety of knowledge within a unified semantic knowledge-base (KB) sets the foundation for the ontological evidence-based approach we are presenting in this work.

To model the patients' medical case, we used contextual information capturing the necessary parameters for making the right diagnosis, including interrogation, clinical examination medical tests, and other complementary examinations.

In this paper, the work will be structured into sections starting in Section 2 with an overview of BC treatments and related SEs. We also present in the same section a summary of related works on automated predictions in oncology and the use of semantic web technologies, with relation to oncology and to evidence-based medicine (EBM) in general [3]. We move in Section Three to a presentation of the set of methods and the methodology we have adopted to develop our ontology-based approach for an automated prediction of BC SEs. The description of our ontology composition and its features will be presented in the results and discussion within Section 5. Finally, at the end of this paper, a general conclusion and a set of future recommendations will also be presented.

2. Background

Following a patient's discovery of BC, the care team develops a personalized treatment plan. This is based on the patient's health and specific information about cancer. When deciding which treatments are to be offered, consideration is given to the stage, grade, risk category, functional index, and other medical conditions that affect the patient and the preferences of the patient concerned. The different types of possible treatment for this pathology include surgeries and in particular Transurethral Resection of the Bladder Tumor (TURBT), Cystectomy and Pelvic lymph node dissection, among the popular treatment options. Immunotherapy, Chemotherapy and Radiation therapy are also common practices for the treatment of BC [4]. However, these procedures have many side and unwanted effects including mouth sores, tiredness, changes in kidney or liver function, diarrhea, dry mouth, changes in fingernails or toenails, changes in mineral levels in the blood, loss of appetite, loss of taste, anemia, dry skin, dry eyes, and hair loss, along with redness, swelling, peeling or tenderness on the hands/feet, constipation, belly pain, nausea, and muscle pain. In addition, eye problems can occur. These include blurred vision, loss of vision or other visual changes. In most cases irritation and a burning feeling in the bladder occur, along with blood in the urine [5]. SEs will vary in type and severity depending on the administered treatment and on the medical case of each patient. Our aim is to capture

and provide the right knowledge for a computer agent to assist the doctor during the process of treatment prescribing by deducing the possible SEs for a selected treatment type, applied to a specific medical case of a patient suffering from a BC case.

Related Work

In the literature, only a few works focus on the application of information technology to optimize oncotherapy treatment processes. To the best of our knowledge, no effort has been put into the relationship to BC oncology. In general, the research effort has been directed to the construction of medical ontologies [6,7], as well as the translation of many existing thesauri, terminologies, and classifications into the ontology web language (OWL) [8,9]. Beyond the construction of ontologies, some works aimed to exploit the potential of the semantic web in medical and clinical applications: for example, computerized patient records [10] or knowledge management in clinical processes [11]. So far, several studies have attempted to suggest predictive computer approaches and models that are based on mathematics, semantics and logic for use in health systems, e.g., the probabilistic models [12–14], the Bayesian network [15] and the rule-based therapeutic recommendations for infectious diseases [16]. These approaches were welcomed at first, but studies have revealed some major inadequacies [17,18]. This is mainly due to the presentation of results in the form of probable treatments with their consequences, but without explanations. These approaches did not convince doctors particularly in the case of probabilistic approaches since they are not able to say explicitly "why" and "how" they produced such results. In contrast, the semantic modelling in association with the rule-based reasoning we provide in this work allows us to identify patients at high risk of oncotherapy SEs in the case of BC. This has also permitted the development of computer-based prediction of treatment for SEs while taking into consideration medical proof and evidence specified as contextual information within our ontology.

Over the last decade, several studies have investigated the effectiveness, vigilance and responses of treatments applied to patients with BC [19–21]. However, no consistent conclusions have been reached among those studies. Thus, this research provides a synthesis of current evidence to investigate and predict the possible SEs of treatments for BC cure. Only a few approaches have been adopted on the prediction of SEs during cancer treatment. Isaksson et al., developed a machine learning-based model for toxicity outcome prediction in Radiotherapy (RT) which was considered as a valid model [22], but there are still loose ends on the clinical applicability of RT-induced toxicity models. However, an effective prediction strategy for SEs is necessary. Hirahara et al. carried out a study to predict postoperative complications and survival after laparoscopic gastrectomy using Risk Index in elderly gastric cancer patients and the Clavien-Dindo (CD) classification for SE evaluation [23]. For statistical analysis they used the non-parametric Mann–Whitney U test, the Chi-squared test, the Kaplan–Meier method, the log-rank test and the Cox proportional hazards regression models within the retrospective cohort study. These methods and the risk index proved their reliability within this approach, but knowledge models still need to be implemented for semantic prediction. Jing et al. used a strategy that combines pharmacovigilance data and omics data, and assessed relationships between multi-omics factors and immune-related adverse events (AEs), reporting odds ratio across different cancer types [24]. They identified a bivariate regression model that predicted complications through LCP1 and ADPGK biomarkers.

As mentioned by Wang et al., current artificial intelligence (AI) was employed for automating and improving several medical aspects such as RT [25]. Many algorithms in RT planning were created to support planners through automated planning and radiation dose optimization. This featured automated rule-making and reasoning, prior knowledge modeling and optimization of many criteria in clinical practice. New treatment planning solutions based on AI used knowledge-based and deep learning. In terms of efficiency and uniformity, this optimized treatment planning. AI models with data-driven approaches such as machine learning and deep learning are improving the clinical RT

workflow. However, a lack of knowledge and of AI models processing can prevent wide and comprehensive use in clinical practice. In a review carried out by Liesbeth et al., it was found that the implementation of AI models in the RT workflow and their quality assurance (QA) were supported by specific guidelines [26]. This measured treatment reliability through comprehensive patient safety monitoring. Commissioning, implementing, and case-specific QA are emphasized for the most used applications in RT.

It is also worth mentioning the work done by Brooks et al., in which they developed a clinical prediction model to assess patient-specific risk of chemotherapy-related hospitalization using the readily available clinical data [27]. They abstracted risk factors, patient, and treatment characteristics from the medical records, to model patient-specific risks. In addition, Tramèr et al. found that learning models such as statistical methods improve precision in additional cases [28]. However, there are major ways in which ontology-based EBM differs from traditional statistics and learning models: predictions are made for categories or groups and can suit individuals belonging to the group. Second, it relies upon a normal bell-shaped curve, based on past treatment outcomes as well as the latest medical research published in scientific journals and databases, to reach the top of the curve of unsuspected new predictive associations [29,30]. Still, in these approaches the user usually has minimal intervention such as supplying machines with administrative data or non-clinical information about the patient. Meanwhile our models enrich the application area by incorporating various personal factors. Hence, it has the potential to improve patient safety by predicting adverse AEs that might not have been observed within the clinical trials. To present the different methods and the research methodology adopted in this work, we rely mainly on a scenario describing an instance of the process a doctor adopts to make a choice of treatment protocol for a patient suffering from BC.

As mentioned by Zang et al. [31], several studies related to BC treatment reported on libraries and databases, such as the Cochrane Library Central database (CENTRAL), PubMed/MEDLINE and Embase, from which randomized controlled trials (RCT) and records were retrieved. Other various biomedical sources were included in BC study-based research, such as the WHO's international clinical trials registry platform (CINAHL) and clinicaltrials.gov.

Many of the works shown below have examined the application of DSS for ontology cooperation. Shen et al. developed a DSS for cancer treatment and prognosis based on an existing Disease Ontology (DO) to improve the reasoning task of the DSS using Case-Based Reasoning (CBR) [32]. This system estimated the stage of the cancer. The system searches result in using the CBR database as reference for future reasoning, instead of using its own outputs. Moreover, this DSS still struggles with assisting doctors in using drugs rationally according to the patient's specific situation. Zhang et al. proposed an ontology-based DSS to solve some issues in multi-level integrative data analysis studies for oncology research, through theory-based guidance for multi-level variables and data source selection, a standardized documentation of this data selection and an ontology-based integration process [33]. Hence, the approach enabled the sharing of reports among scientists. But the system is still not automated and needs a standardized framework for operational use. Redjdal et al. reported that the guideline-based DSS (GL-DSS) of the DESIREE project and OncoDoc are examples of clinical DSS applied to breast cancer [34]. The team reused the OncoDoc multidisciplinary tumor board (MTB) RCTs. The approach included two different knowledge representation models and two formalisms. Therefore, a transformation sequence was proposed, involving synthetic patients, the DESIREE ontology improvement, and the abstraction of RCT outcomes. Complex cases within the approach that were not handled by guidelines needed effective analyses. In a review carried out by Pavithra et al., clinical reasoning ontology (CRO)–based clinical DSS (CDSSs) in oncology were evaluated to identify and classify knowledge, reasoning concepts and properties within these ontologies [35]. The team found that ontology-based methods make inferences according to the relationships implicating EHRs. Moreover, 16% used algorithms, 79% of CDSSs used rule-based computation for inferencing, 5% used fuzzy logic, 58% used an ontology-

based method and 8% used machine learning and natural language processing. Other computational methods included probability, proximity-based, anchor-based, and ranking of weighted option, but more research is needed for high quality ontology-based CDSSs.

Generally, BC therapy is based on international guidelines, including those of the society of urologic oncology (SUO) [36], the National Comprehensive Cancer Network (NCCN) [37], the Canadian Urological Association (CUA) [38], the National Cancer Institute (NCI) [39], the First International Consultation on Bladder Tumors (FICBT), Consultation on Bladder Cancer (SIU-ICUD) [40], the PDQ bladder cancer [41], the American Urological Association (AUA) [42], the European Society for Medical Oncology (ESMO) [43] and the European Association of Urology (EAU) [44]. This practice has the drawback of not necessarily, accurately or appropriately recommending the options and alternatives as mentioned in the local recommendations for local clinical practice or specific cancer states. Recommendations based on international guidelines and other references are not always suitable for all cases, with some drugs and treatment techniques or technologies not licensed for use in some places.

A reasonably substantial number of BC RCTs have been included and been considered appropriate to improve these guidelines by our prediction results and evidence-based reasoning. This ontological guidance provides an overview of BC treatment in the individual clinical stages, followed by clinical questions that encounter issues in daily clinical practice. In a study conducted by Zhang et al., it was found that the quality of the current BC recommendations and guidelines was controversial. Moreover, these guidelines varied in different ways [45]. Despite many similarities, there were several inconsistencies in the recommendations.

3. Materials and Methods

To present the different methods and the research methodology adopted in this work, we rely mainly on a scenario describing an instance of the process a doctor adopts to make a choice of treatment protocol for a patient suffering from BC.

