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Local Recurrence Following Resection of Intermediate-High Risk Non-Metastatic Renal Cell Carcinoma: An Anatomic Classification and Analysis of the ASSURE (ECOG-ACRIN E2805) Adjuvant Trial

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Abstract

Purpose: We describe a novel classification system for local recurrence after surgery for renal cell carcinoma, and assess its prognostic implications using prospective randomized controlled data.

Materials and Methods: The ASSURE (ECOG-ACRIN E2805) trial data were queried for patients with fully resected intermediate-high risk non-metastatic renal cell carcinoma with local recurrence using the following definitions: Type I: single recurrence in remnant kidney or ipsilateral renal fossa; Type II: single recurrence in ipsilateral vasculature, ipsilateral adrenal gland, or lymph node; Type III: single recurrence in other intra-abdominal soft tissues or organs; and Type IV: any combination of Types I-III, or multiple recurrences within a single Type.

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None

Multivariable logistic regression and log-rank test were used to identify clinicopathologic predictors and compare survival, respectively.

Results: Of 300/1,943 (15.4%) patients with local recurrence, 66/300 (22.0%) had Type I, 97/300 (32.3%) had Type II, 87/300 (29.0%) had Type III, and 50/300 (16.7%) had Type IV. Surgical modality (minimally-invasive versus open) and type of surgery (partial versus radical) did not predict any local recurrence. Five-year cancer-specific ($p<0.001$) and overall ($p<0.001$) survival were worse for patients with Type IV recurrence. There was no difference in survival among patients with Types I-III recurrences.

Conclusions: In patients with intermediate-high risk non-metastatic renal cell carcinoma, local recurrence appears to be a function of biology more than surgical modality or type of surgery. The prognosis for solitary intra-abdominal local recurrences appear similar regardless of location (Types I-III). Local recurrences involving multiple sites and/or subdivisions is associated with worse survival (Type IV).

Keywords

Classification; Local Neoplasm Recurrence; Nephrectomy; Renal Cell Carcinoma

Introduction:

Local recurrence (LR) has been reported in 1.8–6.4% of patients undergoing surgery for clinically localized renal cell carcinoma (RCC).[1–4] It is associated with poor prognosis and 18–46% 5-year cancer-specific survival (CSS).[5, 6] Identifying patients with LR is critical because locally directed therapies such as surgery, ablation, and/or radiation may improve survival outcomes, especially in the setting of a solitary recurrence.[2, 6, 7] Furthermore, utilization of systemic therapies have improved the prognosis of patients with multifocal recurrence and may improve the results of consolidative surgery.[8]

There is currently no standardized definition for LR after surgery for RCC, and there is considerable heterogeneity in defining LR in the current literature.[4, 9, 10] Generally, LR refers to microscopic persistence leading to recurrence in the remnant kidney or ipsilateral renal fossa.[4, 5, 10, 11] Other authors have included the ipsilateral adrenal gland and lymph nodes (LN) in their definition.[1, 2, 6] Although the definition of LR is inferred to mean an anatomically adjacent recurrence, this definition is open to significant interpretation. Furthermore, in the absence of a consistent definition of LR, the prognostic implications of these differences are unknown.

Herein, we describe a novel anatomic classification system for LR utilizing prospective randomized controlled data from the ASSURE (ECOG-ACRIN E2805) trial[12] to identify clinicopathologic variables that predict LR and evaluate survival outcomes.

Materials and Methods:

Patient Cohort:

The ASSURE trial was an institutional review board approved, double-blind, placebo-controlled, phase III multi-institutional study in which patients with completely resected

non-metastatic intermediate-high risk RCC were randomly assigned sunitinib, sorafenib, or placebo in a 1:1:1 ratio from April 2006-September 2010. Intermediate-high risk patients were defined as having pT1b G3−4 N0 (or pNX where clinically N0) M0 to T(any) G(any) N+ M0. In patients with cN+, complete resection was required for enrollment. All patients were R0 with negative surgical margins. Tumor samples were centrally reviewed to confirm RCC histology. The primary outcome was disease-free survival among each experimental group in the intention-to-treat population.[12]

After pooling data across the three treatment arms, we identified all patients with LR, which we defined as any intra-abdominal RCC recurrence. Patients with concurrent metastasis, which we defined as any extra-abdominal recurrence (ie. lung, brain, and bone), were excluded. All patients were postoperatively evaluated for recurrent disease via standardized chest and abdominal cross-sectional imaging. Per protocol, imaging was performed every 4–5 months during the 54-week treatment regimen, then every 6 months for 2 years, and then once per year for 10 years.

