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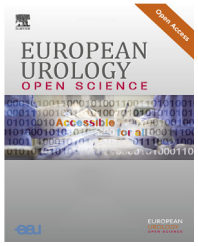

European Association of Urology

Review – Renal Disease

A Systematic Review of Heterogeneity in Outcome Definition and Reporting in Localised Renal Cancer

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Abstract

Context: Outcomes in renal cell carcinoma (RCC) are reported inconsistently, with variability in definitions and measurement. Hence, it is difficult to compare intervention effectiveness and synthesise outcomes for systematic reviews and to create clinical practice guidelines. This uncertainty in the evidence makes it difficult to guide patient-clinician decision-making. One solution is a core outcome set (COS): an agreed minimum set of outcomes.
Objective: To describe outcome reporting, definitions, and measurement heterogeneity as the first stage in co-creating a COS for localised renal cancer.
Evidence acquisition: We systematically reviewed outcome reporting heterogeneity in effectiveness trials and observational studies in localised RCC. In total, 2822 studies (randomised controlled trials, cohort studies, case-control studies, systematic reviews) up to June 2020 meeting our inclusion criteria were identified. Abstracts and full texts were screened independently by two reviewers; in cases of disagreement, a third reviewer arbitrated. Data extractions were double-checked.
Evidence synthesis: We included 149 studies and found that there was inconsistency in which outcomes were reported across studies and variability in the definitions used for outcomes that were conceptually the same. We structured our analysis using the outcome classification taxonomy proposed by Dodd et al. Outcomes linked to adverse events (eg, bleeding, outcomes linked to surgery) and renal injury outcomes (reduced renal function) were reported most commonly. Outcomes

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related to deaths from any cause and from cancer were reported in 44% and 25% of studies, respectively, although the time point for measurement and the analysis methods were inconsistent. Outcomes linked to life impact (eg, global quality of life) were reported least often. Clinician-reported outcomes are more frequently reported than patient-reported outcomes in the renal cancer literature.

Conclusions: This systematic review underscores the heterogeneity of outcome reporting, definitions, and measurement in research on localised renal cancer. It catalogues the variety of outcomes and serves as a first step towards the development of a COS for localised renal cancer.

Patient summary: We reviewed studies on localised kidney cancer and found that multiple terms and definitions have been used to describe outcomes. These are not defined consistently, and often not defined at all. Our review is the first phase in developing a core outcome set to allow better comparisons of studies to improve medical care.

1. Introduction

Renal cell carcinoma (RCC) represents 2.2% of all new cancers worldwide [1,2]. With the increase in reporting of incidental findings, a greater proportion of patients newly diagnosed with renal cancer currently present with stage I disease [3,4]. Historically, surgery has been the standard of care for localised renal cancer, but international guidelines have more recently proposed ablative treatments and active surveillance as alternative options [5,6]. Currently, oncological outcomes across treatments are similar and treatment decision-making is multifactorial [7].

Across many clinical areas including urology, patient-reported outcomes and clinical outcomes are reported inconsistently, with variability in definitions and measurement, for instance in the settings of localised prostate cancer and bladder cancer [8–10]. This makes it very difficult to compare and synthesise outcomes to improve guidelines to better direct and support patients and clinicians during treatment decision-making and ultimately improve results in clinical practice [11,12]. A core outcome set (COS) is a standardised set of prioritised outcomes and is proposed by current research as a solution to decrease heterogeneity in collection, reporting, and analysis of outcomes. COS in urology are needed because inconsistencies and variability cause not only frustration but also potentially problematic conclusions [9]. This issue is also clearly apparent for localised renal cancer, and ultimately results in barriers for the multifactorial process of decision-making [7].

The aim of this systematic review was to identify which outcomes are reported in intervention effectiveness research in localised kidney cancer and to assess heterogeneity in outcome definitions and measurements. It constitutes the initial stage in the development of a COS for localised renal cancer with the intention of identifying a minimum set of outcomes that are potentially important to health care professionals and patients. The outcomes identified in this systematic review are organised under the taxonomy developed by Dodd et al. [13], which helps to structure general health research vocabularies to reduce inconsistencies. It is embedded in a larger project registered in the Core Outcome Measures in Effectiveness Trials (COMET) database [14], and uses the same robust methodology that was already followed for the prostate cancer COS [15] developed in collaboration with the European Association of Urology.