Our primary outcomes included: (i) SEs' prediction and detection rate using knowledge-based reasoning in relation to BC, including NIBC, NMIBC and MIBC; and (ii) overall survival and progression-free survival within AEs' severity grades. Secondary outcomes were SE management, preventing recurrences and occurrences of SE risks and the impact on quality of life.

3.1. Knowledge and Data Collection

In this study, we used a crawler "pubCrawler" as a selective information dissemination service (SDIS) to extract information from various online knowledge sources, particularly evidence-based knowledge and data about past events and facts in BC treatments. This systematic review framework was applied to search, extract, and assess scientific papers. We used a keyword search strategy to find relevant articles that contain knowledge about BC treatment risks and effects and research about BC ontologies. Journals, books, guidelines, and taxonomies are also included in these crawling events. Additionally, research was applied to find clinical anonymized and non-identifiable data and indications about patients and related clinical cases used in previously published studies about BC. Whether a study refers to random samples or is broadly applicable to many different types of samples, data are labelled with good generalizability.

We adopted a comprehensive literature search that included RCTs and data-based knowledge from Pubmed/Medline, Embase, Cochrane CENTRAL and the Allied and Complementary Medicine Database (AMED). Our review process was based on Cochrane guidelines for systematic reviews of interventions [46]. Terms and their combinations were searched following specific criteria as described in Table 1 including the ongoing trials. Within some databases, such as Pubmed, we used the "related articles" function to refine the search. On the other hand, we manually searched in the retrieved studies' references as they were cited. We have retained the most complete and updated studies, to which

the outcomes were different in measures and time. This was to avoid multiplicity and similarities included in reports with the same samples and results. All BC treatment SE-related Knowledge and RCTs will be included. Our search focused on studies with extended research findings and conclusions, from a small sample study to a larger population. The larger the population, the more the data is generalizable. This method provided information on a dedicated web page whenever new hits on articles appeared in PubMed and the US National Library of Medicine (NLM) or when new sequences were found in Science Direct or GenBank that were specific to our customized queries. These targets provided access to their databases.

Table 1. Search criteria and selection of BC treatments risks and effects crawling variables.

Search Lines	Alias	Query Description	Search Terms and Field Filters
Line 1	'Query Alias 1'	Cancer and BC strategy management	'cancer' (J[1]) OR ('bladder' AND 'treatment options' AND 'treatment workflow' OR 'oncology care pathway' AND 'models' AND 'clinical trial') (T[2]/A[3]) AND 'ID' (LID[4])
Line 2 OR	'Query Alias 2' OR	BC Treatments' effects and risks	('bladder cancer' AND 'side effects' AND 'treatments' AND 'patients' AND 'prediction' AND 'grades' AND 'stages' AND 'risk factors' AND 'risks' AND 'severity') (T/A) AND 'ID' (LID) AND 'patient' (J)
Line 3 AND	'Query Alias 3' AND	BC Treatments	('bladder cancer' AND 'immunotherapy' OR 'chemotherapy' OR 'radiation therapy' OR 'surgery' OR 'intravesical instillation') (T/A) AND 'bladder cancer' (Ta[5]) AND 'patient' (J)
Line 4 AND	'Query Alias 4' AND	Patients and trials	('bladder cancer database' AND 'patient' AND 'case study' AND 'samples' AND 'electronic medical record' AND 'age' AND 'Sex' AND 'medical history' AND 'diagnosis' OR 'clinical trial') (A/T) AND 'patient' (B)

Only studies with BC treatment AEs and SE severity grades related to the clinical state of patients were included. Furthermore, any other treatment of BC different from the performed one was used as a comparator, including SEs. On the other hand, we avoided any use of studies with RCTs implicating the same treatments/procedures and the same AE severity grades.

We provide some details about the exclusion and remaining records and papers as described in Figure 1. As detailed in Table 1, four queries were launched together and returned 3858 hits that were received by our crawler as shown in Figure 1.

Inclusion and exclusion criteria are characteristics that prospective studies must have to screen and review searched studies. These criteria are based on our PICOs of interest, with the agreement of all the research team. The PICO method is a process used in evidence-based practices to develop search strategies. It contextualizes and answers questions about healthcare and clinical observations. We referred to the PICO model to define our clinical questions, or PICOs, and to help find relevant evidence in the studies searched. This consists of concepts relating to (P) patient problem/characteristics, (I) intervention, (C) comparison with interventions/where applicable and (O) outcomes to measure.

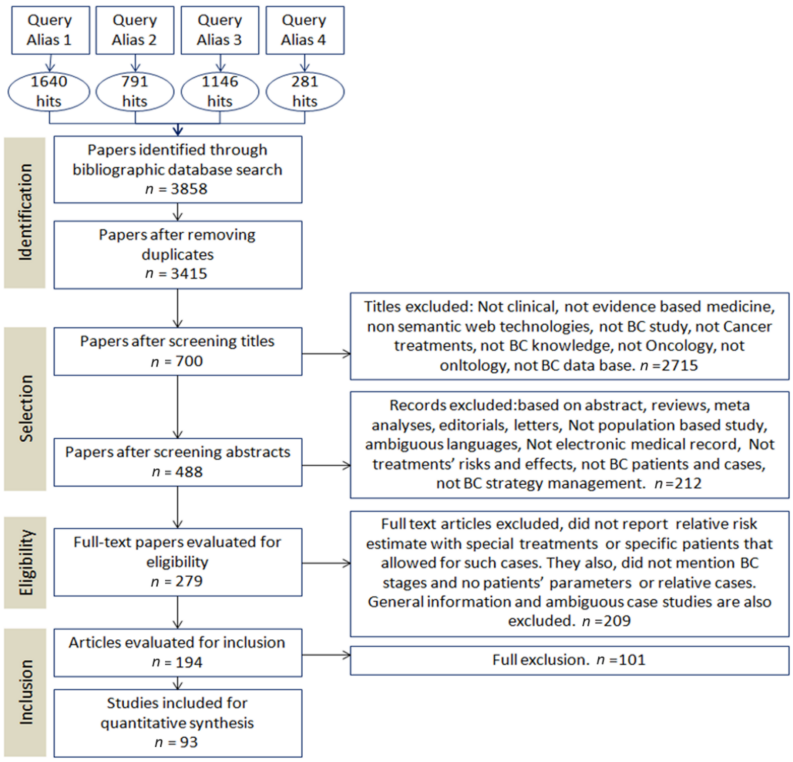


Figure 1. Flow diagram for BC data collection and study selection.

For general knowledge, we used background questions in the form of a *wh*-question about aspects of healthcare in BC treatment. For specific knowledge, we used foreground questions affecting clinical decisions and includes indications about medical and clinical problems, such as treatments' SEs. As follows, we present examples of our PICO questions:

- In a 65-year-old male patient, smoker, diagnosed with BC Papillary Carcinoma (P), does a chemotherapy treatment (I) worsen the situation of the patient more than immunotherapy (C) for more serious SEs (O)?
- In adults with NMIBC (P), what does a TURBT (I) cause as SEs (O)?

First, duplicates were removed. Then, we focused on checking the titles and abstracts. This helped us to reduce the number of articles to 279 to refine the set of records gradually. In this screening phase, we found that there were many papers discussing cancers, and general knowledge about treatments such as numbers and statistics. However, few of these papers reviewed the risks and effects of BC treatments regarding evidence-based medicine and semantic web technologies. Moreover, we only considered articles that strongly focused on providing data about BC patients and cases, which was our main concern in this information gathering. We also focused on knowledge acquisition. We mainly excluded research that did not include examples and patients' parameters and characteristics related to BC treatments. Only 93 remaining papers and records met the criteria to be included for quantitative synthesis and utilization as medical evidence and cases.

3.2. Data Collection and Analysis

For our studies selection we used the EndNote X7.8 as a tool to import our crawled reports and to perform data deduplication on our gathered information from previous studies (literature). Among the authors, two independent researchers browsed the content of all relevant studies and scanned their taxonomy, abstracts, location ID and titles to extract knowledge data from the included RCTs. Furthermore, based on our predefined eligibility criteria as mentioned in Table 1, unassociated contents were excluded from our identified studies. Then, full text evaluation was processed for eligibility and inclusion

as shown in Figure 1. Both researchers independently extracted, selected, and evaluated the quality of the recorded studies using the recommended tool Cochrane risk of bias tool (RoB 2) [47] within the included RCTs and PICOs based on the consolidated standards of reporting trials (CONSORT) [48]. Any conflicting views, disagreement or inconsistencies were resolved by consensus with the help of another researcher, the adjudicating senior author who reached a final decision after discussion.

We used Cohen's kappa, as it determines agreement between both investigators involved in data collection and analysis. The interpretation of kappa results is as follows: poor ($\kappa < 0$), slight ($\kappa = 0.00–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), substantial ($\kappa = 0.61–0.80$), or almost perfect ($\kappa = 0.81–1.00$). We used the following Cohen's kappa formula for agreement between our two investigators:

$$\kappa = (p_0 - p_e)/(1 - p_e) = 1 - [(1 - p_0)/(1 - p_e)] \quad (1)$$

where: p_0 is the relative observed agreement among raters and pe is the hypothetical possibility of chance agreement.

The methodological quality of all included RCTs was appraised by two independent researchers. We used Cohen's kappa as it determines agreement between both investigators involved in data collection and analysis. The interpretation of kappa results is as follows: poor ($\kappa < 0$), slight ($\kappa = 0.00–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), substantial ($\kappa = 0.61–0.80$), or almost perfect ($\kappa = 0.81–1.00$).

We used the crosstabulation table Table 2, to understand the degree to which both raters agreed and disagreed. As described in Table 2, the researchers rated 93 RCT studies targeted for inclusion after evaluation. 80 RCT studies received confirmation for further study as agreed by both investigators. Furthermore, both researchers agreed that there were 6 RCT studies not confirmed for further study. Thus, there were 7 RCT studies for which the investigators could not agree on their status.

Table 2. The investigators' RCT studies agreement and disagreement—kappa data crosstabulation.

Count				
		Researcher 2		
		Confirmed for further study	Not confirmed for further study	Total
Researcher 1	Confirmed for further study	80	5	85
	Not confirmed for further study	2	6	8
Total		82	11	93

Based on data in Table 2 we have $p_0 = 0.92$ and $p_e = 0.81$, $k = (p_0 - p_e)/(1 - p_e)$: then $k = 0.57$. Our Cohen's kappa (k) is 0.57. This states a moderate strength of agreement. It is statically significant (95% CI, $p > 0.0005$).

