



Oncological Outcomes of Patients With Different Pathological Features of pT3a Renal Tumor: A Systematic Review and Quantitative Synthesis

Pengju Guo[†], Yongxing Wang[†], Yili Han, Dechao Wei, Jiahui Zhao, Mingchuan Li, Yongguang Jiang^{*} and Yong Luo^{*}

Department of Urology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

Purpose: To identify the differences in oncological outcomes for patients with different pT3a renal tumor invasion patterns and pathological features.

OPEN ACCESS

Edited by:

Andrea Mari, Careggi University Hospital, Italy

Reviewed by:

Carlo Terrone, San Martino Hospital (IRCCS), Italy Riccardo Campi, Careggi Hospital, Italy

*Correspondence:

Yongguang Jiang jyganzhen@163.com Yong Luo luoyonganzhen@163.com

[†]These authors have contributed equally to this work

Specialty section:

This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: 09 March 2021 Accepted: 06 May 2021 Published: 03 June 2021

Citation:

Guo P, Wang Y, Han Y, Wei D, Zhao J, Li M, Jiang Y and Luo Y (2021) Oncological Outcomes of Patients With Different Pathological Features of pT3a Renal Tumor: A Systematic Review and Quantitative Synthesis. Front. Oncol. 11:678459. doi: 10.3389/fonc.2021.678459 **Methods:** The protocol of this study was registered on PROSPERO (CRD42021234475). Relevant studies were identified by searching the PubMed, Cochrane library, Embase, and Web of Science databases. Cancer-specific survival (CSS) was selected as the endpoint. Pooled hazard ratio (HR) and 95% confidence interval (CI) extracted from multivariate Cox models were evaluated to identify the hazard association.

Results: A total of 22 studies, which enrolled 12384 patients were included for quantitative synthesis. Sinus fat invasion (SFI) + perinephric fat invasion (PFI) was associated with inferior CSS compared to SFI only (p = 0.02). Comparable CSS was observed between SFI and PFI (p = 0.57). SFI ± PFI showed inferior CSS compared to PFI only (p = 0.0002). The presence of pelvicalyceal system invasion significantly increased the risk of cancer-specific mortality (p = 0.0005). Renal vein invasion (RVI) indicated poor oncological outcomes in terms of CSS (p = 0.002). The concomitant RVI and fat invasion (FI) significantly increased the risk of deterioration of CSS compared to RVI or FI (p < 0.0001). Multiple invasion patterns translated into a significantly decreased CSS (p < 0.0001). Aggressive tumor behavior, including lymph node involvement (p = 0.006), distant metastases (p < 0.0001), sarcomatoid differentiation (p < 0.0001), necrosis (p < 0.0001), Fuhrman grade III or IV (p < 0.0001), positive margin (p < 0.0001), and tumor size >7cm (p < 0.0001) were the predictors of inferior CSS. The lymphovascular invasion (p = 0.67) was indolent in terms of CSS.

Conclusion: This study confirmed the heterogenicity of pT3a renal tumors. Multiple invasion patterns could translate into a significantly decreased CSS, and SFI should not be merged in the SFI + PFI group. The presence of PSI or RVI could significantly increase the risk of cancerspecific mortality. Lymph node involvement, distant metastases, sarcomatoid differentiation, necrosis, high Fuhrman grade, positive margin, and size >7cm were the predictors of inferior CSS. A precise-risk grade of CSS for different invasion patterns including comprehensive combinations may be useful for the further refinements of the TNM system.

1

Systematic Review Registration: The current study was registered on PROSPERO, and the registration numbers is CRD42021234475.

