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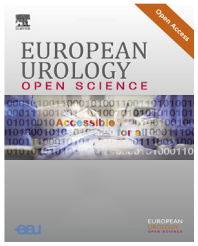

European Association of Urology

Kidney Cancer

Local Treatment of Recurrent Renal Cell Carcinoma May Have a Significant Survival Effect Across All Risk-of-recurrence Groups

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Abstract

Background: Retrospective comparative studies suggest a survival benefit after complete local treatment of recurrence (LTR) in renal cell carcinoma (RCC), which may be largely due to an indication bias.
Objective: To determine the role of LTR in a homogeneous population characterised by limited and potentially resectable recurrence.
Design, setting, and participants: RECUR is a protocol-based multicentre European registry capturing patient and tumour characteristics, risk of recurrence (RoR), recurrence patterns, and survival of those curatively treated for nonmetastatic RCC from 2006 to 2011. Per-protocol resectable disease (RD) recurrence was defined as (1) solitary metastases, (2) oligometastases, or (3) renal fossa or renal recurrence after radical or partial nephrectomy, respectively.
Intervention: Local treatment of recurrence.
Outcome measurements and statistical analysis: Overall survival (OS) and cancer-specific survival was compared in the RD population that underwent LTR versus no LTR. We constructed a multivariate model to predict risk factors for overall mortality and analysed the effect of LTR across RoR groups.
Results and limitations: Of 3039 patients with localised RCC treated with curative intent, 505 presented with recurrence, including 176 with RD. Of these patients,

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97 underwent LTR and 79 no LTR. Patients in the LTR group were younger (64.3 [40–80] vs 69.2 [45–87] yr; $p = 0.001$). The median OS was 70.3 mo (95% confidence interval [CI] 58–82.6) versus 27.4 mo (95% CI 23.6–31.15) in the LTR versus no-LTR group ($p < 0.001$). After a multivariate analysis, having LTR (hazard ratio [HR] 0.37 [95% CI 0.2–0.6]), having low- versus high-risk RoR (HR 0.42 [95% CI [0.20–0.83]), and not having extra-abdominal/thoracic metastasis (HR 1.96 [95% CI 1.02–3.77]) were prognostic factors of longer OS. The LTR effect on survival was consistent across risk groups. OS HR for high, intermediate, and low risks were 0.36 (0.2–0.64), 0.27 (0.11–0.65), and 0.26 (0.08–0.8), respectively. Limitations include retrospective design.

Conclusions: This is the first study assessing the effectiveness of LTR in RCC in a comparable population with RD. This study supports the role of LTR across all RoR groups.

Patient summary: We assessed the effectiveness of local treatment of resectable recurrent renal cell carcinoma after surgical treatment of the primary kidney tumour. Local treatment of recurrence was associated with longer survival across groups with a risk of recurrence.

1. Introduction

Renal cancer is the 15th most prevalent cancer in the world, with over 430 000 new cases diagnosed in 2020 [1]. Depending on tumour and patient characteristics at diagnosis, 35–47% of patients with locally advanced (T2–T4) renal cell carcinoma (RCC) recur after surgery and develop metastasis [2]. Despite proven efficacy of immune checkpoint inhibitors in the treatment of metastatic RCC (mRCC), only a minority of patients developed complete response in the most recent trials (8–16%) [3–6]. Therefore, complete removal of metastatic lesions, when technically feasible and clinically appropriate, may provide a potentially "curative" treatment alternative.

Prior studies consistently suggest a benefit of complete local treatment of recurrence (LTR) in mRCC patients in terms of overall survival (OS), cancer-specific survival (CSS), and delay of systemic treatment. The generally poor quality of the evidence base implies that there is significant uncertainty, and therefore, caution is needed in the interpretation of available retrospective comparative studies of LTR versus no intervention [7,8]. The reported benefit may largely be due to an indication bias on the basis of differences in metastatic load and tumour biology. Potentially, patients with oligometastasis and long metachronous intervals are more likely to be candidates for LTR, whereas those with high-volume metastasis, rapid progression, and reduced performance status often do not undergo resection but were used as comparators in historical retrospective studies [7].