2. Evidence acquisition

This systematic review followed the guidelines of the COMET initiative, an international expert body that established guidelines on how to develop methodologically robust COS. We report our study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the COS-STAR reporting guidelines, which are relevant to this stage of COS development [16]. A project steering committee (S.M., M.V.H., P.Z., A.B., L.M., S.D., R.B., N.K.) supported the development from a methodological and clinical perspective. The study protocol was registered on PROSPERO (ID: CRD42020198605).

2.1. Aims and objectives

The aim of this project was to systematically review which outcomes have been reported in effectiveness trials and observational studies in localised renal cancer, and how they were defined and measured.

2.2. Identification of relevant studies

We searched Medline, EMBASE, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews (via Ovid) from inception to June 2020. We worked with an information scientist to design the search strategy (Supplementary Fig. 1). To balance the feasibility and precision of the search, we used a two-step approach. First, we identified all published systematic reviews and intervention trials related to RCC without limiting the search to localised renal cancer, and we screened the reference lists in all the articles as a pragmatic way to identify primary studies potentially meeting our inclusion criteria. Second, we searched for and screened

all interventional studies on localised RCC from 2015 onwards without limiting the study design. We included randomised controlled trials (RCTs), cohort studies, and case-control studies that reported on eligible interventions for localised renal cancer. We excluded case studies owing to their low level of evidence according to the Oxford Centre for Evidence-Based Medicine (level of evidence 4 or lower [14]) and the unlikelihood of changing clinical practice. We also excluded conference abstracts.

2.2.1. Study participants

Adults (male and female) with suspected localised renal cancer (N0M0 according to the TNM classification; all versions of the TNM staging system) on magnetic resonance imaging, computed tomography, or ultrasound imaging were included.

Those undergoing treatment for renal metastasis or other tumours were excluded.

2.2.2. Intervention and comparator

Studies reporting on any intervention for localised renal cancer were retained, including but not limited to active surveillance, radical nephrectomy (all modes and approaches), partial nephrectomy (all modes and approaches), cryoablation, radiofrequency ablation, microwave ablation, irreversible electroporation, watchful waiting, high-intensity focused ultrasound, or radiotherapy.

2.2.3. Eligibility of studies

All abstracts and full texts were screened independently by at least two reviewers (C.W., K.B.). Any disagreements were arbitrated by a third review author (S.M).

2.3. Data extraction

Data were independently extracted from the studies included by two researchers (C.W., K.B.) and checked for accuracy by another reviewer (S.M.). We extracted data on study design; author details; year and journal of publication; intervention(s) under investigation; each effectiveness outcome reported; whether the outcome was defined or not; the definition used; the indicators and/or tool(s) used to operationalise or measure the outcome; the time point or period for outcome measurement; and how the outcome was reported.

2.4. Data analysis and synthesis

The outcome names extracted were coded and categorised according to the outcome reporting taxonomy developed by Dodd et al. [13], which has been suggested by COMET for classification of outcomes and group domains.

2.5. Assessment of risk of bias

A risk-of-bias assessment was not conducted, as no estimation of the effect size of treatments was conducted and only qualitative information containing terminology was extracted.

3. Evidence synthesis

3.1. Characteristics of the studies included

Our initial search returned 2785 abstracts. Of these, we assessed 319 full-text articles, of which 149 were included (Fig. 1). Of the 149 studies included, 97% were observational studies and five (3%) were RCTs.

3.2. Heterogeneity in outcome reporting, detection, and definitions

A suitable outcome taxonomy for health research must differentiate between high-level outcome domain classifications, and comprehensively classify all outcomes, while also proposing a standardised terminology. Therefore, we reported and organised the outcomes in the studies under the taxonomy developed by Dodd et al. [13] and recommended by the COMET initiative. Taxonomies help to

