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Title

A rapid review of patient-reported outcomes investigated in the context of advanced renal cell cancer or advanced hepatocellular cancer

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Abstract

Background: Patient-reported outcomes (PROs) are key indicators of health status and functioning, coming directly from the patient. Comprehensive monitoring of PROs enables implementation of person-centred care. Currently, the PROs that patients with advanced renal cell carcinoma (RCC) or hepatocellular carcinoma (HCC) consider of greatest importance remains unknown.

Methods: A rapid literature review was carried out to identify PROs commonly reported in clinical studies of patients with advanced RCC/HCC. We searched MEDLINE, CINAHL & PsycInfo for relevant peer-reviewed publications in the period from 2000-2021. Pre-specified selection criteria were applied to all retrieved records. Findings were integrated into a narrative synthesis.

Results: Eighty-one studies met our selection criteria and were retained. Most research was on advanced RCC (n=64, 79%); 46 studies (57%) were drug trials. ~~No qualitative research on PROs was found.~~ Only twenty-six studies (32%) employed PROs as their primary endpoint. Most PROs concerned physical symptoms (45% RCC, 54% HCC) and emotional wellbeing (19% RCC, 16% HCC). The most common outcome measured was quality of life (65% of the total), followed by fatigue (62%) and pain (54%). Whether selection of these PROs was patient-driven was not reported.

Conclusions: A wide range of PROs were assessed. Deficits in PROs often cause patients to seek out help; however, which PROs matter the most to people with advanced RCC/HCC must be further clarified. Targeting, monitoring, and responding to the 'right' PROs can enhance provision of person-centred care in advanced RCC/HCC and augment the clinical efficacy of established and emerging targeted therapies.

Key Words:

Patient-reported outcomes, Advanced Renal Cell Carcinoma, Advanced Hepatocellular Carcinoma, Quality of life, Person-centred care

BACKGROUND

Renal cell carcinoma (RCC) accounts for around 80% of all kidney cancers, while hepatocellular carcinoma (HCC) is the most common type of liver cancer (International Agency for Research on Cancer, 2020). Both types of cancer are most frequent in men, often diagnosed at an advanced stage, and associated with poor survival (Escudier et al., 2019; Ghouri et al., 2017). RCC is often diagnosed in people over 60 and in higher-income settings; conversely, HCC is more frequent in people between the ages of 30 and 50, and those residing in developing countries (Capitanio et al., 2019; Ghouri et al., 2017).

Several treatment modalities are available for advanced RCC and advanced HCC. Surgery or radiotherapy may be prescribed where metastases are localised. Since the development of novel treatments, chemotherapy is not first-line treatment for advanced RCC/HCC as it has not been shown to improve survival (Escudier et al., 2019; Vogel et al., 2018). Instead, targeted therapies and immunotherapy, normally in combination, have taken precedence (Gao et al., 2019; Hato et al., 2016). Until now first-line treatments of advanced HCC and advanced RCC were single targeted therapies while the recommendation is the introduction of combination therapy being Atezolizumab plus bevacizumab the first line treatment. First-line targeted therapy for advanced HCC is atezolizumab plus bevacizumab, a combination of immunotherapy and targeted therapy, while cabozantinib plus nivolumab and is used as first-line for advanced RCC (Escudier et al., 2019; Powles et al., 2021; Vogel et al., 2021, 2018).

While they are known to be better tolerated than traditional anticancer treatment (Gao et al., 2019; Hato et al., 2016), targeted therapies often have persistent low-grade and perhaps long-term unpleasant toxicities, such as fatigue, skin rash or diarrhoea (Zhou and Fountzilias, 2019). Immunotherapy can also have delayed side-effects (e.g. colitis or pneumonitis) that if not treated promptly can be severe (Haanen et al., 2017; Puzanov et al., 2017). These side-effects may not require immediate intervention but are difficult to live with; consequently, health-related quality of life (HRQoL) may gradually be affected, potentially leading to poor treatment adherence (Rapoport et al., 2017).

