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ORIGINAL ARTICLE

Open versus robotic-assisted partial nephrectomy in patients with intermediate/high-complexity kidney tumours: final results of the randomised, controlled, open-label, multicentre trial OpeRa

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Background: The prospective, randomised, open-label, multicentre OpeRa trial (NCT03849820) aimed to determine whether robotic-assisted partial nephrectomy (RAPN) is superior to open partial nephrectomy (OPN) in reducing 30-day post-operative complications during the treatment of intermediate/high-complexity renal tumours.

Patients and methods: Eligible patients aged ≥18 years had a renal tumour suitable for OPN or RAPN, a RENAL score ≥7, and an estimated glomerular filtration rate ≥50 ml/min/1.73 m^2. Patients were randomised from 15 March 2019 to 23 November 2021 in 12 German hospitals and assigned (1 : 1) to undergo RAPN or OPN. Primary endpoint was the 30-day post-operative complication rate [Clavien−Dindo (CD) I-V] in the modified intention-to-treat population. We aimed to recruit 606 patients to detect ≥10% reduction in the primary endpoint for RAPN versus OPN.

Results: A total of 240 patients were randomised to RAPN ($n = 123$) or OPN ($n = 117$). Enrolment was stopped prematurely due to slow recruitment. After patient withdrawal post-randomisation, 117 patients underwent RAPN and 90 OPN. The primary endpoint was assessable in 112 and 89 patients, respectively. The 30-day complication rate did not differ between groups: RAPN 41/112 (37%) versus OPN 41/89 (46%) (one-sided: $P = 0.088$). The difference of −9.5% (95% confidence interval −23.1% to 4.2%) numerically favoured RAPN. The most frequent high-grade complications (CD III-IV) to post-operative day 30 (POD30) were urine leakage [RAPN 4/112 (4%) versus OPN 2/89 (2%)] and post-operative bleeding [2/117 (2%) versus 1/89 (1%)]. Compared with OPN, RAPN patients had longer operative and warm ischaemia times, shorter hospital stay, and reported better recovery, less opioid use, less pain, and improved quality of life (QoL) up to POD30.

Conclusions: There was no statistically significant difference in the 30-day complication rate between RAPN and OPN in this underpowered trial. Few high-grade complications occurred over the whole cohort with intermediate/high-complexity tumours. Despite less intense pain management, patients undergoing RAPN reported less pain and better QoL up to POD30.

Key words: complications, kidney cancer, open surgery, partial nephrectomy, renal cell carcinoma, robotic-assisted surgery

INTRODUCTION

Since its first description in 1969, open radical nephrectomy has been considered the standard intervention for curative therapy of localised renal cell carcinoma (RCC).[1] While surgical techniques have evolved and detection of small tumours has improved, partial nephrectomy (PN) became the standard of care for small renal masses ≤4 cm and an

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accepted alternative for suitably located larger tumours. However, the feasibility of PN is dependent on tumour stage and location.

PN techniques include open PN (OPN), laparoscopy, and robotic-assisted laparoscopic PN (RAPN). Reported benefits of minimally invasive surgery, such as smaller surgical scars, faster recovery, shorter hospital stay,[2] and reduced pain,[3] have led to its increased use.[4] Non-randomised evidence indicated that RAPN reduced complications and pain compared with OPN,[5-7] whereas shorter surgery and warm ischaemia times (WITs) were reported advantages of OPN.[8-13] To date, randomised evidence comparing RAPN and OPN has only been reported in one small, single-centre, feasibility study (ROBOCOP II), suggesting advantages for RAPN ($n = 25$) regarding blood loss, opioid use, rate of minor complications, and quality of life (QoL), while OPN ($n = 22$) required shorter operation times.[14,15] However, most patients had low/intermediate-complexity tumours (approximately three-quarters graded cT1a, the rest cT1b), restricting the evidence to such tumours.

Our prospective, randomised, open-label, multicentre trial OpeRa (Open vs. Robotic-assisted partial nephrectomy) aimed to demonstrate the superiority of RAPN over OPN in reducing 30-day post-operative complications [Clavien–Dindo (CD) I-V[16]] in patients with intermediate/high-complexity renal tumours. We also assessed pain, (health-related) QoL [(hr)QoL], and procedure-related outcomes. Comparative high-level evidence generated from this trial may redefine current standards of care and assist health care providers in selecting the most appropriate surgical approach for intermediate- to high-complexity renal tumours.

PATIENTS AND METHODS

OpeRa (ClinicalTrials.gov: NCT03849820) was a prospective, randomised, controlled, open-label, multicentre, superiority trial. The protocol is available in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.04.005. Patients were recruited from 12 German hospitals (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.04.005). Eligible patients were aged ≥18 years with an intermediate/high-complexity renal tumour (RENAL nephrometry score[17] ≥7) considered a candidate for PN using either OPN or RAPN. The required estimated glomerular filtration rate (eGFR) was ≥50 ml/min/1.73 m^2. Anticoagulation was accepted according to surgeon practice. Exclusion criteria are listed in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.04.005. All enrolled patients provided signed informed consent before trial inclusion. Patients could withdraw consent and discontinue participation at any time.

Access to a da Vinci® Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) was required at all centres. Surgeons had a baseline experience of >50 PN cases in the applied technique(s), and ≥20 cases during the last 12 months according to protocol V1.0, or either ≥10 cases during the last 12 months or ≥5 cases during the last 6 months according to later protocol versions. The prerequisite was adjusted to increase the number of centres. Per centre, >20 RAPN cases and >40 overall PN cases during the last 12 months were required before study entry. Ethical approval was obtained from each participating centre. The study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice.

Procedures

Patients were randomised 1 : 1 to receive RAPN or OPN using a computer-generated, sponsor-provided randomisation schedule that was software-revealed upon patient enrolment. A block design randomisation scheme was used, with a block size of 10 at each centre.

The da Vinci® Si, Xi, or X Surgical System was used in all RAPN cases. RAPN and OPN were carried out according to site standards. Details of study visits, including protocol version-specific information, are provided in the Supplementary Methods and Table S2, available at https://doi.org/10.1016/j.annonc.2025.04.005. The database was closed on 21 June 2023, after the last patient had achieved post-operative year (POYR) 1 (24 October 2022).

