

# Clinical Relevance of Routine Monitoring of Patient-reported Outcomes *Versus* Clinician-reported Outcomes in Oncology

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**Abstract.** *The National Cancer Institute Common Terminology Criteria for Adverse Events classification is the standard classification used by the physicians in oncology for reporting adverse events. This classification has evolved over the last years according to the emergence of new therapies. Reporting symptoms, quality of life (QoL) and toxicities via patient-reported outcomes (PROs) in clinical practice is not yet a standard of care, nevertheless many studies have been conducted recently to assess feasibility and impact of routine monitoring of PROs, which should enable for better management of toxicities and earlier detection of disease progression in a more patient-centered health care delivery system. The aim of this article was to discuss the advantages and limitations of both approaches, clinicians-reported outcomes and PROs. Growing evidence supports that the routine collection of PROs leads to improvement of QoL and overall survival of cancer patients.*

Symptoms in patients with cancer are related to treatment adverse events or cancer itself. These symptoms can impair quality of life (QoL). Collection of symptoms in oncology is

commonly reported by the physicians at each consultation using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) classification (1). This classification is widely used, standardized and helps physicians to report toxicities and allows for a standardized dose adaptation. Nevertheless, this approach has shown several limitations especially the underestimation of symptoms by clinicians (2).

Reporting symptoms, QoL and toxicities *via* patient-reported outcomes (PROs) in clinical practice is not yet a standard of care. Over the last years, several trials have been conducted to assess PROs in routine practice especially using electronic devices (ePROs). This approach would intensify symptoms monitoring, improve symptoms control, help detect relapses earlier and thus improve patients' QoL and survival.

In this paper, we discuss the advantages and limitations of both approaches, clinicians-reported outcomes and PROs.

## Clinician-reported Outcomes

Safety and tolerability are one of the most important endpoints in trials especially in early phases, in order to define benefit risk balance between efficacy and toxicity. The NCI-CTCAE is nowadays the standard classification used for reporting adverse events (AEs) in clinical trials but it is also widely used in clinical practice to evaluate toxicity of oncology therapeutics in routine (1).

The first version CTCAE v1.0 was published in 1982 to address this standardization need for the evaluation of chemotherapy toxicity in cancer clinical trials. Several versions have followed, including in 1993 a second version extended to radiotherapy toxicities, and in 2003 to surgery

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and pediatric evaluation. The fourth version, published in 2009, was largely restructured with the Medical Dictionary for Regulatory Activities (MedDRA) organized by System Organ Class (SOC) based on anatomical, physiological system, etiology, or purpose.

The latest improvement, CTCAE v.5.0, published in November 2017, lists 832 AEs, structured according to 26 SOC. AEs are defined as any unfavorable and unintended sign, symptom, or disease, temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. This includes objective AEs (laboratory results) and subjective symptoms (nausea, dysesthesia, etc.), all collected by the physician himself who plays a key role in the reporting (1).

To evaluate the severity, a grading scale from 0 to 5 was provided: 0 absent, 1 asymptomatic or mild, 2 moderate, 3 severe, 4 life-threatening, 5 death. A grade 3 or more is considered as a cut off for tolerability and may lead to a discontinuation of the treatment and a specific management.

This 5th version needed to be upgraded due to the development of new drug therapies as immunotherapies. Forty six items have been added. For example, items in the SOC Eye disorders (central serous retinopathy, macular edema) or in the SOC skin and subcutaneous tissue disorders (hyperkeratosis, hair color changes, nail changes) were added with the expansion of targeted therapy such as angiogenesis inhibitors or EGFR inhibitors. Many clarifications of grade description and evaluation have also been done.

This method of reporting AEs displays several limitations. It is important to emphasize that CTCAEs were designed to evaluate the impact of treatment in clinical trials and not for the management of toxicities in clinical practice .

In the last few years the emergence of novel therapies such as immunotherapy or targeted therapy has resulted in a change in toxicity profile. Even if the CTCAEs have made some improvement with the last version, it remains insufficient. In that sense the European Society for Medical Oncology (ESMO) elaborated clinical practice guidelines for the management of toxicities from immunotherapy (3). These guidelines provide description and grading for 9 of the most significant categories of AEs: skin toxicity, endocrinopathy, hepatotoxicity, gastrointestinal toxicity, pneumonitis, neurological, cardiac, rheumatological and renal toxicity. They also made specific recommendations for management and treatment of each toxicity according to their severity.

Novel agents may require novel administration protocols and sometimes extended treatment duration over months and years. This chronic administration can lead to delayed and longer lasting toxicities. CTCAE does not take into account the duration of AEs, and underestimate the impact of lower grade toxicities on quality of life (4). For example chronic grade 2 diarrhea persisting several months after treatment

can have more consequences for the patient than an isolated grade 3 episode.

