PROPHECY: Patient Reported Outcomes in Prostate Cancer, a Mobile-Health Experience in Radiotherapy

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Abstract—**The growing relevance of Patient Reported Outcomes (PROs), the increasing importance of mHeatlh and the objective discrepancy documented between Patient Reported Outcomes and Observer Reported Outcomes are important aspects that need to be addressed when dealing with prostate cancer patients. The aim of this work was to develop an electronic Patient Reported Outcomes tool to systematically assess the impact of radiation therapy on prostate cancer patients' quality of life. We elaborated a four-step process. In the first step, a general literature search was made. The next step was to generate a set of adequate questions and answers. The subsequent step was to identify a reliable scale to report adverse events, namely, the Common Terminology Criteria for Adverse Events version 4.03 scale of toxicity. The last phase was to implement a user-friendly interface. We developed a new and innovative comprehensive list of items for prostate cancer patients receiving radiotherapy whose main characteristic is to link the Patient Reported Outcomes obtained from patients to a well-established scale of toxicity. The conclusive validation of this conceptually innovative tool should allow to provide both patients and physicians with a useful tool to reduce, and possibly prevent, adverse events during and after radiotherapy, with a consequence of improvement in terms of Quality of Life.**

Keywords—Mobile-health; Quality of life; Patient reported outcomes; Prostate cancer.

I. INTRODUCTION

Prostate cancer is the most common cancer in men and the recent developments in therapeutic approaches have allowed to obtain very long overall survival rates [1]. A key aspect that needs to be addressed when dealing with such patients is the Quality of Life (QoL) [2]. There are several reasons which, in our view, should be taken into account when considering to develop a QoL questionnaire for prostate cancer patients undergoing radiotherapy to be used specifically through mobile devices:

1) The growing awareness in the scientific community about the relevance of Patient Reported Outcomes (PROs) [3][4].

2) The increasing importance mHeatlh is rapidly gaining [5][6].

3) The objective discrepancy documented in scientific literature between PROs and Observer Reported Outcomes (OROs) [7][8].

On these premises, we decided to develop a specific Health Related Quality of Life (HRQoL) prostate cancer questionnaire which might be included in a much wider electronic application developed in-house called VALEO+ (VAluation Endorsed by Oncology Patient) with the intent to help all cancer patients undergoing radiotherapy treatment by providing useful tools such as scheduling of appointments, suggestions to improve lifestyle and a specific questionnaire developed to assess toxicity.

The rest of the paper is structured as follows. In Section II, we present the materials and methods used. Section III presents the state of the art. In Section IV, we present the results and we discuss them in Section V. We conclude the work in Section VI.

II. MATERIALS AND METHODS

First of all, we identified two main sources from literature. The first is the guidelines issued by the EORTC for developing Questionnaire Modules. The approach proposed is, in this case, a "modular" one [9]: in particular, the development of modules is specific to tumor site, treatment modality, or a QoL dimension. The second major reference for the questionnaire development was the Food and Drug Administration [10]; for the FDA a PRO instrument needs to capture PRO data used to measure treatment benefit or risk in medical product clinical trials.

The conceptual framework is a straightforward expression of the extracted concepts by the questionnaire and can be represented like a diagram with clear relationships between items, the domain, and concepts (the specific measurement goal) measured. Keeping in mind the framework presented in these guidelines, we proceeded with a four-step process to generate the questionnaire.

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In the first phase, in which the relevant QoL issues should be generated, an in-depth literature search was performed [11]-[13]. Since prostate cancer has been widely studied over the years and there is a great amount of literature that extensively covers the issues related to quality of life, we decided to identify the most relevant questionnaires reported in the published reviews. After identifying the most widely reported questionnaires, we started a series of dedicated debates, performed within the urological group of our department, to choose the most relevant items to include in our questionnaire.

In the second phase the list of QoL items was converted into questions in Italian language, keeping in mind the great importance of the major methodological considerations according the guidelines mentioned above in terms of item construction: questions in fact need to be clear, brief and unambiguous.

The third step implied identifying a reliable scale to report adverse events and an accurate literature research was performed to choose a simple and validated system to correlate with the set of items and relative questions generated.

In the last step, a user-friendly interface for patients was realized with the help of graphic experts; this phase was also crucial since this represents a key aspect which differentiates a paper-based from an electronic approach and is a major challenge when dealing with mobile-health PRO [14].