Outcomes

The primary endpoint was 30-day post-operative complications, including any event according to CD I-V[16], assessed by the investigator in the modified intention-to-treat (mITT) population. Complications classified as CD III-V were reviewed by one (MOG) of two coordinating investigators, with the final decision made by the site investigator. Secondary endpoints were intraoperative outcomes [complications, operative times, ischaemia time, surgical conversions (RAPN to OPN, PN to radical nephrectomy), intraoperative blood loss], post-operative outcomes [specimen pathology, eGFR, quality of recovery (QoR-9[18,19]), perioperative transfusion, length of hospital stay, comprehensive complication index (CCI, Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.04.005) for post-operative complications over 30 days, post-operative complications (90 days), procedure-related readmissions/reoperations], pain assessment [Brief Pain Inventory (BPI, short form), pain medication, Douleur Neuropathique 4 (DN4)[20]], hrQoL [EuroQol-5 dimensional-5 level instrument (EQ-5D-5L)], and QoL [European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)[21]] in the mITT population. Further secondary endpoints were overall survival [time between surgery and death from any cause (censoring was carried out at the last known date alive)], disease-free survival (DFS, time between surgery and date of the first recurrence), and local recurrence-free survival (RFS, time between surgery and date of the first local recurrence). For DFS and RFS, patients without recurrence were censored at the date of their last study visit. Complications were recorded until post-operative day (POD) 90.

Statistical analysis

The primary objective was to demonstrate that RAPN was superior to OPN in reducing the number of 30-day post-operative complications (CD I-V[18]) in the mITT population of patients with intermediate/high-complexity kidney tumours. The null hypothesis was that there would be <10% difference in the 30-day post-operative complication rates between the RAPN and OPN groups. The alternative hypothesis was that there would be ≥10% difference in the 30-day post-operative complication rates, with the expectation that RAPN would result in a lower rate. The hypothesis for the primary endpoint was tested at a one-sided 0.05 significance level.

With 80% power to detect this difference at the 5% level, and assuming 10% potential loss to follow-up, a sample size of 303 patients per group was calculated to be adequate to show the intended difference. A secondary endpoint, CCI (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.04.005), was introduced with protocol V2.1 (19 October 2021) using existing data, and powered to detect superiority as an additional means to describe complications.

The mITT population was defined as all patients randomised who underwent the procedure, analysed according to randomisation assignment. The as-treated population comprised all patients who initiated the procedure, grouped by the actual procedure received. Patients were included in the analysis of events through study milestones (POD30, POD90) if either an event was reported within the milestone time-frame or the follow-up information through the milestone was complete and no event was reported. Kaplan—Meier analysis was carried out as a sensitivity analysis for the primary endpoint in the mITT and as-treated populations.

Analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are displayed as the number and percentage in each category, and compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as medians and interquartile ranges (IQRs), and compared using the Wilcoxon rank sum test. Questionnaires were scored at each time point and compared as a continuous measure across the operative approaches. Mixed models for repeated measures were used to adjust for within-patient correlation and to estimate differences in scores across treatment groups. Results are presented as least-squares means and 95% confidence intervals (CIs).

The study was designed with a one-sided test of α level 0.05 regarding the primary endpoint.

RESULTS

Between 15 March 2019 and 23 November 2021, 247 patients consented; 240 were randomly assigned to receive RAPN ($n = 123$) or OPN ($n = 117$). We intended to randomise 606 patients (1 : 1) in up to 20 centres within 4 years. As described, enrolment was stopped prematurely. As some patients discontinued study participation before surgery [RAPN $n = 6$ (5%) of 123; OPN $n = 27$ (23%) of 117], the mITT population included 117 RAPN and 90 OPN patients. The complication status at POD30 was not available for 5 RAPN patients and 1 OPN patient, leaving 112 RAPN and 89 OPN patients available for the primary endpoint analysis. One patient assigned to OPN underwent RAPN. For the as-treated analyses, this patient was counted as being in the RAPN group. A Consolidated Standards of Reporting Trials (CONSORT) diagram is displayed in Figure 1.

Baseline characteristics were comparable between groups (Table 1). The median maximum tumour size was 42 mm (IQR 30-49 mm) in RAPN and 42 mm (IQR 30-55 mm) in OPN patients. The median RENAL score was 8 (IQR 7-9) in both groups. Intermediate-complexity RENAL scores were reported for 98 (84%) of 117 RAPN patients and 78 (87%) of 90 OPN patients. High-complexity RENAL scores were reported for 19 (16%) RAPN and 12 (13%) OPN patients. Post-operative pathology revealed benign tumours in 14 (12%) RAPN and 11 (12%) OPN patients. Most patients had clear-cell RCC [RAPN 69 (59%); OPN 63 (70%)]. Median follow-up time was 12.0 months (IQR 3.1-12.1 months) for RAPN and 11.8 months (3.0-12.0 months) for OPN.

Primary outcome

In the mITT population, post-operative complications to POD30 occurred in 41 (37%) of 112 RAPN patients and 41 (46%) of 89 OPN patients (one-sided: $P = 0.088$). The difference of −9.5% (95% CI −23.1% to 4.2%) numerically favoured RAPN. In the as-treated population, post-operative complications to POD30 occurred in 41 (36%) of 113 RAPN patients and 41 (47%) of 88 OPN patients [one-sided: $P = 0.070$; the difference of −10.3% (95% CI −24.0% to 3.4%) favoured RAPN; Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.04.005]. As a sensitivity analysis, the primary endpoint was further assessed as time from surgery to first post-operative complication via Kaplan—Meier estimates in the mITT and as-treated populations [log-rank $P = 0.143$ (mITT) and 0.119 (as-treated), Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.04.005]. In the mITT population, no grade III/IV complications were reported in 99 (88%) of 112 RAPN patients and 82 (92%) of 89 OPN patients (no significant difference). Details regarding the maximum CD grade to POD30 are provided in Table 2.

In the mITT population, complications were judged to be possibly or definitely procedure-related in fewer RAPN patients [26 (23%) of 112] than OPN patients [33 (37%) of 89]. Serious adverse events occurred in 17 (15%) of 112 RAPN patients and 12 (14%) of 87 OPN patients, respectively. Through to POD30, the following individual high-grade complications occurred: urine leakage [RAPN 4 (4%) of 112 patients versus OPN 2 (2%) of 89 patients], post-operative bleeding [2 (2%) versus 1 (1%), respectively], arteriovenous fistula [1 (1%) versus 1 (1%)], haematoma [0 versus 2 (2%)], and pseudoaneurysm [2 (2%) versus 0; Table 2]. The median CCI through to POD30 did not differ between RAPN and OPN in either the mITT [0 (IQR 0-15)]