Moreover, we used calculable decision-making markers of treatment effects to evaluate studies including RCTs about the rate of AEs in BC treatments (for example the risk of life-threatening AE rate). We also compared SEs of a prescribed treatment (intervention) to another as a standard of care (control). For risk quantification of treatments, we computed the absolute risk reduction (ARR) difference between both treatments (intervention–control). The ARR indicates the treatment with less life-threatening risk. Additionally, the number needed to treat (NNT): NNT = 1/ARR, which indicates the number of patients that must receive the treatment for one patient to benefit. We used the relative risk (RR) as the ratio of risks in intervention treatment subjects to the risks in the control treatment subjects. With a (RR > 1) we have a treatment with a high-risk of bad outcome compared to control trials. However, a (RR < 1) indicates greater treatment benefit with decreased

risks. The relative risk reduction (RRR): RRR = 1–RR indicates the amount of risk reduction performed by the treatment. For the assessment of treatment AEs, we used the absolute risk increase (ARI) which measures the difference between a treatment event rate and a control event rate. Moreover, the inverse of ARI is the number needed to harm (NNH): NNH = 1/ARI and this indicates the number of patients that must receive the treatment to have an AE. In this case, the RR > 1 indicates a greater treatment risk. Identically, the higher the relative risk increase (RRI): RRI = R −1, the higher the harm rates.

Statistical Analysis

For meta-analysis, we used the Cochrane collaboration's software Review Manager (RevMan 5.3) which uses the Cochran–Mantel–Haenszel test method (CMH) [49] to carry out statistical analysis [50]. Treatment SEs of continuous data were considered as a standardized mean difference and dichotomous data as a risk ratio, while 95% confidence intervals were provided. A p-value ≤ 0.05 was considered statistically significant which indicates strong evidence against the null hypothesis (no significant difference) which is rejected, and the alternative hypothesis (difference is anticipated) is retained which states that the results are significant in terms of supporting the investigated study and 95% confidence intervals (CI) are provided.

The CMH-χ^2-test was used to evaluate statistical heterogeneity within the used studies and a p-value < 0.1 was of significance. However, the I^2 statistic was used to quantify heterogeneity across the included RCTs and to examine the null hypothesis. When $I^2 \leq 50\%$, homogeneity is detected, and a fixed-effects model is applied. However, $I^2 > 50\%$ suggests a significant heterogeneity and a random-effects model meta-analytical technique is utilized with a subgroup to specify this heterogeneity.

3.3. BC Story Example

A patient aged 60 years old was initially diagnosed with a high grade (fast growing) non-invasive papillary carcinoma (Ta) BC: Stage 0a: Ta, N0, M0 (no involvement of regional lymph nodes and absence of distant metastases). Cancer was only in the inner lining layer of the bladder. The tumor size was >3 cm. It should be noted that when diagnosing this non-muscle invasive BC (NMIBC), the transurethral resection of the bladder tumor (TURBT) of the second look revealed a low-grade pTa tumor/lesions, so the rate of recurrence after intravesical treatment was not minimal. Moreover, it was diagnosed along with a high level of smoking intoxication.

The doctor chose the resection as a first intention treatment and consulted the ontology system to identify possible risks. As described in Figure 2, the system checks the risks and effects of the selected treatment via SE queries. In addition to the diagnosed cancer type and stage, the queries used take into consideration other contextual information such as the type of the proposed treatment and its extended practice and the patient's medical and demographic data including age, medical history, doses, sex, weight, activity, symptoms, and parallel treatments.

These indicators should match patient information that is usually recorded in their electronic medical record (EMR) [51]. Moreover, the decision-making engine retrieves related knowledge and evidence included in the ontology to reason about the consequences of the selected treatment. Then, it generated a list of SEs associated with this prescribed treatment with reference to their severity grade scale as specified by the Common Terminology Criteria for Adverse Event (CTCAE) [52] and based on expert panel opinions (the International BC Group (IBCG) and the Cancerology Committee of the French Urology Association (CCAFU)) [53,54]. For example, as a result of this TURBT treatment for our specific patient case, our system should report related SEs that belong to the second grade on the severity scale, and that these SEs will not last long with reference to the right standard as listed in Table 3.

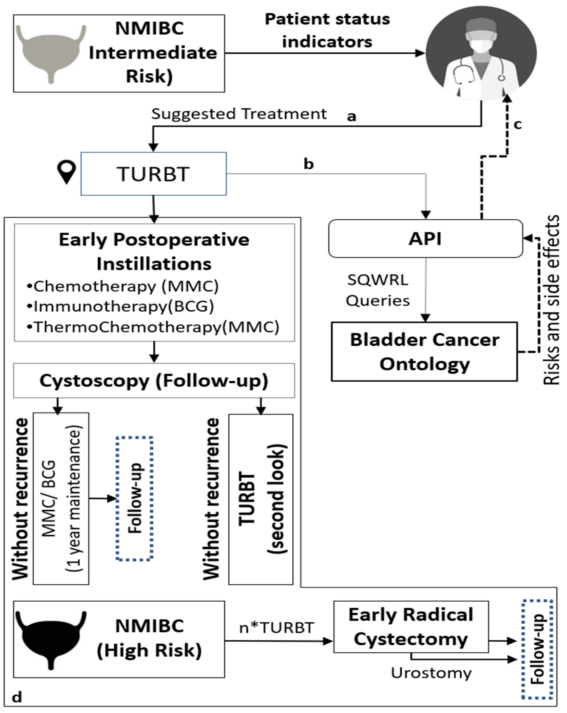


Figure 2. Case scenario of BC treatment process and the required generated SE prediction approach; (a) Treatment suggested for evaluation; (b) Evaluation; (c) Prediction results for decision; (d) Treatment procedure following TURBT.

Table 3. Predicted risks and side effects' results related to the applied treatment.

Treatment	Risks/Effects	Grade of Severity	Reference Standard
TURBT	• Hematuria and painful urination • Incontinence • Tiredness • Lower abdominal ache and cold sweats • Bladder perforation and infection	II	CTCAE v.5 (2017)

3.4. Building an Ontology for BC Knowledge Representation

In this study, a patient was represented by an instance of the class *Patient*, which was mainly expressed by two main subclasses, *PatientBiophysicalInformation* and *PatientClinicalInformation*.

We also introduced *Pathologies* as a class, in which we mainly focused on *BladderCancer* as a subclass describing its grades, characteristics and malignancy using class hierarchy. Besides the *BladderCancer* subclass, we identified *BodyDisease* as a subclass describing other tumors and diseases/illnesses that could be bound to BC or mentioned as a possible-related complication.

The *Treatment* class was designed to categorize BC therapy strategies and protocols in which we record applied treatment-related clinical evidence. This was to model knowledge about *TreatmentType*, *Drug*, *ClinicalTechnique* and *TherapyProtocol*. This class is related to both the *RiskSideEffect* and the *BladderCancer* (grades) classes to obtain possible complication about each suggested clinical act. This class is the clinical evidence basis element of our semantic prediction rules used to reason and decide about prediction results of treatment's SEs.

We included a *RiskSideEffect* class in which we created two main subclasses: *RiskSeverity* and *Complication*. This describes possible treatment SEs threatening the bladder

and other organs when applying a therapy. When matched with BC grade and treatment, severity can help in managing complications correctly. It is important to be mentioned and includes the assessment criteria used to compare patient's BC details with BC treatment's evidence. Moreover, this class includes clinical evidence outcomes as good and bad effects to be compared and anticipated for the treatment decision making.

Another important concept in our ontology is the *Anatomy* class. It contains knowledge and gender-based details about human body organs and describes *AnatomyAbnormality* and *ConventionalAnatomy*. This is to obtain more precise predictive results when locating treatment SEs damages to the patient's health. The subclass *OrgansBiophysicalSensitivity* helps in understanding BC behavior and complications in addition to the body's physical responses to undertaken treatments.

The inferred results were supported by the *TreatmentSEStandard* class, including texts and standards about treatment related SEs, extracted from the international standard CTCAE and the published guidelines of the international cancer research foundations with reference to BC treatment clinical practice guidelines [55–60].

The construction of our ontology was semi-automatic. Information and knowledge representation design was applied to obtain a pre-formal metamodel ontology for rule-based prediction. It included classes, properties and attributes as static components. Additionally, the BC treatment process with SE prediction diagram was a part of the model. This model was a convenient tool to represent and formalize our domain knowledge. Furthermore, our descriptive representation was also understandable by medical team actors (clinicians and technicians) for both assessment and follow-up. This was to provide more semantic clinical evidence details, used as instances and concept values, so that we could obtain an ontology model.

The next step was to represent complex concepts in our ontology, using semantic and logic-based specifications. Regarding the variable conditions of each patient, our semantic-based explicit criteria rules were needed to help in discovering complications and to tag the source causes. We used Protégé to manually transform our model into an ontology OWL-DL model format. Our domain knowledge was represented by a set of classes and instances. *OWL:Thing* is the root class of this model, the set of subclasses representing the common domain terminology used to describe our conceptual knowledge model.

The main concepts in our ontology were modelled in a hierarchical manner which is a feature of OWL inherited from previous languages for graph representation, such as RDF [61]. The higher level of hierarchy was initially reserved for BC treatment domains. The main concepts were modeled as classes or categories of concepts. One class can be a subclass of several series of classes.

Creating a *Cancer* sub-class within the *Pathology* class highlighted this to be prominent. For example, *BladderCancerPapillaryCarcinoma* is both a *Carcinoma* and a *Cancer*. Therefore, we defined a *BladderCancerPapillaryCarcinoma* class as having two levels of super-classes on the hierarchical scale of the *Pathology* class: *Carcinoma* and *Cancer*. All instances of the *BladderCancerPapillaryCarcinoma* class would be instances of both the *Carcinoma* class and the *Cancer* class: a super-class can access sub-classes' instances and attributes. However, the *BladderCancerPapillaryCarcinoma* class inherited attributes and facets from parent classes. We specify a class attribute using OWL Properties (binary predicates/formulae with two free variables). This is a logic descriptor of a given concept modelled as object properties or data type properties, for example, *tumPapillaryCarcinomaOf(x,y)* denotes that y is a papillary carcinoma of a given tumor x; or as atomic properties to denote the set of each objects (instances of a class x) classified under a defined class, for example, *Cancer(x)*, *InvasiveCarcinoma(x)*, etc.

We can also use Data type properties which are a type of predicate capable of linking an instance (or object of a specific class type) to a range of data values (similar to the data types used to define the columns of a database).

An example of the use of a property could be as described in the following triplet:
<*NonInvasivePapillaryCarcinoma has TreatmentName, TURBT*>

This is to say that a BC *NonInvasivePapillaryCarcinoma* object is linked to the range of data values *TURBT* (transurethral resection) by the datatype property *hasTreatmentName*.

