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## 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.

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## 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 (NOMO) 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 con-

ducted 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).

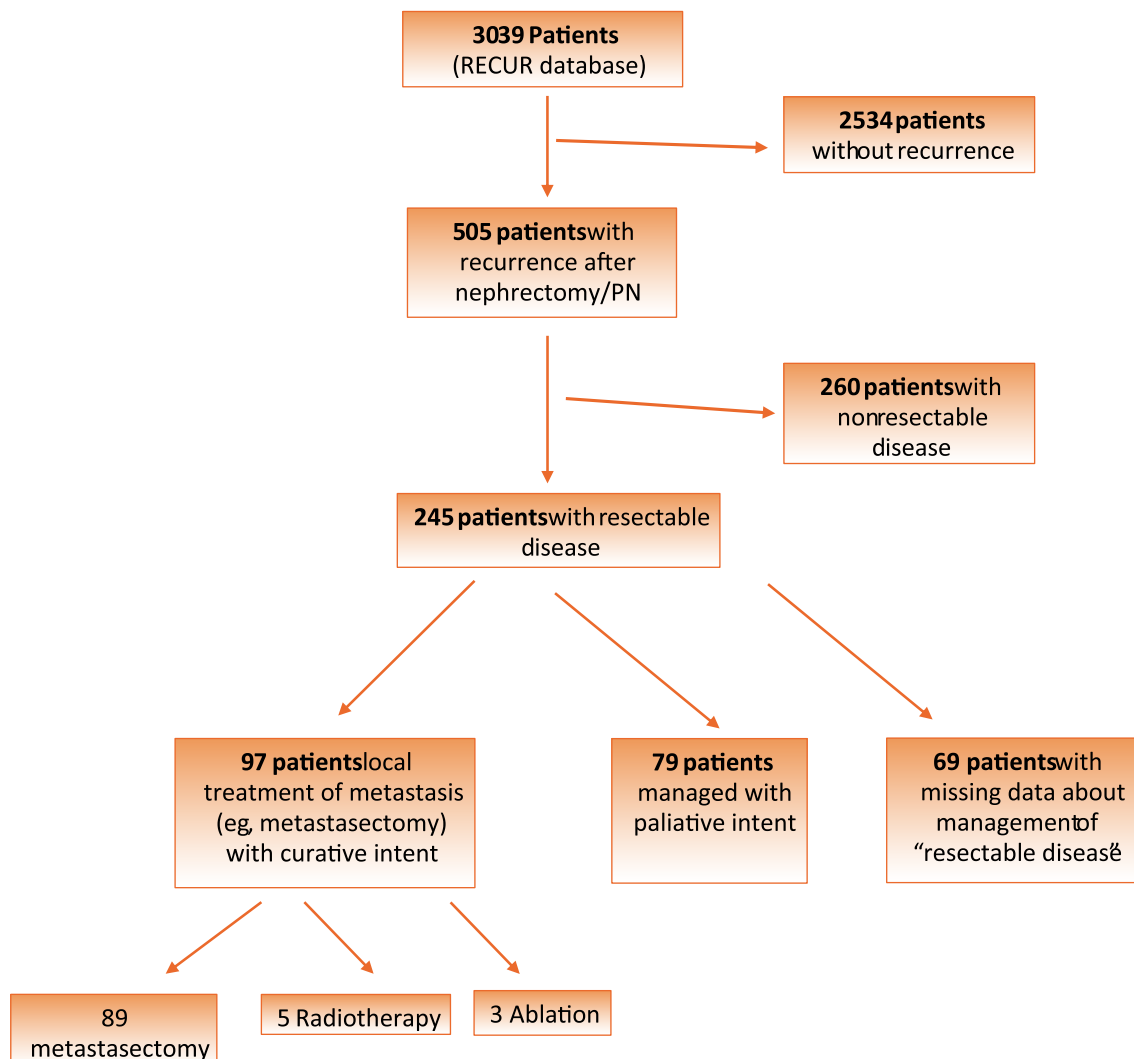


Fig. 1 – Flowchart of the patients included in the study. PN = partial nephrectomy.

