Systematic Review of Comparative Patient Reported Outcomes and Health-Related Quality of Life After Management of Localized Renal Masses or Renal Cell Carcinomas

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Abstract

Objective To perform a systematic review assessing the impact of the different management options on health-related quality of life (HRQoL) of patients with localized renal masses or renal cell carcinomas (LRM/LRCC).

Materials and Methods Searches covering PubMed, Embase (Ovid), CENTRAL, PsycINFO (Ovid), CINAHL (EBSCO), and Cochrane Central Register of Controlled Trials (CENTRAL) databases was conducted for papers published up to 25 April 2021. Methods as per Cochrane Handbook were followed. "Modality" of treatment included radical nephrectomy (RN), nephron-sparing surgery (NSS), thermal ablation (TA), and active surveillance (AS). "Approach" was categorized as open incision and minimally invasive surgery (MIS). Risk of bias was assessed by ROBINS-I and Cochrane RoB 2 for observational studies and randomized controlled trials, respectively and certainty of the evidence by GRADE.

Results Sixteen observational studies and 1 randomized controlled trial (2.370 patients) met inclusion criteria. Fifteen different patient reported outcome measures (PROMs) were identified. Heterogeneity prevented quantitative analysis.

Generic HRQoL decreases after RN and NSS, recovers within 6 to 12 months, and mostly overlaps with baseline values, irrespective of modality. Cancer-specific HRQoL improves faster after open-NSS than open-RN. The detrimental effect of RN may persist long-term in cross-evaluations. QoL scales significantly decrease after open surgery and MIS during the first weeks but improve faster after MIS. They are similar for both approaches at 1 year. Long-term cancer-specific QoL is similar for MIS and open procedures. Fear of recurrence is lower in older patients and affected by neither modality nor approach.

Conclusions Low quality evidence supports the use of MIS over the open approach when HRQoL is considered in the management of LRMs/LRCCs; data regarding the effect of the treatment modality of the LRM/LRCC show contradictory outcomes.

Key Words

HRQoL, PROMs, QoL, localized renal cell carcinoma, surgical management, localized renal mass

Competing Interests

None declared.

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Abbreviations

AS active surveillance
HRQoL health-related QoL
LRCC localized renal cell carcinoma
LRM localized renal mass
MIS minimally invasive surgery
NSS nephron-sparing surgery
PN partial nephrectomy
PROM patient reported outcome measures
RCC renal cell carcinoma
RCT randomized controlled trial
RN radical nephrectomy
TA thermal ablation
VAS visual analog scale

Introduction

Approximately 70% of renal cell carcinomas (RCC) are clinically diagnosed as localized renal masses (LRM)[1]. Of the latter, a non-negligible proportion—between 10% and 30%—will be ultimately confirmed as benign at histological examination[2–4]. The surgical management options include radical nephrectomy (RN) or nephron-sparing surgery (NSS), both of which can be performed by an open or minimally invasive approach (MIS). MIS includes laparoscopic and robotic (R) surgery as well as any modification of these approaches. Furthermore, patients with stage cT1a RCC can be offered active surveillance (AS) or interventional percutaneous thermal ablation (TA)[5].

A previous systematic review synthetising perioperative and quality of life (QoL) outcomes for the management of localized RCC (LRCC) showed inconclusive evidence about QoL while comparing partial nephrectomy (PN) with RN[6]. Although a significantly better short-term physical function was found for laparoscopy than for open approach, only 3 studies reported on generic or cancer-specific QoL measurements, stressing the need for future research[6].

Patient reported outcomes (PROM) are increasingly used in surgery as a practical tool for assessing outcomes[7,8]. Particularly when several management options with similar clinical efficacy coexist[2,8], the impact of a given treatment on patient QoL plays an important role in the clinical decision-making. Health-related QoL (HRQoL) is subjective, multidimensional, and influenced by the nature of the histological diagnosis. Patients diagnosed with a cancer are likely more tolerant of a negative impact of treatment on QoL than patients found to have a benign condition. This is relevant in the management of localized renal masses because a proportion are benign[2–4].

Parallel to the increasing incidence of LRM[9], integration of patient's perception and values in the process of care becomes imperative[7,8] and a number of comparative reports on QoL using PROMs have been published in the last 5 years. Data compilating the current knowledge in the subject seems indicated.

The aim of this systematic review was to critically appraise and synthesise the comparative evidence on HRQoL measured by PROM among the different management approaches in patients with LRMs or LRCCs.

Materials and Methods

Data Sources and Searches

A search for relevant literature published in English was conducted up to 4 April 2019 and updated on 25 April 2021. The following databases were searched: PubMed, Embase (Ovid), CENTRAL, PsycINFO (Ovid), CINAHL (EBSCO) and CENTRAL. The search strategy is included in **Supplementary Appendix 1** (available at siuj.org). We followed the PRISMA guidance and the Cochrane Handbook[10,11]. The protocol was registered with PROSPERO (CRD 42019107456).

Study Selection, Data Extraction and Analysis

Study selection was based on predefined criteria according to the PICO (population, intervention, comparison, outcomes) constructed for this systematic review (**Table 1**).

We sought a response to 2 questions: (1) Is HRQoL after NSS better than after RN? (2) Is HRQoL better after MIS than after open approach? A comparison between surgical management, TA, or AS in small renal masses was planned.

Only studies using original or cross-validated PROMs comparing 2 or more management options for LRMs/LRCCs were included. Studies that reported on surgical or interventional management for other kidney conditions were excluded.

Two reviewers (L.S. and L.O.) independently performed abstract and full-text screening and data extraction. Information collected included patient characteristics, PROM distribution and response, missing data, time-points for evaluation, outcomes and confounders analysis, and interpretation of results. Two senior authors acted as arbitrator (M.P.L. or M.I.O.) in case of disagreement.

"Modality" of treatment included RN, NSS (PN, tumorectomy), TA, and AS. "Approach" was categorized as open incision (any), MIS (laparoscopic or robotic), and percutaneous. Management strategies included all possible combinations of modality of treatment and

TABLE 1.

PICO search strategy for the systematic review

P (Population)	Inclusion criteria • Patients aged ≥ 18 yr with localized renal tumours (cT1-T2, non-metastatic) either RCC or renal masses • Treated by any surgical option (RN or NSS) or alternatives including ablation and active surveillance by any type of approach (open, laparoscopic, robotic or percutaneous) • Use of validated QoL questionnaires (including VAS) to assess health related quality of life • Comparison between or among treatments Exclusion criteria • Presence of metastasis and/or gross or pathological lymphadenopaties • > 20% non-localized (clinical or pathological T3-4) renal tumours • Non-comparative studies
I (Intervention)	• Open radical nephrectomy (ORN) when included as treatment group • If no ORN present in the comparison as denominator any of the other surgical options or alternative treatments can be used as comparator after consensus with the senior reviewer
C (Comparator)	• RN laparoscopic or robotic • Open NSS (open, laparoscopic (or any laparoscopic assisted technique) or Robotic (or any robotic assisted technique) • Ablation either RFA or CA percutaneous or laparoscopic • Active surveillance
O (Outcomes)	• Primary outcome: differences in HR QoL according to the different management strategies • Secondary outcomes: evolution of HRQoL after any management strategy

approach. Studies with response rate ≥70% were considered as "data available for all or nearly all participants."

Evidence synthesis was primarily categorized according to modality or approach. We identified a variety of instruments for measuring HRQoL across studies, and comparisons were based on the use of the same PROM. Study design (longitudinal or cross-sectional) was taken into account in the evidence synthesis.

Risk of Bias Assessment and Strength of Body of Evidence

Two reviewers independently assessed the risk of bias. ROBINS-I tool[12] was used for comparative observational studies, and the Cochrane RoB 2[13] for RCTs. The quality of the evidence was assessed using GRADE[14]. Discrepancies were resolved by senior authors.

Results

From the 1404 identified citations, 16 observational comparative studies[15–30], and 1 RCT[31] met the inclusion criteria. The PRISMA diagram depicts the flow of the literature selection (**Figure 1**).

