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Development of a Decision Support System in Oncology for Prostate Adenocarcinoma

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ABSTRACT

INTRODUCTION: The present paper introduces a knowledge-based Decision Support System, applied to assessment and treatment in Oncology, named Oncology Custom Assistance Tools (OnCATs). It is aimed to evaluate if OnCATs can precisely characterize a patient into a definitive risk group, assess all the available treatment options and individually prescribe every treatment that is part of the chosen treatment course.

METHODS: On the first phase the OnCATs knowledge base was built, resorting to 23 guidelines for the treatment of prostate cancer. On the second phase, the interface itself was built, using Microsoft Visual Studio 2010. Lastly, the system was tested using 10 case reports published on the journal of medical case reports and PubMed websites. The On CATs output was submitted to a pass/fail analysis.

RESULTS:

For risk group assessment, OnCATs was able to perform successfully in every case. As for the assessment of the available treatment courses, it was observed that the system was able to pass in 40% of the cases. Regarding the prescription of each treatment modality, On CATs had a mean passing rate of 80.4%.

CONCLUSIONS: OnCATs can accurately assign a risk group to a prostate cancer patient. As for treatment course assessment, we found that the estimation of the patient's life expectancy can highly impact the output generated by the system. Regarding the prescription of treatments, OnCATs performed better on the prescription of EBRT treatments, in comparison with ADT.

KEYWORDS: Prostate cancer; Clinical decision support system; Radiotherapy; Radical prostatectomy; Androgen Deprivation Therapy (ADT).

INTRODUCTION

Healthcare professionals are constantly faced with new research and discoveries on the medical field and practice [1]. In Oncology, given the high heterogeneity among diseases, a greater need of providing individual healthcare measures exists, in order to achieve optimal results. Individualized medical practices are a constant process of decision-making, as the path followed by a patient has many different stages, with several possible courses of action each [2,3].

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A clinical Decision Support System (DSS) is a computerized system, which is designed to assist a healthcare professional on performing a task that involves making a set of different decisions. This technology has been globally used with the aim of saving time and reducing medical errors [4].

The goal of this study is to develop a method of implementation for knowledge based clinical DSS for assessment and treatment in Oncology. The developed clinical DDS was named Oncology Custom Assistance Tools (OnCATs). We also aim to test the system's algorithm and evaluate its performance and appliance to real clinical cases of prostate adenocarcinoma, by evaluating if the system can successfully characterize a patient into a definitive risk group, evaluate the available treatment courses, and prescribe every single treatment modality that constitutes the chosen treatment course.

Prostate cancer can be treated with several treatment options, such as External Beam Radiotherapy (EBRT), Brach therapy (BT) or Radical Prostatectomy (RP). This variety of treatments produces different side effects, which can cause different impacts on the patient's quality of life. The development of these tools is also necessary to efficiently compare the predicted outcomes of different treatment courses, which plays a great part on the process of deciding a definitive treatment option for a patient[5]. Since having more treatment options available makes the task more demanding in terms of decision-making, since there are more variables that have to be considered. Because of that, localized prostate cancer was chosen as the starting point for the development of OnCATs.

METHODS

Knowledge Base Construction

The first phase consisted on obtaining a fair amount of information to build a database that represented the current practices in Oncology.

To start building the knowledge base, a web search was conducted, including the keywords "prostate cancer", "treatment", "management" and "guidelines". This search led us to obtain a total of 13 international guidelines of well-known associations and committee [6-18].

While analyzing the obtained data, it was noted that information regarding stereotactic radiotherapy and brachytherapy was somewhat scarce. In order to bridge this gap, a second search, using the keywords "prostate cancer", "stereotactic body radiotherapy" and "guidelines", was conducted [19-22]. Following that, a third web search was conducted using the key-words "prostate cancer", "brachytherapy" and "guidelines" [23-28].

At the end, we obtained a total of 23 published guidelines to incorporate on the On CATs original knowledge base.

The obtained information was stored in tables using Microsoft Excel using the following criteria:

1. Risk classification definition: tumor stage, GS and PSA value.
2. Treatment course assessment: patient life expectancy, presence of symptoms and presence of tumor adverse features.
3. RT prescription: total delivered dose and dose fractionation for RT treatments.
4. ADT prescription: first line ADT approach and treatment duration.

System Design

The second phase of development consisted on building the system's interface. The knowledge base was digitally integrated in a way that it allowed communication with the user, while allowing the exportation of outputs, after predetermined information was inserted in the system's platform. The interface was built in the form of computerized software, meant to be used on the Microsoft

Windows operating system, using Microsoft Visual Studio 2010 [29].