Keywords: renal tumor, pT3a, nephrectomy, cancer-specific survival, systematic review

INTRODUCTION

Since the publication of the sixth edition of the TNM staging system for renal tumors, the classification of T3a renal tumors has undergone several modifications. Although currently pT3a is defined as a tumor confined to the Gerota's fascia but exhibiting perinephric fat invasion (PFI), sinus fat invasion (SFI), renal vein invasion (RVI), or/and pelvicalyceal system invasion (PSI) regardless of tumor diameter, a realistic controversy is whether pT3a represents a heterogeneous histological group where different elements or a combination may indicate a significant difference in oncological prognosis. The EAU guidelines on renal cell cancer (RCC) state that tumors with SFI might be more aggressive than tumors with PFI, which was consistent with the findings of Thompson et al. (1, 2). However, several studies evaluating oncological outcomes for different pT3a renal tumor invasion patterns have failed to demonstrate the significant difference (3, 4). Lack of consensus on the outcomes of different extrarenal extension patterns may result from the unstandardized definitions for the histological assessment of fat invasion in the early years and discrepancies in study design (2, 5).

Our understanding of the heterogeneous behavior of renal tumors has been well advanced. The increasing interest in adjuvant treatment, immunotherapy and targeted therapies has prompted the need for more accurate staging of renal tumors (5– 9). In the clinical context, some pT3a renal tumors are confirmed by postoperative pathology, and their incidence is usually underestimated. Therefore, it is important to accurately predict the prognosis of different pT3a renal tumor invasion patterns to guide the follow-up protocols and evaluate the effect of postoperative therapies on survival. Given the continuing controversy over pT3a renal tumor staging, we undertook a systematic review and quantitative synthesis to determine whether pT3a represents a heterogeneous histological group and evaluate the oncological outcomes for different pT3a renal tumor invasion patterns and pathological features.

METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria, and the protocol was registered on PROSPERO for the study (CRD42021234475).

Search Strategy

We searched the PubMed, Cochrane Library, Embase, and Web of Science databases for studies investigating the oncological outcomes of pT3a renal tumors from database inception to April 2021, using search terms integrated subject relevant terms ("renal tumor", "renal neoplasm," "renal cancer," and "renal cell carcinoma") and staging terms ("T3a," "pT3a," "T3," "pT3," "renal vein invasion," and "urinary collecting system"). We also reviewed the references cited in the relevant articles to avoid omissions. The detailed Population, Intervention, Comparison, Outcome and Study design (PICOS) framework of the review was shown in **Table 1**. Only articles written in the English language were searched. All retrieved references were independently screened by two investigators (PG and YW) independently. When discordant decisions occurred, the senior authors (YJ and YL) were consulted to make final decisions.

Study Selection, Data Extraction, and Quality Assessment

The studies on the oncological outcomes for different pT3a renal tumor invasion patterns and pathological features following partial or radical nephrectomy (PN or RN) were included. Cancer-specific survival (CSS) was considered as the single endpoint of oncological outcomes. Conference abstracts, reviews, commentary, editorials, and letters were excluded but checked for cited references. The studies that did not provide CSS with a hazard ratio (HR) and corresponding 95% confidence interval (CI) or p value in the multivariate cox models were also excluded.

Two investigators independently extracted the data from each study. Extracted data included the name of the first author, year of publication, recruitment period, country or region, study type, sample size, surgery types, and size of pathological features of different pT3a renal tumor invasion patterns. HRs and 95% CIs for CSS associated with different pT3a renal tumor invasion patterns and pathological features were extracted for quantitative synthesis. The quality of included studies was assessed using the Quality In Prognosis Studies (QUIPS) tool (10). The six bias domains when evaluating the literatures were study participation, study attrition, prognostic factor measurement,

 TABLE 1 | The Population, Intervention, Comparison, Outcome and Study design (PICOS) framework of the review.

Parameter	Inclusion criteria
Population (P)	Patients with pathological T3a and clinical or pathological N0-1M0-1 renal tumor.
Intervention (I)	Partial or radical nephrectomy
Comparison (C)	The cancer-specific survival of patients with different tumor invasion patterns or pathological features.
Outcome (O)	Cancer-specific survival with the hazard ratio (HR) and corresponding 95% confidence interval (CI) or p values in the multivariate cox models.
Study design (S)	Randomized trials, population-based, single and multi-center observational studies, and retrospective studies which were published in English.

outcome measurement, study confounding, and statistical analysis and reporting. According to the items and considerations, the overall rating assessments were divided into low, moderate, and high risk of bias for each bias domain.