Patients with LR were categorized into four groups:

Type I: Solitary LR involving remnant kidney or ipsilateral renal fossa.

Type II: Solitary LR involving ipsilateral vasculature (i.e. renal vein or inferior vena cava remnant), ipsilateral adrenal gland, or LN. This represents nearby organs that touch the primary organ (ie. kidney). Although a systemic metastatic mechanism is possible, such recurrences may also result from local spread from microscopic persistence.

Type III: Solitary LR involving distant intra-abdominal soft tissue or organ. Some intra-abdominal recurrences may represent local spread rather than systemic disease (ie. liver recurrence in segment 5/6 from right-sided upper pole tumor or pancreatic tail recurrence from left-sided upper pole tumor). As there is no definitive method to distinguish local versus systemic recurrence, we analyzed this as a single subtype.

Type IV: Any combination of Types I-III LR, or multiple recurrences.

Statistical Analysis:

Multivariable logistic regression was used to identify clinicopathologic predictors for each LR type versus non-recurrence. The covariates assessed included age, tumor size, gender, Fuhrman grade (low [1–2] versus high [3–4]), sarcomatoid features (sRCC), papillary pathology, vascular invasion, tumor necrosis, node positive disease at time of primary resection (pN+), type of surgery (partial nephrectomy [PN] versus radical nephrectomy [RN]), and surgical modality (minimally-invasive surgery [MIS] versus open surgery). Backwards elimination with a 5% significance level was used to select variables associated with each LR type. A more stringent significance level (1%) was used for Types I and IV LR due to lower prevalence. Two-way interaction between selected variables were assessed and considered for inclusion in the final model using the same significance level criterion. Bootstrap re-sampling (using 1,000 samples) was used to assess bias in logistic regression coefficients. Deviance, and Hosmer and Lemeshow goodness-of-fit tests were used to assess

logistic regression model fit. Log-rank test and Kaplan-Meier estimates were used to compare CSS, overall survival (OS), and time to recurrence by LR type. Two-sided $p \leq 0.05$ was considered statistically significant.

Results:

Patient Characteristics:

LR without metastasis was noted in 300/1,943 (15.4%) patients who underwent surgical resection of RCC at a median follow-up of 7.9 (IQR 6.5–9) years. Of patients who developed LR, 66 (22.0%) had Type I, 97 (32.3%) had Type II, 87 (29.0%) had Type III, and 50 (16.7%) had Type IV. Patient characteristics by LR type are summarized in Table 1.

Multivariable Logistic Regression Analyses:

Multivariable analyses performed to identify significant clinicopathologic predictors for each LR type are summarized in Table 2. Larger tumor size (p=0.0023) and pN+ (p<0.0001) predicted Type 1 LR. sRCC (p=0.0051), vascular invasion (p=0.0006), tumor necrosis (p=0.0042), and pN+ (p<0.0001) predicted Type II LR. Larger tumor size (p=0.0243), sRCC (p=0.0229), and vascular invasion (p=0.0012) predicted Type III LR. Larger tumor size (p=0.0024), sRCC (p=0.0034), tumor necrosis (p=0.0002), and pN+ (p<0.0001) predicted Type IV LR. Age, gender, Fuhrman grade, papillary pathology, type of surgery (PN versus RN), and surgical modality (MIS versus open surgery) did not predict any type of LR.

Survival and Time to Recurrence Analyses:

Log-rank test results used to compare CSS, OS, and time to LR among the LR types and Kaplan-Meier estimates are summarized in Figures 1–3 and Table 3, respectively. Median five-year CCS [95% CI] was worse for patients with Type IV LR (40.2% [CI 26.1–53.9]) compared to those with Types I-III LR (66.0% [CI 53.1–76.2], 65.1% [CI 54.6–73.8], and 72.0% [CI 60.8–80.4], respectively) (p<0.0001). Median five-year OS [95% CI] was worse for patients with Type IV LR (35.0% [CI 22.1–48.2]) compared to those with Types I-III LR (60.2% [CI 47.3–70.9], 62.2% [CI 51.7–71.1], and 66.0% [CI 54.9–75.0], respectively) (p<0.001). There was no significant difference in 5-year CSS and OS among Types I-III LR. Median two-year LR-free time [95% CI] was worse for patients with Type IV LR (26.0% [CI 14.9–38.6]) compared to those with Types I-III LR (39.4% [CI 27.7–50.9], 39.2% [CI 29.5–48.7], and 51.7% [CI 40.8–61.6], respectively) (p<0.0001).