System Workflow

A summary of the workflow of the OnCATs algorithm can be consulted on [Figure 1]. The first stage of the On CATS workflow is to verify to which risk group a specific patient belongs to, using the given tumor stage, GS and PSA level [6,7,25,8,11,12,14-16,18,23].

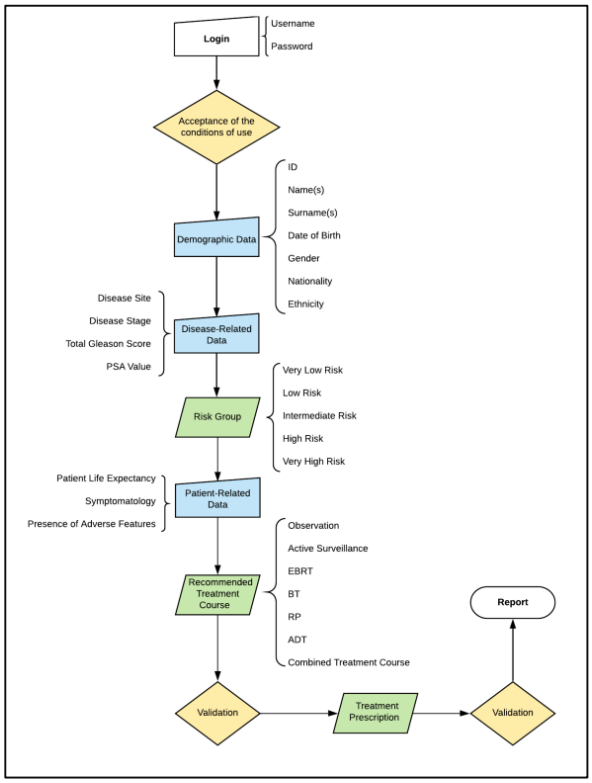

Figure 1: Representation of the OnCAT's clinical workflow.

The second stage of the workflow is to assess all the available treatment options. By evaluating the patient's estimated life expectancy, presence of symptoms and presence of adverse tumor features, the system will recommend at least one of the following treatment courses:

1. Radical Observation.
2. Radical AS.
3. Radical ADT.
4. Radical BT.
5. Radical EBRT.
6. EBRT with ADT.
7. EBRT with adjuvant BT.
8. EBRT with adjuvant BT and ADT.
9. Radical Prostatectomy.
10. RP with adjuvant EBRT.
11. RP with adjuvant EBRT and ADT.
12. RP with adjuvant Observation.
13. RP with PLND and ADT.
14. RP with PLND and adjuvant Observation.
15. RP with PLND and adjuvant EBRT and ADT.

In third stage of the workflow, the system assists the prescription of each individual modality that is part of the chosen treatment course. Each different treatment modality has different prescription criteria, due to their different natures and goals.

System Testing

In order to evaluate if the OnCATs workflow could successfully simulate the clinical workflow for prostate cancer treatments, clinical cases of real patients were necessary. To obtain these cases, we recurred to the Journal of Medical Case Reports and PubMed websites, where a web search was conducted using the keywords "prostate" and "cancer" [30,31]. Using the advanced search function, we searched for articles that contained the words "prostate" and "cancer" in its title. Filters were applied in order to display only case reports, articles with full text available for free, published in last 5 years, and written in English. After revising all the publications, a total of 10 clinical cases were obtained.

The method of Kim et al. was applied to estimate the patients' life expectancy [32]. Regarding the quartile of health, we considered patients who had co morbidities, such as diabetes mellitus or hypertension, to not be healthy, and therefore were placed on the bottom quartile of health (bottom 25%). Patients, who did not suffer from other co morbidities, were considered to be very healthy, belonging on the top quartile of health (top 25%). For the cases in

which there was no mention of the presence of co morbidities, we assumed that they were overall healthy and therefore were placed on the middle quartile of health (between 25% - 75%) [32].

As for the presence of symptoms, for the clinical cases where there was no indication if the patient was symptomatic or not, we assumed the patients on lower stages were asymptomatic, while patients on higher stages were symptomatic [33].

As for defining the presence of adverse features, clinical cases where there was no mention if adverse features were present, we assumed the absence of any of these features.

On [Figure 2] is represented an example of a report generated by OnCATs. After analyzing and compiling the information regarding the reports, a pass/fail analysis was performed, where it was assumed that the system "passed" the analysis when it suggested the same approach that was applied to the patient, and it was assumed the system "failed" when different approaches were suggested.