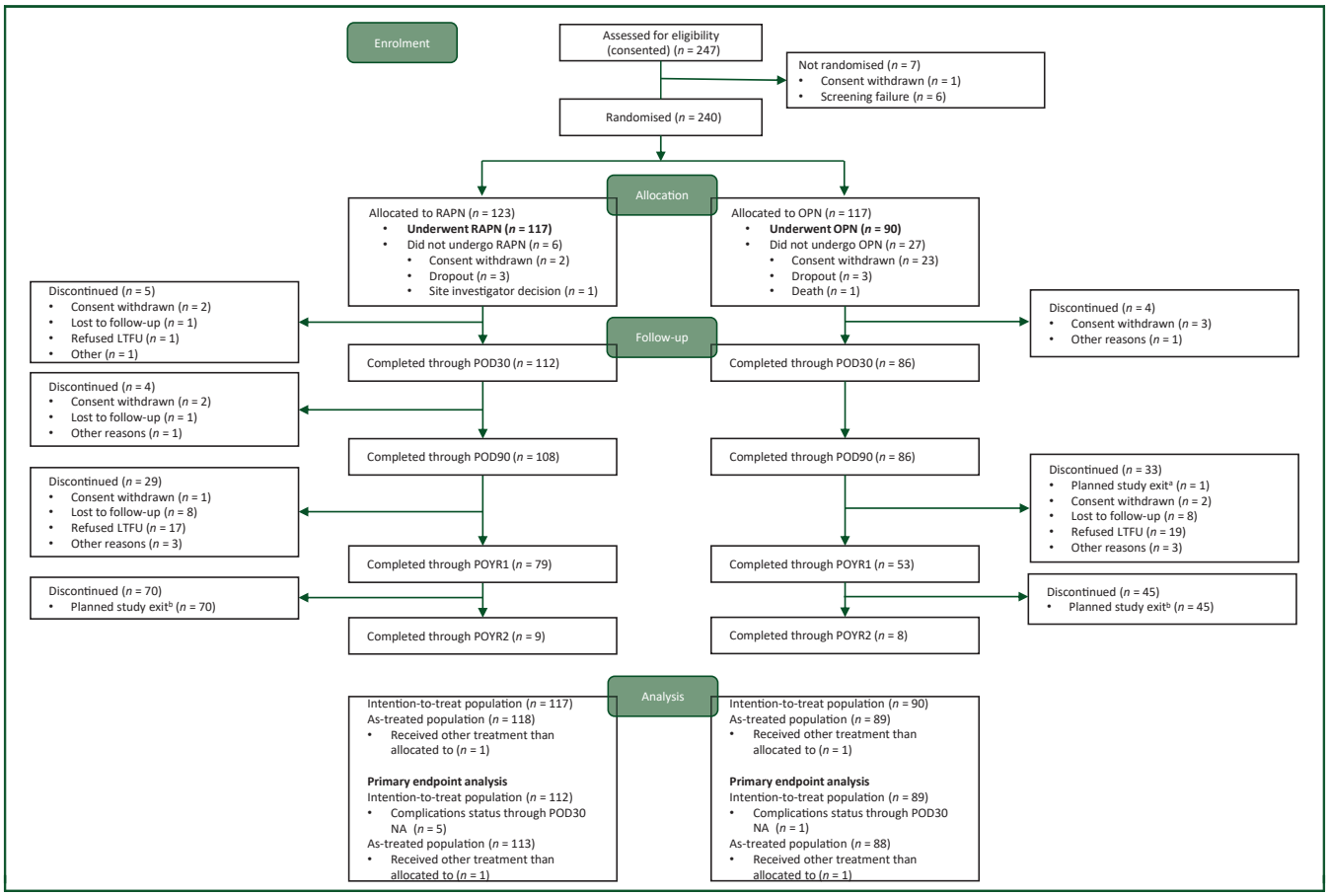

Figure 1. CONSORT flow diagram.
[a]Patients enrolled with protocol V1.0 (16 July 2018) were intended to be followed up until POD90. Study period was extended with protocol V2.0 (20 December 2019). Patients enrolled with V1.0 could consent to LTFU.
[b]With sponsor decision to terminate the study due to slow recruitment of patients (26 November 2021), study visits after the 1-year visit were not continued. CONSORT, Consolidated Standards of Reporting Trials; LTFU, long-term follow-up; NA, not available; OPN, open partial nephrectomy; POD, post-operative day; POYR, post-operative year; RAPN, robotic-assisted partial nephrectomy.

versus [0 (IQR 0-21)] or the as-treated populations [0 (IQR 0-9)] versus [0 (IQR 0-21)]. Intraoperative complications were comparable between groups in the mITT population [RAPN 5 (4%) of 117 patients versus OPN 4 (4%) of 90 patients]. Post-operative complications to POD90 were reported for 45 (41%) of 111 RAPN patients and 42 (48%) of 88 OPN patients.

Secondary outcomes

As a result of the different techniques used, the surgical approach varied between groups in the mITT population, with 100 (85%) of 117 RAPN patients versus 10 (11%) of 90 OPN patients receiving transperitoneal surgery, and 17 (15%) RAPN patients versus 80 (89%) OPN patients undergoing the retroperitoneal approach (Table 3). The median operating time (skin-to-skin) was longer for RAPN [167 min (IQR 142-200 min)] than OPN [122 min (IQR 99-152 min)], as was the median anaesthesia time [250 min (IQR 218-301 min) for RAPN versus 218 min (IQR 195-258 min) for OPN]. Intraoperatively, ischaemia was applied in 102 (87%) RAPN patients and 71 (79%) OPN patients, with a median ischaemia duration of 19 min (IQR 13-23 min) for RAPN and 11 min (IQR 7-17 min) for OPN. The clamping technique most often used was main vessel clamping [74 (64%) of 115 RAPN patients with non-missing data versus 55 (61%) of 89 OPN patients], followed by segmental/selective clamping [RAPN 23 (20%) versus OPN 11 (12%)]. No clamping was applied in 13 (11%) RAPN and 17 (19%) OPN cases.

Positive tumour margins were detected in 11 (10%) of 111 RAPN patients and in 10 (11%) of 88 OPN patients. The median minimum and maximum distances of tumour to surgical margins were 1.0 mm (IQR 1.0-2.0 mm) and 1.0 mm (1.0-4.0 mm), respectively, for RAPN and 2.0 mm (1.0-5.5 mm) and 9.0 mm (1.0-17.0 mm) for OPN. TRIFECTA criteria (negative margins, ischaemia $<$25 min, no complications to POD30) were met in 53 (48%) of 110 RAPN patients and 42 (47%) of 89 OPN patients. Selected procedure and intraoperative data in the as-treated population are provided in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.04.005.