Our objective was (1) to mitigate this selection bias and determine the role of LTR in a population comparable in terms of relapse volume, defined as resectable disease (RD) at time of recurrence, and (2) to determine the association between baseline risk of recurrence (RoR) by Leibovich score or Union for International Cancer Control (UICC) at the time of (partial) nephrectomy with curative intent and OS after LTR.

2. Patients and methods

2.1. RECUR database and study design

The RECUR database collected data from consecutive patients with a primary localised (N0M0) RCC from 15 centres in ten European countries who underwent surgery with curative intent from January 2006 to December 2011. The database collects demographic, surgical, and tumour characteristics, and information on risk scores as well as the type and frequency of imaging according to a protocol to establish associations for guideline recommendations for follow-up [9–11]. RECUR has appropriate institutional review board approval. Patients with <4 yr of follow-up and alive, or with incomplete data regarding subtype or risk scores were excluded.

Patients who recurred after radical nephrectomy (RN) or partial nephrectomy (PN), and presented with RD at recurrence were included in the study. Two groups were compared: patients who underwent LTR (LTR group) versus patients whose recurrence was not treated locally (no-LTR group).

2.2. Definition of RD

In the RECUR protocol, RD was defined as follows:

1. Solitary metastases
2. Oligometastases of up to three metastases at one site
3. Local renal fossa recurrence after RN or renal recurrence after PN

To account for other factors that may have influenced the decision to treat recurrences locally, intent of treatment and factors (comorbidities and sites) that may have contributed were collected.

2.3. Risk scores

All patients were classified according to their risk score of progression after nephrectomy. As per the RECUR protocol, for clear cell RCC (ccRCC), the Leibovich score [12] was used to document the baseline RoR at the time of (partial) nephrectomy with curative intent. The Leibovich score is a scoring algorithm based on tumour stage, regional lymph node

status, tumour size, nuclear grade and histologic tumour necrosis that can be used to predict disease progression after patients undergo RN for clinically localised ccRCC. For non-ccRCC, the UICC risk score was used [13,14].

2.4. Outcomes

OS and CSS were defined from the time of recurrence until death from any cause and death caused by RCC, respectively. Those still alive at the last follow-up were censored. Death from RCC was defined based on death certificate review or death following a recent medical visit for mRCC.

2.5. Statistical analysis

Frequencies and proportions were computed for categorical variables, whereas medians and interquartile ranges were calculated for continuous variables. Statistically significant differences between groups were estimated using the exact chi-square and Mann-Whitney tests for categorical and continuous variables, respectively.

The 1-, 2-, 3-, and 4-yr and median survival rates were obtained using the Kaplan-Meier method. Cox proportional hazard regression analyses including age at recurrence, time to recurrence, risk score, site of recurrence (abdomen, thoracic, and other), and LTR status were conducted to determine the impact of independent risk factors on OS. All statistical comparisons were two sided, with a p value of <0.05 as a threshold of statistical significance. SPSS version 25 (IBM Corporation, Armonk, NY, USA) was used for the analyses.

3. Results

During the study period, a total of 3039 patients with localised RCC were treated with curative intent with either RN or PN. Of these patients, 505 (16.6%) presented with RCC recurrence after curative treatment, of whom 245 had RD. Of the latter, 97 underwent LTR (89, five, and three patients received metastasectomy, radiotherapy, and ablation, respectively), 79 patients did not receive any intervention, and data were missing for 69 patients (Fig. 1).

Table 1 shows baseline characteristics of the two groups. Patients in the LTR group were younger at nephrectomy and had a better risk score profile, longer time to recurrence, and lower pT stages (Table 1). The no-LTR group presented with a higher number of patients with liver (7% vs 0%, p = 0.006) or bone (20.3% vs 4.1%, p = 0.001) metastasis (Table 2).