The impact of treatment on people with advanced RCC/HCC can leave them feeling uncertain and vulnerable (Foster et al., 2018), particularly as they often have to deal with the complexities of a cancer

diagnosis as well as decisions about supportive and palliative care (Moldawer and Wood, 2020). Challenging physical and psychosocial issues may be experienced, such as mood changes, distress, fatigue, pain or insomnia (Cella, 2011; Firkins et al., 2021; Harding et al., 2007; Howell et al., 2015). Commonly, patients and families self-manage targeted therapies at home (most are given orally) and are expected to adhere to complex dosing strategies, and monitor and report symptoms effectively. While at home, such challenges can be augmented by advanced cancer, older age, frailty, availability of family support, perceived burden of treatment, unmet information needs, multimorbidity, polypharmacy, and psychological/emotional burden (Nichol et al., 2016; Ullgren et al., 2018). Support to prepare people for the effects of treatment for advanced RCC/HCC is essential, alongside comprehensive assessment of their emerging supportive care needs (Greenhalgh et al., 2018).

Currently, in the context of advanced RCC/HCC clinical assessments focus predominantly on objective evaluation of physical and functional performance, while the more subjective domains of well-being may be underreported (Toumi et al., 2019; Drury et al., 2022). Furthermore, healthcare professionals' assessment and patients' own perspective of functioning may diverge (Tzelepis et al., 2015). Patients may judge symptoms like fatigue, mucositis or dysgeusia more severe than their physicians (Goebell et al., 2016, 2014). Families and caregivers who are familiar with the ill person can report observable symptoms, but reports of subjective problems such as quality of life or anxiety may not be as accurate (Dawber et al., 2019). It is therefore necessary to directly and holistically assess and measure patients' own experiences.

Evaluating patient-reported outcomes (PROs) is a crucial step to this end. A PRO *"is a report coming directly from patients about how they function or feel in relation to a health condition and its therapy, without interpretation of the patient's responses by a clinician, or anyone else"* (Higgins et al., 2011). PROs provide information which complements clinical evaluation and enhances understanding on how the patient is affected by these treatments. PROs also help patients reflect on their health and can help communication between patients and healthcare providers (Greenhalgh et al., 2018).

PROs are normally assessed via patient-reported outcomes measures (PROMs), i.e., self-report questionnaires that the patient completes, which assess various illness/treatment-related outcomes and experiences directly from the personal perspective (Kingsley and Patel, 2017). PROs recorded via PROMs specifically designed for people with RCC/HCC are the most effective way to capture the patient's wellbeing and changes over the course of the disease (Foster et al., 2018; Howell et al., 2015).

The use of PROMs in clinical practice remains suboptimal. Lack of time or training adversely affect implementation and uptake, meaning that assessment of PROs in the context of advanced RCC/HCC remains inconsistent (Kang et al., 2020). People live with advanced RCC/HCC as a treatable condition for a long time, however, the PROs that they may consider as priorities in their care are yet to be defined. To begin to address this knowledge gap, we aimed to identify what PROs have been investigated in people with advanced RCC/HCC, and how and when these PROs were measured in the illness trajectory.

METHODS

This review is part of a larger project to identify suitable PROMs for use in advanced RCC and advanced HCC practice (https://cancernurse.eu/research/proms_project/).

A rapid review of the literature was conducted to identify common PROs reported in published research in the context of advanced RCC and HCC. Targeted therapies have increased survival and made people affected by these advanced cancers with other problems associated with their disease and treatment. We report our findings in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

A search was conducted in MEDLINE, CINAHL and APA PsycInfo for relevant peer-reviewed publications published between 2000 and 2021. This period was chosen to include the evolution of targeted therapies since their use in cancer practice became mainstream. The searches included terms related to PROs, advanced RCC and advanced HCC (Supplementary Table 1).

Eligibility criteria

Inclusion criteria were based on the research aim:

- Studies in patients with advanced HCC or RCC treated with or without targeted therapies.
- Studies investigating PROs in this population (e.g., symptoms, supportive care needs, quality of life, psychological wellbeing, physical wellbeing, fear of recurrence, physical activity).

Articles were excluded if they were:

- Studies conducted with family members or healthcare professionals about patients' experiences.
- Studies that deal with patient populations other than RCC or HCC. Studies with mixed samples were excluded unless a separate analysis was done for the RCC or HCC sample.
- Studies focused on the development, validation or testing of a new PROM.
- Studies published in languages other than English.
- Grey literature, commentaries, opinion papers.

Screening

Retrieved records were transferred to Mendeley© reference management software and de-duplicated by one author (GK). The records were then transferred to reference manager. One author (CD) screened title and abstract against the eligibility criteria. Retained records were accessed in full-text, evaluated for eligibility by one author (CD), and double-checked by a second author (GK). If studies were excluded the reasons were recorded.