We can also represent the level of risk severity that is associated with a specific treatment option using data type properties, as shown in the following triplet example:

<IntravesicalTherapy has *RiskSeverity, 4>*

This example links the object class *IntravesicalTherapy* to the data value *4*, indicating its risk severity grade, by the use of the datatype property *hasRiskSeverity*. On the CTCAE SEs scale, the grade *4* refers to life-threatening consequences with an urgent intervention to be indicated.

In OWL, we can also use Restrictions on attributes (facets, sometimes called role restrictions) to map pre-identified classes into definitions in a language that is understandable by a reasoning engine and therefore will be understood by a computer or a digital device. Here, our knowledge was explicitly included in our ontology in the form of restrictions. To define these restrictions, we rely on the notation allowed by the OWL language. In these definitions we also use the Existential Restriction most common in OWL ontologies. This restriction describes a class of individuals, which maintains at least one (*some*, $\exists$) relationship with an instance of a specific class.

Example 1. *BladderCancerPapillaryCarcinoma is a Cancer which is not manifested by Adenoma. We can define this class as the combination of the following definitions:*

- *not Adenoma, denoted as* $\neg$ *Adenoma*
- *not BladderCancerPapillaryCarcinoma and (manifestedBy some Adenoma) denoted in OWL as* $\neg$ *BladderCancerPapillaryCarcinoma* $\sqcap$ *(manifestedBy* $\exists$ *Adenoma)*

In addition, we can also use OWL Universal restriction (*only* $\forall$) to describe classes of individuals which for a given relationship are related (only) to individuals of a specific class. For example, the class of individuals which only has anatomy (*hasAnatomy*) and individuals belonging to the *Bladder* denoted as *BladderAnatomy*.

Example 2.

- *BladderCancer has Anatomy only, the DetrusorMuscle and Adventitia, which is only, a part of some BladderWall or Peritoneum.*
- *BladderCancer has Anatomy only (DetrusorMuscle and Adventitia only (partOf some (BladderWall or Peritoneum))*
- *BladderCancer* $\sqcap$ *hasAnatomy* $\forall$ *(DetrusorMuscle* $\sqcap$ *Adventitia* $\forall$ *(partOf* $\exists$ *(BladderWall* $\sqcup$ *Peritoneum)))*

We have also used many features of OWL that could be found in the world wide web consortium reports and Jain et al. [62,63]. These include enclosure, intersection, union, inverse, and equivalence (of classes and properties). All these elements were created to identify the quantitative assessment model and predictions generated by our knowledge-based approach.

3.5. A Semantic Rule-Base for Decision Support in BC Treatment Selection

Based on the given conceptualized domain vocabulary (as provided by our OWL2 ontology in the previous section) and an extended syntax with logic-based descriptions, we can produce sets of decision support rules using the semantic web rule language (SWRL) [64]. As an OWL-DL based language combined with Horn-like logic rules of the rule markup language (Rule-ML), this is used for developing rule-based approaches. The rules assessment and firing tasks were passed to the rule engine (Pellet 2) [65]. This engine played the role of a deductive system which, starting from formulas of the language chosen as premises (axioms already represented in the ontology), made it possible to construct new formulas in the form of new premises to be added to the ontology. The newly generated knowledge by the rule engine will be offered to medical practitioners as decision support guidelines. The set of rules are run in a query-like mode of knowledge reasoning and retrieval. In this sense, a condition that is tested by the first part of a rule is true if its query

is valid. For example, "*All patients who are taking external beam radiation therapies are at risk*" can be written as:

$$ExternalBeamRadiationTherapy\ (x) \rightarrow atRiskOf\ (x,y)$$

where x and y represent some given patient and health risk, respectively.

We could then deduce "*there are radiation therapies that are presenting a health risk to the patient*" which could be recorded in the OWL ontology formalism as:

$\exists\ x\ RadiationTherapy\ (x) \wedge atRiskOf\ (x,y)$

This could be recorded in the ontology thanks to the generalization hierarchy, by minimizing differences between classes by way of extracting their common characteristics. The combination represents a specialization of a superclass with a multileveled hierarchy using inheritance.

To ask and determine cases and possible undesirable events according to the defined evidence, we used semantic query-enhanced web rule language (SQWRL) queries examination. As a SWRL-based query language, this queries OWL ontologies and affords SQL-like services to model the retrieved knowledge [66]. The following example shows a query examination we used in our ontology:

Patient (?P) $\wedge$ *hasStage (?P, ?S)* $\wedge$ *swrlb:greaterThan (?S, 1)* $\wedge$ *hasSideEffect (?P, ?SE)* $\wedge$ *hasStandardReference (?SE, ?SR)* $\wedge$ *hasTreatment (?P, RadiationTherapy)* $\rightarrow$ *sqwrl: select (?P, ?SE)* $\wedge$ *sqwrl: select (?SR)*

This aims to detect all BC SEs within an advanced stage (greater than 1) and associated with a given patient/treatment combination when the treatment is radiation therapy as shown in Table 4. This result is also supported by the afforded standard reference.

Table 4. SQWRL side effects' results and their related standard reference.

?P [1]	?SE	?SR
PMIBC001 [2]	Peeling, Blistering, Diarrhea, Incontinence, Hematuria, Nausea, Painful urination, Cystitis, Tiredness, Anemia, Bruising, Erection problems, Infection	Moschini, et al. (2019) doi.org/10.1016/j.eururo.2018.09.034

[1] Patient, [2] Patient muscle invasive bladder cancer 001(ID).

Patient (?P) $\wedge$ *hasStage (?P, ?S)* $\wedge$ *swrlb:greaterThan (?S, 1)* $\wedge$ *hasSeverityGrade (?SE, ?SG)* $\wedge$ *hasSideEffect (?P, ?SE)* $\wedge$ *hasTreatment (?P, RadiationTherapy)* $\rightarrow$ *sqwrl: select (?P, ?SG)* $\wedge$ *sqwrl: sum (?SG)* $\wedge$ *sqwrl: avg (?SG)*

In this query we added a SEs severity grade criterion to detect each severity grade of the predicted SEs related to a BC patient treated with radiation therapy (stage > I) Table 4. Since *hasSeverityGrade* (SG) is a datatype property of the class *RiskSideEffect*, we can use this semantic relationship to relate each SE to its own severity grade. Moreover, this query gives the total score and the average value of the obtained severity grade using SWRL aggregation operators *sum* and *avg*. Results are shown in Table 5. Severity grades are ranked from 0 to 5 according to the CTCAE related to the cancer therapy evaluation program (CTEP).

Table 5. SQWRL severity grades results related to predicted side effects.

?P1 [1] = p1	Selected Values of ?SG	Returned Sum (?SG)	Returned Avg (?SG)
PMIBC001 [2]	2, 1, 1, 3,1, 1, 2, 2, 1, 2,3, 1, 2, 2	24	2

[1] Patient, [2] Patient muscle invasive bladder cancer 001(ID).

Here, the result shows a severity grade rate of 2, which refers to moderate AEs related to the indicated intervention. The strategic approach that has been adapted for the design and development of our ontology is detailed in Figure 3.

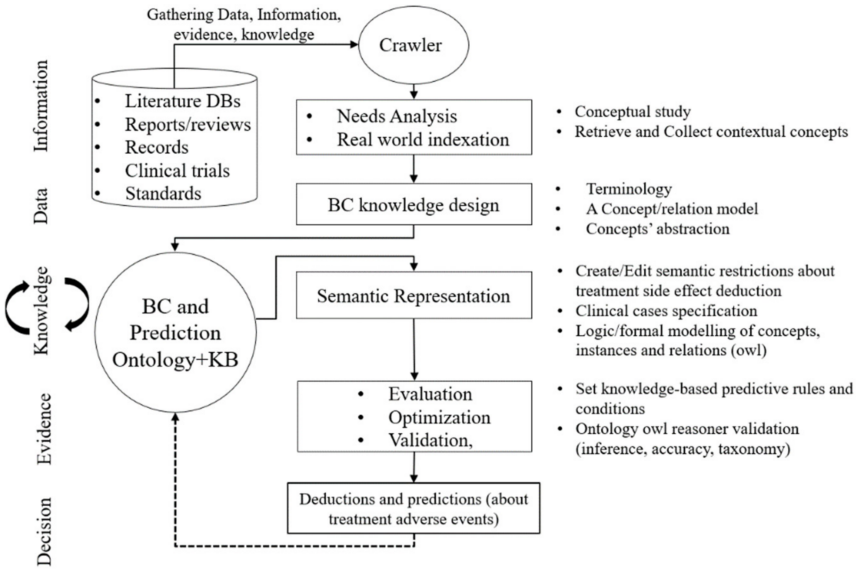


Figure 3. Ontology map and design methodology.

Both SWRL and SQWRL queries rely on OWL inferences since they were both built primarily on OWL-DL. Therefore, the complementarity of these languages made it possible and easier to reach our objective. We have relied on Protégé in its version 3.5 as ontology and rule-base editor [67]. This is a platform and an environment for development and it built and managed our ontology, using tools for the construction of oncology and oncotherapy conceptual models. Clinicians and patients are the potential users of this ontology. Many plugins have helped us to accomplish our mission and enhance our ontology performance while editing the main semantics and test cases for our predictive rules.

4. Results

In order to describe our ontology about BC treatments risks and SEs, we rely on the graph and figures presented in Figure 4. These describe the composition of the ontology in terms of various structured components including:

There are -6 super-classes targeting the BC, treatments, procedures, risks, and evidence, each of which contains a large number of hierarchical subclasses (all types of examinations and existing oncotherapy techniques) linked to instances describing concrete objects about BC cases: 42 subclasses of the second level, 60 of the third levels, 198 of the fourth level, 251 of the fifth level, 284 of the 6th level. Concepts are classified by types and families of medical examination techniques.

- 80 "object-properties" between classes and 176 "data-type-properties" between classes and instances, indicating the values and the parameters related to the occurred examinations.
- 1825 instances with actual objects of knowledge: 35% of these instances are data. 65% of our instances are presented as the finest values of knowledge and evidence. Here, we define data as analysis' elements, while knowledge is the synthesis of evidence and information flow which presents data with a context.
- 621 different rules for the checking of SQWRL and SWRL risk and SE identification queries. These tests deploy as parameters the type of examination in treatment procedure as well as the probable risks, with selective results of examinations.