Post-operative kidney function (eGFR) did not differ between RAPN and OPN from baseline to POD5/discharge in the mITT population (Supplementary Table S6 and Figure S2, available at https://doi.org/10.1016/j.annonc.2025.04.005). When comparing last available eGFR

Table 1. Baseline characteristics of patients and pathology in the mITT population

	RAPN (N = 117)	OPN (N = 90)
Baseline characteristic		
Sex, *n* (%)		
Male	82 (70)	64 (71)
Female	35 (30)	26 (29)
Age, median (IQR), years	63 (55-70)	64 (57-69)
BMI, median (IQR), kg/m^2	28 (25-30)	28 (25-32)
<25 kg/m^2, *n* (%)	34 (29)	22 (24)
≥25 to <30 kg/m^2, *n* (%)	50 (43)	34 (38)
≥30 kg/m^2, *n* (%)	33 (28)	34 (38)
Charlson Comorbidity Index, median (IQR); N_{RAPN} = 116, N_{OPN} = 90	1 (1-2)	1 (1-2)
0, *n* (%)	24 (21)	22 (24)
1, *n* (%)	45 (38)	35 (39)
≥2, *n* (%)	47 (40)	33 (37)
ASA classification, *n* (%)		
I—completely healthy	43 (37)	31 (34)
II—mild systemic disease	48 (41)	37 (41)
III—severe not incapacitating	23 (20)	18 (20)
IV—incapacitating	0	1 (1)
Baseline eGFR, median (IQR), ml/min/1.73 m^2	88 (76-101)	85 (74-95)
Anticoagulant yes, *n* (%)	29 (25)	32 (36)
Laterality right, *n* (%)	56 (48)	37 (41)
RENAL score—numeric part, median (IQR)	8 (7-9)	8 (7-9)
Intermediate-complexity score ≥7, <10, *n* (%)	98 (84)	78 (87)
High-complexity score ≥10, *n* (%)	19 (16)	12 (13)
Max. tumour size preoperative, median (IQR), mm; N_{RAPN} = 113, N_{OPN} = 87	42 (30-49)	42 (30-55)
Nearness to collecting system or sinus, *n* (%)		
≤4 mm	106 (91)	78 (87)
>4 to <7 mm	7 (6)	9 (10)
≥7 mm	4 (3)	3 (3)
Exophytic/endophytic properties, *n* (%)		
Endophytic	19 (16)	12 (13)
<50% exophytic	59 (50)	46 (51)
≥50% exophytic	39 (33)	32 (36)
Primary location relative to polar lines, *n* (%)		
Entirely above the upper polar line	21 (18)	11 (12)
Crosses a polar line	42 (36)	42 (47)
Crosses axial renal midline	20 (17)	14 (16)
Entirely below the lower polar line	15 (13)	11 (12)
>50% across polar line	6 (5)	5 (6)
Entirely between polar lines	13 (11)	7 (8)
Primary location relative to hilar vessels, *n* (%)		
Neither	42 (36)	33 (37)
Posterior	41 (35)	33 (37)
Anterior	34 (29)	24 (27)
Hilar tumour, touch renal artery/veins, *n* (%)	95 (81)	79 (88)
cT score stage group at screening, *n* (%)		
TX, T0, T1a	55 (47)	38 (42)
T1b	50 (43)	44 (49)
T2a, T2b, T3a	12 (10)	8 (9)
Pathology		
pT score stage group post-surgery, malignant only, *n* (%)		
TX, T0, T1a	46 (39)	36 (40)
T1b	44 (38)	30 (33)
T2a, T2b, T3a	13 (11)	12 (13)
Histology, *n* (%)		
Clear-cell RCC	69 (59)	63 (70)
Chromophobe	12 (10)	6 (7)
Papillary RCC type I/II	14 (12)	6 (7)
Unknown	1 (1)	0
Other	6 (5)	3 (3)
Benign	14 (12)	11 (12)

Data are presented as *n* (%) or median (IQR). Proportions are calculated based on column totals. Percentages may not sum up to 100% due to missing data. Numbers (*N*) for continuous variables are noted in the characteristic label if different from column *N*.

ASA, American Society of Anesthesiologists; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; mITT, modified intention-to-treat; OPN, open partial nephrectomy; RAPN, robotic-assisted partial nephrectomy; RCC, renal cell carcinoma.

measurements before hospital discharge, no difference was detected between RAPN and OPN in value (73 ± 22 versus 69 ± 21 ml/min/1.73 m^2, respectively) or compared with baseline (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.04.005).

For the mITT population, two surgical conversions occurred in the RAPN group, one to OPN and one to open radical nephrectomy. The median estimated blood loss during surgery was 200 ml (IQR 100-400 ml) for RAPN and 250 ml (100-400 ml) for OPN. Five (4%) RAPN and two (2%) OPN patients needed perioperative transfusions. The median length of hospital stay was numerically shorter in RAPN [6 days (IQR 5-7 days)] versus OPN patients [7 days (6-8 days)]. Post-operatively, 10 (9%) of 117 RAPN patients were readmitted compared with 4 (4%) of 90 OPN patients. Re-interventions were reported in nine (8%) RAPN and four (4%) OPN patients, of which four (44%) and three (75%), respectively, were ureteral stent insertions.

No deaths occurred. There were no differences in the distributions of DFS or local RFS rates (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.04.005).

Epidural anaesthesia was used in 14 (12%) RAPN and 38 (42%) OPN patients (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2025.04.005). Use of non-opioid analgesics was comparable between groups for application of any non-opioid analgesic or each of the three most commonly used compounds (metamizole, paracetamol, ibuprofen) and regardless of whether all patients or only those without epidural anaesthesia (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2025.04.005) were analysed. Opioids were administered less frequently in RAPN patients than in OPN patients [all patients: 80 (68%) versus 77 (86%); patients without epidural anaesthesia: 69 (67%) of 103 versus 40 (77%) of 52]. In a pooled analysis with all applied opioids being

Table 2. Complications in the population with adverse event information through to POD30