Data extraction and synthesis

A customised data extraction table was developed, and data was extracted by two authors (CD, GK) onto a bespoke data extraction form created for this rapid review and inserted into an Excel spreadsheet

for ease of use. Data about the characteristics of the study, the PROs collected, including measuring points were extracted. The PROs were then classified into separate domains. Each of the domains based on the categories used in the PROMs such as physical, wellbeing, social, functional, and overall HRQoL outcomes. Studies that investigated similar PROs or variations of the same PRO were included in the same domain. We calculated the percentage of studies investigating each PRO / domain out of the total studies reviewed. A narrative synthesis per domain was provided.

RESULTS

Results of searches

A total of 1255 original articles were identified and 1102 were excluded based on title and/ or abstract. The remaining 153 articles were read in full; 72 articles were excluded as they did not meet the inclusion criteria (Figure 1). Ultimately, we included 81 articles in this review. Sixty-four studies (79%) investigated PROs in advanced RCC, while 17 investigated PROs in advanced HCC.

Characteristics of the included studies

The included studies involved 18,992 patients in total. Drug RCTs were the most common study design (53%; n=35 RCC; n=8 HCC). Of these, 31 involved targeted therapies (n=30 RCC; n=1 HCC), there were 3 non-randomised drug trials in RCC patients with targeted therapies. The second most common study design included were non-experimental studies (36%) (n=25 RCC; n=4 HCC), of which 17 involved targeted therapies (n=15 RCC; n=2 HCC). The selected studies also included trials with other treatments such as acupuncture (n =4 HCC; n=1 RCC). There was one case study included (n=1 HCC). No findings from qualitative data analyses were reported in any of these studies.

Types of RCC and HCC treatment

Fifty-one studies (63%) involved patients treated with targeted therapy (n=48 RCC; n=3 HCC). Most RCC studies involved patients treated with sunitinib (n=21), sorafenib (n=13) or axitinib (n=11) (Figure 2). The three HCC studies involved patients treated with sorafenib.

In fifteen studies (19%), patients were treated with immunotherapy (n=14 RCC; n=1 HCC). In three HCC studies, patients were treated with hormone therapy, while 3 RCC studies involved patients on chemotherapy. The remaining studies (n=4 RCC; n=9 HCC) involved patients receiving ultrasound, radiotherapy, or acupuncture, either alone or in combination with other therapies.

Seven studies (9 %) looked at combination of treatments with immunotherapy and targeted therapies or two immunotherapies (n=7 RCC) such as atezolizumab plus bevacizumab or sunitinib or atezolizumab with bevacizumab.

Twenty-six studies (32%) employed PROs as their primary endpoint. However, PROs were mainly featured as secondary end points, particularly where treatment efficacy (survival) was the focus of the study. Looking at when these PROs were measured, most studies employed PROs before and during treatment (n=34 (42%); n=27 RCC; n=7 HCC) or before, during and after treatment (n=28; 25 RCC; 3 HCC, 35% total) (Table 1).

Evaluated PROs

In the included studies, 109 different PROs were evaluated. Diversity in terminology was observed. In some studies, the constructs were divided into different aspects and called differently depending on the PROM used. For example, some studies reported fatigue, while others separated 'physical fatigue' and 'fatigue interference with daily life'. Similarly, some studies evaluated 'sleep disturbance', while other studies considered 'sleep quality' or 'sleep duration', depending generally on the PROMs used to measure the outcomes.

Across studies, the assessed PROs were similar for both RCC and HCC. The most common PRO measured in both groups was quality of life, reported in 53 of the 81 studies included (65% n=44 RCC studies and n= 11 HCC studies). Fatigue (n=50; 62%), pain (n=44; 54%), shortness of breath (n=35; 43%), lack of appetite (n=34, 42%) and sleep disturbances (n=34; 42%) were also among the top 5 most common PROs.