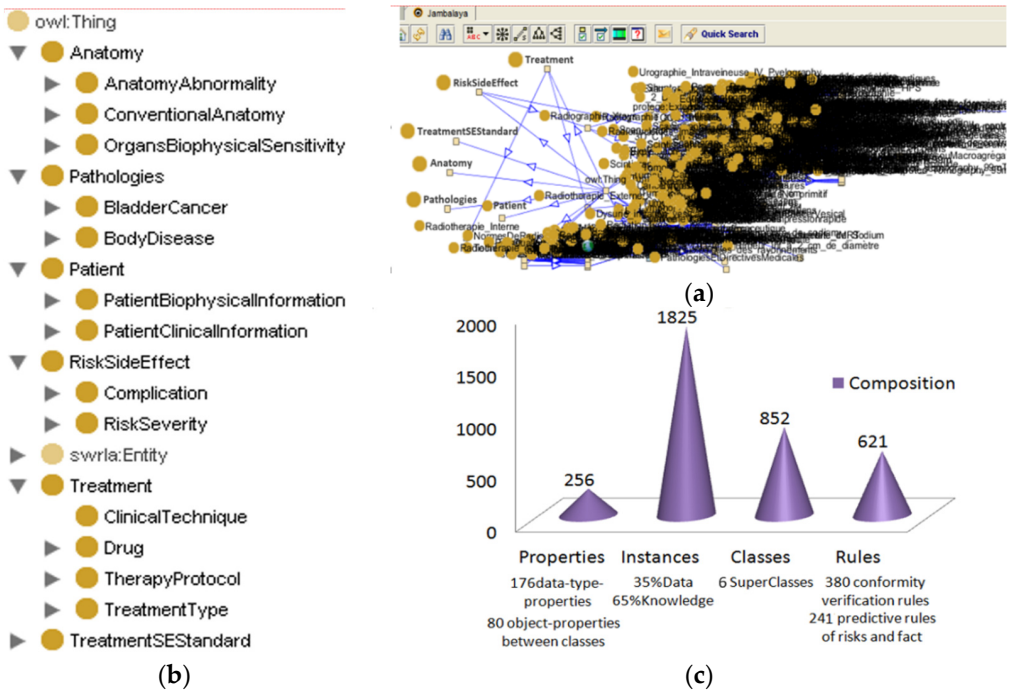


Figure 4. Knowledge-based model for bladder cancer treatment side effects using Protégé; (**a**) Model Classes hierarchy; (**b**) OWL view of the ontology graph using Jambalaya plugin; (**c**) Composition of our ontology.

The validation of our produced ontology is an essential step. We followed special criteria according to which the ontology had to be validated in terms of consistency, taxonomy, and inference Figure 5. This checking validates the SWRL rules which are based on valid relationships to predict and detect SEs from the given prediction criteria (as mentioned in Section 3.3).

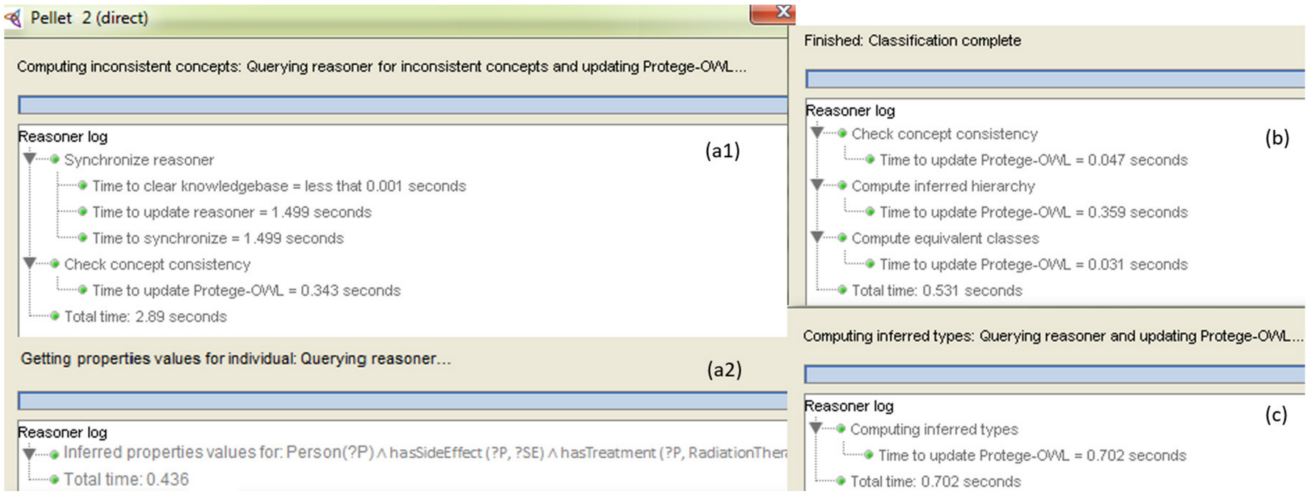


Figure 5. Checking the consistency of the classes (**a1**) and their properties (**a2**), the taxonomy (**b**) and the inference (**c**) within the model through Pellet reasoner dialogue.

Furthermore, formal correctness was evaluated according to criteria as disjunction errors which aimed to identify a class as a conjunction of distinct classes. We also checked the consistency and coherence to verify the accuracy and the semantic and syntactic representation of BC treatment and SEs knowledge without contradictory conclusions. Moreover, we checked duplication errors to remove redundant elements which can be

deduced from the others. Completeness was also evaluated to measure the conformance and compatibility of both ontology and our domain-model. This criterion was based on covering all elements and terms related to BC treatments by proving the incompleteness of elements to check the completeness of the ontology as mentioned by Gómez et al. [68,69]. To do this, we used Pellet as a java based OWL2DL reasoner [70].

The semantic reasoner and SWRL Rules are the constructive elements of the system's rule engine within our model. For application, the SWRLTab interface plugin allows the creation and the management of our SWRL and SQWRL (SQL-like query features). A graphical format sample of these rules is shown in Figure 6.

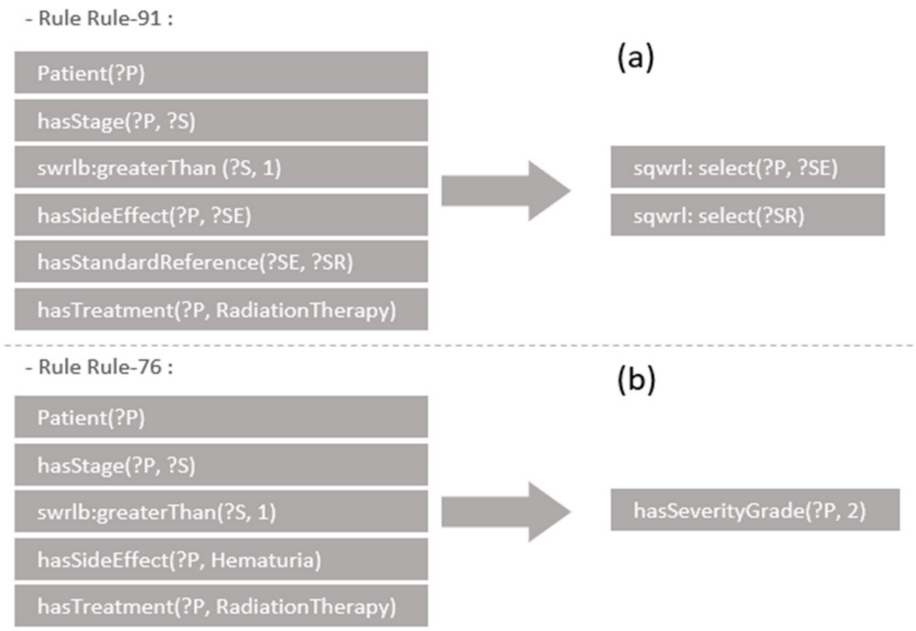


Figure 6. The graphical format of SQWRL (**a**) and SWRL; (**b**) rules.

To reason about a prescribed treatment and anticipate SEs and possible complications, the model is performed within a clinical administration unit. When the healthcare provider supplies the queries by the required predefined criteria through an application programming interface (API), the model requests its query processor. Accordingly, the model checks the relations between SEs, complications, and treatments with reference to guidelines and elements identified in the edited SQWRL and SWRL rules. The model manages the interactions of both KB and user. Therefore, the model generates a detailed decision about the treatment SEs, its severity grade and the required reference standard. Then, results are displayed on the user interface as an output of the model.

JessTab is used in Protégé to perform the querying tasks. The key forms of performance for retrieving knowledge from ontology are SWRL and SQWRL queries. SWRL rules are launched in the Jess inference engine after the class consistency checking. The results and the validation process of the Jess inference tab are shown in Figure 7.

The generated SQWRL and Jess results are shown in Figures 8 and 9.

The obtained outputs were considered as new evidence to supply the model by being stored in the properties of class instances.

As shown in Figure 9, the instance PMIBC001 of the class Patient who has a stage 2 MIBC and has radiation therapy as a planned treatment is predicted to have anemia, blistering, etc., as listed in Figure 9 with a severity grade 2. This is the output of the SWRL rule that we defined previously, including all the factors of predicting treatment SEs. The obtained outcome is stored in our model to supply our ontology for future reasoning Figure 9. Before rules processing, the content of SEs, severity grade and standard reference was empty, and then supplied by the inferred results of prediction.

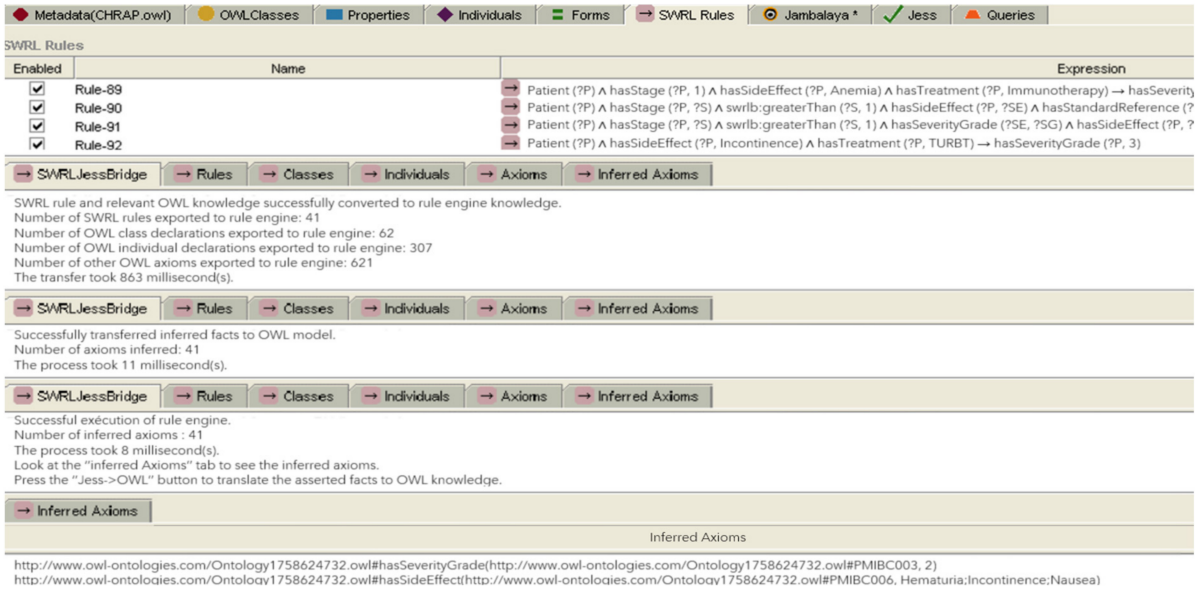


Figure 7. Results and validation of Jess and axioms inferences.