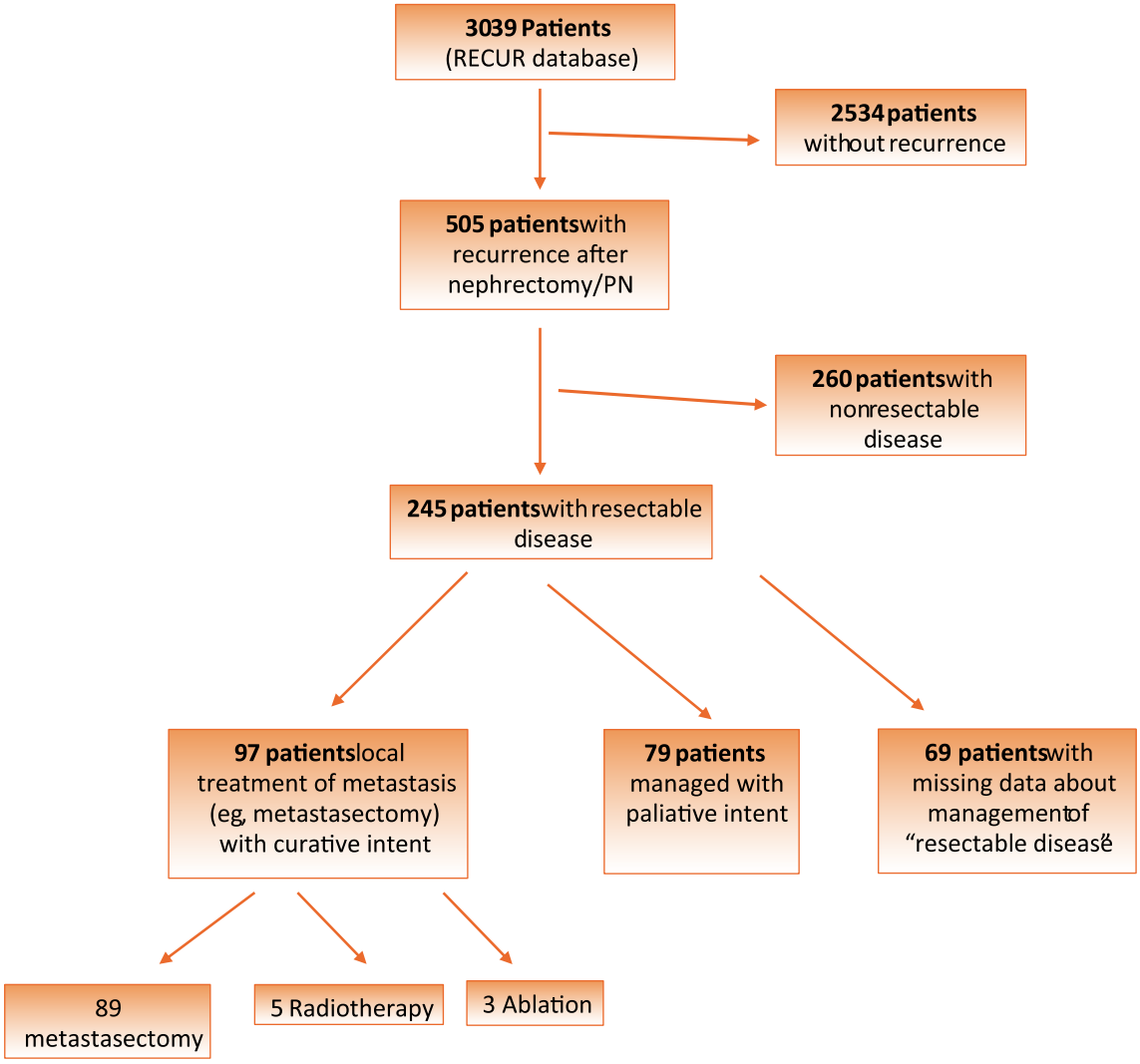


Fig. 1 – Flowchart of the patients included in the study. PN = partial nephrectomy.