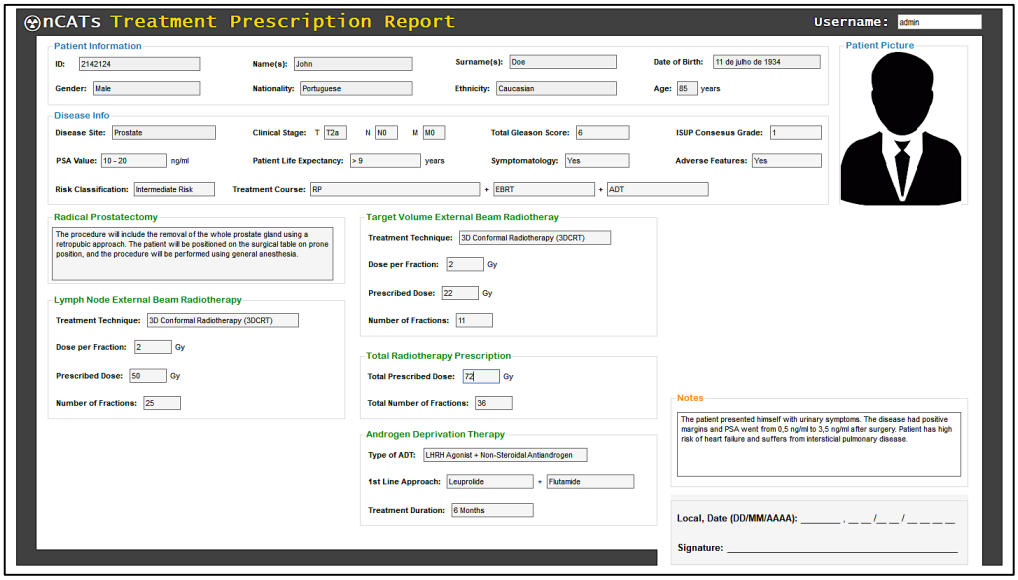

Figure 2: Example of a final report generated by on CATs for a patient who underwent RP with adjuvant EBRT and ADT.

	CC01	CC02	CC03	CC04	CC05	CC06	CC07	CC08	CC09	CC10
Authors	Tisman et al.	Nishimura et al.	Hiyama et al.	Chang et al.	Coyle et al.	Tisman et al.	Brahm bhatt et al.	Shen et al.	Castro-Alonso et al.	Yamashita et al.
Year of Publication	2009	2014	2011	2016	2015	2011	2008	2019	2019	2017
Age (Years)	75	68	59	70	64	71	71	77	65	77
GS	5	7	7	9	9	7	8	9	8	6
Lead Time (Years)	10	0	0	0	0	0	0	10	0	10
Quartile of Health	**Healthy**	**Not Healthy**	**Not Healthy**	**Not Healthy**	**Very Healthy**	**Very Healthy**	**Not Healthy**	**Healthy**	**Not Healthy**	**Healthy**
Risk of Mortality by Cancer (%)	1.2	6.5	6.5	12.1	12.1	6.5	12.1	12.1	12.1	3
Life Expectancy (Years)	10.1	4.4	5.2	2.8	9.4	11.7	2.8	8.5	3.1	8.9
Life Expectancy Category (Years)	> 9	< 6	< 6	< 6	> 9	> 9	< 6	6 – 9	< 6	6 - 9

Table 1: Summary of the characteristics of the clinical cases obtained for testing the OnCATs' algorithm.

RESULTS

A summary of the demographics and disease related characteristics of the clinical cases used for testing the on CATs system can be consulted on (Table 1).

The sample of patients has a mean age of 69,7 ± 59 years (59 years - 77 years) [32,34–42].

Variable Assessment

As for the presence of symptoms, 7 out of 10 (70 %) reports did not mention if the patient manifested symptoms at the time of assessment. For CC02, CC04, CC05, CC08 and CC09, we assumed those patients were symptomatic. Opposed to that, for CC06 and CC10, we assumed those patients were asymptomatic.

As for the presence of adverse features, 4 out of 10 (40 %) of the case reports did not mention if adverse features were present or not. For CC02, CC05, CC09 and CC10, we assumed those patients did not exhibit any adverse features.