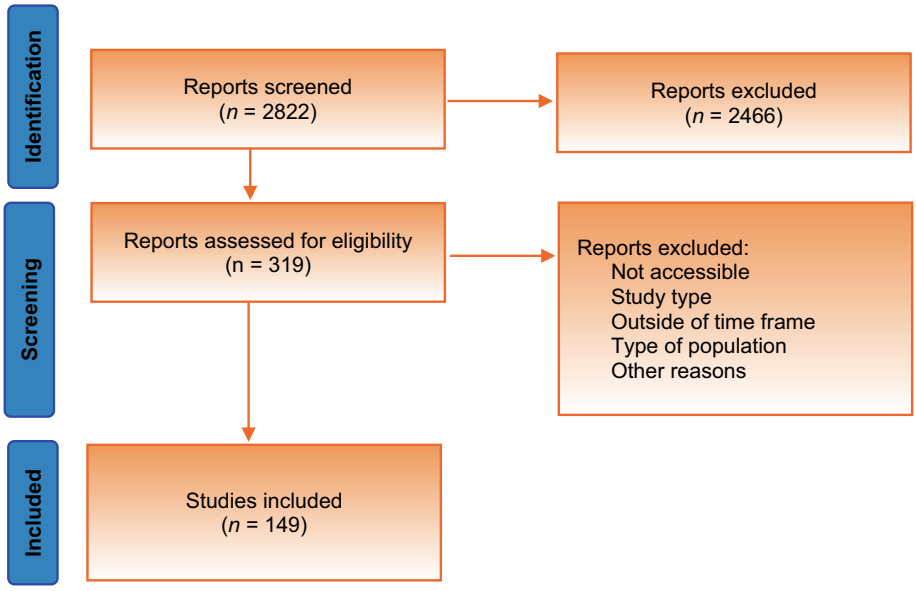

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

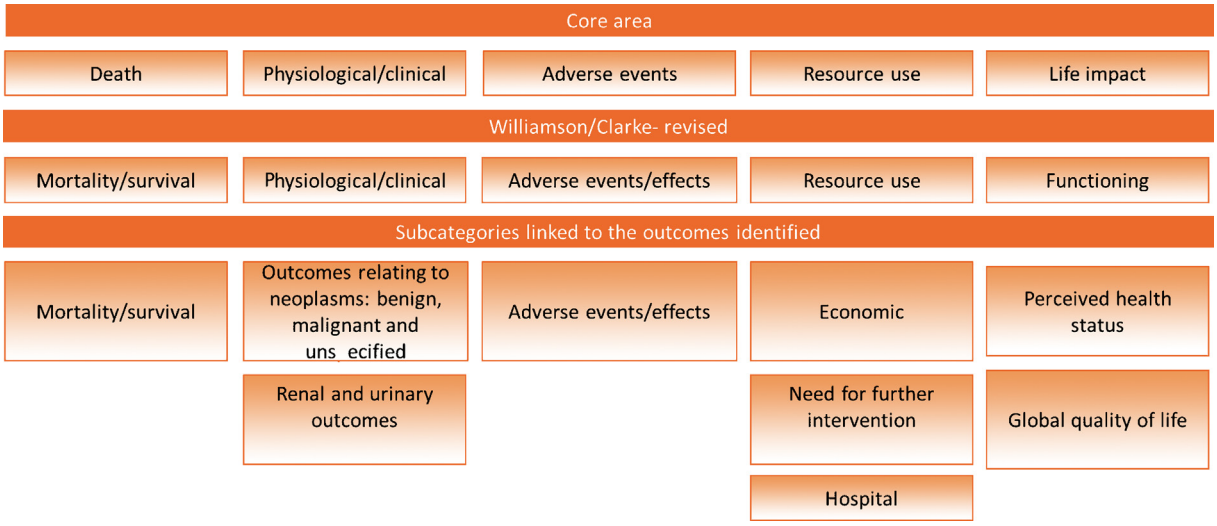

Fig. 2 – The Dodd [13] taxonomy applied for classification.

structure vocabularies for general health research to reduce inconsistencies and ambiguities in how current studies describe and define outcomes. The Dodd taxonomy has been proposed to increase the reuse value of outcome data. The taxonomy comprises 38 outcome domains within five core areas: death, adverse events, life impact, physiological/clinical, and resource use [13]. The core outcomes are further subclassified as shown in Figure 2.

Table 1 lists the outcomes reported by the studies by domain and highlights the heterogeneity of outcomes identified. We have merged the synonyms and redundant terms. The next section explains the heterogeneity of the terminology in more detail. Table 2 shows which outcomes were reported in the studies included in the review.

3.3. *Death (mortality/survival)*

Death was reported 103 times. We categorised these outcomes according to the Dodd mortality/survival classification into "overall survival" and "cancer-specific survival". Overall survival (OS) was measured in 65 studies (44%; Table 2) as OS, death, or mortality; more details are provided in Table 1. Cancer-specific survival (CSS) was reported in 43 (29%) of the studies (Table 2) as CSS, death from renal cancer, or cancer-specific mortality.