	RAPN (N = 112)	OPN (N = 89)	Difference (95% CI)
Any post-operative AE through to POD30, *n* (%)	41 (37)	41 (46)	−9.5 (−23.1 to 4.2)[a] P = 0.088 (one-sided)
Maximum Clavien−Dindo classification through to POD30, *n* (%)			
No post-operative AE	71 (63)	48 (54)	9 (NA)[b]
Grade I	13 (12)	17 (19)	−7 (NA)[b]
Grade II	15 (13)	17 (19)	−6 (NA)[b]
Grade III-a	6 (5)	3 (3)	3 (NA)[b]
Grade III-b	5 (4)	3 (3)	2 (NA)[b]
Grade IV-a	2 (2)	1 (1)	1 (NA)[b]
No grade III/IV complications, *n* (%)	99 (88)	82 (92)	−3.7 (−11.9 to 4.4)[a]
Complications possibly/definitely related to procedure, *n* (%)	26 (23)	33 (37)	−14 (−26.6 to −1.1)[a]
Serious AEs through to POD30, *n/N* (%)	17/112 (15)	12/87 (14)	1.4 (−8.4 to 11.2)[a]
Post-operative high-grade complications through to POD30, *n* (%)[c]			
Urine leakage	4 (4)	2 (2)	1.3 (−5.0 to 7.0)[a]
Post-operative bleeding	2 (2)	1 (1)	0.7 (−4.6 to 5.4)[a]
Arteriovenous fistula	1 (1)	1 (1)	−0.2 (−5.4 to 4.0)[a]
Haematoma	0	2 (2)	−2.2 (−8.0 to 1.2)[a]
Pseudoaneurysm	2 (2)	0	1.8 (−2.5 to 6.4)[a]
CCI through to POD30, median (IQR)	0 (0-15)	0 (0-21)	0 (−9 to 9)[d]
Any post-operative AE through to POD90, *n/N* (%)	45/111 (41)	42/88 (48)	−7.2 (−21.1 to 6.7)[a]

Data are presented as *n/N* (%) when the denominators is not the column *N*. Data not available for all patients, see CONSORT diagram. Proportions are based on subjects with non-missing data.

AE, adverse event; CCI, Comprehensive Complication Index; CI, confidence interval; mITT, modified intention-to-treat; NA, not applicable; OPN, open partial nephrectomy; POD, post-operative day; RAPN, robotic-assisted partial nephrectomy.

[a]Rate difference (95% CI).

[b]Rate difference (95% CI is inappropriate, because other categories should not be combined).

[c]Clavien−Dindo III/IV.

[d]Median difference (bootstrap 95% CI).

calculated as oral morphine equivalents (mEq), median cumulative doses through to POD5/discharge were lower in the RAPN versus OPN groups [all patients with opioids: 100 mEq (IQR 60-285 mEq) versus 410 mEq (132-1090 mEq); patients without epidural anaesthesia with opioids: 80 mEq (50-200 mEq) versus 160 mEq (59-440 mEq)].

The QoR-9 total score did not differ between groups at baseline, POD1, POD2, or POD5/discharge, but was improved at POD3 for RAPN versus OPN (Figure 2A). For details see Figure 2H and Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2025.04.005.

While the BPI pain interference subscale was ameliorated for RAPN versus OPN at POD3, a tendency towards better outcomes for RAPN was visible from POD2 to POD90 (Figure 2B). The pain severity subscale was lower for RAPN on POD3, POD5/discharge, and POD30 (Figure 2C). As for the other BPI subscales, better outcomes were reported for worst and average pain from POD3 to POD30, for least pain at POD3 and POD5/discharge, and for current pain at POD5/discharge and POD30. With RAPN, pain interfered to a lower extent with walking ability at POD1, enjoyment of life and mood at POD2 and POD3, general activity at POD3 and POD/discharge, and normal work including outside home and housework at POD30 (Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2025.04.005, Figure 2H). Furthermore, less pain for RAPN was evidenced on the EQ-5D-5L pain/discomfort dimension (POD5/discharge and POD30) and EORTC QLQ-C30 pain subscale (POD30) (Figure 2D, E, and H). The POD90 and POYR1 questionnaires did not reveal any differences between groups regarding (hr)QoL and pain.

The DN4 questionnaire showed no differences between groups for neuropathic pain in a pooled analysis of any pain quality through to POD30. On POD90, fewer RAPN patients reported neuropathic pain, again in a pooled analysis of any pain quality. At POYR1, no patient reported neuropathic pain of any quality (Supplementary Table S11, available at https://doi.org/10.1016/j.annonc.2025.04.005).

QoL was improved for RAPN versus OPN at POD30 for both the EQ-5D-5L visual analogue scale (Figure 2F) and EORTC QLQ-C30 global health status/QoL (Figure 2G). At this time point, the EQ-5D-5L mobility and usual activities dimensions were improved for RAPN versus OPN. Also, EORTC QLQ-C30 physical functioning and fatigue subscales and QoL during the past week showed benefits for RAPN at POD30. For details, see Supplementary Tables S12 and S13, available at https://doi.org/10.1016/j.annonc.2025.04.005; for an overview of all patient-reported outcomes with differences at any time point assessed, see Figure 2H.

DISCUSSION

The OpeRa trial was intended to demonstrate that the perioperative complication rate through to POD30 was lower in patients undergoing RAPN than OPN for intermediate/high-complexity renal masses. The study was negative, since we observed a 9.5% lower complication rate for RAPN, but failed to demonstrate the prespecified

Table 3. Procedure and intraoperative data in the mITT population

	RAPN (N = 117)	OPN (N = 90)	Difference (95% CI)
Da Vinci® surgical system used, *n* (%)			
Xi	52 (44)	0	NA
X	7 (6)	1 (1)	5 (NA)[a]
Si	56 (48)	0	NA
Surgical approach, *n* (%)			
Transperitoneal	100 (85)	10 (11)	74.4 (65.3 to 83.5)[b]
Retroperitoneal	17 (15)	80 (89)	−74.4 (−83.5 to −65.3)[b]
Ischaemia applied, *n* (%)	102 (87)	71 (79)	8.3 (−2.1 to 18.7)[b]
Ischaemia duration, median (IQR), min	19 (13-23)	11 (7-17)	8 (3 to 10)[c]
Clamping technique, *n* (%)			
Main vessel clamping	74 (64)	55 (62)	2 (NA)[a]
No clamp/zero ischaemia	13 (11)	17 (19)	−8 (NA)[a]
Segmental/selective	23 (20)	11 (12)	8 (NA)[a]
Early unclamping	4 (3)	6 (7)	−4 (NA)[a]
Local compression instead of pedicle clamping	1 (1)	0	1 (NA)[a]
Operation time, median (IQR), min[d]; N_{RAPN} = 117, N_{OPN} = 89	167 (142-200)	122 (99-152)	45 (23 to 71)[c]
Anaesthesia time, median (IQR), min; N_{RAPN} = 115, N_{OPN} = 88	250 (218-301)	218 (195-258)	32 (−1 to 60)[c]
Surgical procedure conversions, *n* (%)	2 (2)[e]	NA	NA
Estimated blood loss, median (IQR), ml; N_{RAPN} = 113, N_{OPN} = 83	200 (100-400)	250 (100-400)	−50 (−150 to 100)[c]
Perioperative transfusions, *n* (%)	5 (4)	2 (2)	2.1 (−4.0 to 7.9)[b]
Intraoperative complications, *n* (%)	5 (4)	4 (4)	−0.2 (−7.3 to 6.1)[b]
Hospital days, surgery to discharge, median (IQR); N_{RAPN} = 116, N_{OPN} = 90	6 (5-7)	7 (6-8)	−1 (−2 to 0)[c]
Tumour margin, *n* (%)			
Positive, R1	11 (10)	10 (11)	−1.5 (−10.1 to 7.2)
Negative, R0	100 (90)	78 (89)	78.7 (70.1 to 87.4)
Minimum distance of tumour to surgical margin, median (IQR), mm; N_{RAPN} = 72, N_{OPN} = 64	1.0 (1.0-2.0)	2.0 (1.0-5.5)	−1 (−3 to 0)[c]
Maximum distance of tumour to surgical margin, median (IQR), mm; N_{RAPN} = 34, N_{OPN} = 34	1.0 (1.0-4.0)	9.0 (1.0-17.0)	−8 (−17 to 1)[c]
TRIFECTA (negative margins, ischaemia <25 min, no complications through to POD30), *n* (%)			
Yes	53 (48)	42 (47)	1.0 (−13.0 to 14.9)[b]
No	57 (52)	47 (53)	−1.0 (−14.9 to 13.0)[b]