Discussion:

There is currently no standardized definition of LR for RCC. Simplistically, there are two ways to define LR: biologically or anatomically. Biologically, LR refers to microscopic persistence of tumor at the surgical site, rather than tumor that spreads hematologically. In contrast, an anatomic definition refers to LR based on proximity to the original primary. Currently, clinicians infer biology when classifying a LR anatomically by making an implicit assumption that the recurrence represents a microscopic persistence rather than a hematogenous spread. While most would agree that LR represents microscopic persistence of tumor at the surgical resection site,[4, 5, 10, 11] recurrences at nearby sites such as soft

tissues, LN, or adjacent organs are open to debate.[1, 2] This discrepancy in defining LR is therefore a function of our inability to fully understand the biologic processes of LR versus hematogenous spread. Our anatomic classification system accounts for these variations and allows for consistent characterization of all recurrences that could potentially be considered local.

Furthermore, our classification system addresses three limitations in defining RCC LR that exist in the literature. First, current definitions do not differentiate between recurrence in the remnant kidney or ipsilateral renal fossa (Type I) and those in the ipsilateral vasculature, adrenal gland or LN (Type II). We make this distinction because they potentially represent different processes. Type 1 LR may more likely result from incomplete resection of the primary tumor or mechanical tumor spillage and seeding, rather than hematologic spread.[13] Indeed, prior reports have found that larger tumor size[14] and positive surgical margins[9, 14, 15] are associated with LR in the remnant kidney and ipsilateral renal fossa. However, the fact that our cohort only included patients with negative surgical margins and our finding that pN + ($p<0.0001$) predicted Type I LR suggests that at least some Type I LR may reflect systemic disease. Similarly, we found that pN+ ($p<0.0001$) predicted Type II LR. Since well-established markers of aggressive tumor behavior such as sRCC ($p=0.0051$), vascular invasion ($p=0.0006$), and tumor necrosis ($p=0.0036$) also predicted Type II LR, such recurrences could possibly represent anatomic persistence or perhaps more likely systemic recurrence.

Second, current definitions for LR do not usually include intra-abdominal soft tissue or organ (Type III) recurrence because they (along with recurrences in the lung, brain, and bone) have generally been considered to be systemic metastases.[4, 11, 13] As such, the risk factors associated and the natural history of patients with isolated RCC recurrence in the peritoneum, bowel, and other intra-abdominal organs is unclear. We found that larger tumor size ($p=0.0243$), sRCC ($p=0.0229$) and vascular invasion ($p=0.0012$) predicted Type III LR, perhaps suggesting that most Type III LR are systemic. Unfortunately, this supposition is by no means definitive as recurrence in visceral organs juxtaposed to the primary tumor may lead to LR without systemic disease.

Third and lastly, current definitions for LR do not account for differences in patients with multiple recurrences or at multiple sites (Type IV). For example, using current definitions for LR,[1, 2, 6] if a patient developed synchronous RCC recurrences in the renal fossa and LN, the patient would be classified in the same category as someone with solitary recurrence in the renal fossa. As such, the prognostic implications of having multiple sites of LR are unclear. To address this limitation, we defined Type IV LR as multiple recurrences within a given type or any combination of Types I-III LR. Larger tumor size ($p=0.0002$), sRCC ($p=0.0034$), tumor necrosis ($p<0.0001$), and pN+ ($p<0.0001$) predicted Type IV LR.

With regards to survival outcomes, we did not find any difference in 5-year CSS and OS among Types I-III LR. This finding is significant as it suggests that in the tyrosine kinase inhibitor era, the prognosis for solitary intra-abdominal RCC recurrences appear to be similar regardless of location. This is consistent with the results of Paparel et al., who found that differences in location of recurrence among the ipsilateral adrenal gland, LN, and renal

fossa were associated with similar CSS.[6] Although data comparing CSS between patients with LR (recurrence in remnant kidney) and metastasis (any recurrence outside of remnant kidney) exist,[11] there are no studies evaluating survival in patients with solitary recurrence distinguished by location (Types I-II) or in the distant intra-abdominal soft tissue or organ (Type III). We found that patients with Types I-III LR had similar prognoses. This finding suggests that patients with Type III LR may benefit from more aggressive local treatments, as is the standard for healthy patients with Types I-II LR.