A total of 2370 patients were included. Characteristics of the studies and the patients, PROMs used, time-points of evaluation, outcomes, confounders, and variables of interest of the included studies are summarized in Tables 2 and 3. Eleven studies included exclusively LRCCs [16–18,20,23,25–29,31] and 6 LRMs[15,19,21,22,24,30].

There were 6 longitudinal[15,17,21,22,26,30] and 9 cross-sectional studies[16,18–20,24,25,27–29]. In 1 study, cross-sectional and longitudinal cohorts overlapped but outcomes were reported separately[23]. The RCT reported outcomes at 1 month[31]. Ten studies reported correction for possible confounders [15–23,30] using several statistical methods for adjustment, and 1 study considered only the effect of complications on HRQoL[29] (**Tables 2 and 3**).

PROMs used to assess QoL and distribution

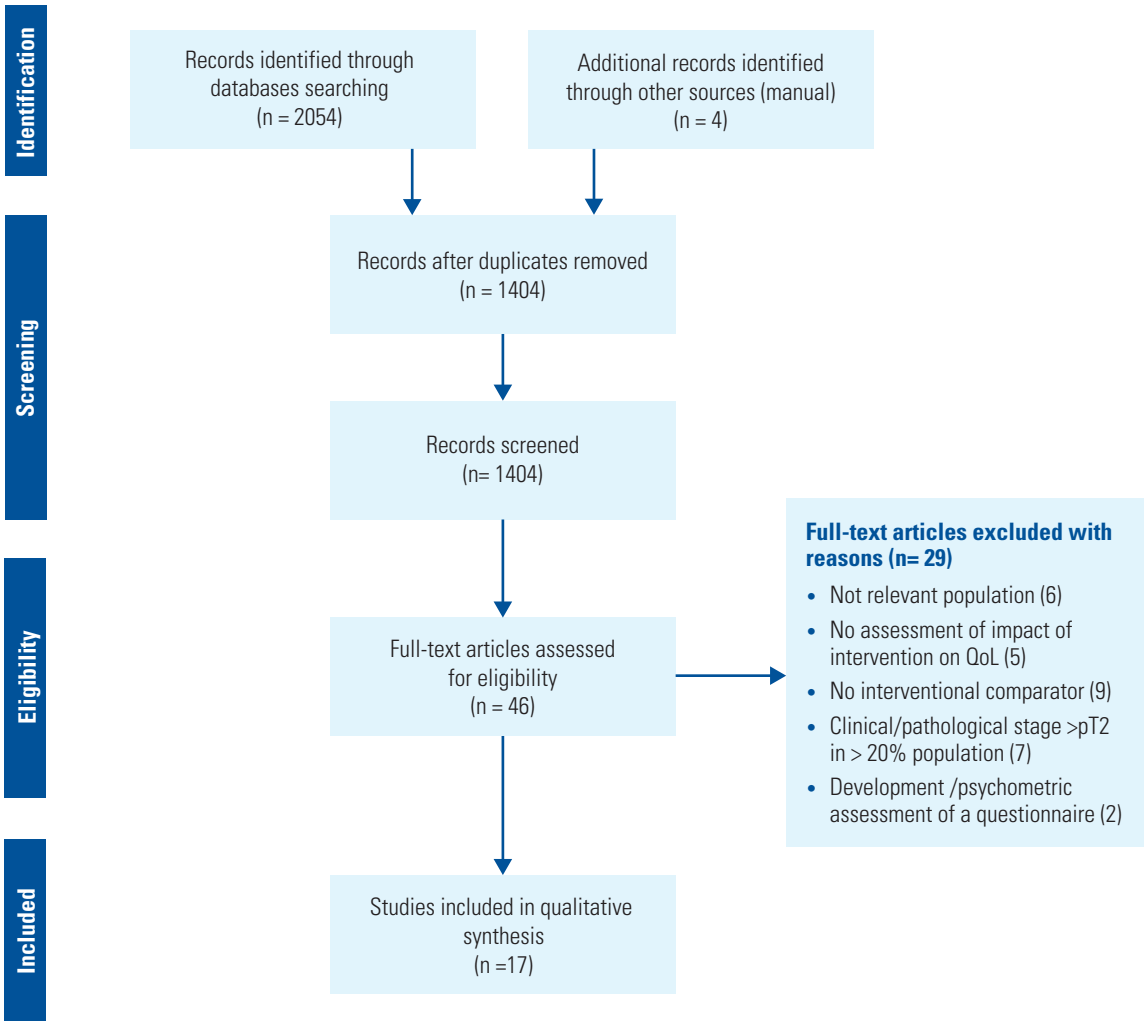
Supplementary Table 1 (available at siuj.org) summarizes the intended measure and the targeted population of the 15 English original or cross-culturally validated PROMs used. Three were generic (SF-36, SF-12 and VAS), 3 cancer- specific, including one for kidney cancer, and 9 condition-specific, assessing aspects imbricated in HRQoL.

Ten studies used a single PROM[15,16,19,20,22,24–26,28,29] and 7 more than 1[17,18,21,23,27,30,31] (3 and 2 studies used 2 and 3 PROMs respectively, 2 studies, 4 and 5 respectively). The most frequently used PROMs were SF-36, EORTC QLQ-C30, and IES by 8, 5, and 2 studies respectively. The remaining PROMs were used once each. VAS was used in 4 studies to evaluate pain or cosmetic outcomes.

In 10 studies, PROMs were distributed by mail [16,18,20,21,23-25,28–30], 5 were described as self-administered[15,17,22,26,27], and in 2 studies distribution method was not described[19,31].

The response rate was reported in 16 studies[15–26, 28–31], and varied from 37.2% to 93.4%; it was >70% in all but 2 studies[19,21]. Rates of completeness of the

FIGURE 1.
Preferred reporting Items for systematic reviews and meta-analysis (PRISMA) flow diagram



questionnaire were reported in only 2 studies[16,21] and were 74% and 37.2%.

Standards for comparison

There were 3 standards for comparison:

- head-to-head comparison between or among management strategies in 6 longitudinal[15,17,21,26,30,31] and 9 cross-sectional[16,18–20,24,25,27–29] studies.
- comparison with the corresponding baseline scores in 6 longitudinal cohorts[17,21,23,26,30].
- comparison with the age–sex normative scores of the country's general population in 2 longitudinal[22,26] and 5 cross-sectional[18–20,23,29] studies.

Outcomes

Six studies presented comparative outcomes on modality[15,16,18,22,23,27], 6 on approach [17,19,20,24,25,31] and 4 reported separately outcomes stratified by modality or approach[21,28,29,30]. Two articles compared an open approach with MIS (RN, PN, or ablation by PCA or PRFA) [26,30].

Is HRQoL after NSS better than after RN?

Follow-up in longitudinal studies was up to 1 year, although 1 reported up to 7 years[15,21–23,26,30]. The cross-sectional time-points evaluations ranged from 12 months to a mean of 40 to 62 months[16,18,23,27–29] (Table 2).

At baseline there was no statistically significant difference in generic or cancer-specific scores between open RN and open NSS[21–23,30]. Small but significant changes were seen at 3 and 6 months in most of the scales compared with median baseline scores for RN (open/MIS) and open-NSS[22,23], with the exception of physical functioning, that was similar to baseline at 6 months[22]. At 1 year, all scales overlapped baseline

values in 52% to 80% of patients[22] and no differences were seen in mean scores between open-RN and open-NSS or compared with baseline values[29,30]. There were no long-term differences between patients receiving open-RN and open-NSS[18,23], although several scores were higher in the subset of elective-NSS compared with RN or mandatory-NSS[23].

Two longitudinal studies showed earlier improvement in cancer-specific QoL in the NSS group than in the RN group[21,23]. However, better scores than at baseline were reached in RN at 2 months with a clear time-effect improvement up to 1 year[21,30]. At 1-year post procedure, RN was shown to have a detrimental effect on physical and emotional scores, although one series showed all scales returned to baseline levels in NSS[23].

Cross-sectional evaluations showed a negative impact of RN compared with NSS on cancer-specific QoL at 2 years. General health and physical and functional roles improved significantly in both modality groups at 4 years[16], although NSS patients reported better scores, mostly on physical scales[16,23,28].