**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 (%) <sup>a</sup>			<b>0.009</b>
Low risk	29.9	13.9	
Intermediate risk	33.0	27.8	
High risk	37.1	58.2	
Time to recurrence (mo)	31	24	<b>0.023</b>
Chest recurrence (%)	25.8	38.0	0.082
Abdomen recurrence (%)	27.8	46.4	<b>0.012</b>
Other site of recurrence (%)	21.6	27.8	<b>0.034</b>
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	<b>0.048</b>
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.

<sup>a</sup> 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)

### 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).

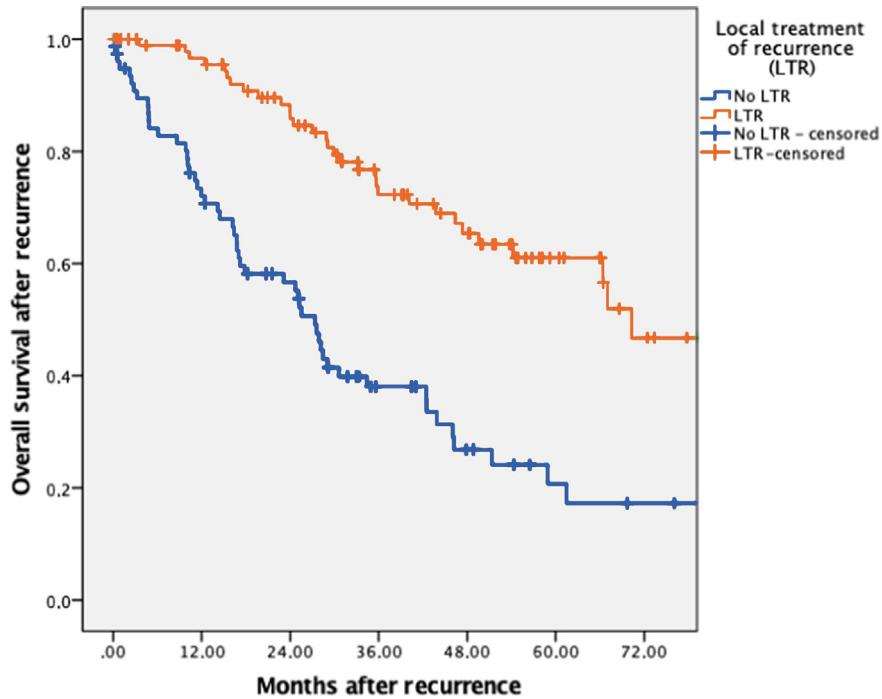
Within the group of patients submitted to LTR, despite the superior numerical survival in those patients with favourable and intermediate RoR, no statistically significant differences were found (log rank p = 0.107; Supplementary Fig. 3)

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).

**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	<b>0.006</b>
Pancreas	3.1	3.8	0.8
Adrenal	9.3	2.5	0.067
Contralateral kidney	19.6	2.5	<b>0.001</b>
Bone	4.1	20.3	<b>0.001</b>
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.



Number at risk

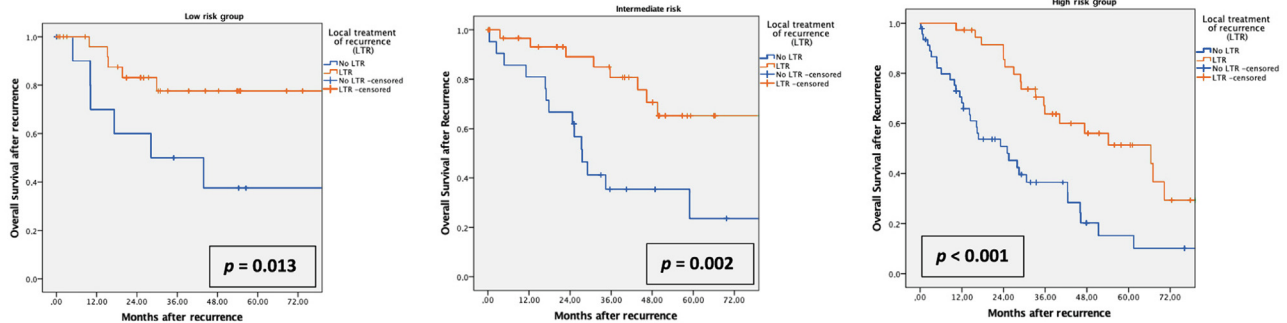
	0 mo	12 mo	24 mo	36 mo	48 mo	60 mo
LTR	97	85	69	49	37	18
No LTR	79	53	38	19	11	6