Overarching PRO categories

All PROs identified were categorised into overarching themes with the domains normally used in the PROMs (Cella et al., 2015; "Patient-reported outcomes (PROs) assessment - EUPATI Toolbox," n.d.). Most PROs concerned three main categories: physical symptoms (cancer-related and treatment-related) in around half of the RCC and HCC studies, followed by emotional wellbeing in around 19% of the RCC studies and 16% of HCC studies. The next most commonly used category for RCC studies was practical concerns (15%), for HCC studies it was practical concerns, general health, and social issues; each of them representing 9% of the total PROs used (Figure 3)

Physical Symptoms

PROs related to physical symptoms included disease-related issues (e.g., fatigue, lack of appetite) as well as treatment-related issues (e.g., skin changes, diarrhoea, or mouth sores) (Figure 4). Pain (RCC 92%; HCC 88%) and fatigue (RCC 86%; HCC 94%) were the most evaluated symptoms. Nausea (RCC 30%; HCC 76%) and lack of appetite (RCC 34%; HCC 71%) were more commonly assessed in HCC studies. Cough (RCC 24%; HCC 12%) was more assessed in RCC studies. Fever was not evaluated in any HCC studies and was evaluated in n=17 RCC studies (27%).

Emotional / psychological well-being

Included PROs related to psychological state such as motivation, distress or mood changes, were outcomes that indicate positive or negative impacts of the disease and its treatment. There were similarly assessed in HCC and RCC studies. Enjoyment of life (RCC 25%; HCC 18%), worry condition will get worse (RCC 23%; HCC 12%) were the most commonly evaluated in RCC studies alongside mental health concerns in HCC studies (RCC 20%; HCC 24%) (Figure 5).

Practical concerns and daily activity

PROs related to the functional status and ability of the patient to perform daily activities was described using terms such as: decreased activity (RCC 17%; HCC 18%), vitality (RCC 16%; HCC 6%), ability to

work (RCC 25%; HCC 12%), financial concerns (RCC 14%; HCC 29%) or ability to engage in activities of daily living (RCC 36%; HCC 29%).

For the remaining categories, cognitive symptoms comprised confusion (RCC 12%; HCC 0%), difficulty concentrating (RCC 3%; HCC 12%), or difficulty remembering things (RCC 6%; HCC 6%). PROs related to HRQoL focussed on evaluating perceived health status and general well-being of the patient. PROs specifically related to sexuality (RCC 11%; HCC 18%) or spirituality (RCC 2%; HCC 0%) were included in different domains, although they are not always measured with generic cancer PROMs. Finally, PROs concerning social issues included problems or limitations in relationship with others such as with family (RCC 8%; HCC 6%) or friends (RCC 12%; HCC 12%) or social support (RCC 6%; HCC 6%).

DISCUSSION

This rapid review illustrates the extent to which PROs are assessed in research pertinent to advanced RCC/HCC. Over half of the included studies were clinical trials, and almost all had PROs as a secondary outcome. Clinical trials for HCC and RCC primarily focus on how long treatment can delay disease progression, and how tolerable side effects are, although survival rates do not always translate into patient priority (Toumi et al., 2019).

HRQoL and physical symptoms were the most frequently assessed PROs in people with advanced RCC/HCC. HRQoL is unique to each person and is difficult to accurately capture in proxy reports from carers and healthcare providers. Therefore, it is important to focus on self-reports as the main indicator on how the person is tolerating their cancer and its treatment (Flannery et al., 2021). Physical symptoms such as fatigue, nausea or pain were very commonly assessed in the reviewed studies. Whether these were necessarily the most important or relevant outcomes to be assessed from the patient perspective is unclear, although perhaps their monitoring makes sense from a clinical perspective. That said, focussing too much on the physical aspects of health might steer attention away from wider health needs and issues that health professionals cannot predict (e.g. financial worries, sexuality issues, anxiety), but that patients want to report and discuss with the clinical team in search for support (Chaar et al., 2018; Denouel et al., 2018; Hansen et al., 2017; Kyte et al., 2014; Maiko et al., 2019; Mercieca-Bebber et al., 2018).

Previously, Cella et al. (2011) looked into the symptoms and concerns of people with advanced cancer, including patients with renal and hepatobiliary cancer patients (Cella et al., 2011). Their study suggested that the most important concerns of these patients were included in the available PROMs. However, studies looking at the validation of PROMs in people with advanced cancer were conducted in the context of chemotherapy alone (Rothrock et al., 2013). New treatment options for advanced RCC/HCC, including targeted therapies, are now associated with additional survival benefit and have different side effects (Cella, 2011).

Recent studies have identified the need to research HRQoL and further develop PROMs specific to advanced cancer (Firkins et al., 2021) as well as the need to capture how evolving treatments impact on patients (Bhavsar et al., 2017). Indeed, previous research in advanced RCC has shown that non-

RCC-specific PROMs may not be accurate measures of PROs if the 'right' PROs for these patients are not targeted in the first place (Cella et al., 2018). PRO measurement before, after and/or during treatment (as evidenced in 72 in 81 of the reviewed studies) may allow for longitudinal assessment of changes in patient wellbeing, and across different health domains and needs (Higgins et al., 2011).