Proportions are based on subjects with non-missing data. Numbers (*N*) for continuous variables are noted in the characteristic label if different from column *N*.
CI, confidence interval; mITT, modified intention-to-treat; NA, not applicable; OPN, open partial nephrectomy; POD, post-operative day; RAPN, robotic-assisted partial nephrectomy.
[a]Rate difference (95% CI is inappropriate, because other categories should not be combined).
[b]Rate difference (95% CI).
[c]Median difference (bootstrap 95% CI).
[d]Skin-to-skin.
[e]One conversion to OPN, one to open radical nephrectomy.

difference of ≥10% between the two approaches. One probable reason was premature termination of the trial before reaching the powered sample size, a decision made as per protocol because of low recruitment.

OpeRa failed to demonstrate differences between RAPN and OPN in most secondary endpoints, suggesting that we can expect similar complication and safety profiles despite the intermediate to high complexity of the tumours. Overall, RAPN was shown to be a safe surgical method in the OpeRa setting; almost 90% of patients did not experience high-grade perioperative complications, being comparable to OPN. Fewer complications were deemed by the investigators to be possibly or definitely procedure-related for RAPN than for OPN. We observed no difference in intraoperative complications and blood loss between both surgical approaches. The shorter operation time for OPN is, however, an advantage for conventional surgery which may have implications on staffing requirements, operating theatre capacity, and economics. In OpeRa, there were a number of hospital readmissions and re-interventions with a numerically higher number for RAPN. However, the small number of events precludes conclusions. Most of the re-interventions in both groups were minimally invasive, mainly ureteral stent insertions for urine leakage. In the similar but much smaller feasibility trial ROBOCOP II, which included renal tumours of all complexities, similar results were reported, including lower overall complication rates for RAPN versus OPN (4.9% ± 14.7% versus 14.0% ± 15.9%, P = 0.008), driven mainly by minor complications, significantly lower blood loss for RAPN, and longer operation time.[14,15]

In OpeRa, the frequently reported TRIFECTA rate (negative surgical margins, ischaemia time, no complications) indicated that both surgical methods were comparable in terms of oncologic and functional outcomes. TRIFECTA rates were rather low compared with literature, probably due to the complexity of the tumours included.[22-24] The complication rate was (numerically) lower with RAPN, in line with retrospective data, whereas ischaemia time was shorter with OPN, suggesting better preservation of kidney function