We found that patients with multiple LR sites (Type IV) had a 5-year CSS and OS that was approximately half of that of patients with Types I-III LR ($p<0.001$). Furthermore, those with Type IV LR had a shorter median time to LR compared to those with Types I-III LR ($p<0.0001$). These findings suggest that patients with multiple sites of intra-abdominal LR have a worse prognosis than those with a solitary intra-abdominal LR. This is consistent with a report by Hafez et al. that found that patients with isolated LR (recurrence in the kidney remnant after PN) had better survival compared to those with LR and metastatic disease.[11]

With regards to surgical modality (MIS versus open surgery), some authors have suggested that patients undergoing MIS for RCC may have an increased risk for tumor seeding and port-site recurrence.[16] One proposed mechanism for this hypothesis is that pneumoperitoneum causes a chimney effect due to the leakage of gas carrying viable tumor cells to the area of gas leak.[17] Despite this, aerosolization alone has not been shown to have a major role in port-site metastasis.[18] Furthermore, reports of tumor seeding and port site metastasis of RCC after MIS are extremely rare and limited to small case series.[16] In our prospective data, we did not find that the use of MIS predicted any LR types.

With regards to type of surgery (PN versus RN), current guidelines recommend PN as the standard surgical treatment for cT1a renal masses.[19, 20] However, emerging data suggest that PN may have equivalent oncologic outcomes as RN for higher stage RCC.[21, 22] In a meta-analysis evaluating PN versus RN for large (≥7 centimeter) renal tumors by Deng et al., there was no significant difference in CSS.[21] In our prospective data, we did not find that PN predicted any type of LR. However, it should be noted that only 107/1944 (5.5%) patients underwent PN, and the decision to perform PN versus RN is undoubtedly subject to selection bias.

The results of our study must be interpreted in the context of its limitations. As our cohort was restricted to intermediate-high risk patients, the results of our study may not be applicable to lower risk patients. However, the ASSURE trial cohort was ideal for applying our anatomic classification. While prior studies have been limited by small numbers of LR, [1–4] our study represents the largest experience of patients with LR without metastases. The increased incidence of LR in our series may be attributed to our patient cohort, rigorous protocoled imaging, and/or our expanded definition of LR to include all intra-abdominal recurrences. Also, as management of patients with LR was not standardized across all participating institutions, our survival outcomes may be subject to institutional variations in care. Despite this, given the lack of standardized treatment paradigms for LR, our report may be an accurate real-world representation of current outcomes. Lastly, although our study

was a secondary review of the ASSURE trial data, the fidelity of our centralized pathology review and follow-up data related to LR and survival outcomes were likely better in this prospective and highly annotated clinical trial than what would be expected in a retrospective study.

Conclusions:

We propose a standardized definition for LR following resection of intermediate-high risk non-metastatic RCC that may be used to categorize any intra-abdominal recurrence based on location and tumor burden. Since the biology of LR versus distant metastases has not been well defined, our definition uses an expansive yet incremental anatomic approach. Such a system is necessary to more clearly evaluate the clinical implications and prognostic significance of LR. We demonstrate that LR after full resection of RCC is more a function of biology than surgical modality (MIS versus open surgery) or type of surgery (PN versus RN). Compared to a solitary LR at a single anatomic subdivision, LR involving multiple sites and/or subdivisions (Type IV) is associated with worse 5-year CSS and OS, and shorter time to LR. When LR is limited to a solitary lesion, there appears to be no difference in CSS and OS, regardless of its intra-abdominal anatomic subdivision (Types I-III). These findings have implications for utilization of current and novel systemic therapies and may improve results of consolidative surgery for local recurrences.

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Legend of Abbreviations:

LR	Local recurrence
RCC	Renal cell carcinoma
CSS	Cancer-specific survival
LN	Lymph nodes
sRCC	Renal cell carcinoma with sarcomatoid features
pN+	Node positive disease at time of primary resection
PN	Partial nephrectomy
RN	Radical nephrectomy
MIS	Minimally-invasive surgery
OS	Overall survival