Table 1 – Baseline characteristics

		LTR group (n = 97)	No LTR group (n = 79)	p value
Age at recurrence, yr (range)		64 (40–80)	69 (45–87)	0.001
Age at nephrectomy, yr (range)		61 (37–77)	67 (43–85)	**<0.001**
Primary tumour size (cm)		7.06	7.98	0.1
Risk score (%)[a]	Low risk	29.9	13.9	**0.009**
	Intermediate risk	33.0	27.8	
	High risk	37.1	58.2	
Time to recurrence (mo)		31	24	**0.023**
Chest recurrence (%)		25.8	38.0	0.082
Abdomen recurrence (%)		27.8	46.4	**0.012**
Other site of recurrence (%)		21.6	27.8	**0.034**
Male (%)		67.0	65.8	0.97
NSS (%)		21.6	16.5	0.39
Histologic subtype (%)				
ccRCC		85.6	87.3	0.804
Papillary RCC		10.3	8.9	
Chromophobe RCC		3.1	3.8	
Other		1	0	
Tumour grade (%)				
1		2.1	3.9	0.741
2		37.2	38.2	
3		44.7	38.2	
4		16	19.7	
pT (%)				
pT1a		23.7	10.1	**0.048**
pT1b		15.5	7.6	
pT2a		10.3	12.7	
pT2b		11.3	7.6	
pT3a		30.9	52.4	
pT3b		7.2	16.5	
pT3c		0	1.3	
pT4		1	2.5	
pN				
pN0		21.6	27.8	0.059
pN1 or N2		2.1	8.9	
pNx		76.3	63.3	

ccRCC = clear cell RCC; LTR = local treatment of recurrence; NSS = nephron-sparing surgery; RCC = renal cell carcinoma; UICC = Union for International Cancer Control.
[a] Leibovich or UICC.

Systemic treatment after recurrence was administered to 21.8% (n = 17) and 39% (n = 30) in the LTR and no-LTR group, respectively (p = 0.02).

3.1. Survival analysis

The mean study follow-up was 34 mo. The median OS was 70.3 mo (95% confidence interval [CI] 58–82.6) versus 27.4 mo (95% CI 23.6–31.15) in the LTR and no-LTR group, respectively (log rank p < 0.001; Fig. 2). OS periods at 12, 24, 36, and 48 mo after recurrence were, respectively, 97%, 86%, 72%, and 65% for the LTR Group versus 72%, 57%, 38%, and 27% for the no-LTR group. Both OS analysis excluding contralateral kidney recurrences and CSS findings mirrored those from OS (Supplementary Fig. 1 and 2)

Table 2 – Location of recurrence per study group

	LTR (n = 97), %	No LTR (n = 79), %	p value
Lung	27.8	32.9	0.47
Pleura	1	1.3	0.88
Retroperitoneal LN	2.1	2.5	0.84
Liver	0	7	**0.006**
Pancreas	3.1	3.8	0.8
Adrenal	9.3	2.5	0.067
Contralateral kidney	19.6	2.5	**0.001**
Bone	4.1	20.3	**0.001**
Brain	3.1	5.1	0.5
Other	9.3	6.3	0.472
Local recurrence (after RN)	11.3	11.4	0.99
Local recurrence (after PN)	10.3	6.3	0.35

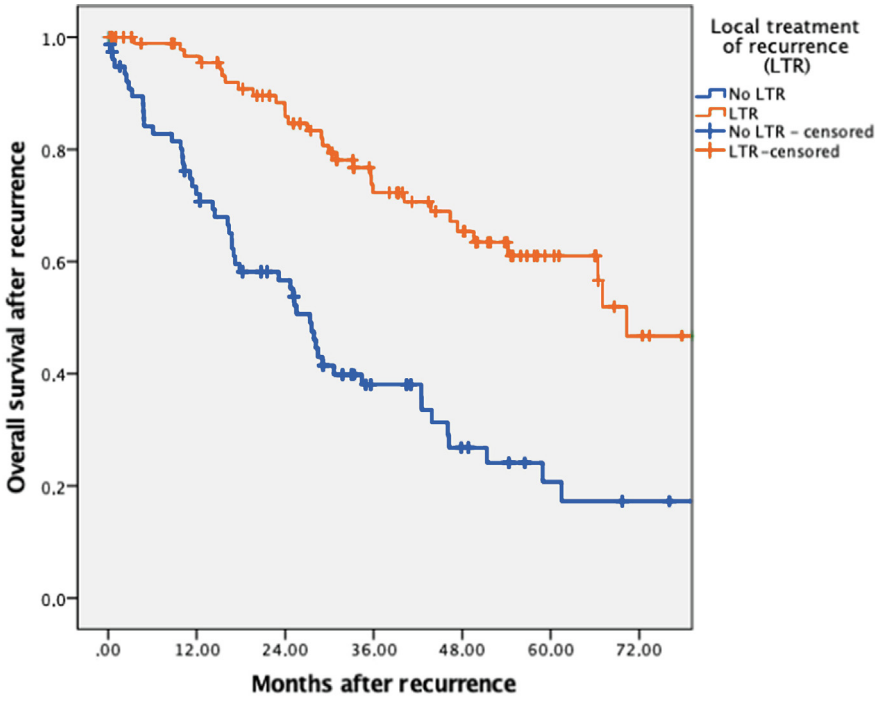
LN = lymph node; LTR = local treatment of recurrence; PN = partial nephrectomy; RN = radical nephrectomy.