There were no differences between RN and NSS groups on intrusive thoughts and fear of recurrence at baseline or at 6 months[21,23]. The significant trend to fewer intrusive thoughts about kidney cancer and avoidance behaviour at 1 year for open-NSS, was no longer apparent in the longer term[18,21,23].

Other less frequently used questionnaires showed overlap in the functional impairment for open-NSS and open-RN and a lower level of anxiety and depression in elective open-NSS than in open-RN[27].

Is HRQoL better after MIS than after open approach?

Three longitudinal[17,21,30] and 3 cross-sectional [19,25,29] studies compared MIS with open approach. Two studies compared MIS with LESS[24,31], and 1 compared 2 open approaches[28] (**Table 3**). The time-points for evaluation varied from 1 week to 1 to 3 months, and 2 studies conducted an additional assessment at 6 and 12 months[17,21].

In 1 study, general health at baseline was significantly lower in patients undergoing open procedures than in those undergoing MIS-RN[17], whereas no difference was found between MIS and open-RN/NSS in other studies[21,30]. A significant decrease in physical and general health scales occurred in both approaches during the first postoperative weeks, more so for open procedures[21,30]. Patients showed faster improvement on physical scales after MIS than after open approach, irrespective of modality (2 versus 3 months). At 6 and 12 months, scales were similar for open and MIS approach[21,25,29,30] and higher or similar to baseline[17,30]. Mental component scales remained unchanged across the follow-up in both groups[21].

At mid- and long-term, cancer-specific QoL was similar between MIS and any open incision for either PN or RN[19,21,30], but patients who underwent MIS reported a short period of convalescence defined as recovery to a performance level of 80%[19].

A small RCT showed better postoperative recovery after LESS-RN than conventional LRN[30]. Short-postoperative VAS pain and analgesic requirements were similar between MIS and open approaches[17], while LESS approaches showed inconclusive pain outcomes compared with conventional MIS[24,30].

Overall, older individuals had significantly fewer intrusive thoughts and avoidance behaviour across the first year, regardless of surgical approach[21].

Comparison with matched age–sex normative scores for the general population

Two longitudinal[22,26] and 3 cross-sectional[18,23,29] studies compared the impact of modality on HRQoL with the country normative population values (**Tables 2** and **3**).

At baseline, general QoL median scores of RN (open/MIS) or open-NSS patients were within 1 SD of the age–sex matched population scores[22]; however, the scales of patients receiving percutaneous TA were significantly lower[26]. Whether generic or cancer-specific QoL, median physical or mental scores of RN and NSS at 1-year or at long-term did not differ from those of the matched general population[18,22,23,29] with the exception of 1 study that reported higher physical scores than those of the matched population in all groups[29].

Regarding approach, there were no differences at baseline or at 12 months in generic HRQoL between open and MIS (RN/NSS)[29]. Long-term cancer-specific general health and social functioning were higher than in the normative population, irrespective of the approach, although one study reported that treated individuals had more symptoms than the general population[19]. Others found that only laparoscopically treated patients (RN/NSS) scored at the same level as the normative population, while those treated by an open approach experienced a detrimental impact on general health, as well as functional and symptom indices[20].

HRQoL outcomes in clinical or pathological T1a

Four studies comparing treatment modality included exclusively cT1a RMs or pT1a RCCs[15,18,26,28] and 1 also approach[28]. Adjustment for confounders was tested in 2 studies[15,18] (**Tables 2** and **3**).

At baseline, patients choosing AS or receiving subsequent treatment by RN or TA had significantly lower

TABLE 2.

Comparative HRQoL outcomes between or among modalities of treatment

Author, year of publication	Questionnaires	Country/ study period	No patients	Time of evaluation	Interventions	
Longitudinal studies						
Novara et al. (2010)[22]	SF-36	Italy 2006–2007	129	Baseline 6 – 12 months	ORN LRN OPN	

[a]Included two overlapping cohorts: longitudinal assessment in a sub-cohort of 51 patients and cross-sectional assessment in a cohort of 306 patients [b]Parker percentage of patients that received different management combinations. [c]Not assessed by validated questionnaire [d]Approach not specified [e]Data not reported on LTE questionnaire outcomes. [f]Median or mean follow-up

ORN: open radical nephrectomy ; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; e-ONSS: elective open nephron sparing surgery; LPN: laparoscopy partial nephrectomy; PN: partial nephrectomy; RN: radical nephrectomy; PRFA: percutaneous radiofrequency ablation; NSS: nephron sparing surgery; Open; L: laparoscopy ; m-ONSS: mandatory open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; e-OPN: elective open partial nephrectomy; m-OPN: mandatory open partial nephrectomy; MIS: minimally invasive surgery; AS: active surveillance

generic QoL scores than those preferring upfront PN, after controlling for time, age, sex, CCI, and BMI[15]. Total scores remained significantly lower in AS than in RN for up to 2 years, while mental health scores were comparable across groups during follow-up[15].

Baseline scales of patients receiving PRFA were significantly lower than the national norm or than those of LRN patients[26]. After LRN, several physical and emotional scores were significantly lower than at baseline, while no changes occurred in PRFA patients. LRN scales recovered between 4 and 12 weeks. Overall, there were no significant differences in scales between the 2 groups during follow-up[26].

Two cross-sectional long-term comparisons between open-RN and PN did not show any impact of modality in HRQoL or differences with the normative population whether generic or cancer-specific PROMs were used[18,28]. Nevertheless, the physical functioning scale was higher for the NSS group[28].

Confounders and predictive factors

Overall, 25 covariables were considered across studies as interacting or confounding with general and cancer-specific HRQoL outcomes, or as predictive factors at different time-points in the management process[15–23,29,30] (**Supplementary Table 2**; available at siuj.org).

Risk of Bias assessment and certainty of evidence

RoB assessment of the 16 observational studies was critical in 6[24–28] and serious in 10[15–23,30] **Supplementary Table 3**; available at siuj.org). The RCT was judged at high risk of bias for all outcomes[31] (**Supplementary Appendix 2a and b**; available at siuj.org). Certainty of the evidence was very low for all studies (**Table 4**).

Discussion

Our systematic review confirms the post-treatment deleterious effect of both RN and NSS on HRQoL of

	Outcomes (Comparison between/among interventions or with baseline scores)	**Outcomes** (Comparison with median normative scores of general population)	**Predictors/ interactions**

	• **SF-36:** at 6 and 12 months
	  • Significant modification of median values in all domains except PF and GHP when - compared with baseline.
	  • RP and BP domains lower than baseline (<0.05).
	  • EWB, RE, EF and SF significantly higher than baseline (<0.05)
	  • At 6 months 59%-81% of patients scores overlapping baseline values.
	  • At 12 months 52%-80% of patients scores overlapping with baseline values.
	  • Similar patterns of evolution with respect to baseline for ORN and e-NSS
		• **SF-36:**
		  • At baseline, no significant differences with the general Italian population (all within 1 SD of normative data).
		  • At 6 and 12 months the mean scores for each domain within 1 SD of age-gender matched normative data for the Italian population.
			• **Associated with recovery of SF-36 baseline scores at 6 months:** educational level and NYHA class in RE domain; BMI in EWB; NYHA class in RP; mode presentation in GHP; indication for NSS in PF and tumor histology in BP.
			• **Associated with recovery of SF-36 baseline scores at 12 months:** Age and NYHA class with PF; occupational level with RP; BMI and pathological size with BP; indication for NSS with SF; tumor histology with RE; clinical Stage with GHP and EF domains.
			• e-ONSS higher chances to return to baseline PF at 6 months and significantly higher probability of returning to baseline scores at 12 months.

PF: physical functioning; GHP: general health perception; RP: role limitations due to physical health problems; BP: bodily pain; EWB: emotional well-being; RE: role limitations due to emotional problems; EF: energy /fatigue; SF: social functioning; SD: standard deviation; NYHA: New York Heart Association ; BMI: body mass index; RF: role functioning; PCS: physical component summary; MCS: mental composite summary; CCI: Charlson comorbidity index; GH : general health; VT: vitality; MH: mental health.