Definitions of OS and CSS differed across studies (Table 1). The heterogeneity for the definitions was linked to time points. For instance, some studies started measurement at diagnosis, whereas others used the treatment date as the starting point for survival. The time endpoint also differed, with studies reporting either a rate at a defined time (eg, at 10 yr) or a hazard ratio based on survival analyses.

3.4. *Adverse events (adverse events/effects)*

Adverse events (AEs) were the most common outcome reported ($n = 101$, 68%). However, many different types of AE were reported, sometimes as the number or percentage of patients experiencing the outcome and sometimes subsumed in a classification system linked to severity or consequences (eg, the Clavien-Dindo scheme). Examples of events that play a role in AE assessment include bleeding, operation time, warm ischaemia time, intra-abdominal pressure, surgical time, drainage time, serum creatinine, blood loss, trifecta/pentafecta outcomes, and dialysis, which are linked to the complexity of the surgery. Many articles reported several AEs within one study, but the AEs reported varied across studies (eg, surgical complications were measured as intraoperative complications, conversion to nephrectomy, or short-term complications).

"Adverse events/effects or resource use: hospital" outcomes were reported in six studies (4%). Outcome reporting and measurement were inconsistent; examples include dialysis-free probability, number requiring dialysis, temporary dialysis, and permanent dialysis (Table 1).

3.5. *Life impact/functioning (perceived health status; global quality of life)*

Only eight studies (5%) reported outcomes reflecting life impact. Five studies (3%) reported outcomes classified as perceived health status. Three studies (2%) reported on global quality of life (QoL), one study using the Short Form (SF)-36 and another using the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-15 patient-reported outcome measures (PROMs; Table 2).

3.6. *Physiological/clinical (physiological or clinical)*

Physiological or clinical outcomes were subclassified as "renal and injury outcomes" (eg, new chronic kidney disease [CKD], CKD stage, time to CKD), which were defined very heterogeneously and reported in 87 (58%) of the studies; and "outcomes relating to neoplasms" (linked to cancer follow-up and progression, reported in 55 studies [37%]) according to the Dodd taxonomy [13] (Tables 1 and 2).

3.7. *Resource use (economic, need for further intervention, hospital)*

Resource use consisted of the subcategories "economic resource" (eg, health care expenditure; reported in four

Table 1 – Outcomes classified according to the taxonomy of Dodd et al. [13]