The mean estimated life expectancy for this sample of patients was 6.7 years ± 3.4 years (2.8 years – 11.7 years). Following those results, 5 out of 10 patients (50%) were placed on the category of life expectancy bellow 6 years, 2 patients (20%) were placed on the category of life expectancy between 6 and 9 years and 3 patients (30%) were placed on the category of life expectancy above 9 years.

Regarding the quartile of health, 5 patients (50%) were considered to be on the bottom quartile of health (not healthy) due from suffering from co morbidities, such as myocardial infarction, diabetes mellitus type 2 or hypertension. 3 patients (30%) were considered to be in the middle quartile of health (healthy), and the 2 other patients (20%) were considered to be in top quartile of health (very healthy) due to being described as not suffering from any co morbidities.

Risk Group Assessment

Regarding the risk group assessment, OnCATs was able to successfully characterize each patient into a risk group using the NCCN nomenclature. The results of the risk group stratification for each clinical case is demonstrated on (Table 2) [11,32,42,34-41].

ID	Tumor Stage	GS	PSA Value (ng/ml)	PSA Category (ng/ml)	Risk Group
CC01	T1c N0 M0	5	4	< 10	Very Low
CC02	T2b N0 M0	7	62.1	> 20	High
CC03	T2b N0 M0	7	9.5	< 10	Intermediate
CC04	T2b N0 M0	9	1.8	< 10	High
CC05	T4 N0 M0	9	< 10	< 10	Very High
CC06	T1c N0 M0	7	8	< 10	Intermediate
CC07	T4 N0 M0	8	5874	> 20	Very High
CC08	T4 N0 M0	9	52.736	> 20	Very High
CC09	T4 N0 M0	8	32	> 20	Very High
CC10	T1c N0 M0	6	10.35	20-Oct	Intermediate

Table 2: Results of the risk group assessment for the clinical cases used for testing OnCATs, using the NCCN nomenclature.

According to the system's algorithm, 1 patient (10%) was characterized as having a very low risk disease, 3 patients (30%) were characterized as having intermediate risk diseases, 2 patients (20%) were characterized as having high risk diseases and 4 patients (40%) were characterized as having very high-risk diseases.

Treatment Course Assessment

Regarding the OnCATs performance on assessing the available treatment courses for all clinical cases, the detailed results can be consulted on (Table 3) [11,26,34-42].

ID	Risk Group	Life Expectancy Category (Years)	Symptomatology	Presence of Adverse Features	Applied Treatment Course	Treatment Courses Suggested by OnCATs	Pass/Fail
CC01	Very Low	> 9	Asymptomatic	Present	Observation	AS EBRT RP + Observation RP + EBRT RP + EBRT + ADT	Fail
CC02	High	<6	Symptomatic	Not Present	ADT + EBRT	EBRT + ADT EBRT + BT + ADT RP + PLND	Pass
CC03	Intermediate	<6	Symptomatic	Present	RP + EBRT + ADT	Observation BT EBRT + ADT EBRT + BT + ADT	Fail
CC04	High	< 6	Symptomatic	Present	ADT + EBRT	EBRT + ADT EBRT + BT + ADT RP + PLND + ADT RP + PLND + EBRT + ADT RP + PLND + Observation	Pass
CC05	Very High	> 9	Symptomatic	Not Present	ADT	EBRT + ADT EBRT + BT + ADT RP + PLND	Fail
CC06	Intermediate	> 9	Asymptomatic	Present	ADT	AS BT EBRT + ADT EBRT + BT EBRT + BT + ADT RP + Observation RP + PLND + Observation RP + PLND + EBRT + ADT	Fail
CC07	Very High	< 6	Symptomatic	Present	ADT	EBRT + ADT EBRT + BT + ADT RP + PLND + ADT RP + PLND + EBRT + ADT RP + PLND + Observation	Fail
CC08	Very High	6 – 9	Symptomatic	Present	RP + PLND + EBRT + ADT	EBRT + ADT EBRT + BT + ADT RP + PLND + ADT RP + PLND + EBRT + ADT RP + PLND + Observation	Pass
CC09	Very High	< 6	Symptomatic	Not Present	EBRT + ADT	EBRT + ADT EBRT + BT + ADT RP + PLND	Pass
CC10	Intermediate	6 – 9	Asymptomatic	Not Present	EBRT + BT	Observation EBRT BT	Fail

Table 3: Results of the treatment course assessment for the clinical cases used for testing the OnCATs algorithm.