III. STATE OF THE ART

Table I summarizes the results of the relative items from the seven questionnaires included in the analysis [15]-[21].

As shown in Table II, the number of possible choices for patients significantly changes across the different questionnaires already existing and, in some cases, even within the same questionnaire.

IV. RESULTS

After choosing the questionnaires included in the reviews, we created a collection of all the questions presented in the different questionnaires, grouping them according to the relative item of interest.

After identifying the list of the items and of the domains, the list was discussed by prostate experts at our institution and the result was the identification of 3 main domains including urinary symptoms, bowel symptoms and sexual function/hormonal therapy related problems for a total of 14 items, as shown in Figure 1, The first domain (urinary) includes hematuria, urinary incontinence, urinary tract pain and urinary frequency. The second domain (bowel symptoms) includes abdominal pain, diarrhea, rectal hemorrhage and proctitis. The last domain (sexual function and hormonal therapy) includes sexual desire reduction, hot flashes, breast pain, memory or concentration problems, erection problems and ejaculatory problems.

Questions and answers have been formulated while trying to keep the number of words as low as possible, considering the means of delivery that is a smartphone or a tablet.

All questions were subsequently revised by psycho-oncologists with great expertise in cancer patients questionnaires; in this phase, several changes were made in order to make the question not only clear for patients, but also to reduce any possible problem related to the question itself.

TABLE I. NUMBER OF ITEMS IDENTIFIED IN DIFFERENT QUESTIONNAIRES IN LITERATURE.

	U.F.	***U.D.***	***U.I.***	***U.B.***	***I.F.***	***I.D.***
EORTC QLQ - PR25	5	1	2	0	0	0
UCLA - PCI	1	0	3	0	0	1
EPIC	2	2	4	2	3	2
FACT-P	1	1	0	0	0	0
PORPUS	1	0	1	0	1	1
PC-QoL	0	0	5	0	1	1
PCSI - SDS	4	4	4	0	2	2
	A.P.	***I.B.***	***H.F.***	***B.P.***	***Er.P.***	***Ej.P.***
EORTC QLQ - PR25	1	1	1	1	1	1
UCLA - PCI	2	0	0	0	3	0
EPIC	4	2	2	2	5	0
FACT-P	1	0	0	0	1	0
PORPUS	0	0	0	0	1	0
PC-QoL	3	1	0	0	2	0
PCSI - SDS	5	1	0	0	4	1

U.F.=Urinary frequency; U.D.=Urinary tract pain; U.I.= Urinary Incontinence; U.B.= Hematuria; I.F.= Diarrhea; I.D.= Proctitis, A.P.= Abdominal pain; I.B.= Rectal Hemorrhage; H.F.=Hot flashes; B.P.=Breast pain; Er.P.=Erection problems; Ej.P.=Ejaculatory problems

These differences might generate at least two kinds of problems in our view.

The first problem is in patients' perspective because, when they answer questions, patients face diversity, in the range of possible choices, which could, in theory, be a confounding factor in attributing the choice of symptom severity.

The second problem is the physicians' perspective because it is difficult to compare the results from the different questionnaires.

A possible solution to both problems could be found in the third phase of our process since we chose to use the

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severity scale found in the CTCAE V 4.03, which is a scale going from 1 to 5 from the less severe to the more severe symptoms due to either frequency or entity increase according to the different definitions [22].

TABLE II. DIFFERENT NUMBER OF RESPONSES IDENTIFIED IN QUESTIONNAIRES IN LITERATURE.

EORTC - PR25	1→4 1=no symptom→4=worst
UCLA - PCI	0→6 with a range of 3 to 6 answers and no fixed correlation between severity and number
EPIC	0→5 with a range of 3 to 5 answers and correlation between severity and increasing number
FACT-P	0→4 with correlation between severity and increasing number
PORPUS	No definite number of answers
PC-QoL	1→7 with a range of 3 to 7 answers and correlation between severity and increasing number
PCSI - SDS	1→5 1=no symptom→5=worst

Knowing the severity of the symptoms also includes potentially life-threatening conditions (grade 4) and death (grade 5); the absence of the symptom is not included in the scale, so there is no zero.

We decided to exclude the two higher grades that is to say grade 4 and 5, since they are not compatible with a patient reported symptom and, therefore, we chose a 4 way possible answers with one answer including the absence of the symptom and a growing severity (in frequency or entity, according to the CTCAE definition) for the remaining three answers.