Quantitative Synthesis and Analysis

The comparisons of CSS between different tumor invasion patterns were evaluated by the pooled HRs with corresponding 95% CIs. The statistical heterogeneity among studies was evaluated by the Cochrane Q test and quantified by I² value. $I^2 \leq 50\%$ indicated no or moderate heterogeneity, and a fixedeffect model was applied. On the contrary, $I^2 > 50\%$ indicated obvious heterogeneity, and a random-effect model was applied. The quantitative synthesis of HRs was evaluated by the inverse variance technique, and the quantitative synthesis of risk differences was evaluated by the Mantel-Haenszel test. The sensitivity analysis was conducted by one-removed analysis. Based on the recommendations of the Cochran manual, the evaluation of publication bias was conducted by using Egger's test only when there were 10 or more included studies (11). The certainty of the evidence were evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, which yields four levels of evidence (i.e., very low, low, moderate, and high) (12). All statistical tests were performed using Review Manager 5.4 (Cochrane Collaboration, Oxford, UK) and Stata 15.1 (StataCorp., College Station, Texas). Statistical significance was set at p < 0.05, and all specified p values were two-sided.

RESULTS

Among the 655 potential studies that were identified from the aforementioned databases, 139 studies were excluded due to duplication. After screening the titles and abstracts, 363 studies were found to be unsuitable for full text screening and were excluded. Based on the inclusion criteria, we conducted the fulltext evaluation of the remaining 153 studies, among which 23 studies did not focus on the patients with pT3a renal tumor, 16 studies did not report the HRs of the CSS, 52 studies did not compare the CSS for patients with different invasion patterns or pathological features, 13 studies were reviews, 10 study were comments, 13 studies were not published in English, and two studies were case reports. Among the 24 full-text articles assessed for eligibility, two studies that only reported the relevant HRs in the univariate Cox models were also excluded. Finally, 22 studies enrolling 12,384 patients were included in the quantitative synthesis (Figure 1) (2-7, 13-28).

The enrolled studies were published between 2005 and 2021, and included 12 (54.5%) studies published over the past five years. All the enrolled studies were retrospective, and the recruited patients had no direct ipsilateral adrenal invasion. The recruited patients were from Asia, Europe, and USA. Ten studies focused only on patients following RN, 12 studies included patients who received PN or RN (**Table 2**). Using the QUIPS tool, the risk of bias for each enrolled study was assessed and the results are shown in **Figure 2**. Also, two enrolled studies used data from the Surveillance, Epidemiology, and End Results



TABLE 2 | Characteristics of the included studies.