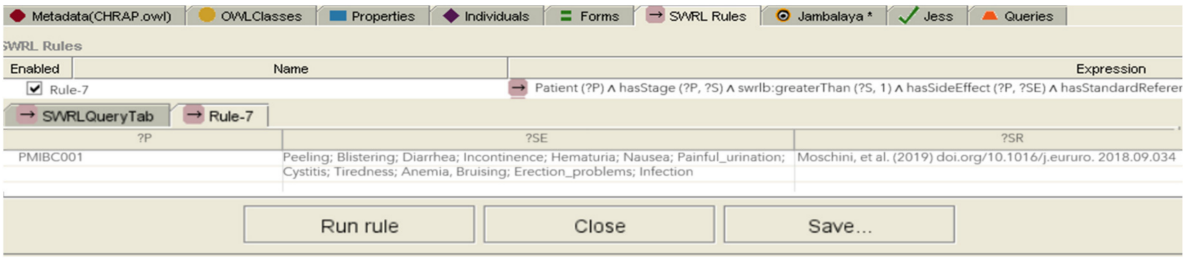


Figure 8. Model-based SQWRL results displayed in Protégé.

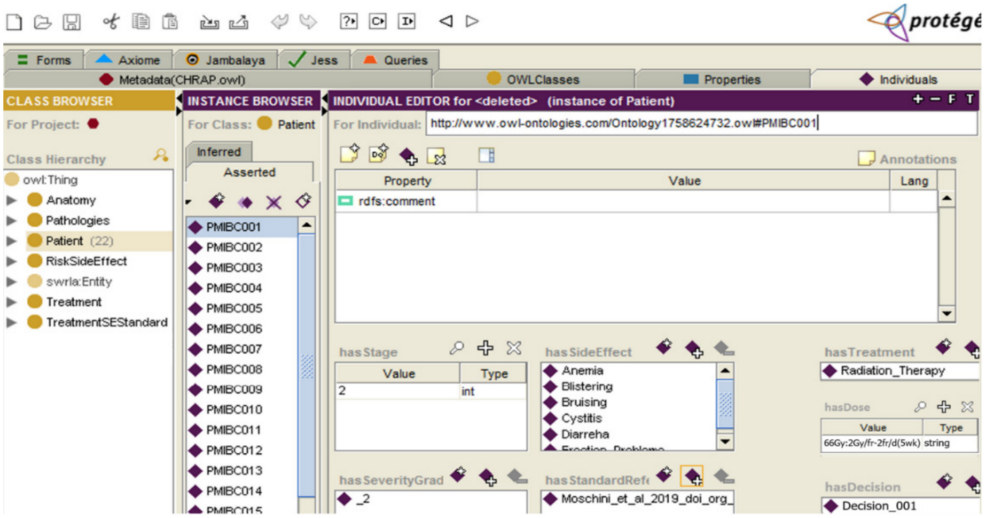


Figure 9. Jess query results generation and output reintegration into the ontology model.

Thus, we customized an easily accessible java swing-based user interface API, to let healthcare providers and clinicians anticipate AEs of prescribed BC treatment and support their decision making. This provided options to query our ontology model directly and predict BC treatment SE elements according to the required criteria. As inspired by the work of Kayes et al. [71], we present, in Table 6, examples of operator-defined reasoning

rules from our rule-base followed by a descriptive simplified conceptual model of our ontology with details of the *Pathology* concept, as shown in Figure 10.

Table 6. Examples of operator-defined reasoning rules from our rule-base.

No	Rule
Rule 1	Patient (?P) ∧ hasStage (?P, ?S) ∧ swrlb:greaterThan (?S, 1) ∧ hasSideEffect (?P, ?SE) ∧ hasStandardReference (?SE, ?SR) ∧ hasTreatment (?P, RadiationTherapy) → sqwrl: select (?P, ?SE) ∧ sqwrl: select (?SR)
Rule 2 . . .	Patient (?P) ∧ hasStage (?P, ?S) ∧ swrlb:greaterThan (?S, 1) ∧ hasSeverityGrade (?SE, ?SG) ∧ hasSideEffect (?P, ?SE) ∧ hasTreatment (?P, RadiationTherapy) → sqwrl: select (?P, ?SG) ∧ sqwrl: sum (?SG) ∧ sqwrl: avg (?SG)
Rule 7 . . .	Patient (?P) ∧ hasStage (?P, ?S) ∧ swrlb:greaterThan (?S, 1) ∧ hasSideEffect (?P, ?SE) ∧ hasStandardReference (?SE, ?SR) ∧ hasTreatment (?P, RadiationTherapy) → sqwrl: select (?P, ?SE)
Rule 92	Patient (?P) ∧ hasSideEffect (?P, Incontinence) ∧ hasTreatment (?P, TURBT) → hasSeverityGrade (?P, 3)

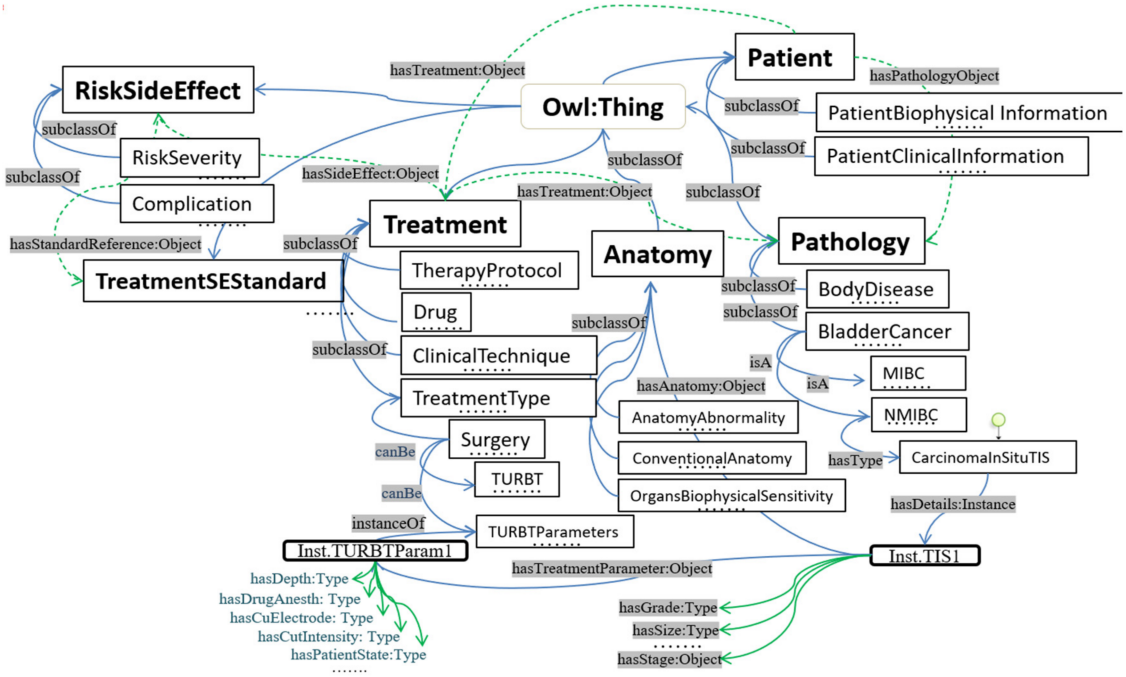


Figure 10. Conceptual knowledge model of our bladder cancer treatment side effects ontology.

Based on the previously published RCTs in the literature, the performed model resulted in elements constructing prediction conclusions that were displayed on the user interface for consideration by the clinicians Figure 11.

When the prediction inference is processed, the newly registered patient (e.g., PMIBC001) within the *Patient* class of the model is tagged and its demographic (e.g., age, gender) and biophysical (e.g., medical history, BC type and stage) data are imported in the queries for the required reasoning. Launching the reasoning process through the interface involved patient identification, the required treatment selection among the imported list of the prescribed treatments for the whole therapy to this patient (including procedure details and treatment dose) and the BC stage retrieval. All the used data, knowledge, rules, and queries were retrieved automatically from our performed knowledge model. The output of the Java-based API is displayed on the user-interface as treatment SE prediction information (AEs and severity grade) with reference to the prediction knowledge standard references and guidelines (related to the obtained SEs severity grade), as shown in the validation example of Figure 11. A decision is also displayed within the interface importing the content of the instance (Decision_001) generated by the model and stocked in the KB.

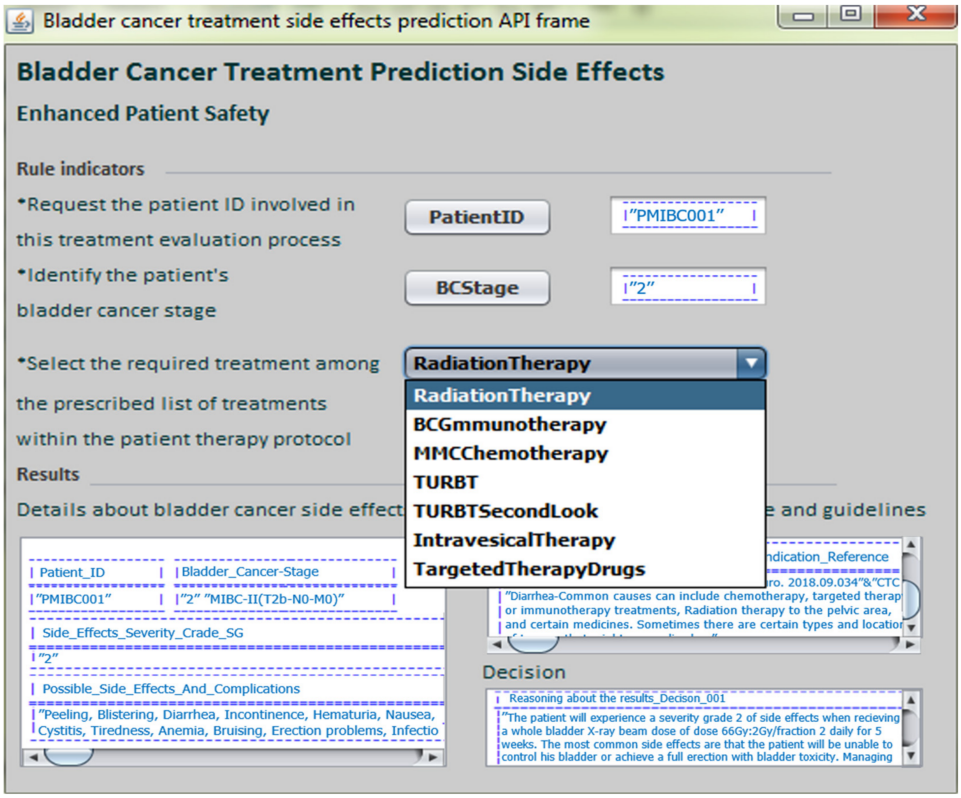


Figure 11. Results displayed on the bladder cancer treatment side effects prediction API frame.