As for the applied treatment course, 3 out of 10 patients (30%) were submitted to radical ADT, 2 patients (20%) were submitted to EBRT with neoadjuvant ADT, 1 patient (10%) was submitted to radical observation, 1 patient (10%) was submitted with RP with PLND and adjuvant EBRT with ADT, 1 patient (10%) was submitted to EBRT with adjuvant ADT and 1 patient (10%) was submitted to EBRT with adjuvant BT.

By analyzing each applied treatment course as individual modalities, it is possible to observe that that 8 out of 10 patients (80%) were submitted to ADT, 6 patients (60%) were submitted to EBRT, 2 patients (20%) were submitted

to RP, 1 patient (10%) was submitted to Observation, 1 patient (10%) was submitted to PLND and 1 patient (10%) was submitted to BT.

After analyzing the treatment course assessment using the on CATs algorithm, it was observed that the system passed in 4 out of 10 clinical cases (40%) and failed in 6 out of 10 clinical cases (60%).

The mean number of options that on CATs suggested for all cases was 4.4 ± 1.6. For the cases in which on CATs passed the analysis, the mean number of options suggested was 4 ± 1.2. For the cases where on CATs failed the analysis, the mean number of options suggested was 4.7 ± 1.9 (Table 4).

EBRT Prescription																
ID		**Treatment Technique**				**Fractionation**			**Dose per Fraction** (Gy)		**Prescribed Dose** (Gy)					
CC02	**Report**	IMRT				Conventional Fractionation			2		74					
	On CATs Suggestions	3DCRT	IMRT	VMAT	SBRT	Conventional Fractionation	Moderate Hypo fractionation	Extreme Hypo fractionation	1.8	2	72	74	76	78	80	
CC03	**Pass/Fail**	Pass				Pass			Pass		Pass					
	Report	Not Mentioned				Conventional Fractionation			2		50					
	On CATs Suggestions	3DCRT	IMRT	VMAT		Conventional Fractionation			1.8	2	64	66	68	70	72	
	Pass/Fail	Not Assessable				Pass			Pass		Fail					
CC04	**Report**	3DCRT				Conventional Fractionation			2		76					
	On CATs Suggestions	3DCRT	IMRT	VMAT	SBRT	Conventional Fractionation	Moderate Hypo fractionation	Extreme Hypo fractionation	1.8	2	72	74	76	78	80	
	Pass/Fail	Pass				Pass			Pass		Pass					
CC08	**Report**	Not Mentioned				Conventional Fractionation			2		74					
	On CATs Suggestions	3DCRT	IMRT	VMAT		Conventional Fractionation			1.8	2	64	66	68	70	72	
	Pass/Fail	Not assessable				Pass			Pass		Fail					
CC10	**Report**	Not mentioned				Conventional Fractionation			2		50					
	On CATs Suggestions	3DCRT	IMRT	VMAT	SBRT	Conventional Fractionation			1.8	2	46	48	50			
	Pass/Fail	Not assessable				Pass			Pass		Pass					

Table 4: Results of the performance of On CATs algorithm for the prescription of EBRT.

Treatment Prescription

The results of the test of performance for OnCATs prescription of EBRT can be consulted on (Table 4) [35-37,40,42]. As for ADT, the results for the test of performance for on CATs can be consulted on (Table 5) [36-41,43].

ID		**Type of ADT**				**1st Line Approach**									**Treatment Duration**			
CC02	**Report**	Not mentioned				Not mentioned									Not Mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non- Steroidal Antiandrogen	LHRH Antagonist	Bilateral Orchidectomy	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide	Degarelix	1.5 Years	2 Years	2.5 Years	3 Years
	Pass/Fail	Not Assessable				Not Assessable									Not Assessable			
CC03	**Report**	LHRH Agonist + Non-Steroidal Antiandrogen				Leuprolide		Flutamide				Bicalutamide			3.5 Years			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non- Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide			On CATs was not able make a suggestion			
	Pass/Fail	Pass				Pass									Fail			
CC04	**Report**	LHRH Agonist				Leuprolide									9 Months			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non- Steroidal Antiandrogen	LHRH Antagonist	Goserelin		Histrelin			Leuprolide		Triptorelin		1.5 Years	2 Years	2.5 Years	3 Years
	Pass/Fail	Pass				Pass									Fail			
CC05	**Report**	LHRH Agonist				Goserelin									Not Mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non- Steroidal Antiandrogen	LHRH Antagonist	Goserelin		Histrelin			Leuprolide		Triptorelin		1.5 Years	2 Years	2.5 Years	3 Years
	Pass/Fail	Pass				Pass									Not Assessable			
CC06	**Report**	LHRH Agonist + Non-Steroidal Antiandrogen				Leuprolide				Flutamide					Not Mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non- Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide	6 Months		6 Months			
	Pass/Fail	Pass				Pass									Not Assessable			
CC07	**Report**	LHRH Agonist + Non-Steroidal Antiandrogen				Leuprolide					Bicalutamide				Not Mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non- Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide	Triptorelin		Nilutamide	Flutamide	Bicalutamide	1.5 Years	1.5 Years	2 Years	2.5 Years	3 Years
	Pass/Fail	Pass				Pass									Not Assessable			
CC08	**Report**	LHRH Agonist + Non-Steroidal Antiandrogen				Goserelin			Leuprolide			Bicalutamide			Not Mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non- Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide	6 Months		6 Months			
	Pass/Fail	Pass				Pass									Not Assessable			
CC09	**Report**	LHRH Antagonist				Degarelix									Not Mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non- Steroidal Antiandrogen	LHRH Antagonist	Degarelix									1.5 Years	2 Years	2.5 Years	3 Years
	Pass/Fail	Pass				Pass									Not Assessable			