Author	Year	Country	Recruitment period	Study design	Institution	Stage	Surgery type	Outcome	Cox model	Follow-up (mo)
Thompson (2)	2005	USA	1970–2002	RTP	Single	N0-1 M0-1	RN	CSS	Multi	72(24–408)*
Margulis (13)	2007	USA	1990-2006	RTP	Single	NO-1 MO-1	PN, RN	CSS	Uni, Multi	33.5(6.1-158.6)*
Poon (4)	2009	USA	1988-2007	RTP	Multiple	N0-1 M0-1	PN, RN	CSS	Uni, Multi	24(9-48)*
Bedke (14)	2009	Germany	1990-2007	RTP	Single	N0-1 M0-1	RN	CSS	Uni, Multi	34.8(14.4-109.2)*
Bertini (15)	2009	Italy	1989–2006	RTP	Single	N0-1 M0-1	RN	CSS	Uni, Multi	38(2-240)*
Kresowik (16)	2010	USA	1997–2007	RTP	Single	N0-1 M0-1	PN, RN	CSS	Multi	25.3(0-96.4)**
Chen (24)	2017	China	2006-2015	RTP	Single	N0 M0	RN	CSS	Uni, Multi	31 (3.4-109.7)
Park (17)	2017	South Korea	1997-2012	RTP	Single	N0 M0	PN, RN	CSS	Multi	58.1(37.2-86.5)*
Guo (18)	2019	China	1979–2014	RTP	Multiple	N0 M0	RN	CSS	Uni, Multi	NA
Shah (5)	2019	USA	1970-2011	RTP	Single	N0 M0	RN	CSS	Uni, Multi	111.6(81.6–160.8)*
Wang (6)	2020	China	2010-2016	RTP	Multiple	N0-1 M0-1	PN, RN	CSS	Multi	24(10-46)*
da Costa (19)	2012	Brazil	1992-2009	RTP	Single	N0-1 M0-1	PN, RN	CSS	Multi	28.6(3-60)**
Baccos (20)	2013	Italy	2000-2011	RTP	Single	N0-1 M0-1	RN	CSS	Uni, Multi	31(12-68.2)*
Flood (21)	2020	Canada	2011-2017	RTP	Single	N0-1 M0-1	RN	CSS	Multi	33.8(20.6-55.4)*
Schiavina (22)	2015	Italy	2000-2013	RTP	Single	N0-1 M0	RN	CSS	Uni, Multi	32(18-62)*
Brookman-May (3)	2015	Germany	1992-2010	RTP	Multiple	N0 M0	PN, RN	CSS	Multi	NA
Peng (23)	2017	China	2007-2012	RTP	Single	N0 M0	PN, RN	CSS	Multi	35.5(10-86)*
Oh (7)	2018	South Korea	1988–2015	RTP	Multiple	N0 M0	PN, RN	CSS	Uni, Multi	38.8(NA)**
Capitanio (25)	2018	Italy	1988–2015	RTP	Multiple	N0 M0	PN, RN	CSS	Multi	52(NA)**
Bailey (26)	2017	USA	2001-2010	RTP	Single	N0-1 M0-1	RN	CSS	Uni, Multi	98.4 (72-129.6)*
Garcia Marchinena (27)	2019	Argentina	2000-2016	RTP	Multiple	NO MO	PN, RN	CSS	Uni, Multi	21(1–194)*
Lai (28)	2021	China	2000-2018	RTP	Single	N0-x M0	PN, RN	CSS	Uni, Multi	48(NA)*

Addioi	i cai	No.proa			10.511+111(70)	NO.511 ± F11(70)	110.11 (70)		10.1101111 (70)		NO.P 51 (70)
Thompson (2)	2005	205	162 (79.0)	16 (7.8)	27 (13.2)	43 (21)	NA	NA	NA	NA	NA
Margulis (13)	2007	365	199 (54.5)	96 (26.3)	70 (19.2)	166 (45.5)	NA	NA	NA	NA	331 (90.7)
Poon (4)	2009	230	167 (72.6)	NA	NA	63 (27.4)	NA	NA	NA	NA	NA
Bedke (14)	2009	106	58 (54.7)	27 (25.5)	21 (19.8)	48 (45.3)	NA	NA	NA	NA	NA
Bertini (15)	2009	105	70 (66.7)	16 (15.2)	19 (18.1)	35 (33.3)	NA	NA	NA	NA	NA
Kresowik (16)	2010	110	36 (32.7)	41 (37.2)	33 (30)	74 (67.3)	NA	NA	57 (51.2)	NA	NA
Chen (24)	2017	163	79 (48.5)	11 (6.7)	NA	NA	NA	87 (53.4)	NA	NA	40 (24.5)
Park (17)	2017	266	92 (34.6)	51 (19.2)	29 (10.9)	80 (30.1)	172 (64.7)	94 (35.3)	69 (25.9)	25 (9.4)	NA
Guo (18)	2019	1869	687 (36.8)	381 (20.4)	105 (5.6)	486 (26.0)	1173 (62.8)	NA	696 (37.2)	NA	NA
Shah (5)	2019	563	114 (20.2)	51 (9.1)	NA	NA	NA	NA	NA	163 (29.0)	NA
Wang (6)	2020	5290	2569 (48.5)	1975 (37.3)	746 (14.1)	NA	NA	NA	NA	NA	NA
da Costa (19)	2012	46	NA	NA	NA	NA	24 (52.1)	NA	11 (23.9)	11 (23.9)	NA
Baccos (20)	2013	122	NA	NA	NA	NA	63 (51.6)	59 (48.4)	41 (33.6)	18 (14.8)	NA
Flood (21)	2020	160	NA	NA	NA	NA	NA	97 (61)	NA	NA	24 (15)
Schiavina (22)	2015	185	NA	NA	NA	NA	NA	NA	NA	NA	NA
Brookman-May (3)	2015	1247	NA	NA	NA	NA	1036 (83.1)	211 (16.9)	NA	NA	NA
Peng (23)	2017	125	NA	NA	NA	NA	89 (71.2)	NA	NA	36 (28.8)	NA
Oh (7)	2018	211	NA	NA	NA	NA	124 (58.8)	87 (41.2)	47 (22.3)	40 (19.0)	NA
Capitanio (25)	2018	309	164	68	NA	NA	NA	NA	NA	NA	NA
Bailey (26)	2017	325	NA	NA	NA	NA	NA	NA	NA	NA	27 (8.3)
Garcia Marchinena (27)	2019	293	111 (37.9)	36 (12.3)	35 (11.9)	118 (40.3)	253 (86.3)	91 (31.1)	57 (19.5)	34 (11.6)	35 (11.9)
Lai (28)	2021	89	NA	NA	NA	NA	71 (79.8)	36 (40.4)	18 (20.2)	18 (20.2)	NA