Death	Adverse events/effects	Physiological or clinical	Resource use	Life impact
Mortality/survival	38. Adverse events/effects	2–24. Physiological/clinical	Resource use	Functioning
Mortality/survival *Overall survival* • OS rate • Cumulative survival • Stage-related OS • Mean OS • Survival probability 1 yr *Deaths* • Deaths • Death from any cause *Mortality* • Other-cause mortality • Mortality events • Overall mortality • Total mortality • X-day mortality *Cancer-specific survival* • RCC-specific survival • Recurrence-free survival *Death from kidney cancer* • Number of patients deceased at last follow-up • Death from kidney cancer • RCC death • Death from RCC • Death due to cancer *Cancer-specific mortality* • Cancer-specific mortality • Death from nonRCC, other-cause mortality	**38. Adverse events** *Complications* • Surgical complications • Intraoperative complications • Conversion to nephrectomy • Short-term complications • Conversions • Grade I and grade II complications • Highest complication grade • Overall complications • 30-d postoperative complications *Bleeding* • Bleeding severity • Units of blood transfused during hospitalisation • Estimated bleeding • Bleeding-related complications • Haemoglobin postoperatively ***Perioperative*** *Surgical margins* • Surgical margins • Negative margins • Positive surgical margins *Outcomes linked to surgery* • Operation time • WIT • Surgical time • Drainage time • Procedure time • Pneumoperitoneum time • Suture time • WIT ≤25 min • Conversions • Open conversion • Average clamping time • Haemoglobin after surgery • Postoperative drainage time • Intra-abdominal pressure • Adverse health outcomes • Clampless rate *Blood loss* • Mean estimated blood loss • Estimated blood loss • Changes in estimated blood loss • Units of blood transfused during surgery • Transfusion requirement • Transfusion rate • Intraoperative transfusion • Intraoperative ES transfusion • Transfusions received • Perioperative allogenic blood transfusion	**19. Renal and injury outcomes** *New CKD* • CKD probability *CKD stage* • CKD stage • Upgrading to CKD grade III–V • CKD upstaging • No CKD upstaging • Postoperative CKD stage • Postoperative new onset of stage III or IV CKD • Final CKD stage • Patients with acquired stage III–V CKD at follow-up, compared to preoperative *Time to CKD* • Decline in CKD stage • Progression to CKD • CKD upstaged–free survival • De novo CKD stage III • Survival without CKD upstaging • Time to diagnosis of CKD *Outcomes linked to procedure* • Mean ablation time • Laser excision time • Median procedure time • Renal outcomes • Urinary function • Oncological outcomes • Collecting system entry • Haemostatic agent *eGFR* • Mean eGFR change • Median eGFR preservation • Median percentage eGFR change • Change in GFR • eGFR preservation (%) • Latest eGFR preservation • Δ GFR change • Last eGFR • eGFR 1-yr post operation • Percentage change in eGFR • eGFR decrease • Postoperative eGFR change (%) from baseline to 1-yr follow-up *Serum creatinine* • Preoperative creatinine • Creatinine level • Serum creatinine • Difference in serum creatinine between preoperative and postoperative levels • Postoperative creatinine level • Postoperative creatinine • Latest creatinine level • Percentage change in creatinine • Variation of creatinine	**34. Economic** *Cost* • Health care expenditure • Medical cost • Total cost • Imaging (linked to costs) • *Medications?* **36. Need for further intervention** • Readmission **35. Hospital** • Length of stay • Postoperative HSP time • HSP time • Hospital stay • Average hospital stay • Duration of HSP • Duration of postoperative hospital stay • Median hospital stay • Surgical supplies and devices • Operating room	**31. Perceived health status** • Perceived health • Pain • Adverse health outcomes **30. Global quality of life** • Health-related quality of life

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Table 1 (*continued*)

Death	Adverse events/effects	Physiological or clinical	Resource use	Life impact
	• Percentage blood transfusion • BUN after 1 d and 1 mo *Trifecta/pentafecta* • Trifecta • Trifecta rate • Pentafecta reached • Highest complication grade • Low-grade complication	• Δ creatinine *Recurrence-free survival* • RFS + time		
	38. Adverse events/effects or 35. Resource use: hospital • Dialysis free probability • No. requiring dialysis • Temporary dialysis • Permanent dialysis	**16. Outcomes relating to neoplasms: benign, malignant and unspecified (including cysts and polyps)** *Metastasis* • Distant metastasis–free survival • Distant metastasis • Extrarenal metastasis *Follow-up* • Follow-up • Long-term outcomes • Median postoperative follow-up time • Average length of follow-up • Median follow-up time *Progression-free survival* • PFS • Systemic PFS • Clinical PFS *Progression* • Local tumour progression • Disease progression *Recurrence* • Local recurrence • Disease-free survival • Recurrence rate • Recurrence-free survival • Recurrence result *Recurrence linked to time* • Time to local recurrence • Events of local recurrence • Delayed recurrence • Time to recurrence • Local recurrence rate • Local recurrence–free survival • Recurrence (local or metastatic) • Local ipsilateral recurrence • Disease-free survival		

BUN = blood urea nitrogen; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ES = erythrocyte suspension; HSP = hospitalisation; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma; WIT = warm ischaemia time.

Table 2 – Outcomes reported in each study after classification according to the taxonomy suggested by Dodd et al. [13]