IQR	Interquartile range

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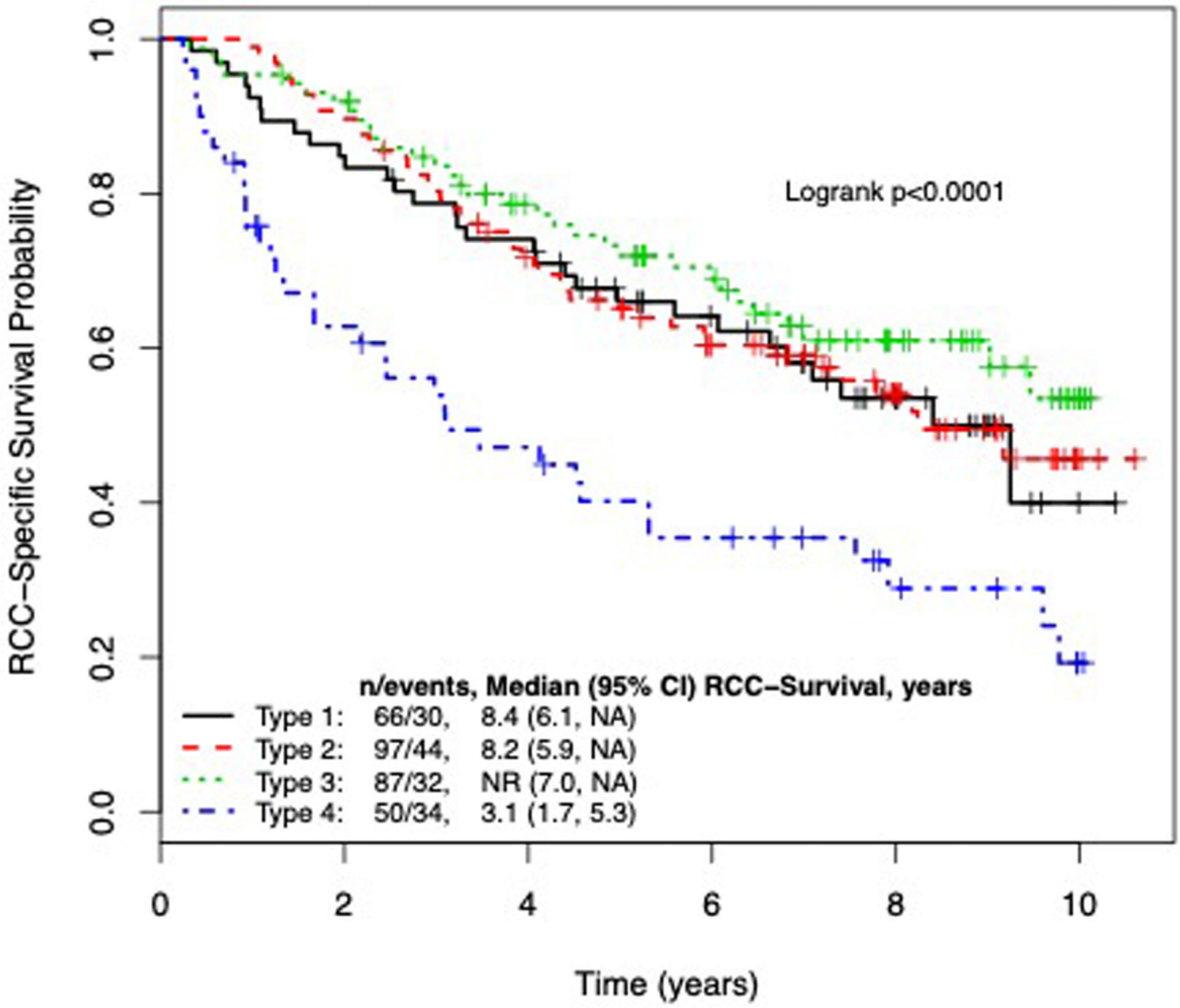

Figure 1:
Kaplan-Meier Estimate of RCC-specific Survival by Local Recurrence Type