RTP, retrospective; PN, partial nephrectomy; RN, radical nephrectomy; NOS, Newcastle-Ottawa Scale; NA, not applicable; SFI, sinus fat invasion; PFI, perinephric fat invasion; RVI, renal vein invasion; FI, fat invasion; PSI, pelvicaliceal system invasion.

*Median (IQR).

**Mean (range).

June 2021 | Volume 11 | Article 678459



(SEER) database (6, 18). However, due to the recruitment period and the fact that most reported pathological features were different, it was reasonable to include these two studies. When two studies reported the endpoints of the same pathological features, we selected the most recent outcomes, i.e., those reported by Wang et al., because of the enrolled patients identified between 2010 to 2016 (6).

Cancer-Specific Survival of Different Invasion Patterns

CSS results were available from 19 studies for different tumor invasion patterns. Although the pooled results revealed that SFI only (n = 631) had comparable CSS to PFI only (n = 903) (HR, 0.92; 95% CI, 0.69–1.23; p = 0.57; $I^2 = 20\%$; Figure 3A), SFI + PFI (n = 138) was associated with inferior CSS as compared to SFI only (n = 422) (HR, 1.97; 95% CI, 1.13–3.42; p = 0.02; $I^2 = 2\%$; Figure 3B). SFI \pm PFI (n = 126) showed inferior CSS as compared to PFI only (n = 290) (HR, 1.81; 95% CI, 1.33-2.47; p = 0.0002; $I^2 = 0\%$; Figure 3C). The pooled results revealed that patients with PSI (n = 102) had inferior CSS as compared to those without PSI (n = 676) (HR, 1.91; 95% CI, 1.33-2.75; p = 0.0005; $I^2 = 0\%$; Figure 3D). Patients with RVI (n = 531) had inferior CSS as compared to those without RVI (n = 1484) (HR, 1.45; 95% CI, 1.15–1.82; p = 0.002; I² = 47%; **Figure 3E**), and the coexistence of RVI and fat invasion (FI) (n = 168) showed further deterioration of CSS as compared to RVI or FI (n = 477) (HR, 2.13; 95% CI, 1.52–2.99; p = 0.002; $I^2 = 0\%$; Figure 3F). The multiple invasion pattern (n = 1266) was associated with inferior CSS as compared to single pattern (n = 1226) (HR, 1.77; 95% CI, 1.49–2.09; p < 0.00001; I² = 0%; **Figure 3G**). Using the GRADE approach, the certainty of SFI only vs. PFI only was low, while that of RVI+FI vs. RVI or FI was high. The certainty of SFI+PFI vs. SFI only, SFI ± PFI vs. PFI only, PSI vs. non-PSI, RVI vs. non-RVI and multiple vs. single pattern were all moderate (Table 3).