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patients with LRMs/LRCCs during the early post-surgery phase. The effect is more pronounced for RN, mainly affecting the physical and emotional domains. Although the majority of patients in both modalities recover to baseline levels between 6 and 12 months post surgery, the impact of RN may be long-lasting. Reports are more consistent on the lower impact of MIS on QoL scores and on a faster recovery when compared with open approach, especially regarding the physical component scales. Overall, levels of intrusion and avoidance behaviour remained low across the follow-up, irrespective of modality or approach.

Studies comparing HRQoL between surgical management and AS or percutaneous ablation did not allow for a firm conclusion as in both cases a unique comparative study was available. Data on patient baseline QoL suggest a strong directional management selection bias for AS and ablation[15,26,30] in accordance with the clinical selection criteria established for both types of management[32].

Overall, the included studies were heterogenous, most of them with small cohorts, and a wide variety of PROMs were used to assess QoL. Although straightforward comparisons of modality or approach were found, the diversity in reporting and the patient selection bias precluded meta-analysis[10].

As indications for modality depend on tumour and patient characteristics, selection bias may be unavoidable in HRQoL assessments, even in longitudinal studies. However, the likelihood of bias in cross-sectional evaluations was high, not only because of the lack of baseline assessment but also because unforeseen new factors coexist at evaluation that mask causality even when adjusted analyses are conducted[33].

Apart from the previously mentioned reasons for apparent discordances in outcomes, with respect to modality comparisons, it is the lack of standardization in reporting that stands out as the most important when generic QoL PROMs are used (total global

TABLE 2.

Comparative HRQoL outcomes between or among modalities of treatment, *Cont'd*

Author, year of publication	Questionnaires	Country/ study period	No patients	Time of evaluation	Interventions	
Poulakis et al. (2003)[23][a]	EORTC QLQ-C30 SF-36 IES-R FCR	Germany 1991–2001	Last 51	Baseline 3–6–9 – 12 months[f] (20 months)	ORN e-ONSS	

[a]Included two overlapping cohorts: longitudinal assessment in a sub-cohort of 51 patients and cross-sectional assessment in a cohort of 306 patients [b]Parker percentage of patients that received different management combinations. [c]Not assessed by validated questionnaire [d]Approach not specified [e]Data not reported on LTE questionnaire outcomes. [f]Median or mean follow-up

ORN: open radical nephrectomy ; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; e-ONSS: elective open nephron sparing surgery; LPN: laparoscopy partial nephrectomy; PN: partial nephrectomy; RN: radical nephrectomy; PRFA: percutaneous radiofrequency ablation; NSS: nephron sparing surgery; Open; L: laparoscopy ; m-ONSS: mandatory open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; e-OPN: elective open partial nephrectomy; m-OPN: mandatory open partial nephrectomy; MIS: minimally invasive surgery; AS: active surveillance

	Outcomes (Comparison between/among interventions or with baseline scores)	**Outcomes** (Comparison with median normative scores of general population)	**Predictors/ interactions**

	Overall type of operation no influence on patients QoL. Several scores higher in NSS in generic or cancer-specific PROMs
	• **EORTC QLQ C30:**
	  • at 3 months, patients after ORN showed significant changes in a higher number of scales (significantly decreased) than in e-ONSS
	  • at 12 months in e-ONSS all scales returned to baseline values. PF, RF, emotional function and global QoL significantly higher in e-ONSS than in ORN
	• **SF-36:** at 12 months
	  • RE ($P < 0.001$) and RP ($P < 0.001$) significantly lower than baseline after ORN.
	  • All scales similar to baseline in e-ONSS.
	  • Statistically significant difference in favour of e-ONSS when compared to ORN in PF, RP, vitality and RE (compared US population).
	• **IES-R:** at 12 months
	  • no statistically significant changes were observed for either group.
	  • e-ONSS significantly lesser intrusive and avoidance thoughts.
	• **FCR:**
	  • at 12 months significantly greater in ORN than in e-NSS.
		—	—

PF: physical functioning; GHP: general health perception; RP: role limitations due to physical health problems; BP: bodily pain; EWB: emotional well-being; RE: role limitations due to emotional problems; EF: energy /fatigue; SF: social functioning; SD: standard deviation; NYHA: New York Heart Association ; BMI: body mass index; RF: role functioning; PCS: physical component summary; MCS: mental composite summary; CCI: Charlson comorbidity index; GH : general health; VT: vitality; MH: mental health.

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TABLE 2.

Comparative HRQoL outcomes between or among modalities of treatment, *Cont'd*

Author, year of publication	Questionnaires	Country/ study period	No patients	Time of evaluation	Interventions	
Parker et al. (2012)[21][b]	SF-36 IES CARES-SF FCR	United States 2001–2007	64	Baseline– 3 weeks 2–3–6–12 months	ORN (14%) LRN (32%) LPN (12%) OPN (42%)	

[a]Included two overlapping cohorts: longitudinal assessment in a sub-cohort of 51 patients and cross-sectional assessment in a cohort of 306 patients
[b]Parker percentage of patients that received different management combinations. [c]Not assessed by validated questionnaire [d]Approach not specified
[e]Data not reported on LTE questionnaire outcomes. [f]Median or mean follow-up

ORN: open radical nephrectomy ; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; e-ONSS: elective open nephron sparing surgery; LPN: laparoscopy partial nephrectomy; PN: partial nephrectomy; RN: radical nephrectomy; PRFA: percutaneous radiofrequency ablation; NSS: nephron sparing surgery; Open; L: laparoscopy ; m-ONSS: mandatory open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; e-OPN: elective open partial nephrectomy; m-OPN: mandatory open partial nephrectomy; MIS: minimally invasive surgery; AS: active surveillance

	Outcomes (Comparison between/among interventions or with baseline scores)	**Outcomes** (Comparison with median normative scores of general population)	**Predictors/ interactions**

	• At baseline no significant differences among groups in any questionnaire
	• No statistically significant differences for any treatment group across follow-up with baselines scores in any questionnaire.
	• **SF-36**
	  • PCS and MCS lower at 3 weeks
	  • steady recuperation from 2 until 12 months
	• **CARES-SF**
	  • at 3 weeks only PN lower global score (better specific QoL).
	  • RN lower average global scores (p 0.03) indicating better cancer specific QoL than PN at 2, 3, 6 and 12 months (p 0.03) compared to baseline
	• **IES**
	  • older individuals' fewer intrusive thoughts and avoidance behaviours (p 0.04). Time effect (fewer at 2, 6 and 12 months compared with 3 weeks)
	• **Fear of recurrence:**
	  • Increases non-significantly across the follow-up in all groups.
		—	• **SF-36:** PCS significantly associated to postoperative GFR (*P* 0.015).
			• **CARES-SF:** time interaction/effect (predictor) at 2, 3, 6 and 12 months significantly lower scores (all *P* = 0.001) compared with 3 weeks (improvement in QoL).
			  • Pre- and postoperative GFR significantly associated with CARES-SF global score.
			• **IES:** age, significant predictor of total scores and time effect.
			  • No effect of type of surgery.
			Postoperative GFR significantly associated (*P* = 0.012).
			• **Fear of recurrence** associated with age. Older significantly higher scores and increased significantly at all time points compared with 3 weeks.
			No effect of type of surgery.
			Postoperative GFR significantly associated (*P* = 0.002).

PF: physical functioning; GHP: general health perception; RP: role limitations due to physical health problems; BP: bodily pain; EWB: emotional well-being; RE: role limitations due to emotional problems; EF: energy /fatigue; SF: social functioning; SD: standard deviation; NYHA: New York Heart Association ; BMI: body mass index; RF: role functioning; PCS: physical component summary; MCS: mental composite summary; CCI: Charlson comorbidity index; GH : general health; VT: vitality; MH: mental health.

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TABLE 2.