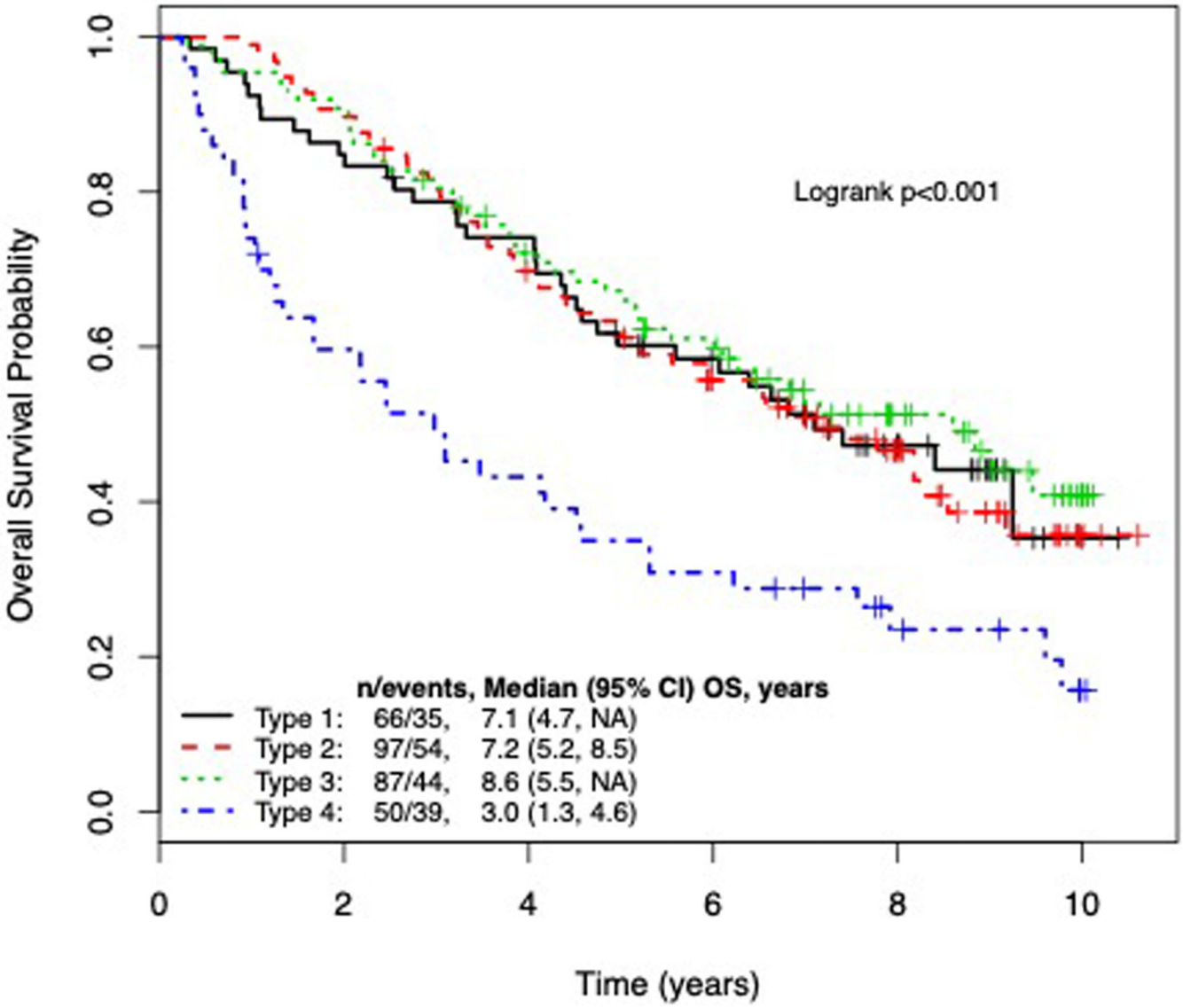

Figure 2:
Kaplan-Meier Estimate of Overall Survival by Local Recurrence Type

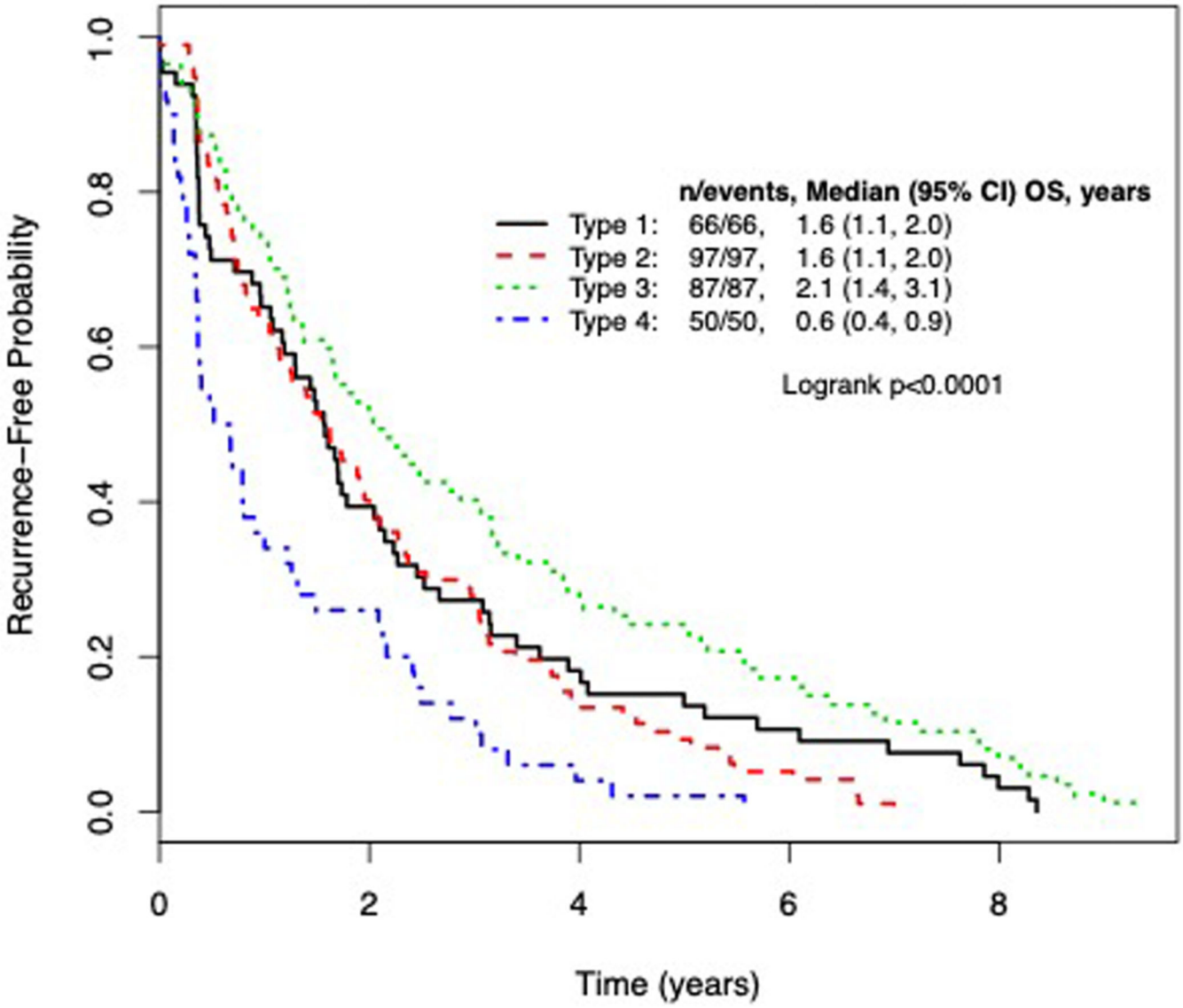

Figure 3:
Kaplan-Meier Estimate of Time to Local Recurrence by Local Recurrence Type

Table 1:

Baseline Patient Characteristics by Local Recurrence Type

Variable	Local Recurrence Type			
	Type I (n=66)	**Type II (n=97)**	**Type III (n=87)**	**Type IV (n=50)**
Median Age [IQR] (Years)	56 [47–63]	58 [49–65]	58 [49–67]	58 [51–65]
Median Tumor Size [IQR] (cm)	10 [7–12]	9 [6–11]	8 [7–12]	10 [8–12]
Gender:				
Male (%)	43 (65.2%)	75 (77.3%)	50 (57.5%)	41 (82.0%)
Female (%)	23 (34.8%)	22 (22.7%)	37 (42.5%)	9 (18.0%)
Fuhrman Grade:				
1 (%)	1 (1.5%)	0 (0%)	2 (2.3%)	0 (0%)
2 (%)	14 (21.5%)	18 (19.0%)	30 (34.5%)	10 (20.0%)
3 (%)	33 (50.8%)	48 (50.5%)	37 (42.5%)	17 (34.0%)
4 (%)	17 (26.2%)	29 (30.5%)	18 (20.7%)	23 (46.0%)
Missing:	1	2	0	0
sRCC:				
Yes (%)	11 (16.7%)	20 (20.6%)	13 (14.9%)	14 (28.0%)