Table 5: Results of the performance of OnCATs algorithm for the prescription of ADT.

For CC01, since the case report did not mention the Observation protocol that was as applied for the treatment of the patient, the comparison with the default protocol suggested by OnCATs was not possible, so further results regarding the treatment prescription for this clinical case were not possible to obtain.

Prescription of External Beam Radiotherapy

In general, on CATs passed 15 out of the 20 tasks (75%) that consisted the workflow of CC02, CC03, CC04, CC08 and CC10 OnCATs. In 2 of the tasks (10%), the system failed and in 3 tasks (15%) a comparison was not possible due to that information not being disclosed on the case report.

More specifically, regarding the treatment technique, fractionation and dose per fraction, OnCATs was able to suggest the applied choice in all the clinical cases simulations. Regarding the dose prescription, OnCATs had a 60% passing rate, meaning that 3 cases out of 10 cases had a successful dose prescription and 2 cases (40%) had a failed dose prescription.

By analyzing each case individually, on 60% of the cases (CC02, CC04 and CC10), On CATs was able to recreate all the phases of the clinical workflow that those patients were submitted to. On the other 40% (CC03 and C008), OnCATs did not only suggest the applied prescription dose, but succeeded on the other phases of the workflow.

Prescription of Androgen Deprivation Therapy

OnCATs managed to pass on 14 out of the 21 tasks (66.67%) that consisted the workflow of CC03, CC04, CC05, CC06, CC07, CC08 and CC09. In 2 of the tasks (9.52%), the system failed and in 5 tasks (23.91%) a comparison was not possible due to that specific information not being disclosed on the case report.

More specifically, regarding the type of ADT and first line approach, On CATs was able to successfully suggest the option applied to the clinical case in all cases. However, on the prescription of the treatment duration, in CC03 and C004, where we had indication of the total treatment duration, On CATs was not able to recommend the right treatment duration in either of them.

Prescription of Brachytherapy

On our sample of clinical cases, only a single case (CC10) underwent a BT treatment. Lastly, the results of the on CATs analysis for the BT treatment of CC10 can be consulted on (Table 6) [42].

BT Prescription							
CC10		**Type of BT**		**Radioactive Isotope**	**Prescribed Dose and Number of Fractions**		
	Case Report	HDR		Iridium-192	18 Gy in 2 Fractions		
	On CATs	LDR	HDR	Iridium-192	12 Gy in 1 Fraction	15 Gy in 1 Fraction	21.5 Gy in 2 Fractions
	Pass/Fail	Pass		Pass	Fail		

Table 6: Results of the performance of on CATs algorithm for the prescription of BT.

	Number of Successful Tasks	**Number of Failed Tasks**	**Total**	**Passing Rate** (%)
CC01	1	1	2	50
CC02	6	0	6	100
CC03	5	3	8	62.5
CC04	8	1	9	88.9
CC05	3	1	4	75
CC06	3	1	4	75
CC07	3	1	4	75
CC08	6	1	7	85.7
CC09	4	0	4	100
CC10	6	2	8	75
Total	45	11	56	80.4

Table 7: **Number of successful and failed tasks by the OnCATs system, by clinical case.**

For the adjuvant BT prescription of CC10, it is possible to observe that on CATs was able to pass on the definition of the type of BT and radioactive isotope, but failed on the dose prescription and number of fractions.

General Analysis

Table 7 are summarized the number of successful and failed tasks, by clinical case, performed by OnCATs during the testing of the algorithm [32,34-42].