First author	Design	Location	Death		Adverse events		Physiological or clinical		Resource use			Life impact	
			OS	CSS	AEs	AEs/ ERUH	RIO	ORN	E	H	NFI	PHI	GQL
Patel	OBS	US	X				X	X					
Li	OBS	China			X		X			X			
Wang	OBS	China			X		X			X			X
Morkos	OBS	USA	X	X		X	X	X					
Alshyarba	OBS	Saudi Arabia	X		X								
Wu	OBS	China			X		X			X			
Packiam	OBS	USA			X		X			X			
Yang	OBS	Not stated	X		X					X			
Rembeyo	OBS	France	X	X	X		X	X					
Uhlig	OBS	USA	X										
Yu	OBS	China	X	X	X		X	X					
Kartal	OBS	Turkey	X		X		X	X					
Jalbani	OBS	Pakistan			X		X			X			
Seon	OBS	South Korea	X	X	X		X	X					
Choi	OBS	South Korea			X		X			X			
Tan	OBS	USA, Puerto Rico	X										
Grant	OBS	USA	X										
Chen	RCT	China			X		X			X			
Liu	OBS	China			X		X			X			
Sandbergen	OBS	Netherlands			X								X
Shapiro	OBS	USA		X	X		X	X					
De Cobelli	OBS	Italy			X		X						
Nayan	OBS	Canada	X	X			X	X					
Jin	OBS	China			X		X			X			
Mourao	OBS	USA, Spain	X	X	X		X			X			
Anglickis	OBS	Lithuania			X		X	X		X		X	
Marchioni	OBS	USA	X	X									
Li	OBS	China		X									
Liao	OBS	USA	X	X									
Simone	OBS	Italy	X	X	X		X	X					
Shao	OBS	Taiwan			X			X		X			
Antonelli	RCT	Italy			X		X			X			
Kitley	OBS	USA	X										
Zhou	OBS	China			X		X						
Andrews	OBS	USA		X				X					
Zhou	OBS	USA		X			X	X					
Fraisse	OBS	France	X		X			X				X	
Hu	OBS	China			X								
Abu-Ghanem	OBS	Israel	X	X			X	X					
Kavaric	OBS	Montenegro			X		X			X			
Ziegelmueller	OBS	Germany	X				X	X					
Talenfeld	OBS	USA	X	X	X								
Bhindi	OBS	USA	X	X	X		X	X					
Larcher	OBS	Netherlands, Italy	X		X		X	X		X			
Xing	OBS	USA	X	X								X	
Ristau	OBS	USA, Puerto Rico	X										
Zhao	OBS	China			X		X	X		X			
Gershman	OBS	USA	X	X			X	X					
Benoit	OBS	France			X		X	X		X			
Paulucci	OBS	USA			X		X	X		X			
Abdel Raheem	OBS	South Korea		X	X		X	X		X			
Lourenco	OBS	Canada	X		X		X	X		X			
Hasegawa	OBS	Japan					X	X			X		
Streja	OBS	USA		X			X						
Borghesi	OBS	Globally			X		X			X			
Uhlig	OBS	USA	X							X	X		
Ye	OBS	China			X			X		X			
Park	OBS	Not stated											
Venkatramani	OBS	USA	X							X			
Uhlig	OBS	USA		X									
Zhang	OBS	USA	X	X									
Lee	OBS	South Korea	X	X	X			X					
Chong	OBS	USA			X			X			X		
Chang	OBS	Taiwan			X				X	X			
Yang	OBS	China			X			X		X			
Veys	OBS	Belgium	X	X	X		X	X					
Banapour	OBS	USA			X		X			X			
Cai	OBS	China	X	X			X						
Lanchon	OBS	France			X		X			X			
Venkatramani	OBS	USA	X								X		
Karalli	RCT	Sweden										X	

(*continued on next page*)

Table 2 (*continued*)