Comparative HRQoL outcomes between or among modalities of treatment, *Cont'd*

Author, year of publication	Questionnaires	Country/ study period	No patients	Time of evaluation	Interventions	
Alam (2018) [15][d]	SF-12	United States 2009–2016	531	Baseline 6 months 1–2–3–4–5–6–7 years	PN RN Ablation AS	
Onishi et al. (2007)[26]	SF-36	Japan 2004–2006	37	Baseline- 1–4–12–24 weeks	LRN PRFA	

[a]Included two overlapping cohorts: longitudinal assessment in a sub-cohort of 51 patients and cross-sectional assessment in a cohort of 306 patients [b]Parker percentage of patients that received different management combinations. [c]Not assessed by validated questionnaire [d]Approach not specified [e]Data not reported on LTE questionnaire outcomes. [f]Median or mean follow-up

ORN: open radical nephrectomy ; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; e-ONSS: elective open nephron sparing surgery; LPN: laparoscopy partial nephrectomy; PN: partial nephrectomy; RN: radical nephrectomy; PRFA: percutaneous radiofrequency ablation; NSS: nephron sparing surgery; Open; L: laparoscopy ; m-ONSS: mandatory open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; e-OPN: elective open partial nephrectomy; m-OPN: mandatory open partial nephrectomy; MIS: minimally invasive surgery; AS: active surveillance

	Outcomes (Comparison between/among interventions or with baseline scores)	**Outcomes** (Comparison with median normative scores of general population)	**Predictors/ interactions**

	• **SF-12:**
	  • at enrolment and at 2–3 years total scores significantly lower in AS when compared only to PN (after controlling for time, age, gender, CCI and BMI).
	  • At enrolment AS, Ablation and RN similar scores.
	  • PCS significantly lower amongst AS patients when compared to PN at enrolment and annually until year 5.
	  • MCS comparable across all management groups at each point of follow up.
		—	• **SF-12:** lower scores associated with female and increased CCI and BMI.
			• Lower PCS for AS associated to female, increased CCI and BMI, each additional year of follow up and older age at enrolment.
			• MCS score higher with each year of follow-up, with older age at enrolment and for males

	• **SF-36**
	  • at baseline PRFA significantly lower PF (0.008), RP (0.035), VT (0.003) and MH (0.009) than LRN.
	  • comparing with baseline no reduction of any scores in PRFA 1 week after surgery
	  • comparing with baseline, PF, RP and RE scores mean values of the LRN group significantly lower at 1 week
	  • recovery of PF, RP and RE scores in LRN group at 4-12 weeks after surgery.
	  • no significant difference in any domain of SF- 36 between the two groups during follow up period.
		• At baselines PRFA group SF RE GH SF, RE and MH scales significantly lower than nation normative.
		• LRN: at baseline only SF (p 0.034) significantly lower than national-normative.
			—

PF: physical functioning; GHP: general health perception; RP: role limitations due to physical health problems; BP: bodily pain; EWB: emotional well-being; RE: role limitations due to emotional problems; EF: energy /fatigue; SF: social functioning; SD: standard deviation; NYHA: New York Heart Association ; BMI: body mass index; RF: role functioning; PCS: physical component summary; MCS: mental composite summary; CCI: Charlson comorbidity index; GH : general health; VT: vitality; MH: mental health.

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TABLE 2.

Comparative HRQoL outcomes between or among modalities of treatment, *Cont'd*

Author, year of publication	Questionnaires	Country/ study period	No patients	Time of evaluation	Interventions	
Sandbergen et al. (2020) [30]	SF-36 FKSI-15 VAS	Netherlands 2011–2014	98	Baseline 1–3–12 months	NSS (Open, MIS) RN (Open, MIS)	
Cross-sectional studies						
Azawi et al. (2015)[16][c]	EORTC QLQ-C30	Denmark 2008–2013	162	<2 years, 2–4 years, >4 years	ORN and LRN ONSS and LNSS	

[a]Included two overlapping cohorts: longitudinal assessment in a sub-cohort of 51 patients and cross-sectional assessment in a cohort of 306 patients [b]Parker percentage of patients that received different management combinations. [c]Not assessed by validated questionnaire [d]Approach not specified [e]Data not reported on LTE questionnaire outcomes. [f]Median or mean follow-up

ORN: open radical nephrectomy ; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; e-ONSS: elective open nephron sparing surgery; LPN: laparoscopy partial nephrectomy; PN: partial nephrectomy; RN: radical nephrectomy; PRFA: percutaneous radiofrequency ablation; NSS: nephron sparing surgery; Open; L: laparoscopy ; m-ONSS: mandatory open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; e-OPN: elective open partial nephrectomy; m-OPN: mandatory open partial nephrectomy; MIS: minimally invasive surgery; AS: active surveillance

	Outcomes (Comparison between/among interventions or with baseline scores)	**Outcomes** (Comparison with median normative scores of general population)	**Predictors/ interactions**

	• **SF-36:**
	  • at baseline, no differences among modalities
	  • at 1 month: social functioning and role physical significantly better in PCA than in NSS.
	  • At 3 months significant better health transition and mental health in RN than CA
	  • At 12 months only health transition scale significantly better in RN than in CA (other scales recovered baseline values).
	• **FKSI-15:** No differences at baseline or in follow up.
	• **VAS:** At s at baseline significantly more pain in CA than in RN. No differences in follow-up
		—	• Data did not change substantially when corrected for the following confounders Charlson-age adjusted comorbidity index, PADUA and RENAL anatomic complexity scores, clinical TNM, definitive histopathology and the presence of complications across the different study time points.

	• **EORTC QLQ C30:**
	  • Low overall global health status for whole cohort
	  • RN significant negative impact on QoL.
	  • PN significantly higher QoL score than RN
	  • Patients > 4 year after operation better GH-QoL and better PR and RF than patients < 2 year of surgery.
		—	• RN negative predictor of GH-QoL, PF, RF, and fatigue.
			• Recurrence status, operation <2 years and symptomatic disease negative impact on QoL.
			• RCC recurrence negative effect on most domains of QoL

PF: physical functioning; GHP: general health perception; RP: role limitations due to physical health problems; BP: bodily pain; EWB: emotional well-being; RE: role limitations due to emotional problems; EF: energy /fatigue; SF: social functioning; SD: standard deviation; NYHA: New York Heart Association ; BMI: body mass index; RF: role functioning; PCS: physical component summary; MCS: mental composite summary; CCI: Charlson comorbidity index; GH : general health; VT: vitality; MH: mental health.

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TABLE 2.

Comparative HRQoL outcomes between or among modalities of treatment, *Cont'd*

Author, year of publication	Questionnaires	Country/ study period	No patients	Time of evaluation	Interventions	
Poulakis et al. (2003)[23][a]	EORTC QLQ-C30 SF-36 IES-R FCR	Germany 1991–2001	306	ONSS [f] 54.5 (± 27.8) months ORN [f] 62 (± 34.7) months	ORN m-ONSS e-ONSS	
Shinohara et al. (2001) [28]	EORTC QLQ-C30	Japan 1986-1996	50	ONSS[f] 47 (±40) months ORN[f] 60 (±31) months	ORN ONSS	

[a]Included two overlapping cohorts: longitudinal assessment in a sub-cohort of 51 patients and cross-sectional assessment in a cohort of 306 patients
[b]Parker percentage of patients that received different management combinations. [c]Not assessed by validated questionnaire [d]Approach not specified
[e]Data not reported on LTE questionnaire outcomes. [f]Median or mean follow-up

ORN: open radical nephrectomy ; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; e-ONSS: elective open nephron sparing surgery; LPN: laparoscopy partial nephrectomy; PN: partial nephrectomy; RN: radical nephrectomy; PRFA: percutaneous radiofrequency ablation; NSS: nephron sparing surgery; Open; L: laparoscopy ; m-ONSS: mandatory open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; e-OPN: elective open partial nephrectomy; m-OPN: mandatory open partial nephrectomy; MIS: minimally invasive surgery; AS: active surveillance

	Outcomes (Comparison between/among interventions or with baseline scores)	**Outcomes** (Comparison with median normative scores of general population)	**Predictors/ interactions**