By analyzing the show results, it is possible to observe that each clinical case had a mean passing rate of 78.7% ± 15.6%. The clinical cases where the OnCATs algorithm performed better where CC02 and CC09 (100%), followed by CC04 (88.9%), CC08 (85.7%), CC05, CC06, CC07 and CC10 (75%), CC03 (62.5%) and CC01 (50%).

DISCUSSION

To the extent of our knowledge, OnCATs is the only developed system that is applied to assisting decision making in all phases of prostate cancer treatment, including risk group assessment, treatment course assessment and treatment prescription, based on relevant and up to date clinical guidelines.

Watson for Oncology (WFO) is a DSS developed by IBM, in cooperation with the Memorial Sloan Kettering Cancer Center, whose knowledge base consists on literature, protocols and patient charts consulted on the web [44]. WFO suggest treatment options for a specific patient based on those sources, and also references the evidence that support said claims [44]. WFO was found to be the developed clinical DSS most similar to on CATs.

Yu et al. conducted a retrospective study where the treatment options suggested by WFO for 201 prostate cancer patients were compared with their actual course of treatment. The authors found that the concordance rate was 73,6 %, demonstrating a high similarity between the suggestions made by the system and the treatment courses applied to the patients on the urology department of the Chonnam National University Medical School. The authors concluded that clinical DSSs can actively assist physicians on decision making, especially when expert resources are lacking [44].

Regarding the few cases where on CATs output did not match the same option that was part of the patient's course of action, it was analyzed in detail every case report in order to investigate which reasons might have led to that occurrence.

For CC01, since Observation is reserved for older patients with one or more co morbidities that will compete with the cancer for mortality cause, the system did not suggest that option, given the estimated life expectancy for patient was 10,1 years [7,11,12,32,45]. Despite having no indication that this patient was not healthy, if we assumed that this patient belonged to the bottom quartile of health (not healthy), the estimated life expectancy would be 4.7 years [32]. As for the presence of symptoms at the time of diagnosis, on the case report it was only stated that the patient had no urological complaints, which usually are the first symptoms to be manifested on a prostate cancer patient. If we assumed that this patient had an estimated life expectancy inferior to 6 years and was symptomatic, on CATs would be able to suggest Observation as a viable treatment approach. Based on these facts, the mismatch of results could be due to the fact of the estimation of the patient's life expectancy and symptomology not being accurate, given the missing information from the case report.

Regarding CC03, on CATs was not able to suggest RP with adjuvant EBRT and ADT as a viable chosen treatment course. This is due to RP being more indicated to patients with an estimated life expectancy superior to 9 years, and adjuvant EBRT with ADT being reserved to patients who display adverse features [11,12,24]. On the case report is mentioned that the patient has high risk of heart failure and interstitial pulmonary disease, because of that, it was fair to assume that the patient was on the bottom quartile of health

(not healthy) [36]. If it was instead assumed that the patient was on the middle quartile of health (overall healthy), the estimated life expectancy would be 16.4 years [32]. By assuming the patient had an estimated life expectancy superior to 9 years, was symptomatic and had adverse features, RP with adjuvant EBRT and ADT would have been suggested by on CATs. Once again, the mismatch of results could be related with the estimation of the patient's life expectancy. As for the EBRT prescription, 50 Gy is not commonly prescribed for the irradiation of the prostate bed, but is common on initial treatment phases in which the pelvic lymph nodes are irradiated [7]. On this case, it was possible to assume, since a PLND was not performed, that EBRT was applied as an adjuvant therapy, to irradiate the whole pelvis, which includes both the pelvic lymph nodes and the prostate bed, without applying a boost to the prostate bed.

For CC04, regarding the ADT prescription, on CATs was not able to suggest treatment duration of 9 months. Based on the guidelines, for high risk patients, the ADT treatment should be prescribed for at least 1.5 years and up to 3 years [7,11,18]. On the case report, is stated that the patient was submitted to ADT with leuprolide for 9 months, another ADT drug or approach could have been prescribed after that, without being disclosed on the case report [37].

As for CC05, CC06 and CC07, the system could not recommend radical ADT as a viable treatment option, since, by the guidelines, radical ADT is only indicated for high and very high patients with life expectancy inferior to 6 years and asymptomatic [11,39,46].