First author	Design	Location	Death		Adverse events		Physiological or clinical		Resource use			Life impact	
			OS	CSS	AEs	AEs/ ERUH	RIO	ORN	E	H	NFI	PHI	GQL
Dong	OBS	Not stated					X						
Wang	OBS	USA	X										
Tang	OBS	USA	X	X									
Yin	OBS	China	X					X					
Shah	OBS	USA					X						
Annino	OBS	Italy			X			X					
Wang	OBS	China	X					X					
Shum	OBS	USA	X					X		X	X		
Luo	OBS	USA	X	X									
Lee	OBS	South Korea	X	X	X			X					
Caputo	OBS	USA	X	X	X		X						
Lu	OBS	China			X		X			X			
Maric	OBS	Serbia			X								
Matei	OBS	Italy			X	X	X	X		X			
Paulucci	OBS	USA			X		X						
Rassweiler	OBS	Germany			X								
Larcher	OBS	USA	X		X			X	X	X	X		
Lenis	OBS	USA	X		X								
Wang	OBS	USA			X					X			
Peng	OBS	China		X	X		X	X		X			
Malkoc	OBS	USA			X			X		X	X		
Long	OBS	France	X	X	X	X	X	X		X			
Yoo	OBS	South Korea					X						
Redondo	OBS	Spain			X					X			
Carrion	OBS	Spain			X		X						
Shah	OBS	USA			X		X						
Moskowitz	OBS	USA	X										
Huang	RCT	China			X		X			X			
Larcher	OBS	USA		X									
Jang	OBS	South Korea	X	X	X		X	X					
Forbes	OBS	Canada	X		X		X	X					
Kara	OBS	Not stated			X		X	X		X			
Takagi	OBS	Not stated			X		X	X		X			
Oh	OBS	Not stated			X								
Andrade	OBS	Not stated			X	X			X	X			
Dong	OBS	Not stated	X		X		X	X		X			
Trudeau	OBS	USA	X		X								
Lai	OBS	China	X	X	X					X			
Liu	OBS	China	X		X		X			X			
Pantelidou	OBS	UK			X		X	X		X			
Liu	OBS	China	X		X		X	X					
Larcher	OBS	USA			X		X						
Hossein	OBS	Iran			X		X						
Komatsuda	OBS	Japan			X		X						
Janicic	OBS	Serbia	X	X									
Lyon	OBS	USA			X					X			
Satkunasivam	OBS	USA	X		X	X	X			X			
Thompson	OBS	USA	X				X	X					
Tabayoyong	OBS	USA						X					
Alanee	OBS	USA		X									
Zargar	OBS	USA			X		X	X					
Mano	OBS	USA	X		X		X	X		X			
Chang	OBS	China	X	X	X		X	X		X			
Serni	OBS	Italy	X	X	X		X	X					
Chung	OBS	Korea	X	X			X						
Yu	OBS	Not stated	X		X								
Weinberg	OBS	USA			X				X	X			
Park	RCT	South Korea			X					X		X	X
Balasar	OBS	Turkey			X		X						
O'Malley	OBS	USA	X	X			X						
Kim	OBS	South Korea			X		X						
Chang	OBS	China	X		X								
Cooper	OBS	USA			X		X						
Alam	OBS	USA	X	X			X						
Çömez	OBS	Turkey			X		X			X			
Kopp	OBS	USA			X		X	X		X			
Danzig	OBS	USA			X		X						
Hussein	OBS	Egypt					X						
Simsek	OBS	Turkey			X		X			X			
Fossati	OBS	Italy		X	X					X			
Ji	OBS	Italy, China	X	X	X	X	X	X		X			

Table 2 (*continued*)

First author	Design	Location	Death		Adverse events		Physiological or clinical		Resource use			Life impact	
			OS	CSS	AEs	AEs/ ERUH	RIO	ORN	E	H	NFI	PHI	GQL
Mason	OBS	USA					X						
Chehab	OBS	Not stated			X								
An	OBS	USA			X					X			
Rosen	OBS	USA			X		X						
Ramirez	OBS	USA			X		X						
Malkoc	OBS	Turkey			X		X				X		

AEs = adverse events; CSS = cancer-specific survival; E = economic resource use; ERUH = effects or resource use: hospital; GQL = global quality of life; H = hospital resource use; NFI = need for further intervention; OBS = observational study; ORN = outcomes relating to neoplasms; OS = overall survival; PHI = perceived health impact; RCT = randomised controlled trial; RIO = renal and injury outcomes.

studies (3%) as mean or median costs), "need for further intervention" (eg, readmission; reported in eight studies [5%] as a binary yes/no result or median value), and "hospital" (eg, length of hospital stay, reported in 58 studies [39%] as mean or median length of hospital stay in days).

3.8. Discussion

To the best of our knowledge, this is the first systematic review of outcome reporting heterogeneity in the literature on localised renal cancer. Our results build a framework for developing a COS for localised renal cancer with the aim of reducing heterogeneity for outcome definitions, measurement, and reporting.

Our systematic review highlights the persisting problem of outcome reporting heterogeneity in studies on localised renal cancer. Multiple terms are used to refer to conceptually similar outcomes, and there is variation in the outcome definitions used. This has not improved over time and is problematic when summarising the evidence base for treatment effectiveness to inform decision-making, because it is not advisable to synthesise data with different outcome definitions within a meta-analysis. Such a practice can produce meaningless summary statistics that may be given more credibility than they are due. Therefore, a cumbersome and often less-informative narrative synthesis must be undertaken instead. Furthermore, our work highlights variety in data reporting and measurement. For instance, if dichotomous outcomes such as OS and CSS are reported using different methods (eg, some studies report adjusted and some unadjusted hazard ratios, others report a rate at median follow-up or at specified time points such as 1 yr or 5 yr), then these data cannot be easily or reliably synthesised in a meta-analysis. When these problems all occur together, then it is difficult to interpret the body of evidence and clinical practice guideline panels encounter challenges in drawing up recommendations and applying certainty-of-evidence attributes such as those proposed by the GRADE working group [17].