	Overall type of operation no influence on patients QoL. Several scores higher in NSS in generic or cancer-specific PROMs
	• **EORTC QLQ-C30:**
	  • e-ONSS scored significantly better (P<0.05) on PF, RF, fatigue, and pain than ORN or m-ONSS.
	• **SF-36**
	• e-ONSS significantly greater scores on PF, RF and lower scores on bodily pain than ORN or m-ONSS (P<0.005).
	  • no statistically significant difference in any QoL domains between ORN and m-ONSS or between ORN and ONSS groups.
	• **IES-R:**
	  • Low mean scores for the 3 groups.
	  • No differences between ORN and ONSS (e- or m-).
	• **FCR:**
	  • No differences between ORN and e-ONSS
		• **EORTC QLQ-C30** scores for each domain within 1 SD of the normative for German general population.
		• **SF-36** Cross evaluation mean scores for each domain with 1 SD of the values for United States general population.
			• **SF-36:** factors with the most pronounced influence in all domains were comorbidity, tumor size and type of operation (e-ONSS vs ORN). PF, RF, and bodily pain scores correlated with tumor size in e-ONSS (r2 = 0.83, 0.71 and 0.88 respectively) and with creatinine in mandatory NSS (r2 = 0.96, 0.83, 0.78 respectively).
			• **EORTC C-30:** in functioning domains comorbidity was an independent factor. In symptomatic domains most significant predictors were gender, nephrectomy type and comorbidity \- EORTC after ONSS, PF, RF, fatigue, and pain scores correlated with tumor size (r2 0.83, 0.83, 0.78 and 0.72 respectively)
			• The patients reporting better overall QOL as measured by the physical component summary of the SF-36 were female patients and those with incidental tumor, tumor 4cm, who underwent elective O-NSS, having normal kidney function, with low comorbidity, or with uncomplicated recovery.
			• **IES-R:** in e-ONSS, tumor size < than 4 cm significantly associated to decrease levels of hyperarousal, intrusion and avoidance scores (P < 0.001) than larger size tumors.
			• **FCR:** m-ONSS highest probability of high scores (19.19, 95%CI 17.85-20.54). After ONSS, FCR correlated with tumor size and significantly greater when tumor≥ 4 cm.

	• **EORTC QLQ-C30:**
	  • ONSS significantly higher scores on physical functioning than ORN (P< 0.05).
	  • No differences in the other five functional scales between the two groups.
	  • ONSS lower scores than ORN in the symptom constipation.
		—	—

PF: physical functioning; GHP: general health perception; RP: role limitations due to physical health problems; BP: bodily pain; EWB: emotional well-being; RE: role limitations due to emotional problems; EF: energy /fatigue; SF: social functioning; SD: standard deviation; NYHA: New York Heart Association ; BMI: body mass index; RF: role functioning; PCS: physical component summary; MCS: mental composite summary; CCI: Charlson comorbidity index; GH : general health; VT: vitality; MH: mental health.

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TABLE 2.

Comparative HRQoL outcomes between or among modalities of treatment, *Cont'd*

Author, year of publication	Questionnaires	Country/ study period	No patients	Time of evaluation	Interventions	
Gratzke et al. (2009)[29]	SF-36	Germany Switzerland 2001-2005	85	[f]22 months	ORN, ONSS, Retroperitoneoscopy-RN	
Clark et al. (2001)[18]	SF-36 IES	United States 1990–1997	97	Overall cohort[f] 41.6 (11-91) months (ORN [f]54 ±20 months OPN [f] 39 ±23 months)	ORN e-OPN m-OPN	
Ficarra et al. (2003)[27][e]	ECOG GHQ HADS SPQ LTE	Italy 1985–1999	144	Interval between surgery and evaluation[f] 55 ± 36 months (6–146) ORNf 58 ± 32.6 (6–130) months e-NSS 62.25 ± 41.4 (6–146) months	ORN e-ONSS	

[a]Included two overlapping cohorts: longitudinal assessment in a sub-cohort of 51 patients and cross-sectional assessment in a cohort of 306 patients [b]Parker percentage of patients that received different management combinations. [c]Not assessed by validated questionnaire [d]Approach not specified [e]Data not reported on LTE questionnaire outcomes. [f]Median or mean follow-up

ORN: open radical nephrectomy ; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; e-ONSS: elective open nephron sparing surgery; LPN: laparoscopy partial nephrectomy; PN: partial nephrectomy; RN: radical nephrectomy; PRFA: percutaneous radiofrequency ablation; NSS: nephron sparing surgery; Open; L: laparoscopy ; m-ONSS: mandatory open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; e-OPN: elective open partial nephrectomy; m-OPN: mandatory open partial nephrectomy; MIS: minimally invasive surgery; AS: active surveillance

	Outcomes (Comparison between/among interventions or with baseline scores)	**Outcomes** (Comparison with median normative scores of general population)	**Predictors/ interactions**

	• **SF-36:**
	  • Mean scores for each domain did not differ significantly among groups (*p* 0.325 to 0.960)
	  • ORN group trend to higher MCS than Retro-RN and O-NSS groups
	  • no differences in PCS physical among groups-
		• Mean scores for each domain within 1 SD of age-sex matched normative German population
		• Physical scores higher than the ones of age-sex matched population in all groups
			• When compared to no postoperative complications, the presence of postoperative complications trend towards worse QoL scores regardless of the type of operation. This difference was statistically significant in the GH domain ($P < 0.05$).

	• **SF-36:**
	  • type of operation (ORN vs e- or m- OPN) no impact in QoL.
	• **IES:**
	  • low levels of intrusive thoughts about Kidney cancer or avoidance of coping with anxiety in both groups.
		• **SF-36:** no differences between the overall investigational group and the normative age-gender matched scores of United States population in physical or mental domains.	• Type of operation (RN vs PN) did not correlate with physical or mental composites of SF-36.
			• Only m-OPN had the highest probability of being concerned about having less than two kidneys (*p* 0.039), decreased levels of intrusion and avoidance behaviour and less impact on cancer overall health[c]
			• Mean low scores for the whole group decreased as the self-amount of parenchyma reported increased[c]

	• **ECOG**
	  • overlapping impairment of functional capacity in both groups
	  • no statistically significant differences between groups
	• **GHQ**
	  • no statistically significant differences in scores between groups ($P = 0.46$)
	• **HADS**
	  • e-ONSS lower levels of anxiety ($P = 0.003$) and depression ($P = 0.01$) than ORN
	• **SPQ**
	  • *no statistically significant differences between both groups scores*		

PF: physical functioning; GHP: general health perception; RP: role limitations due to physical health problems; BP: bodily pain; EWB: emotional well-being; RE: role limitations due to emotional problems; EF: energy /fatigue; SF: social functioning; SD: standard deviation; NYHA: New York Heart Association ; BMI: body mass index; RF: role functioning; PCS: physical component summary; MCS: mental composite summary; CCI: Charlson comorbidity index; GH : general health; VT: vitality; MH: mental health.

TABLE 3.

Comparative HRQoL outcomes between or among approaches

Author, year of publication	Questionnaires	Country/study period	No patients	Time of evaluation	Interventions	
Longitudinal studies						
Acar et al. (2014)[17]	SF-36 VAS-pain	Turkey 2007–2010	111	Baseline 1–6mo	ORN LRN	
Parker et al. (2012)[21]	SF-36	United States 2001–2007	64	Baseline, 3 weeks 2-3-6 -12 months	ORN OPN LRN LPN	

[a]secondary outcomes [b]outcomes for comparison of ORN with retroperitoneoscopy-RN [c]not assessed by validated questionnaire
[d]at mean or median follow-up

ORN: open radical nephrectomy; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; LPN: laparoscopy partial nephrectomy; LESS-RN: laparo-endoscopic single site radical nephrectomy; F-ORN: flank open radical nephrectomy; F-ONSS: flank open nephron sparing surgery; T-ORN: transabdominal open radical nephrectomy; T-ONSS: transabdominal open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; HALRN: hand assisted laparoscopy radical nephrectomy; C-RAPN: conventional robotic assisted radical nephrectomy; LESSS-RAPN: laparo-endoscopic single site robotic assisted partial nephrectomy.