Moreover the limit of the high-grade severity has been arbitrarily decided to be grade 3 which is not reflective of real-world patient experiences.

Although the majority of adverse events refers to objective criteria such as blood disorders (laboratory), or cardiac disorders (electrocardiogram, echocardiography, etc.), about 10% corresponds to symptomatic toxicities whose presence, even in low grade, highly impacts quality of life.

Recent studies demonstrated that physicians underreport the prevalence and severity of patient's symptoms (2). The phase III randomized trial from The French Genito-Urinary Oncology Group (GETUG) evaluating the efficacy and safety of docetaxel combined with androgen deprivation therapy (ADT) compared to ADT alone in non-castrate metastatic prostate cancer (GETUG 15), investigated prospectively patient-physician differences in reporting adverse events (5). They showed that physicians systematically underestimate the symptoms whether they are specific side-effects of docetaxel (neuropathy) or hormonal therapy (hot flushes), but also very usual side-effects such as nausea, pain, fatigue. Discordance between patients and physicians regarding the level of disturbing symptom is overwhelming, for example sexual dysfunction was declared disturbing or very disturbing by 104 patients, whereas clinicians did not report this symptom for 85 of them. Differences in symptom reporting may be more important for subjective symptoms such as fatigue (2, 6).

In this context, it became necessary to improve the collection of symptomatic AEs and place the patient at the center of this evaluation using patient-reported outcomes (PROs) measures.

### Patient-reported Outcomes

A PRO is defined as a measurement of the patient's condition, reported directly by the patient, without interpretation by a clinician or anyone else. In 2009, the US Food and Drug Administration (FDA) published a guidance document for industry recommending the incorporation of PRO instruments in trial (7). To allow a standardization of PROs evaluation in trial, the NCI elaborated the PRO-CTCAE, including 78 symptomatic AEs represented by 124 distinct items (8). PROs measurement could also be implemented in the routine practice but this approach is not yet a standard of care. Many studies have been conducted to assess feasibility and impact of PROs monitoring in routine clinical care, especially using electronic devices.

*Benefits in patients' management.* The first study which assessed routine measurement of PROs was published in 1997 by Trowbridge *et al.* (9). All the patients completed

assessments of their pain, their pain regimens, and the degree of relief received. The intervention group's clinical charts contained a summary of the completed pain scales; the oncologists who treated these patients were instructed to review the summary sheet prior to an evaluation. This summary was not available for the oncologists treating the patients in the control group. In the intervention group, analgesic prescriptions changed for 25% of the patients, decreasing in 5% and increasing in 20% and a decrease in the incidence of pain described was found for the intervention group.

In 2000, Taenzer *et al.* (10) published the first study which assessed electronic routine measurement of QoL. Patients with lung cancer were randomized to either a usual care control group or the experimental group, which completed a computerized version of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire in order to provide the clinical staff with QoL information prior to the clinic appointment. In the experimental group, more QoL issues identified by the patient on the EORTC QLQ-C30 were addressed during the clinical appointment than in the control group and a trend towards more actions being taken was seen in the experimental group.

The study of Bash *et al.* (11) randomized 766 patients with metastatic breast, genitourinary, gynecologic, or lung cancers between a weekly web-based self-reporting of 12 symptoms graded on a five-point scale from 0 (not present) to 4 (disabling) compared to usual care. In case of a patient-reported symptom worsened by  $\geq 2$  points or reached an absolute grade  $\geq 3$ , an e-mail alert was triggered to nurses. Patients receiving intervention were less frequently admitted to the emergency room (34% vs. 41%;  $p=0.02$ ) or hospitalized (45% vs. 49%;  $p=0.08$ ) or remained on chemotherapy longer (mean, 8.2 vs. 6.3 months;  $p=0.002$ ).

*Benefits in patients' satisfaction.* Many studies have demonstrated a very good satisfaction of patients managed with PROs.

In 2000, Mooney *et al.* (12) proposed a system of daily reporting on seven common chemotherapy-related symptoms during a single cycle of chemotherapy and if symptoms met a preset threshold of severity a fax notification to the physician was generated. Twenty-seven patients were enrolled and the mean level of satisfaction was 7.9 on a scale between 0 and 10.

*Benefits in overall survival and quality of life.* The study of Velikova *et al.* (13) published in 2004 randomized 286 cancer patients to either the intervention group (regular completion of European Organization for Research and Treatment of Cancer–Core Quality of Life Questionnaire version 3.0 (EORTC QLQ-C30), and Hospital Anxiety and Depression Scale (HADS) on touch-screen computers in clinic and

feedback of results to physicians); attention-control group (completion of questionnaires, but no feedback); or control group (no completion of questionnaires). Patients in the intervention arm rated their continuity of care better than the control group for 'Communication' subscale of the Medical Care Questionnaire ( $p=0.03$ ). Moreover, patients rated their health-related quality of life (HRQoL) with the Functional Assessment of Cancer–General (FACT-G) questionnaire; an improvement in the global score of the FACT-G and in the emotional well-being dimension of the FACT-G was observed in the intervention arm *versus* the control arm ( $p=0.006$  and  $p=0.008$ ) (13).