Worryingly, we identified very few patient-reported outcomes (PROs), which might be related to the limited number of specific tools available for capturing QoL for renal cancer. In their systematic review, Rossi et al. [18] identified three generic PROMs (RAND medical outcome survey SF-36 and SF-12, EuroQol [EQ-5D], Convalescence and Recovery Evaluation [CARE]) and eight cancer-specific PROMs (Cancer Rehabilitation Evaluation System-Short Form [CARES-SF], European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ]-C30, Functional Assessment of Cancer Therapy-General [FACT-G], FKSI, Renal Cell Carcinoma-Symptom Index [RCC-SI], Instruments to assess psychological wellbeing Impact of Events Scale [IES], Hospital Anxiety and Depression Scale [HADS], Mishel Uncertainty in Illness Scale (MUIS)) which are currently being used in renal cancer. However, of the PROM instruments used, only two are specific to renal cancer and are not stage-specific (FKSI, RCC-SI) [18].

In their study of the symptom index most commonly used for renal cancer, Rosenblad et al. [19] assessed the psychometric properties of the FKSI-19 (which captures physical and emotional disease-related symptoms, function/wellbeing, and treatment side effects) among patients with RCC and reported that it is barely fit for this purpose. Decat Bergerot et al. [20] conducted a patient survey that identified many of the FKSI-19 questions as irrelevant from a patient perspective and stressed the need to incorporate patients in the development of PRO tools to determine areas of importance to them. The EORTC Quality of Life group is currently developing an RCC-specific module to be used in combination with their QLQ-C30 instrument.

Our project steering group includes clinical RCC experts, patient advocacy groups, methodologists, and guideline developers from the European Association of Urology (most are co-authors of this study). We aim to use these networks to improve recruitment to our research stages, and to subsequently endorse and disseminate the final COS as part of our implementation strategy.

We curated the different terms used and collated them using a standardised outcome classification taxonomy [13] as a first step in creating a COS for localised renal cancer. In the next step we will use consensus processes in a multistakeholder group to prioritise which outcomes are core and to recommend definitions for each outcome. Once we know which outcomes are considered core by our stakeholders, we will systematically review the psychometric properties of PROMs available, with coverage of core outcomes using the COSMIN criteria [21,22] and will recommend one to be used in future research on treatment effectiveness. This is a medium- to long-term vision to standardise the definition, measurement, and reporting of

outcomes in research on localised renal cancer, with the ultimate aim of improving the decision-making process at all levels.

3.9. Limitations

We may have missed studies reporting PROs and/or QoL because we did not search specifically for primary qualitative studies of patient experiences of renal cancer treatment. However, we will supplement the list of outcomes presented here with outcomes identified in our own primary interview study with patients who have been treated for renal cancer, and further review work. Furthermore, as part of our prioritisation process, participants will be able to propose outcomes they think are missing from our list.

4. Conclusions

Our review indicates that clinical research on localised renal cancer is impeded by heterogeneity in outcome selection, definitions, and reporting. This work represents the first step in the development of a COS that will ultimately improve the evidence basis for treatment of patients with localised renal cancer and the process for creating clinical practice guidelines, and will facilitate treatment decision-making by health care professionals and patients.

Author contributions: Katharina Beyer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Beyer, Widdershoven, Van Hemelrijck, Bex, Zondervan, MacLennan.
Acquisition of data: Beyer, Widdershoven, MacLennan.
Analysis and interpretation of data: Beyer, Zondervan, MacLennan.
Drafting of the manuscript: Beyer, Zondervan, MacLennan.
Critical revision of the manuscript for important intellectual content: Beyer, Widdershoven, Wintner, Dabestani, Marconi, Moss, Kinsella, Yuan, Giles, Barod, Van Hemelrijck, Bex, Zondervan, MacLennan.
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Appendix A. Supplementary data

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