Fig. 2 – Kaplan-Meier 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-Meier 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	<b>&lt;0.001</b>
Age (at recurrence)	1.03	1.0–1.05	<b>0.012</b>
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	<b>0.016</b>
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	<b>0.042</b>

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.

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*Analysis and interpretation of data:* Marconi, Bex.

*Drafting of the manuscript:* Marconi, Bex.

*Critical revision of the manuscript for important intellectual content:* Marconi, Kuusk, Klatté, Capitanio, Beisland, Lam, Pello, Stewart, Volpe, Ljungberg, Dabestani, Bex.

*Statistical analysis:* Marconi.

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*Supervision:* Bex.

*Other:* None.

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## Appendix A. Supplementary data

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## References

- [1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
- [2] Dabestani S, Thorstenson A, Lindblad P, Harmenberg U, Ljungberg B, Lundstam S. Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study. *World J Urol* 2016;34:1081–6.
- [3] Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2021;384:829–41.
- [4] Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med* 2021;384:1289–300.
- [5] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1116–27.
- [6] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378:1277–90.
- [7] Dabestani S, Marconi L, Hofmann F, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. *Lancet Oncol* 2014;15:e549–61.
- [8] Ouzaid I, Capitanio U, Staehler M, et al. Surgical metastasectomy in renal cell carcinoma: a systematic review. *Eur Urol Oncol* 2019;2:141–9.
- [9] Dabestani S, Beisland C, Stewart GD, et al. Intensive imaging-based follow-up of surgically treated localised renal cell carcinoma does not improve post-recurrence survival: results from a European multicentre database (RECUR). *Eur Urol* 2019;75:261–4.
- [10] Dabestani S, Beisland C, Stewart GD, et al. Increased use of cross-sectional imaging for follow-up does not improve post-recurrence survival of surgically treated initially localized R.C.C.: results from a European multicenter database (R.E.C.U.R.). *Scand J Urol* 2019;53:14–20.
- [11] Dabestani S, Beisland C, Stewart GD, et al. Long-term outcomes of follow-up for initially localised clear cell renal cell carcinoma: RECUR database analysis. *Eur Urol Focus* 2019;5:857–66.
- [12] Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer* 2003;97:1663–71.
- [13] Rosiello G, Larcher A, Fallara G, et al. Head-to-head comparison of all the prognostic models recommended by the European Association of Urology guidelines to predict oncologic outcomes in patients with renal cell carcinoma. *Urol Oncol* 2022;40:271.e19–.
- [14] Usher-Smith JA, Li L, Roberts L, et al. Risk models for recurrence and survival after kidney cancer: a systematic review. *BJU Int* 2022;130:562–79.
- [15] Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology guidelines on renal cell carcinoma: the 2019 update. *Eur Urol* 2019;75:799–810.
- [16] Bedke J, Albiges L, Capitanio U, et al. 2021 Updated European Association of Urology guidelines on the use of adjuvant pembrolizumab for renal cell carcinoma. *Eur Urol* 2022;81:134–7.
- [17] Motzer RJ, Jonasch E, Boyle S, et al. NCCN guidelines insights: kidney cancer, version 1.2021. *J Natl Compr Canc Netw* 2020;18:1160–70.