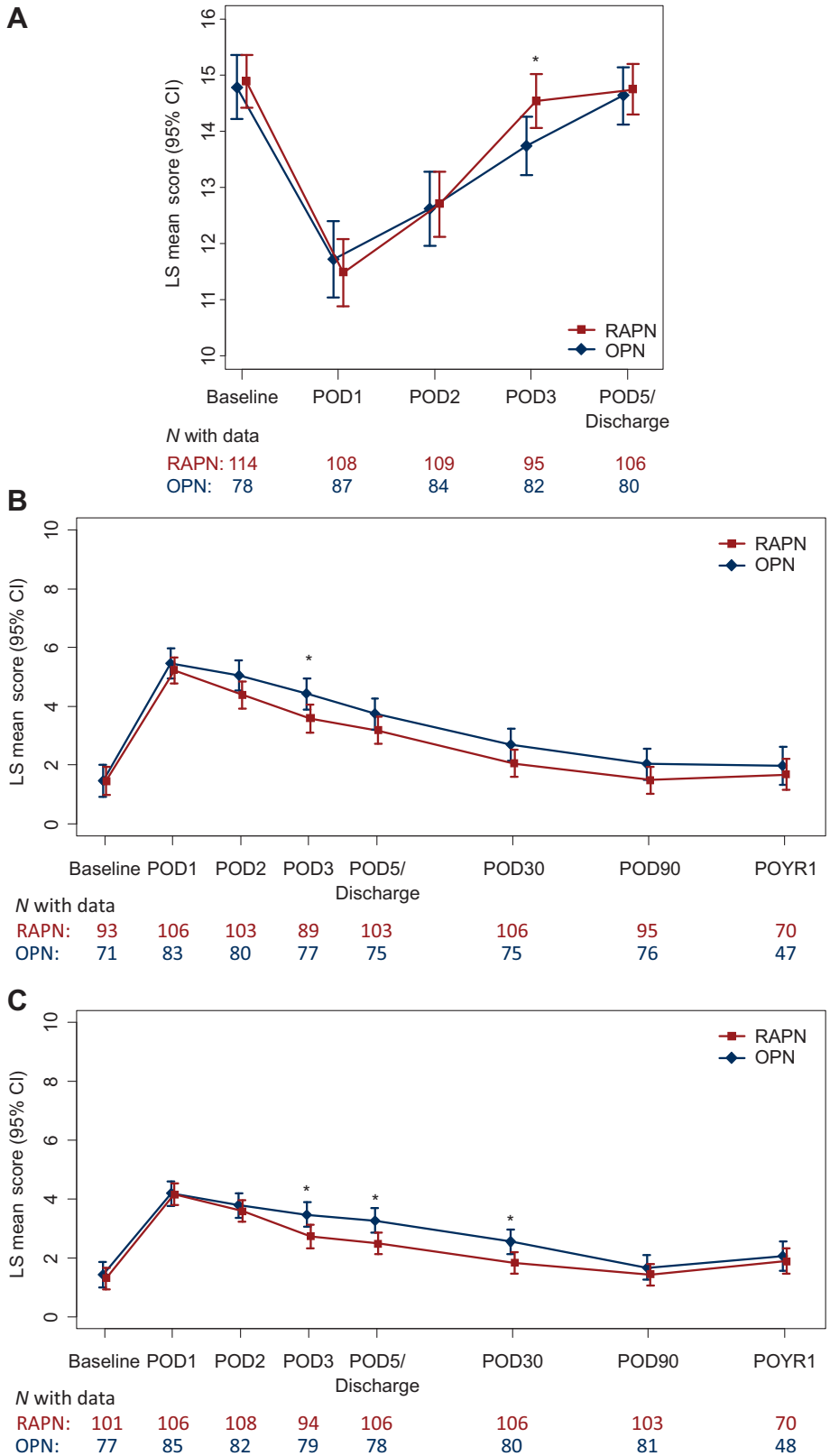

Figure 2. Patient-reported outcomes and pain assessment. (A) Quality of recovery (questionnaire: QoR-9) total score; (B) pain interference domain and (C) pain severity subscale of the Brief Pain Inventory (BPI, short form) questionnaire; (D) pain/discomfort dimension of the EQ-5D-5L questionnaire; (E) pain subscale of EORTC QLQ-C30 questionnaire; (F) health-related quality of life [questionnaire: EuroQol-5 dimensional-5 level instrument—visual analogue score (EQ-5D-5L—VAS)]; (G) quality of life [questionnaire: EORTC QLQ-C30—global health status/quality of life (GHS/QoL)]; (H) overview of patient-reported outcomes with differences between groups at any time point assessed.

BL, baseline; CI, confidence interval; DN4, Douleur Neuropathique 4; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; LS, least squares; OPN, open partial nephrectomy; POD, post-operative day; POYR, post-operative year; RAPN, robotic-assisted partial nephrectomy. *$P < 0.05$.

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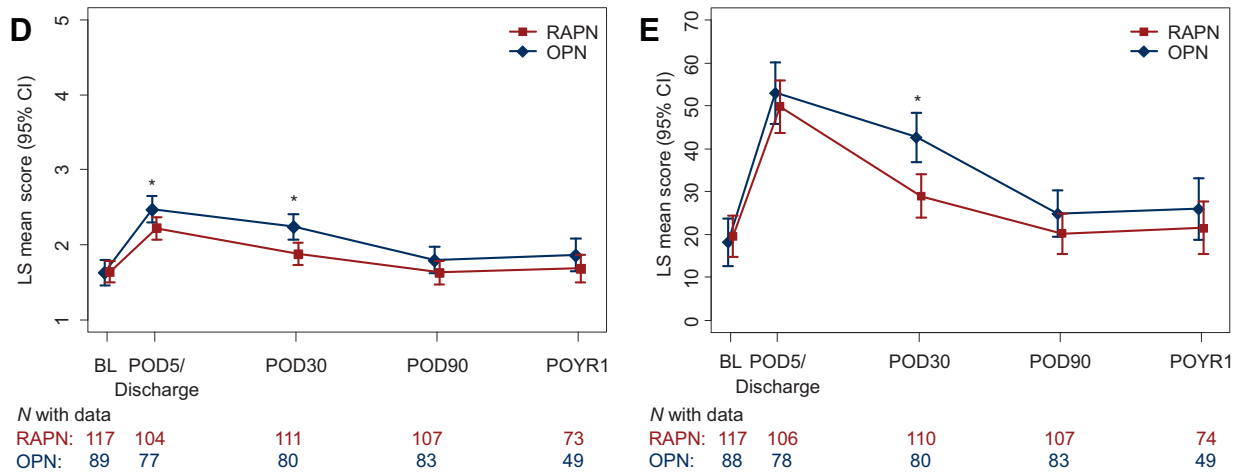