In the study of Bash *et al.* (11, 14), QoL (the primary endpoints using the EuroQol EQ-5D index) improved in a higher number of participants in the intervention group than in the usual care group (34% vs. 18%) and worsened in a fewer number (38% vs. 53%;  $p<0.001$ ) (11). Moreover, they observed a better overall survival (OS) in the PRO group than in the usual care group [(Median OS=31.2 months (95%CI=24.5-39.6) in the PRO group and 26.0 months in the usual care group (95%CI=22.1-30.9); hazard ratio(HR)=0.83; 95%CI=0.70-0.99;  $p=0.04$ ] (14).

The study of Denis *et al.* (15) published in 2017 randomized 133 patients with non-progressive small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) staged as at least cTxN1/pTxpN1 to TxNxM+ cancer between a weekly web-based self-reporting of 12 symptoms with a routine follow-up. According to predefined criteria, an e-mail alert was sent to the oncologist. The median OS was 19.0 months (95%CI=12.5 to non-calculable) in the experimental and 12.0 months (95%CI=8.6-16.4) in the control arm (one-sided  $p=0.001$ ) (HR)=0.32, 95%CI=0.15-0.67,  $p=0.002$ ) (15).

*Benefits for the physicians.* So far, no study has been focused on the impact of routine electronic monitoring of PROs on the physicians in oncology. Nevertheless, a multi-hospital system in Boston, USA, which introduced a PROs system wide across 21 specialties, performed 25 qualitative interviews with physicians on how routine electronic monitoring of PROs affect them. Interestingly, there seems to be an improvement in physician's satisfaction. Indeed, according to the physicians, electronic monitoring of PROs can foster patient-provider communication, improve shared decision making, facilitate conversations about sensitive issues and most surprisingly, improve the workflow efficiency and save time. All these elements contribute to enhanced physician satisfaction and thus well-being. Further researches are needed to confirm these results (16).

## Discussion

There is growing evidence supporting the routine collection of PROs to enable better treatment of adverse events, early recognition of symptoms, pro-active symptoms management

to avoid dose modification, earlier relapse detection, improvement of patients' satisfaction, improvement of patient-physician relationship and thus, for all these reasons improvement in patient's OS and QoL. Nevertheless, there are also some limitations.

First of all, patients and physicians can face difficulties with the electronic tools especially when collection of electronic PROs is implemented for the first time. Moreover, patients who are not familiar with electronic devices or with communication difficulties might be excluded from this approach. Nevertheless, many systems have been developed to facilitate implementation of electronic PROs routine monitoring.

Another limitation may be compliance, as patients must fill the questionnaires regularly (weekly in both, Bash and Denis studies), especially with patients who are not familiar with electronic devices, or computer-inexperienced or do not consult their e-mails regularly. Moreover, compliance could decrease over time. The setting up of such system needs teaching and training sessions for the patients. Of note, in the Basch *et al.* study, on average, 73% of participants assigned to the intervention arm completed a self-report at any given clinic visit (11).

Furthermore, electronic monitoring of PROs may be a burden for care providers which could be a considerable barrier to sustainable use. Therefore, the tasks must be well-defined and split between care providers. Moreover, ease of use of the system is necessary for sustainability. Nevertheless, in the qualitative study conducted across the multi-hospital system in Boston, the clinicians declared it as a burden initially but as comfort with PROs has grown, clinicians find collecting PROs to be beneficial rather than burdensome. Future studies focused in cancer patients should assess rigorously how electronic routine monitoring of PROs affects the workflow and physicians (16).

Then, routine PROs monitoring may lead to an increase cost of the care delivery process and cost-utility analysis of such system should be performed in future trials as it has never been done so far.

Additional research is warranted to refine the technology: identify subpopulations who would benefit the most from this strategy, select the best PROs tools according to the cancer and the setting, determine the best timing of PROs measurement, assess cost-utility, evaluate the burden for physicians and assess its weight within the workflow of oncology.

## Conclusion

The NCI-CTACE is the standard classification used for reporting AEs in clinical trials and in clinical practice. There is growing evidence that routine monitoring ePROs can improve OS and/or QoL of patients with cancer, and may

enhance patient-provider communication, patient satisfaction, and physician's well-being, therefore, routine collection of PROs could be complementary to clinician reported outcomes. This approach is going to change the health delivery care in a more patient-centered perspective. PROs measurement will be implemented in the electronic health record and the examination of PROs prior to each chemotherapy prescription and during follow-up will be a routine for physicians as the examination of blood tests or imaging. Nevertheless, further research is warranted to refine the technology.

## Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

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