On the reports of CC06 and CC07, there was no indication if the patients had any co morbidities or symptoms. If we were to assume that both patients belonged on the last quartile of health (not healthy), despite having no indication to support that statement, the estimated life expectancy would instead be 3.1 years and 3.9 years respectively [32]. Following that, by assuming both patients had an estimated life expectancy inferior to 6 years, and both diseases were asymptomatic, which would be unusual giving the tumor stage, On CATs would have been able to correctly suggest radical ADT as a treatment approach.

For CC08, On CATs did not suggest the prescribed dose for adjuvant EBRT. Based on the NCCN® Guidelines for Prostate Cancer, the prescribed dose for adjuvant EBRT after RP should be between 64 and 72 Gy, delivered in conventional fractionation [11]. For this clinical case, the prescribed dose was 74 Gy, which means that comparing to the guidelines, an additional fraction of 2 Gy was delivered [40]. The reasons behind the dose prescription were not discussed on the case report, so it is not possible to assess if this had any relevant clinical advantage.

Lastly, regarding CC10, OnCATs was not able to suggest EBRT with adjuvant BT as a viable treatment option, since this therapy is reserved for intermediate risk patients with life expectancy superior to 9 years and with adverse feature [8,18,11,24]. Since there was no mention if the patient had any co morbidities or adverse features, it was assumed that the patient was in the middle quartile of health (overall healthy) and had no adverse features. If instead it was assumed that the patient was on the top quartile of health (very healthy), the estimated life expectancy would have been 11.4 years [32]. Assuming the patient had an estimated life expectancy superior to 9 years and had adverse features; OnCATs would be able to suggest EBRT with adjuvant BT as a valid option for treatment course [11].

Following these results, it was apparent that the estimation of the life expectancy was the biggest contributor to the accuracy of OnCATs. In 2014, Kent et al. published a study were 14 publications related to models for estimating a prostate cancer patient life expectancy were reviewed [47]. Of the 14 studies, only 3 studies used life tables to predict the life expectancy. The authors found that most approaches

did not take into account if the patient had any relevant co morbidities. The simple act of defining to which quartile of health a given patient belongs to, leads to a biased result, since it is only based on a simple subjective analysis. On this study, the method of Kim et al. for calculating the estimate life expectancy for prostate cancer patients was also reviewed. Regarding this method, the authors found its results to be implausible, since they found no reliable connection between the output risk of death by prostate cancer and the patient's age, which is not in concordance with clinical experience. In general, the authors found that even though clinical guidelines include the estimated life expectancy of a patient as a key factor for assessment of the optimal treatment course, no appropriate tool exists to accurately estimate this value, and this may constitute a setback for the development of clinical DSS tools [47].

CONCLUSIONS

In general, it was observed that the OnCATs algorithm can recreate the clinical workflow described on guidelines for treatment of localized prostate cancers patients, including valuable steps such as risk group assessment, treatment assessment and treatment prescription.

As for treatment course assessment, we found that the estimation of the patient's life expectancy can highly impact the output generated by the system. The method developed by Kim et al. showed to not always provide a reliable result to this system's workflow, as it forces the estimation of subjective parameters such as the definition of the quartile of health in which the patient belongs to [32]. Since any optimal methods for estimating to automatically estimate the life expectancy of a prostate cancer patient were not found, new methods should be investigated and researched in the future.

Besides that, OnCATs also gives its output on a universal well-known medical language, easy to comprehend by all healthcare professionals, which allows the generated outputs to be shared between professionals in an efficient way and to be easily used on future clinical research.

This study allowed the comprehension of the workflow to which a cancer patient is put through when diagnosed with a tumor. Besides prostate cancer being chosen as the starting point for the development of the system, due to providing a solid learning curve, we believe that the method applied to develop this algorithm can be exploited in order to expand the system's applicability, showing great promise on its future applications.

Despite the positive results, the testing of OnCATs system could be optimized if more clinical case reports containing key information for the system's testing were available. Most of the reviewed clinical case reports did not mention crucial information that would allow the comparison of the workflow in all stages of prostate cancer treatments, such as the presence of symptoms during the time of diagnosis and the duration of the applied treatment protocol. As for the prescription of treatments, it was noticed that OnCATs was found to perform slightly better on the prescription of EBRT treatments, in comparison to ADT treatments. This can be due to the fact that EBRT treatments are usually better reported on clinical case reports in comparison to ADT treatments.

Regardless of the results obtained by applying clinical cases to the systems, it is important to mention that majority of prostate cancer patients have multiple treatment options and different prescriptions. This translates to different physicians being able to choose different courses of action for the same patient, while applying different prescriptions, based on their experience and judgment, without compromising the patient's outcomes and quality of life.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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