The fact that symptoms were initially derived from the CTCAE, which is not a PRO tool, poses a problem for grade 1 asymptomatic situation such as, for example, for hematuria or rectal bleeding. In these two cases, in order to confirm the real absence of the symptom, we propose to add a urine and stool test.

After choosing the questions and the relative answers, we went on with the fourth phase to generate the graphical interface. We relied on the support from personnel experienced in graphical design and tool creation for cancer patients. The entire graphical interface has been completed and is already fully available, as it can be seen in Figure 2.

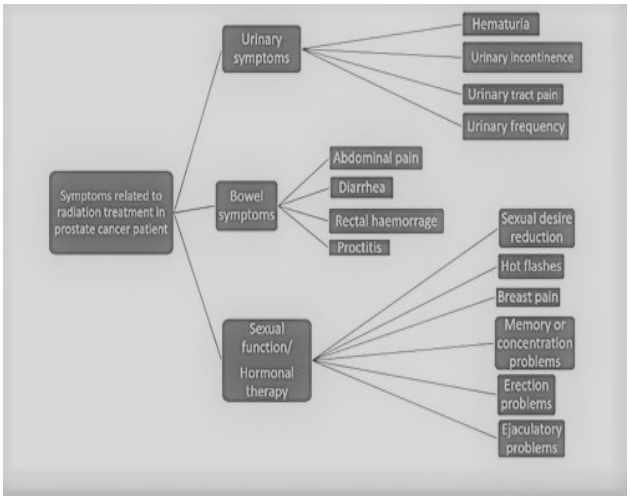

Figure 1. Symptoms domains [27].

Figure 2. VALEO+ graphical interface.

V. DISCUSSION

Assessing PROs has turned out to be a central part of healthcare by measuring the impact of both disease and medical intervention on patients. The first attempts to develop wireless mobile health-related quality of life assessment started more than a decade ago [23]. Few authors have reported about the evaluation of the reliability, usability, and acceptability of point- of-care electronic PRO

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assessments implemented in prostate cancer clinics [24]-[27] and the available result is that mean scores and standard deviations are similar between the paper-pencil and electronic forms across instrument domains with no assessment bias [28]-[31].

In our work, we followed an item pooling procedure, which was mainly based on previous questionnaires; searching in literature, we found that an item pooling procedure for extracting items based mainly from pre-existing questionnaires is an option that has already been described [32][33]. The advantages of this choice are important because it is possible to obtain a correspondence between the patient reported symptoms and the chance to implement a toxicity record.

The choice of the CTCAE has been used by other groups actively involved in the development of quality of life tools for cancer patients [34]; such choice is a key factor which distinguishes our proposed questionnaire from the existing ones in literature because the CTCAE links the indication of a medical intervention to the severity of the symptom. In this way, it is also possible to generate electronic alerts for the patients who report experiencing certain grades of severity. The chance to generate such alerts has at least two other advantages. The first one is that the alert suggesting to contact a doctor allows the doctor himself to confirm (or not) the severity of the symptom reported (thus implicitly validating the correspondence between the patient reported outcome and the CTCAE). The other important aspect is relative to prevention of severe symptoms: in fact, in case of repeatedly reported low severity symptoms, which by definition require no medical intervention, the system may generate an alert signal to contact the doctor as well so that an in depth analysis can be made of the result to prevent further deterioration of the symptom.

Moreover, CTCAE does not distinguish acute from late side effects, but it is focused on the symptoms themselves so that the same question can actually be used both in the treatment setting and, subsequently, in the follow-up of the patients.

The importance of our choice of integrating a modified version of the CTCAE scoring system in a mobile-health system is, in our view, further strengthened by the very recent release of a PRO- CTCAE item library [35][36].

VI. CONCLUSION

A specific questionnaire for prostate cancer patients undergoing radiotherapy was developed to realize an electronic PRO. A combined approach was used, both traditional and innovative, in order to obtain a HRQOL tool that may help patients, caregivers and physicians to improve the quality of the treatment by focusing on the patient's active role. The subsequent phase will require the testing of the developed questionnaire by patients, in order to fully validate it.

ACKNOWLEDGMENT

The abstract of this paper was presented at the 29th Annual Meeting of the Italian Society of Uro- Oncology (SIUrO) as a poster with interim findings. The poster's abstract was published in "Poster Abstracts" in Anticancer Research 39: 1507-1629 (2019).

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