For clinical practice, the proposed model is implemented using OWL as described in the implementation and clinical application process presented in Figure 2. Furthermore, adopting the W3C-based web service activity ensures interoperability and services communication. This will aid in the identification of the desired and most effective treatment, as well as the restrictions that must be adhered to.

This helped to verify the absence of contradictions between ontological elements, in addition to the conceptual matching between them. We also checked the completeness, ensuring that all ontological elements are either explicitly declared or inferable. In our ontology all defined elements obey the principle of concision. Furthermore, we can add new knowledge without changing the old ones originally specified in our ontology, which satisfies the criteria of extensibility which an effective conceptual model should hold.

After formal validation and inconsistencies evaluation, we were concerned by the validation of the domain conceptualization. Experts' feedback was an important step in validating and modifying the ontology. This step allowed us to obtain a confirmation about the accuracy and the correctness of our knowledge with object-oriented explanations. Positive feedback had no impact on our knowledge model, but it was a valid confirmation. Only feedback with domain conceptual notes was considered to make updates and modifications using RDFS rules. To help in the validation task, we used factual questions to improve and enrich our ontology. Feedback showed a rate of 0.48% (compared with our ontology composition: 2933 elements) representing 14 elements to add as knowledge representation items (concepts, relationships, and individuals) and logical chaining suggestions. Moreover, Boolean-like questions about BC treatments relating SEs to risk indicators helped in correcting and updating our knowledge model. This survey resulted in nine questions with "no" answers from a total of 210 Boolean questions, representing a rate of 18.90%. Modifications and suggestions represented 19.38%. Hence, this step showed a total satisfaction rate of 80.62%.

For decision-making markers of treatment effects calculation, we took this example: in a stage I BC patient in which the tumor had spread to the connective tissue layer of the

bladder but has not reached the muscle layer, we indicate that the tumor was removed, then intravesical BCG (immunotherapy) or mitomycin (chemotherapy) was delivered. Table 7 shows the AE results of a RCT that compares the intravesical BCG treatment to mitomycin treatment.

Table 7. AE results of a RCT that compares the intravesical BCG treatment to mitomycin treatment.

Treatment		Mitomycin (*N* = 1210)	Intravesical BCG (*N* = 430)
Life-Threatening AE Rate		9 (0.7%)	13 (2.8%)
Adverse events	Nausea and vomiting	23 (1.9%)	8 (1.8%)
	Autoimmune reactions	9 (0.7%)	77 (17.9%)
	peripheral neuropathy	54 (4.5%)	12 (2.8%)

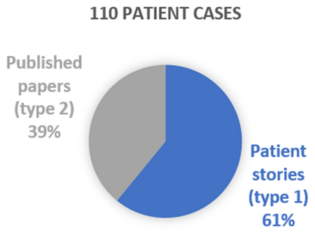
A major efficacy prediction endpoint is the life-threatening AE rate, which was higher in intravesical BCG subjects (2.8%) than in the mitomycin ones (0.7%). The RR calculation for life-threatening AE rate is: $0.007/0.028 = 0.25$ (25%). The RRR is $1 - 0.25 = 0.75$, which means that there is a 75% decreased risk of life-threatening AE in patients receiving the mitomycin treatment compared to those receiving intravesical BCG. The ARR is $0.028 - 0.007 = 0.021$ (2.1%). The NNT is $1/0.021 = 47.6$ ($\approx$48): This means that 48 patients need to receive mitomycin so that one patient gets benefit.

For treatments' SEs measurement prediction and comparison, we take the example of peripheral neuropathy. Based on data in Table 7, we find that mitomycin treatment subjects (4.5%) had a significantly higher rate of peripheral neuropathy than intravesical BCG (2.8%). The associated RR for infusion reactions is $0.045/0.028 = 1.6$. The RRI is $1.6 - 1 = 0.6$ (60%) which means that the rate of peripheral neuropathy occurrence is 60% higher in subjects receiving mitomycin. The ARI for mitomycin treatment subjects relative to intravesical BCG is the difference between the rates of peripheral neuropathy: $0.045 - 0.028 = 0.017$ (1.7%). The NNH is $1/0.017 = 58.8$, which means that 59 subjects need to receive mitomycin to arrive at one more case of peripheral neuropathy.

To evaluate our approach, we performed tests on 110 BC anonymized cases collected from different sources. Around 67 open BC stories were found to be useful and informative, as they include details about specific BC treatment journeys and witnessed SEs. These type 1 cases were extracted from sources such as the Urology Care Foundation and American Urological Association guides and patients' stories [72], Fox Chase Cancer Center Health [73], Temple Health [74], BC advocacy Network (BCAN) [75,76], Action BC UK and Patient Resource Publishing [77]. On the other hand, we obtained 43 more cases from reviewed research papers including post and pre-treatment information and clinical details collected from studies involving BC patients. These type 2 cases were found in 43 papers among our 93 selected studies as described in the "Materials and Methods" section. From each paper we chose one case that meets the criteria of testing (treatment type, cancer type and effects).

The number of these cases is considered adequate, considering the type of BC related to each case, the age, sex, weight and performed treatments (as detailed within patients' treatment protocol stories including procedures and delivered therapeutic doses), along with some behavioral factors as mentioned in the descriptions, such as post/perioperative smoking, alcohol drinking and chronic diseases [78]. To cover most possible scenarios of our ontology-aided BC treatment SE prediction, we were referred to BC types, for which a sample of cases has been assigned. We describe these types as non-invasive bladder cancer (NIBC) which covers non-invasive papillary carcinoma (stage 0a) and carcinoma in situ (Cis) (stage 0is), non-muscle invasive bladder cancer (NMIBC) (stage I) and muscle invasive bladder cancer (MIBC) (stages > I). The tested scenarios were processed as described in Table 8.

Table 8. BC sample cases distributed according to treatment and BC stage.

Type	Stage	Cases	Sample	Sources
NIBC	0a	19	S1	
	0is	18	S2	
NMIBC	I	20	S3	
MIBC	II	17	S4	
	III	16	S5	
	IV	20	S6	

These cases were carefully collected and formed the core of the KB upon which our ontology was created. The queries that were tested and executed by the Pellet2 rule engine [79] focused on inferring possible SEs related to each type of treatment, administrated for the considered cases of BC to predict its impact on patient health and safety. Each treatment type was tested by a query. Results were obtained including the possible SEs related to each type of treatment. The inferred results also contain a reference to the patient identifier (as mentioned in Table 4). An average score of severity grade was also concluded for each predicted SE using semantic queries (as mentioned in the Section 3.5). In Table 9, we present the resulted average severity grade score per sample. Then, we compared our predicted SEs to AEs that were reported in patients' descriptions and stories: this was processed by manual check. For example, and as described in Table 9, a patient represented by sample (S1), diagnosed with low grade NIBC (stage 0a), was predicted to develop mild SEs with a (SG = 1) considering all indicators that we defined previously. This patient's prediction results showed SEs such as pain when urinating, low grade bladder infection, hematuria, and incontinence when applying TURBT treatment, and bladder irritation and burning feeling in the bladder when receiving a post-TURBT intravesical chemotherapy (mitomycin). However, the reported AEs showed that the patient developed pain when urinating, hematuria, low grade bladder infection, but no incontinence effect as post-TURBT SEs. Real SEs were bladder irritation, burning feeling in the bladder, loss of appetite and insomnia for post-intravesical chemotherapy. As a result, our reasoning predicted 75% of AEs for post-TURBT procedure and 80% for post-intravesical chemotherapy. This means that for this case, results were compatible at 77%.

Table 9. Results for average severity grade score per sample SG and a comparison with real reported side effects.

Sample	Results		
	Average Severity Grade Score per Sample SG		Comparison with Real Reported Side Effects
	SG	Sample Rate	(% of Compatibility)
S1	2	73%	86%
	1	27%	
S2	2	87%	81%
	1	13%	
S3	2	11%	78%
	3	89%	
S4	4	36%	82%
	3	64%	
S5	5	07%	79%
	4	93%	
S6	5	10%	76%
	4	90%	

5. Discussion

Thanks to the capability of OWL's terminology, in particular its expressiveness, our ontology's concepts have been represented in a syntax as close as possible to natural language. Composite concepts were classified according to their semantics. Hence, the initial semantics were preserved by the proposed formal representation.

In general, our results presented 80.3% of the real reported BC treatment SEs prediction. These results also showed that the more we go through the advanced stages of BC, the more the treatment protocol becomes complex and presents important and serious SEs. Moreover, the results obtained from our ontology prediction approach were close to real AEs recorded within the collected test samples.

For heterogeneity, a part of our records, four cross-sectional studies [80–83] reported on the overall cystitis AEs and complications, allowing for different time intervals relative to the treatment of patients with high-risk T1G3 BC (TURBT-Radiation therapy versus TURBT-BCG Immunotherapy). We excluded all BC types and stages different than T1G3 (cross-sectional studies).

24.5% of patients who received TURBT-Radiation therapy compared with 16.8% of patients who received TURBT-BCG Immunotherapy (controls) had cystitis. According to Figure 12 (df: degree of freedom; M-H: Mantel-Haenszel), meta-analysis showed that the overall cystitis AEs and complications relative to TURBT-Radiation therapy versus TURBT-BCG Immunotherapy ranged from 2% to 27%. This showed a significantly higher cystitis SE rate by TURBT-Radiation therapy than TURBT-BCG Immunotherapy (rate difference 11%; 95% CI; 2–27%; $p = 0.03$; $I^2 = 81$; $\chi^2 = 16.13$).