3.2. Survival analysis stratified by baseline risk score

The survival analysis stratified by RoR shows median OS of 66.39 (95% CI 33.67–99.11) versus 25.1 (95% CI 12.2–37.9) mo for high-risk patients in the LTR versus no-LTR group (log rank p < 0.001). In intermediate-risk patients, the median OS was not estimable versus 27.6 (95% CI 22.2–32.9) mo for the LTR versus no-LTR group (log rank p = 0.02). For low-risk patients, the median OS was not estimable versus 28.19 (95% CI 0–64.8) mo for the LTR versus no-LTR group (log rank p = 0.013; Fig. 3).

Within the group of patients submitted to LTR, despite the superior numerical survival in those patients with favourable and intermediate RoR, no statistically significant differences were found (log rank p = 0.107; Supplementary Fig. 3)

The effect of LTR on survival was consistent across risk groups: high-risk patients had an OS HR of 0.36 (0.2–0.64), intermediate-risk groups had an OS HR of 0.27 (0.11–0.65), and low-risk groups had an OS HR of 0.2 (0.08–0.8).



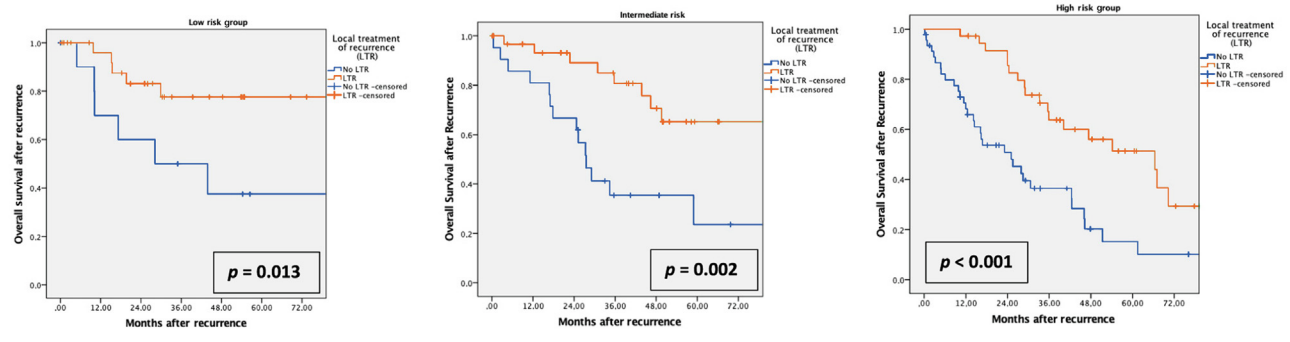
Number at risk

	0 mo	12 mo	24 mo	36 mo	48 mo	60 mo
LTR	97	85	69	49	37	18
No LTR	79	53	38	19	11	6

Fig. 2 – Kaplan-Meyer curves for overall survival after recurrence (log rank $p < 0.0001$). LTR = local treatment of recurrence.

3.3. *Multivariate analysis*

After a multivariate analysis, LTR (HR 0.37 [95% CI 0.23–0.59], $p < 0.001$), low versus high RoR (HR 0.42 [95% CI 0.21–0.83], $p = 0.016$), and longer time to recurrence (HR 0.98 [95% CI 0.97–0.996], $p = 0.01$) were prognostic factors of longer OS. Having a nonthoracic/nonabdominal recurrence (HR 1.96 [95% CI 1.02–3.77], $p = 0.042$) was a risk factor for shorter OS (Table 3).