No (%)	55 (83.3%)	77 (79.4%)	74 (85.1%)	36 (72.0%)
Primary Histology:				
Clear Cell (%)	47 (71.2%)	60 (61.9%)	76 (87.4%)	33 (66.0%)
Papillary (%)	12 (18.2%)	12 (12.4%)	7 (8.0%)	4 (8.0%)
Chromophobe (%)	5 (7.6%)	6 (6.2%)	2 (2.3%)	1 (2.0%)
Mixed (%)	2 (3.0%)	7 (7.2%)	2 (2.3%)	9 (18.0%)
Unclassified (%)	0 (0%)	12 (12.3%)	0 (0%)	3 (6.0%)
Vascular Invasion:				
None Seen	32 (54.2%)	39 (45.9%)	38 (47.5%)	23 (51.1%)
Intrarenal	6 (10.2%)	14 (16.5%)	3 (3.8%)	3 (6.7%)
Renal	19 (32.2%)	27 (31.8%)	31 (38.8%)	18 (40.0%)
IVC, Subdiaphragmatic	0 (0%)	3 (3.5%)	4 (5.0%)	1 (2.2%)
IVC, Supradaphragmatic	0 (0%)	1 (1.2%)	1 (1.3%)	0 (0%)
Unknown	2 (3.4%)	1 (1.2%)	3 (3.8%)	0 (0%)
Missing:	7	12	7	5
Tumor Necrosis:				
Yes (%)	29 (49.2%)	49 (57.7%)	33 (41.3%)	33 (73.3%)
No (%)	30 (50.9%)	36 (42.3%)	47 (58.7%)	12 (26.7%)
Missing:	7	12	7	5
Nodal Status:				
pN1/pN2 (%)	12 (18.2%)	34 (35.0%)	4 (4.6%)	12 (24.0%)
pN0/pNx (%)	54 (81.8%)	63 (65.0%)	83 (95.4%)	38 (76.0%)
Type of Surgery:				