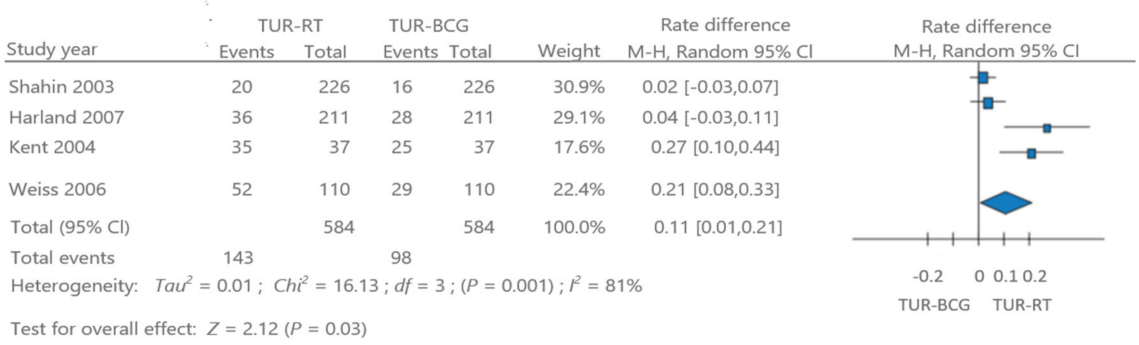


Figure 12. Overall AEs and complications in patients treated with TURBT-Radiation therapy (TUR-RT) versus in patients who received TURBT-Immunotherapy BCG (TUR-BCG), excluding all BC types and stages different than T1G3 (cross-sectional studies).

Our evidence-based reasoning approach, combined with the semantic KB model, helped to generate predictions related to possible patient health issues during and even before treatment application. Integrating a diversity of knowledge and evidence into a single KB and ontology has improved the process of predicting treatment risks and the SEs associated with oncotherapy in BC. Furthermore, improving and adding more inheritance edges between concepts helped to obtain better prediction accuracy. This makes it more robust, especially in the BC domain, involving highly complex and specialized knowledge and semantics.

With reference to previous studies, our approach highlighted digital SE prediction through information technology to optimize oncotherapy treatment processes in BC oncology. Besides the knowledge representation method, we adopted a crawler-based knowledge gathering method to overcome difficulties encountered within computerized patient records or knowledge management in clinical processes, as reported in the study of Masters et al. and Manika et al. This fact helped in supervising most of the useful digital resources and covered more specific reports to enhance the validation of our results. So far, our ontological approach combined the conceptual semantics and the fundamentals of the probabilistic models and Bayesian network, instead of using them separately as

reported in previous studies which revealed some major fuzziness and inaccuracies in results. However, our results represented treatments with their detailed consequences and explanations, which enhanced their credibility as compared to patient-reported SEs. Identifying patients at high risk of BC treatment SEs through a semantic-based prediction method included medical proof and evidence. Compared to the studies of Brooks et al. and Tramèr et al., which only abstracted risk factors about patients and used statistical models for prediction, we found that predictions made for categories or groups (classes) can suit individuals belonging to the group. The approach also relies on past treatment outcomes as well as the latest medical research published in scientific journals and databases, to reach the curved top of unsuspected new predictive associations. This adds to the conclusions of Malterud et al. and Hang et al. in their studies of rule-based and EBM studies. Our approach incorporates various personal factors and improves patient safety by predicting SEs that can be hidden for some patients with specific factors. Our approach could be extended in the future to cover other cancers and help in solving theoretical and technical problems, such as the real-time procedural confusions and difficulties that oncologists can face within medical protocols and standards for clinical pathways and treatment provision.

Our study findings could influence decisions and clinical practices at many levels of BC treatment. Clinicians can apply the presented methods of predicting and estimating BC treatment SEs that are commonly reported in published studies. Furthermore, measures of treatment of SEs can be calculated by clinicians themselves for use in clinical practice even when these indicators are not directly provided by the system. As a result, both patients and clinicians can predict and interpret the results. Following this assessment, users can introduce these measures for treatment of AEs into the system to increment the system's KB, thus contributing to generating clinical decisions for future medical cases.

Our knowledge-based model can be easily deployed within clinical information systems (CIS), communicating with many unit information systems. Featuring our findings with electronic health record (EHR) information allows access to evidence-based tools that providers can use to make decisions about a patient's care. Information about patient treatment and SEs embedded in a clinical document architecture (CDA) [84]—as a health level 7 (HL7 V.3) [85] standard—within an EHR can communicate easily with our OWL mapping model to supply our ontology with information. Thus, our semantic decision rules are fired to predict and decide about treatments' SEs. Even more, within a decision support system (DSS), our findings improve patient safety and health quality through computerized alerts that prompt clinicians regarding possible treatment SEs and their severity grades. This helps in better optimizing treatment management plans in a risk-aware manner. Our approach serves as a Supplementary Material source of proof for evidence-based practice. This includes the integration of available evidence, clinical expertise, and health policy decision-making. Furthermore, clinicians can agree or disagree about the system's output with relation to a treatment of their choice and recommend or rate the decision for future use. If they disagree, they can override the decision by introducing justification from their own previous experience in an anonymous way. Security issues should also be studied in the future, following the approach that data and documents should normally be shared on a health information system (HIS).

Using a knowledge-based approach provided the study with an extensive KB. This allows healthcare providers to shape a strategy for working with the patient based on trusted, credible resources and to improve both focus and precision within healthcare practice. Thus, clinicians with a knowledge-based background have a wide marketing edge. As a main feature of our approach, heterogeneous data inclusiveness enables the support and the reuse of the semantics when building decisions. This is essential to prepare the environment to extensible host evidence-based practice knowledge and to integrate additional utilities in the future. It is important to model the flow of information necessary to simulate a cancer treatment case and to allow reasoning about possible undesirable effects and consequences. It is also reassuring to link the system generating results to scientific references and publications from which the generated knowledge was retrieved.

This approach shows how to benefit from previous research studies and how to consider their outcome as historical knowledge (how to benefit from past clinical and research experience to enhance patient experience in an actual clinical context). In comparison with data driven approaches, there is less dependence on human participation and primary research. In our context, we did not have to deal with occurrences of data incompleteness. It is a fact that the outcome of data-driven studies is usually affected by an insufficient amount of data. A knowledge-based model is more effective at predicting effects and future events than data driven models with a high prediction accuracy [86]. Moreover, calculating measures of treatment effect and providing clinicians with SEs' severity grades empower the clinical practice. This also helps clinicians to set a solid strategy for AE management when referring to our prediction results, including knowledge standard references and guidelines as provided by the *TreatmentSEStandard* class, as defined in our ontology.

Despite our rigorous methodology, our approach only supports clinical decisions and does not afford an ultimate commitment regarding clinical trials. The inherent limitations related to the included studies disallowed us from reaching definitive conclusions. Statistical results are also influenced by patient historical backgrounds, biological mutations, and clinical analysis methods. The community-based transfer of outcomes may also need more effort, because of the extended range of studies and their high-volume of organization. Through our feasibility study we are looking to test other types of cancer in the future, to cover both cancerology and oncology disciplines. Data was partially automated to the ontology feeding channel, which makes human intervention necessary. In addition, we would like to optimize our method of risk severity evaluation. In fact, treatment of SEs and AEs cannot be adequately concluded using a single measure. Along with measures of treatment of SEs, it is recommended also to report the standard of care and the control event rate (CER) [87] as a standard rate. We are looking forward to extending a data driven approach in which tests will use data extracted directly from electronic health records and cancer registries. Thus, integrating the work with a hospital information system and a real electronic health record management system will require adoption of the Fast Healthcare Interoperability Resources (FHIR) [88] standard data model.

6. Conclusions

This paper presented a model-driven evidence-based medicine for predicting BC treatment risks/effects. It is based on the use of ontologies and semantic models to allow sharing and managing of cancer research outcomes and knowledge in this field. Particularly, this was related to increasing patient safety by helping the doctor to choose treatment with less SEs taking into consideration the specific medical case and demographic information.

Our results showed the effectiveness of our approach in predicting risks before applying the prescribed treatment process, not only to prevent potential effects, but also to improve prescriptions with less sides effects, and helping in deciding between complex therapy approaches. Moreover, developing automated evidence-based medical tools is essential to advance the way cancer treatment is managed. However, success in this mission relies on the explicit formal representation of the terminology used by experts in the field. The use of an ontology of BC allowed us to encompass the maximum number of concepts with structural, regulatory, and standardized oncotherapy knowledge. We relied on recent domain studies to obtain the required knowledge and medical cases. In addition, the formal representation of clinical knowledge and evidence allowed us to effectuate clinical reasoning about the collected knowledge which is very close to human cognitive processes usually effectuated by oncologists to assess the SEs of a selected treatment. In contrast with the human cognitive process of thinking, the use of an automated reasoning allowed links between a great deal of evidence, proofs and contextual information about the medical case of the patient. Hence, by referring to this tool, doctors could be seamlessly assisted while deciding about patient treatment adequacy and efficiency. In addition, this decision support approach allows healthcare professionals to review the choices of BC treatment they previously offered to their patient to evaluate their treatment protocols.

Deciphering future medical future populations is not without societal consequences and must be accompanied and anticipated to allow a safe usage of the automated prediction tool. This work will be extended in the future to help generate contextualized clinical pathways and strategic action plans through an evidence-based approach for BC treatment processes.

Extending our biomedical ontology will be a challenging task that can never be deemed to be complete because of the continuously increasing understanding of cancer behavior and treatment advances. Extension can profit from the automation of certain procedures and therefore allow specialists to concentrate on more serious concerns. We are working on a strategy to reinforce the automation of updated and semantic capturing within ontology extension, where the need is found for specific properties or concepts. We are planning to apply supervised learning to features of our current ontology. We will identify the concerns of prediction for our ontology evolution, and build a general framework for ontology extension and prediction of treatment of SEs. The idea is to help focus either manual or semi-automated extension methods on areas that need to be expanded into any other ontology, moreover, helping in reducing the risk of bias or confusion between diseases or treatments generating the same complications when compared to other type of cancer. This will help in increasing the availability of the data and enhance interoperability between HISs. Hence, it reduces time and highlights resource investment. This extensibility aims to improve the interoperability among our domain's growing number of ontologies and solve term redundancy among ontologies to avoid issues of achieving data. We will ensure term reuse and semantic alignment within our ontology and work on community extensibility by application to more clinical trials and by using cases in a broader community. To reinforce our algorithm and make certain that the approach is extremely reliable, we will compare the results to treatment standards and care labels, and carry out an automated text mining of the scientific literature. The risk faced by future participants during the first non-human clinical trials might then be reduced and the risk for patients minimized if a treatment or a drug is approved by the FDA and enters clinical application.

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