Number at risk (low-risk group)

	0 mo	12 mo	24 mo	36 mo	48 mo
LTR	29	23	18	11	10
No LTR	11	7	6	4	3

Number at risk (intermediate-risk group)

	0 mo	12 mo	24 mo	36 mo	48 mo
LTR	32	27	22	19	14
No LTR	22	17	14	5	4

Number at risk (high-risk group)

	0 mo	12 mo	24 mo	36 mo	48 mo
LTR	36	35	29	19	14
No LTR	46	29	18	10	4

Fig. 3 – Kaplan-Meyer curves for overall survival per risk-of-recurrence group. LTR = local treatment of recurrence.

Table 3 – Multivariate Cox regression—predictors of overall mortality

	HR	95% CI	*p* value
LTR (vs no LTR)	0.37	0.23–0.59	**<0.001**
Age (at recurrence)	1.03	1.0–1.05	**0.012**
Time from nephrectomy to recurrence	0.98	0.97– 0.99	0.004
Risk of recurrence score			
Poor vs favourable	2.4	1.2–4.8	**0.016**
Intermediate vs favourable	1.2	0.58–2.6	0.608
Thoracic recurrence	0.79	0.41–1.54	0.49
Abdominal recurrence	1.07	0.56–2.06	0.833
Other site of recurrence	1.96	1.02–3.77	**0.042**

CI = confidence interval; HR = hazard ratio; LTR = local treatment of recurrence.

4. Discussion

In this series of RCC patients with comparable, potentially resectable, low-volume cancer recurrence after nephrectomy, we report superior OS and CSS in those submitted to any form of local treatment of the lesions. This finding was confirmed after a multivariate analysis where local treatment conferred a 63% reduction in the risk of death. In this population, longer time to recurrence and a low baseline RoR at the time of (partial) nephrectomy were also found to be prognostic factors for longer OS after recurrence. We demonstrate that LTR of well-selected mRCC patients is associated with long-term OS across all RoR groups at the time of nephrectomy with curative intent.

Current guidelines recommend LTR for metachronous RCC in patients with metastatic disease and favourable disease factors, and in whom complete resection is achievable [15,16]; in patients who develop oligometastases after a prolonged disease-free interval from nephrectomy [17]; and in patients with good performance status, solitary metastases or oligometastases, metachronous disease with disease-free interval of >2 yr, absence of progression on systemic therapy, low or intermediate Fuhrman grade, and possibility of complete resection [18]

A survival benefit with complete metastasectomy versus either incomplete or no metastasectomy for RCC metastases to parenchymal organs was found in previous studies [7,19]. The current body of evidence is composed of retrospective, often noncomparative, studies and is hampered by a high risk of confounding regarding previous treatments, tumour histology, grade, and especially size, number, and volume of metastases [20–24]. Several recent studies from the tyrosine kinase inhibitor era found favourable survival outcome with metastasectomy compared with nonmetastasectomy in patients treated with targeted therapy [25–27].

In the current study, we analysed a contemporary population from a multicentre European registry that started to include patients after widespread availability of targeted therapy [9]. We attempted to control heterogeneity in number, size, and volume of recurrence by including only patients with RD, as defined according to the RECUR protocol. Reported general and site-specific factors associated with a favourable outcome after local treatment of metastases from RCC are good performance status, Memorial Sloan Kettering Cancer Center (MSKCC) favourable and intermediate risk, solitary or oligometastatic disease, long disease-free interval, absence of sarcomatoid component, clear cell subtype, and complete surgical resection [7]. Especially the number of lesions and their sites seem to have an important prognostic impact [28]. In our study, RD was defined as three or fewer recurrences at a single site. Interestingly, this cut-off was used for eligibility to enter the phase 2 randomised open-label RESORT trial, which investigated the potential benefit of postoperative treatment with sorafenib compared with observation alone after complete metastasectomy in mRCC patients [29].