	Outcomes (Comparison interventions)	Outcomes (Comparison norm values)	Predictors/ interactions

	• **SF-36:**
	  • At baseline GHP score significantly lower in ORN compared to LRN (*P*< 0.01).
	  • PF and GHP scores significantly lower at 1 month than pre-surgery in both groups.
	  • PF and GH significantly higher at 6 months than pre- surgery in both groups.
	• **VAS-pain:**
	  • Analgesic requirements and scores similar between groups at 48 hours.
	• Technical advantages in postoperative events for LRNb
		—	• SF-36 predictive factors for low PF scores: female gender (OR 14.2), low preop Hb (OR 4.5) and high T stage (OR 2.16).
			  • The GHP scores were positively affected by performing LRN (OR 13) and by young age (OR 0.39)

	• No significant baseline scores differences among the 4 surgical groups for any measure or questionnaire.
	• **SF-36:**
	  • O approach lower PCS scores at 3 weeks than Laparoscopic (*P* = 0.004).
	  • L approach scores improved by 2 months and only minor changes thereafter.
	  • O approach steady improvement for the first 3 months and then slowly up to 12 months.
	  • by 12 months similar PCS scores for O and L approaches
		—	• Mixed model regression statistically significant interaction between O and L surgery and time in PCS scores and general QoL scores (*p* 0.04).
			  • No factor examined was significantly associated with MCS scores at any time.

GHP: general health perception; PF: physical functioning; PCS: physical composite score; MCS: mental composite score; GH: general health; ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group;BMI: body mass index, eGFR: estimated glomerular filtration rate, PF: physical functioning, RP: role limitations due to physical health problem, BP: bodily pain, VT: vitality, SF: social functioning, RE: role limitations due to emotional problems; MH: mental health.

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TABLE 3.

Comparative HRQoL outcomes between or among approaches, *Cont'd*

Author, year of publication	Questionnaires	Country/study period	No patients	Time of evaluation	Interventions	
Park et al. (2015)[31][a]	QoR-40 VAS-pain VAS-cosmetic satisfaction	Korea 2010–2011	33	QoR-40 at baseline and at 1month. VAS-cosmetic satisfaction at 1 month VAS-pain up to D+3	LRN LESS-RN	
Sandbergen et al. (2020)[30]	SF-36 FSKI-15 VAS	Netherlands 2011–2014	98	Baseline 1–3–12 months	O (RN, PN) MIS (L, P)	

[a]secondary outcomes [b]outcomes for comparison of ORN with retroperitoneoscopy-RN [c]not assessed by validated questionnaire
[d]at mean or median follow-up

ORN: open radical nephrectomy; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; LPN: laparoscopy partial nephrectomy; LESS-RN: laparo-endoscopic single site radical nephrectomy; F-ORN: flank open radical nephrectomy; F-ONSS: flank open nephron sparing surgery; T-ORN: transabdominal open radical nephrectomy; T-ONSS: transabdominal open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; HALRN: hand assisted laparoscopy radical nephrectomy; C-RAPN: conventional robotic assisted radical nephrectomy; LESSS-RAPN: laparo-endoscopic single site robotic assisted partial nephrectomy.

	Outcomes (Comparison interventions)	Outcomes (Comparison norm values)	Predictors/ interactions

	• **QoR-40:**
	  • in preoperative similar scores between groups
	  • Postoperative scores higher in LESS-RN group in emotional state, physical comfort, psychological support, physical independence but not for pain.
	  • Global score significantly better for LESS-RN (*P* = 0.005) at 1 month
	• **VAS-pain:**
	  • No significant differences at day 3
	• **VAS-cosmetic satisfaction:**
	  • better in LESS-RN group at 1 month (1.3 vs 1.9, *P* 0.001)
		—	—

	• **SF-36**
	  • At baseline L significantly better role physical than O or P and Role emotional and Health transition significantly better than O;
	  • At one month L and P significant better role physical and health transition than O; P significantly better role emotional and bodily pain than O.
	  • At 3 months all scales returned to baseline and there were no differences among approaches
	• **FKSI-15**
	No differences at baseline or in follow- up
	• **VAS**
	No differences at baseline or in follow- up
		—	• Data did not change substantially across the different study time points when corrected for confounders (Charlson-age adjusted comorbidity index, PADUA and RENAL anatomic complexity scores, clinical TNM, definitive histopathology and the presence of complications)

GHP: general health perception; PF: physical functioning; PCS: physical composite score; MCS: mental composite score; GH: general health; ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group;BMI: body mass index, eGFR: estimated glomerular filtration rate, PF: physical functioning, RP: role limitations due to physical health problem, BP: bodily pain, VT: vitality, SF: social functioning, RE: role limitations due to emotional problems; MH: mental health.

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TABLE 3.

Comparative HRQoL outcomes between or among approaches, *Cont'd*

Author, year of publication	Questionnaires	Country/study period	No patients	Time of evaluation	Interventions	
Cross-sectional studies						
Becker et al. (2015)[19]	EORTC QLQ-C30	Germany 1996–2011	110	Mean 60 months, median 49 months (IQR 30-80) (LPN mean 43/ median 44 months (IQR 32–51) (OPN mean 66 / median 56 months (IQR 28-101))	OPN LPN	
Beisland et al. (2014)[20]	EORTC QLQ-C30	Norway 1996–2010	185	[d]All 59 (±3) months (OFI 52mo (±5) OTI 77mo (±5) L 24 (±3))	Flank ORN/ONSS Transabdominal ORN/ ONSS LRN/NSS (In all groups not specified % of RN or NSS)	
Gratzke et al. (2009)[29][b]	SF-36	Germany Switzerland 2001–2005	85	[d]22 months	ORN, O-NSS, Retroperitoneoscopy -RN	

[a]secondary outcomes [b]outcomes for comparison of ORN with retroperitoneoscopy-RN [c]not assessed by validated questionnaire
[d]at mean or median follow-up

ORN: open radical nephrectomy; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; LPN: laparoscopy partial nephrectomy; LESS-RN: laparo-endoscopic single site radical nephrectomy; F-ORN: flank open radical nephrectomy; F-ONSS: flank open nephron sparing surgery; T-ORN: transabdominal open radical nephrectomy; T-ONSS: transabdominal open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; HALRN: hand assisted laparoscopy radical nephrectomy; C-RAPN: conventional robotic assisted radical nephrectomy; LESSS-RAPN: laparo-endoscopic single site robotic assisted partial nephrectomy.

	Outcomes (Comparison interventions)	Outcomes (Comparison norm values)	Predictors/ interactions

	• EORTC QLQ-C30
	  • no significant differences in global median scores or any domain or QoL between L and O (all $P > 0.05$).
	  • LPN patients stated having a shorter period of convalescence (defined as recovery to a performance level of 80%)[b]
		• Male patients significantly higher QoL global score (70.6 vs 65.6, $P = 0.33$) and social functioning (82.5 vs 65.6, $P < 0.001$) and reported less nausea and vomiting (0.7 vs 2.2, $P < 0.001$) but more fatigue constipation and diarrhoea than normative population values.
		• Female patients no significant differences within any domain of QOL with normative-population scores.
			• In EORTC QL-C30 after multivariable regression analysis adjustment for age, gender symptoms at presentation, tumour size and time from surgery no significant factor found.
			• Intuitively LRN stated shorter time to recovery[b]

	—	• Flank and abdominal approaches followed by reduced HRQoL compared to a sample of the general Norwegian population. • GH-QoL, functional and symptom indexes (fatigue, pain, sleep, nausea and vomiting, constipation, and diarrhoea) particularly affected by O approach. • HRQoL of Laparoscopically treated patients at the same level of the general Norwegian population, the rest of the groups lower than general population	• Inverse association with recuperation of EORTC QLQ-C30 HRQoL domains: gender (males better), ASA, ECOG, BMI, Smoking, eGFR at survey, Diabetes at survey and Lung medication at survey. • Tumor size (> 10cm) predictor functional HRQoL sum. • When corrected for age and sex still significant group allocation effect on the functional sum of QoL (L better).

	• **SF-36:**
	  • mean scores for each domain did not differ significantly between groups (P 0.325 to 0.960).
	  • ORN group trend to higher MCS than Retroperitoneoscopy-RN
	  • No differences in PCS among groups
		• Mean scores for each domain within 1SD of age-sex matched normative German population
		• Physical scores higher than the ones of age-sex matched population in all groups
			• Postoperative complications trend towards worse SF-36 QoL scores regardless of the type of operation, compared with the no presence of postoperative complications. This difference was statistically significant in the GH domain ($P < 0.05$).