Variable	Local Recurrence Type			
	Type I (n=66)	Type II (n=97)	Type III (n=87)	Type IV (n=50)
Partial (%)	2 (3.0%)	3 (3.1%)	4 (4.6%)	2 (4.0%)
Radical (%)	64 (97.0%)	94 (96.9%)	83 (95.4%)	48 (96.0%)
Surgical Modality:				
MIS (%)	24 (36.4%)	31 (32.0%)	31 (35.6%)	26 (52.0%)
Open (%)	42 (63.6%)	66 (68.0%)	56 (64.4%)	24 (48.0%)

Table 2:

Multivariable Logistic Regression Analyses Assessing Clinicopathologic Variables Associated with Type of Local Recurrence versus Non-Recurrence

Type I LR			
Variable	**Coefficient ± SE**	**Odds Ratio (95% CI)**	**p-value**
Model Intercept	−3.92±0.36		<.0001
Tumor Size (cm)	0.10±0.03	1.11 (1.04–1.19)	0.0023
pN+ Disease at Time of Primary Resection	1.69±0.39	5.40 (2.51–11.61)	<.0001
Type II LR			
Variable	**Coefficient ± SE**	**Odds Ratio (95% CI)**	**p-value**
Model Intercept	−3.60±0.23		<.0001
sRCC	0.92±0.33	2.51 (1.32–4.79)	0.0051
Vascular Invasion	0.85±0.25	2.35 (1.44–3.81)	0.0006
Tumor Necrosis	0.73±0.25	2.07 (1.26–3.40)	0.0042
pN+ Disease at Time of Primary Resection	2.29±0.30	9.86 (5.45–17.84)	<.0001
Type III LR			
Variable	**Coefficient ± SE**	**Odds Ratio (95% CI)**	**p-value**
Model Intercept	−3.61±0.34		<.0001
Tumor Size (cm)	0.07±0.03	1.08 (1.01–1.15)	0.0243
sRCC	0.79±0.35	2.21 (1.12–4.38)	0.0229
Vascular Invasion	0.78±0.24	2.19 (1.36–3.52)	0.0012
Type IV LR			
Variable	**Coefficient ± SE**	**Odds Ratio (95% CI)**	**p-value**
Model Intercept	−5.29±0.48		<.0001
Tumor Size (cm)	0.12±0.04	1.13 (1.04–1.22)	0.0024
sRCC	0.11±0.38	3.04 (1.45–6.40)	0.0034
Tumor Necrosis	1.34±0.36	3.81 (1.88–7.71)	0.0002
pN+ Disease at Time of Primary Resection	1.82±0.41	6.20 (2.77–13.88)	<.0001

Table 3:

Survival and Time to Local Recurrence Estimates

Local Recurrence Type	5-year Cancer Specific Survival (95% Confidence Interval)	5-year Overall Survival (95% Confidence Interval)	2-year Local Recurrence-free Time (95% Confidence Interval)
Type I	66.0% (53.1–76.2)	60.2% (47.3–70.9)	39.4% (27.7–50.9)
Type II	65.1% (54.6–73.8)	62.2% (51.7–71.1)	39.2% (29.5–48.7)
Type III	72.0% (60.8–80.4)	66.0% (54.9–75.0)	51.7% (40.8–61.6)
Type IV	40.2% (26.1–53.9)	35.0% (22.1–48.2)	26.0% (14.9–38.6)