- [18] Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019;30:706–20.
- [19] Hsieh PY, Hung SC, Li JR, et al. The effect of metastasectomy on overall survival in metastatic renal cell carcinoma: a systematic review and meta-analysis. *Urol Oncol* 2021;39:422–30.
- [20] Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012;82:1744–8.
- [21] Zerbi A, Ortolano E, Balzano G, Borri A, Beneduce AA, Di Carlo V. Pancreatic metastasis from renal cell carcinoma: which patients benefit from surgical resection? *Ann Surg Oncol* 2008;15:1161–8.
- [22] Dragomir A, Nazha S, Wood LA, et al. Outcomes of complete metastasectomy in metastatic renal cell carcinoma patients: the Canadian Kidney Cancer information system experience. *Urol Oncol* 2020;38:799.e1–e10.
- [23] Eggener SE, Yossepowitch O, Kundu S, Motzer RJ, Russo P. Risk score and metastasectomy independently impact prognosis of patients with recurrent renal cell carcinoma. *J Urol* 2008;180:873–8, discussion 878.
- [24] Fuchs B, Trousdale RT, Rock MG. Solitary bony metastasis from renal cell carcinoma: significance of surgical treatment. *Clin Orthop Relat Res* 2005;431:187–92.
- [25] Sun M, Meyer CP, Karam JA, et al. Predictors, utilization patterns, and overall survival of patients undergoing metastasectomy for metastatic renal cell carcinoma in the era of targeted therapy. *Eur J Surg Oncol* 2018;44:1439–45.
- [26] Li JR, Ou YC, Yang CK, et al. The impact of local intervention combined with targeted therapy on metastatic renal cell carcinoma. *Anticancer Res* 2018;38:5339–45.
- [27] Tornberg SV, Visapaa H, Kilpelainen TP, et al. Surgery for metastases of renal cell carcinoma: outcome of treatments and preliminary assessment of Leuven-Udine prognostic groups in the targeted therapy era. *Scand J Urol* 2018;52:419–26.
- [28] Psutka SP, Master VA. Role of metastasis-directed treatment in kidney cancer. *Cancer* 2018;124:3641–55.
- [29] Procopio G, Apollonio G, Cognetti F, et al. Sorafenib versus observation following radical metastasectomy for clear-cell renal cell carcinoma: results from the phase 2 randomized open-label RESORT study. *Eur Urol Oncol* 2019;2:699–707.
- [30] Takagi T, Fukuda H, Ishihara H, et al. Predictive factors for recurrence after complete metastasectomy in patients with metastatic renal cell carcinoma in the targeted therapy era. *Urol Oncol* 2020;38:515–20.
- [31] Verbiest A, Couchy G, Job S, et al. Molecular subtypes of clear-cell renal cell carcinoma are prognostic for outcome after complete metastasectomy. *Eur Urol* 2018;74:474–80.
- [32] Liu Y, Long W, Zhang Z, et al. Metastasis-directed stereotactic body radiotherapy for oligometastatic renal cell carcinoma: extent of tumor burden eradicated by radiotherapy. *World J Urol* 2021;39:4183–90.
- [33] Stenman M, Sinclair G, Paavola P, Wersall P, Harmenberg U, Lindskog M. Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005–2014. *Radiother Oncol* 2018;127:501–6.
- [34] Siva S, Bressel M, Wood ST, et al. Stereotactic radiotherapy and short-course pembrolizumab for oligometastatic renal cell carcinoma—the RAPPOR trial. *Eur Urol* 2022;81:364–72.
- [35] Kalra S, Verma J, Atkinson BJ, et al. Outcomes of patients with metastatic renal cell carcinoma and bone metastases in the targeted therapy era. *Clin Genitourin Cancer* 2017;15:363–70.
- [36] Ruatta F, Derosa L, Escudier B, et al. Prognosis of renal cell carcinoma with bone metastases: Experience from a large cancer centre. *Eur J Cancer* 2019;107:79–85.
- [37] Itano NB, Blute ML, Spotts B, Zincke H. Outcome of isolated renal cell carcinoma fossa recurrence after nephrectomy. *J Urol* 2000;164:322–5.
- [38] Amano H, Kondo T, Hashimoto Y, et al. Contralateral metachronous tumor occurrence is more frequently associated with distant metastases or postoperative intrarenal recurrence in renal cell carcinoma patients. *Int J Urol* 2010;17:615–22.
- [39] Bedke J, Albiges L, Capitanio U, et al. The 2021 updated European Association of Urology guidelines on renal cell carcinoma: immune checkpoint inhibitor-based combination therapies for treatment-naive metastatic clear-cell renal cell carcinoma are standard of care. *Eur Urol* 2021;80:393–7.