GHP: general health perception; PF: physical functioning; PCS: physical composite score; MCS: mental composite score; GH: general health; ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group;BMI: body mass index, eGFR: estimated glomerular filtration rate, PF: physical functioning, RP: role limitations due to physical health problem, BP: bodily pain, VT: vitality, SF: social functioning, RE: role limitations due to emotional problems; MH: mental health.

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TABLE 3.

Comparative HRQoL outcomes between or among approaches, *Cont'd*

Author, year of publication	Questionnaires	Country/study period	No patients	Time of evaluation	Interventions	
Jiang et al. (2009)[25]	SF-36	China 2001–2006	71	d 12 months	ORN HALRN	
Shin et al. (2014) [24]	VAS-pain	Korea, China, Greece 2006–2012	159	At discharge (2.2 days C-RAPN 2.1 days LESS-RAPN)	C-RAPN LESS-RAPN	
Shinohara, et al. (2001)[28]	EORTC QLQ-C30	Japan 1986–1996	50	[d]ONSS 47 months (±40) ORN 60 months (±31)	Extraperitoneal ORN/ ONSS Transabdominal ORN/ONSS	

[a]secondary outcomes [b]outcomes for comparison of ORN with retroperitoneoscopy-RN [c]not assessed by validated questionnaire
[d]at mean or median follow-up

ORN: open radical nephrectomy; LRN: laparoscopy radical nephrectomy; OPN: open partial nephrectomy; LPN: laparoscopy partial nephrectomy; LESS-RN: laparo-endoscopic single site radical nephrectomy; F-ORN: flank open radical nephrectomy; F-ONSS: flank open nephron sparing surgery; T-ORN: transabdominal open radical nephrectomy; T-ONSS: transabdominal open nephron sparing surgery; LNSS: laparoscopy nephron sparing surgery; HALRN: hand assisted laparoscopy radical nephrectomy; C-RAPN: conventional robotic assisted radical nephrectomy; LESSS-RAPN: laparo-endoscopic single site robotic assisted partial nephrectomy.

health score versus domain scales)[21,23,28]. For both modality and approach, the different composition of the cohorts with variable proportions of management combinations[17,20,21,30], the different percentage of responders[19,21,23,30], and the lack of adjustment for confounders justified differences in generic and cancer-specific HRQoL outcomes across reports. In some cases, comparison was disparate with respect to modality and approach, so precluding any sound conclusion[26]. A specific questionnaire was used only in a single study[31], or comparisons were conducted between modifications of a unique conceptual approach[24,31].

Importantly, minimal clinically relevant difference in scales or scores was not pre-specified in any study, which precluded any sound comparison and raised the question of whether the QoL values of the normative population should be used as the standard for comparison[34,35].

Regarding cancer-specific HRQoL, different outcomes among studies were mainly related to the use of PROMs designed to measure different aspects of HRQoL[16,23,28]. While EORTC QLQ-C30 measures cancer patients' physical, psychological, and social functions in general[36], SFKI-15 focuses on renal cancer-specific symptoms and concerns[37] and CARES- SF assesses rehabilitation needs and day-to-day problems of cancer patients[38]. Each instrument has strengths and weakness, but so far there is no evidence on the equivalence among them, and notably none is designed for the specific population of our review.

The strength of this systematic review is the robust and transparent methodological approach, as well as the critical assessment of the risk of bias of the observational studies[13]. The limitations are related to the heterogeneity in the design, methodology, and reporting of the studies assessing HRQoL in LRMs or LRCC.

Although we considered only reports using cross-cultural validated PROMs, there was a surprising variety of instruments used across studies, and this complicated data interpretation and weakened possible differences in comparative outcomes either in modalities or approaches[33]. Although most of them investigated dimensions related to QoL, conclusions are restricted to those used in the majority of studies (SF-36 and EORTC QOL-C30) when used optimally[39,40].

	Outcomes (Comparison interventions)	Outcomes (Comparison norm values)	Predictors/ interactions
	• **SF-36** • No significant differences in eight dimensions (PF, RP, BP, GH, VT, SF, RE and MH) between the two groups (all $P > 0.05$).	—	—
	• **VAS-pain** • score significantly higher in C-RAPN -than in LESS-RAPN ($P = 0.048$).	—	—
	• **EORTC QLQ-C30:** • No differences between approaches in PF scores or any symptoms score.	—	—

GHP: general health perception; PF: physical functioning; PCS: physical composite score; MCS: mental composite score; GH: general health; ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group;BMI: body mass index, eGFR: estimated glomerular filtration rate, PF: physical functioning, RP: role limitations due to physical health problem, BP: bodily pain, VT: vitality, SF: social functioning, RE: role limitations due to emotional problems; MH: mental health.

Lastly, although most of the papers reviewed were published relatively recently, none of them adhered to contemporary checklists or guidelines to report on HRQoL assessed by PROMs[41–44] (in some cases because the guidelines were published even more recently).

Although the study limitations confer a critical risk of bias on our review and the quality of evidence is low, we have identified important shortcomings that can help to guide future research. There is no PROM specifically designed to measure HRQoL of patients with LRMs, raising the question of whether one is needed. On the rationale that cure rate and competing risk of death are high in the majority of patients with LRMs[45], the goal might very well be to reach age–sex adjusted normative HRQoL scores. The decision belongs to the consensus among the different stakeholders involved in the process of care of LRMs and the increasing acceptance of evaluate outcomes beyond the clinical frame[8,46]. Furthermore, some benefits of MIS approaches that may have a meaningful impact on patient perception of QoL—eg, decreased effect on body image dysmorphism and/or enhanced cosmetic aspect—are difficult to ascertain in the current PROMs.

When designing studies on HRQoL, a strict methodology should be followed[43,45,47,48], which has not been the case so far with LRMs. Precise, valid, reliable, responsive, and user-friendly PROMs combined with robustly designed studies and computer adaptative testing offer the chance to include large cohort populations and minimize the burden for patients and physicians[44,48].

Conclusions

Our systematic review on HRQoL following management of LRMs /LRCC shows evidence that the impact of surgery is considerable during the first weeks and months, although this rarely persists in the longer term. There is no conclusive evidence supporting the superiority of NSS over RN. Nevertheless, there is low evidence to support the use of MIS approaches over open surgery on the basis of earlier postoperative recovery. The impact of surgical management on global mental health seems to be negligible in the long term.

TABLE 4.
GRADE certainty of the evidence of the studies included in the systematic review

GRADE rating quality of evidence										
	Initial level of confidence estimated effect		GRADE assessment for RCT and Observational studies					Additional factors Observational studies (only considered if not downgraded for study design, INC, IND, IMP or PB)		Final level of confidence rating
Study ID	Design	IR	RoB	INC	IND	IMP	PB	LE	DR	
Parker et al. (2012)[21]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low
Novara et al. (2010)[22]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low
Onishi et al. (2007)[26]	Observational	Low confidence	Critical	NA	No	No	No	NA	NA	Very low
Acar et al. (2014)[17]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low
Park et al. (2015)[31]	RCT	High confidence	High	NA	No	NA	No	NA	NA	Very low
Alam et al. (2018)[15]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low
Poulakis et al. (2003)[23]	Observational	Low confidence	Serious	NA	No	No	No	No	No	Very Low
Gratzke et al. (2009)[29]	Observational	Low confidence	Critical	NA	No	No	No	NA	NA	Very low
Clark et al. (2001)[18]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low
Becker et al. (2015)[19]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low
Beisland et al. (2014)[20]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low
Azawi et al. (2015)[16]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low
Shinohara et al. (2001)[28]	Observational	Low confidence	Critical	NA	No	No	No	NA	NA	Very low
Ficarra et al. (2002)[27]	Observational	Low confidence	Critical	NA	No	No	No	NA	NA	Very low
Jiang et al. (2009)[25]	Observational	Low confidence	Critical	NA	No	No	No	NA	NA	Very low
Shin et al. (2014)[24]	Observational	Low confidence	Critical	NA	No	No	No	NA	NA	Very low
Sandbergen et al. (2020)[30]	Observational	Low confidence	Serious	NA	No	No	No	NA	NA	Very low

IR: initial rating; RoB: risk of bias; INC: inconsistency; IND: indirectness; IMP: imprecision; PB: publication bias; LE: large effect; DR: dose response; NA: not applicable

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