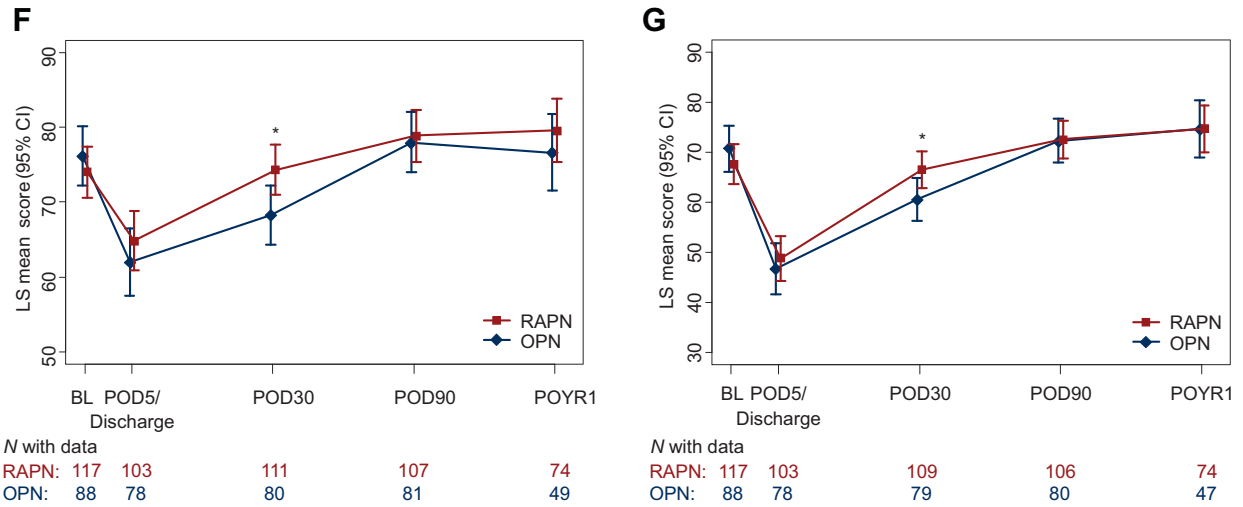

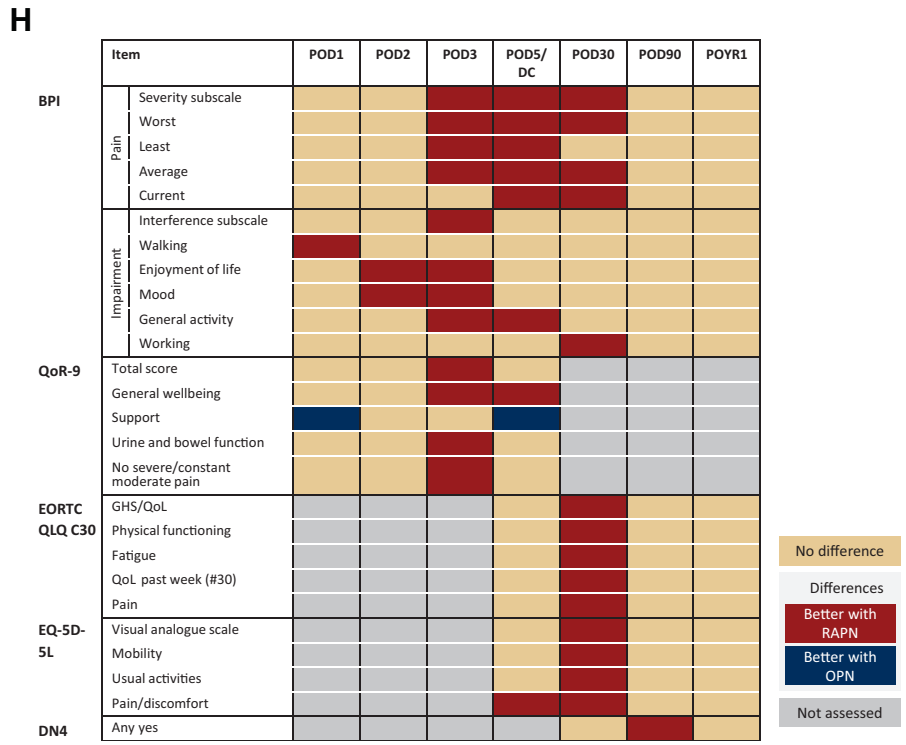

Figure 2. Continued.

in the OPN group. However, renal function (measured via eGFR until POD5/discharge) did not differ between RAPN and OPN, although it had not recovered to baseline in either surgical group by this time. In OpeRa, post-operative evaluation of eGFR was recorded as carried out in clinical routine, without obligation to be conducted on each POD studied. This might have biased our data, as patients with good renal function might have had fewer assessments. Comparing patients' last in-hospital record of eGFR to baseline revealed no difference between groups; we suppose that WIT played a subordinate role for short-term renal function. Similar findings have been presented in a meta-analysis (no prospective randomised data): despite shorter or comparable WIT for OPN, renal function was in favour of RAPN.[8]

Regarding the remaining TRIFECTA criterion, the absence of positive surgical tumour margins, we again report comparable rates between groups. Overall, the R1 rate appeared relatively high, probably reflecting tumour complexity.[23,24] However, the data reported in this article were collected in a multicentre, randomised, controlled trial, reflecting the highest standard of data quality. We noticed that the minimum and maximum distances of the tumour to the surgical margin measured were significantly lower for RAPN than for OPN. Although presumably of little clinical relevance, we interpret this to mean that robotic-assisted surgery has high precision in cutting and may be better suited to preserving as much normal tissue as possible. As a prerequisite for participation in the OpeRa study, minimum requirements for centres and surgeons had to be proven. The individual experience of each surgeon was, however, not recorded. Therefore, a correlation between the experience of the individual surgeons and the complication or TRIFECTA rates could not be examined.

More patients withdrew consent after randomisation when assigned to OPN, suggesting a preference for RAPN, probably due to its minimally invasive nature and anticipated better post-operative recovery. One important advantage of RAPN was the shorter hospital stay that accompanied improved recovery, especially evident on POD3. The fact that there were hardly any differences in the response to the QoR-9 questions at POD1 and POD2 [exception: question 2 ("had support from others") favoured OPN] might be related to pain management. While patients received standard analgesia during the first few PODs, pain management became more individualised and tailored to the patient's actual needs as time passed after surgery. While the use of non-opioid analgesics was comparable between the two surgical groups in terms of both patient numbers and dosage, more OPN patients were administered higher doses of opioids. This could be related to the more frequent use of epidural anaesthesia (OPN 42% versus RAPN 12%), often applying opioid-containing combinations as standard therapy (e.g. ropivacaine plus sufentanil). However, the cumulative dose of morphine equivalents remained elevated for OPN versus RAPN when excluding patients who received epidural anaesthesia. This observation is particularly interesting when considering patient replies to the BPI. No differences in pain were found at POD1 and POD2, but were evident from POD3, when pain management became more individualised. Looking at the questions on how much pain interfered with different aspects of life, walking ability was improved for RAPN versus OPN from POD1 and was a post-operative milestone at this stage of recovery. At POD2 and POD3, mood and enjoyment of life were less impaired for RAPN, attributable to less pain and possibly to the higher percentage of OPN patients receiving higher doses of opioids and their potential influence on the patient's mood. With increasing activity post-surgery, pain again impaired general activities to a lesser extent with RAPN at POD3 and discharge. Finally, the benefits of reduced pain in the RAPN group were reflected in decreased impairment of normal work at POD30, not usually a patient concern during hospital stay. At this time point, (hr)QoL had also improved more with RAPN versus OPN. At POD90 and POYR1, however, no differences in QoL and pain were observed between the two approaches anymore, indicating that the observed benefits were short term. The amount of opioids administered may furthermore be seen from another perspective: (excessive) opioid prescribing after surgery can lead to addiction and is a major contributor to the current opioid abuse epidemic. Withdrawal can be difficult and lengthy.[25,26] In OpeRa, we did not analyse post-discharge opioid use, but it is conceivable that a reduced opioid use during hospitalisation could be beneficial in general and also in terms of opioid use after discharge.

The main limitation of our trial was its premature termination due to slow recruitment, leading to limited statistical power to detect differences. Different numbers of patient withdrawals post-randomisation and of patients without complication status per group through to POD30 might bias the results.

Conclusions

OpeRa failed to achieve its primary endpoint. Given the increased adoption of RAPN and its growing availability, the window of opportunity for randomised trials appears to be closed. The numerically lower rate of complications through to POD30 for RAPN might be seen as indicative. Also, regarding most secondary endpoints, we did not see differences between RAPN and OPN, suggesting that similar complication and safety profiles can be expected despite the intermediate to high complexity of the tumours. However, better (hr)QoL was reported for RAPN through to POD30. Furthermore, RAPN required less intense pain management, with fewer patients receiving epidural anaesthesia and opioids, the latter at lower doses. Nevertheless, less pain was reported by patients undergoing RAPN. However, the experience of the surgeon and patient trust in the physician remain important.

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DATA SHARING

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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