Some progress in the RCC/HCC clinical area should however be noted. For instance, Functional Assessment of Chronic Illness Therapy (FACIT) developed the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index (NFKSI) (Cella et al., 2006) for renal cancer (used in 57% of the RCC studies in this review), and the latest version (NFKSI-19) also includes non-physical items such as 'worry that my condition will get worse' or 'I am able to enjoy life'. For liver cancer, the Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep (Butt et al., 2012)) used in 17.7% of the HCC studies in this review, divides the items in domains and includes physical, social (e.g. sexuality, family relationships and friends support), emotional and functional items. These PROMs have been developed for liver and kidney cancer in general, not RCC or HCC. Qualitative research (e.g. interviews, focus groups) has been conducted in the early stages of PROM development to identify relevant content and support the content validity of topic-specific PROMs. However, further work is needed to ensure existing PROMs are appropriate for the needs of people with advanced RCC/HCC, in order to support comprehensive assessment of the impact of cancer treatments on peoples' lives.

Review strengths and limitations

While the search and analysis in this review were conducted following a systematic and methodical approach, this is not a systematic review. Some studies might have been missed in the searches because we did not include an exhaustive list of databases, multiple publication languages, or the grey literature. Moreover, the methodological quality of the reviewed studies was not evaluated.

This review aimed to include studies in patients with advanced HCC or RCC regardless of the treatment however there were not many studies included with the current combination of treatments with immunotherapy and targeted therapy or with two immunotherapies and therefore it does not completely capture the current situation of PROs in the actual treatments.

CONCLUSION

This rapid review has created new evidence in relation to what PROs are most frequently (e.g. physical symptoms and quality of life) and less frequently reported as assessed in advanced RCC/HCC (e.g. sexuality, difficulty remembering things). Our findings will serve to further discussion what PROs people with advanced RCC/HCC prioritise and would like to be asked about by the clinical team. ~~what PROs are most important for people with advanced RCC/HCC.~~ For health professionals to address and support health needs associated with advanced RCC/HCC, an effort must be made to identify most important concerns and needs, and then regularly assess and monitor these. Currently, most PROs in advanced RCC/HCC are collected as part of clinical trials, with excessive focus on physical symptoms and ambiguity about their actual use or value in clinical practice. PROMs must be incorporated in the clinical workflow to allow patients to have a voice and enable effective person-centred and person-led

cancer care. For this to be useful, patient-validated PROs should be collected using appropriately validated PROMs for use in the advanced RCC/HCC patient population. All members of the healthcare team must be involved in developing PRO-driven supportive care that is appropriate to meet the needs of people with advanced RCC/HCC as and when they arise (Kelly et al., 2021).

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Availability of data and material: All data are available from the authors upon request.

Authors' contributions: CD has led the data analysis and manuscript preparation. All co-authors have contributed in the project and in preparing and reviewing the manuscript. All listed authors have seen and approved the final version of the manuscript.

Ethics approval: Not applicable as this is a literature review.

Consent to participate: Not applicable as this is a literature review.

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Supplementary Table 1: Free-text and MESH terms pertinent to three strings of search. String A was first combined with string B, and subsequently with string C.

Table 1: Measurement points used in the reviewed studies, also broken down by type of cancer (HCC v. RCC)

	Total	HCC	RCC
baseline only	4	2	2
before and after treatment	6	2	4
before and during treatment	34	7	27
before during and after treatment	28	3	25
during treatment only	5	2	3
during and after treatment	4	1	3

Fig. 1 PRISMA diagram of the article selection / screening process (adapted from Moher et al. 2009)

Fig. 2 Breakdown of targeted therapy agents used in the 48 reviewed studies that involved patients with RCC.

Fig. 3 PRO categories broken down by type of cancer. % Indicates number of studies reporting the PRO divided by the total number of PROs identified in each type of cancer

Fig. 4 Frequency of physical symptoms being reported in the reviewed studies by type of cancer. % Indicates number of studies reporting the physical symptom divided by divided by the total number of PROs identified in each type of cancer

Fig. 5 Frequency of emotional wellbeing items being reported in the reviewed studies by type of cancer. % Indicates number of studies reporting the physical symptom divided by divided by the total number of PROs identified in each type of cancer