A recent study on 51 patients with metastasectomy concluded that the number of metastatic sites and sarcomatoid features but not MSKCC score were associated with recurrence after complete metastasectomy [30]. It is very important to accurately estimate a patient's prognosis related to both the tumour and the patient's competing comorbidities, and to weigh the risks and benefits of LTR and its associated toxicity. We have shown that the baseline RoR at the time of (partial) nephrectomy with curative intent has a prognostic value even after recurrence and that LTR is associated with a significant survival benefit across all risk groups compared with no LTR. Nevertheless, despite OS benefits following LTR, the downward trend of the survival curves especially in high-risk disease suggests that patients experience further disease progression after local treatment and that cure is unlikely with this approach. We hypothesised that the RoR at the time of nephrectomy might also maintain a role as a prognostic factor after LTR. In the survival analysis by risk score in those patients who underwent LTR, we found that the baseline RoR lost its prognostic discrimination. This could be explained by the low number of events in the low- and intermediate-risk groups. To our knowledge, this is the first study that controls for baseline RoR by either Leibovich score or UICC in the comparison of LTR versus no LTR, and explores its prognostic value after LTR. We believe that there is currently only the Leuven-Udine metastasectomy prognostic score available for contemporary risk assessment; however, its validation could not be repeated externally [27]. Until biomarkers are available to select patients for local or systemic therapy, decision-making supporting metastasectomy can be guided by the previously mentioned factors [31]. In addition to surgical LTR, stereotactic body radiotherapy is an attractive approach gaining further evidence [32–34].

The current study has several limitations due to its retrospective nature. Both groups were well balanced in terms of primary tumour size, histologic subtype, and tumour grade; however, we could observe evidence of a selection bias in baseline features that predict disease aggressivity such as stage, Leibovich risk score, and time to recurrence. While we controlled for RoR in our comparison, we acknowledge that other inherent patient confounders, such as differences in comorbidities, age, and performance status, may have influenced the decision to undergo LTR in the current series. We have also found a higher proportion of patients with bone metastasis in the no-LTR group, which has been identified as an independent prognostic variable associated with poor survival [35,36]. Further, it needs to be acknowledged

that local recurrence is not distant metastatic disease. However, there were no major imbalances between both groups, and local recurrence in the renal bed portends a similarly poor prognosis to distant oligometastatic disease [37]. Notably, the LTR groups had more contralateral kidney recurrences. Metachronous occurrence of RCC in the contralateral kidney is associated with an unfavourable prognosis, suggesting that metachronous contralateral tumours might be metastases from the original tumours [38]. To exclude confounding by de novo contralateral tumours that carry a better prognosis, we repeated the analysis without patients with contralateral recurrences and continued to observe a survival advantage in the LTR group. In RCC, survival is influenced by systemic therapy, and although we know the percentage of patients treated upon progression, data on the type and duration of treatment were not recorded. Finally, data regarding complications after LTR were not available.

We have witnessed a major paradigm change in first-line therapy for mRCC with the introduction of immune checkpoint inhibitor–based combination as standard of care [39]. In unselected patients, durable overall responses with these combinations are achieved in 60% and complete responses in up to 16% [39]. Therefore, the role of LTR in the era of immune checkpoint inhibition needs to be investigated, in prospective trials, with a focus on surgical options and radiotherapy, observation, perioperative or adjuvant systemic therapy, and sequencing of immunotherapy in oligoprogressive disease.

5. Conclusions

In comparison with previous retrospective studies comparing metastasectomy with no metastasectomy, our study assessed the effectiveness of LTR in RCC in a comparable population with RD. This study supports the role of LTR across all RoR groups in a selected population.

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

Study concept and design: Marconi, Bex.
Acquisition of data: Marconi, Capitanio, Beisland, Lam, Pello, Stewart, Volpe, Ljungberg, Dabestani, Bex.
Analysis and interpretation of data: Marconi, Bex.
Drafting of the manuscript: Marconi, Bex.
Critical revision of the manuscript for important intellectual content: Marconi, Kuusk, Klatte, Capitanio, Beisland, Lam, Pello, Stewart, Volpe, Ljungberg, Dabestani, Bex.
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Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.11.008.

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