Cancer-Specific Survival of Different Pathological Features

The pooled results revealed that lymph node involvement (n = 398; HR, 1.71; 95% CI, 1.17–2.50; p = 0.006; I², 67%; **Figure 4A**), distant metastases (n = 726; HR, 3.36; 95% CI, 2.88–3.91; p < 0.00001; I² = 42%; **Figure 4B**), sarcomatoid differentiation (n = 436; HR, 2.09; 95% CI, 1.78–2.46; p < 0.00001; I² = 12%; **Figure**

4C), Fuhrman grade III or IV (n = 1737; HR, 2.70; 95% CI, 2.18– 3.34; p < 0.00001; I² = 0%; **Figure 4D**), necrosis (n = 640; HR, 1.96; 95% CI, 1.54–2.49; p < 0.00001; I² = 0%; **Figure 4E**), tumor size >7 cm (n = 1571; HR, 1.77; 95% CI, 1.46–2.15; p < 0.00001; I² = 1%; **Figure 4F**), and positive margin (n = 28; HR, 7.61; 95% CI, 4.12-14.04; p < 0.00001; I² = 32%; **Figure 4G**) were associated with inferior CSS. The lymphovascular invasion (LVI) (n = 159; HR, 1.11; 95% CI, 0.69-1.80; p = 0.67; I² = 0%; **Figure 4H**) was not a predictor of inferior CSS. Using the GRADE approach, the certainty of lymph node involvement and LVI were low. Tumor size >7 cm and necrosis showed moderate certainty. The certainty of metastases, sarcomatoid differentiation, Fuhrman grade III or IV, and positive margin status were all high.

Sensitivity Analysis

The sequential omission of a single study was conducted to test the stability of pooled results. The merged HRs for CSS did not significantly change, which revealed the robustness of the results. (**Figure 5**).

Publication Bias

The evaluation of publication bias was conducted using Egger's test only when there were 10 or more included studies. There was no significant publication bias in CSS study of sarcomatoid differentiation (Egger's test p = 0.232).

DISCUSSION

Classifying tumors from the surgical perspective and optimizing prognostic discrimination are the cardinal principles in the refinements of the TNM system as T3a renal tumor contains a wide range of four patterns of extrarenal extension regardless of tumor diameter and is confirmed by postoperative pathology in general. Nevertheless, the accuracy and rationality of T3a classification have been questioned in the context of inconsistency of individual oncological outcomes reported in the last fifteen years (3, 16, 18, 21). In the current study, we integrated the available clinical evidence and experience by conducting this systematic review and quantitative synthesis.

The major findings of the current study are the following: First, the moderate-certainty evidence suggests that SFI + PFI was associated with inferior CSS as compared to SFI only. The low-certainty evidence of comparable CSS between SFI only and PFI only and the moderate-certainty evidence of inferior CSS of SFI \pm PFI compared to PFI only further support the above findings. Several studies, which merged SFI only and SFI + PFI into a single group given the oncological equipoise derived from their cohorts, may be imprecise (2, 15). Second, moderatecertainty evidence suggests that the presence of PSI indicated significantly poor oncological outcome, with a 1.91 times increased risk of cancer-specific mortality (CSM). Although numerous studies have highlighted the adverse effect of PSI on oncological outcomes, the independent prognostic value of PSI has been excluded from the second to seventh edition of AJCC

	Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95%	CI		IV. Fixed.	95% CI		
	Bedke 2009	0.5008 0	.4446	27	58	11.2%	1.65 [0.69, 3.94	9		_		-	
	Capitanio 2018	-0.5108 0	.5605	68	161	7.0%	0.60 [0.20, 1.80	0]	-				
	Guo 2019	-0.2877 0	.2721	381	367	29.8%	0.75 [0.44, 1.28	3]			_		
	Kresowik 2010	-0.4829 0	.4488	41	36	11.0%	0.62 [0.26, 1.49	1		-			
	Shah 2019	-0.2107 0	.3114	51	114	22.8%	0.81 [0.44, 1.49	9]			_		
	Total (95% CI)			631	903	100.0%	0 92 [0 69 1 23	1		-	•		
	Heterogeneity: Chi ² = 6 Test for overall effect: 2	5.21, df = 5 (P = 0.29); Z = 0.56 (P = 0.57)	² = 20%	001	200	100.070	0.32 [0.03, 1.23	0.1 (0.2	0.5 1	2	5	10
B	1	, ,								PELONIX	SELONIA		
	Chudu as Cubaraus	leaflighter Retici	SFI	+PFI S	SFI only	Mainht	Hazard Ratio	~		Hazard	Ratio		
2	Guo 2019	0 4121	0 385	105	381	53 4%	1 51 IO 71 3 21	1		IV. Fixed.	95% 01		
	Kresowik 2010	0.9821 0	.4123	33	41	46.6%	2.67 [1.19, 5.99	1					
	Total (95% CI)			138	422	100.0%	1 97 [1 13 3 42	1			-		
	Heterogeneity: Chi ² = 1	1.02. df = 1 (P = 0.31):	$^{2} = 2\%$	100	722	100.070	1.07 [1.10, 0.42	' —	1	+	<u> </u>		
	Test for overall effect:	Z = 2.41 (P = 0.02)						0.1 (0.2	0.5 1 SFI only	2 SFI+PFI	5	10
С	;		SEI	+DEI D	Fonly		Hazard Patio			Havard	Patio		
	Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV. Fixed. 95% (CI		IV. Fixed.	95% Cl		
	Bedke 2009	0.8065 0	.3446	48	58	21.2%	2.24 [1.14, 4.40	1			-	_	
	Bertini 2009	0.2897 0	.3252	35	70	23.8%	1.34 [0.71, 2.53	i		-+	· · · ·		
	Thompson 2005	0.6419 0	.2136	43	162	55.1%	1.90 [1.25, 2.89]					
	Total (95% CI)			126	290	100.0%	1.81 [1.33. 2.47]	1			•		
	Heterogeneity: Chi ² = 1	1.31, df = 2 (P = 0.52);	² = 0%					' <u></u>	1			-	
	Test for overall effect:	Z = 3.74 (P = 0.0002)						0.1 (0.2	0.5 1 PFI only	SFI±PF	5	10
D)				DCI		Uses and Datia			Hanand	Detie		
	Study or Subgroup	log[Hazard Ratio	1 SE	Total	Total	Weight	IV. Fixed, 95% C			IV. Fixed.	95% CI		
	Bailey 2017	0.57	0.2521	27	298	54.5%	1.77 [1.08, 2.90]			-			
	Flood 2020	0.357	0.4023	40	120	21.4%	1.43 [0.65, 3.15]			-			
	Garcia Marchinena 201	1.0784	0.3785	35	258	24.2%	2.94 [1.40, 6.17]						
	Total (95% CI)			102	676	100.0%	1.91 [1.33, 2.75]				•		
	Heterogeneity: Chi ² = 1	.91, df = 2 (P = 0.39); P	= 0%					0.1 0).2 (0.5 1	2	5	10
	l est for overall effect: 2	2 = 3.48 (P = 0.0005)							N	Non-PSI F	PSI		
Е			R	VI No	n-RVI		Hazard Ratio			Hazard F	Ratio		
	Study or Subgroup	Iog[Hazard Patio]	SE TO	otal	Total \	Veight	IV Fixed 95% CI			V Eived	95% CI		
		log[nazard Natio]					11. T IACG. 00/0 OI			IV. FIXEU.			
	Brookman-May 2015	0.157	0.1571	211	1036	56.3%	1.17 [0.86, 1.59]				F		
	Brookman-May 2015 Flood 2020	0.157 0.892 0.1222	0.1571 2	211 97	1036 63	56.3% 10.1%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20]				⊢_,	_	
	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021	0.157 0.892 0.1222 0.9002	0.1571 2 0.3707 0.3403 0.4542	211 97 57 36	1036 63 53 71	56.3% 10.1% 12.0% 6.7%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99]				F 	_	
	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017	0.157 0.892 0.1222 0.9002 1.1817	0.1571 2 0.3707 0.3403 0.4542 0.4204	211 97 57 36 94	1036 63 53 71 172	56.3% 10.1% 12.0% 6.7% 7.9%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43]						_
	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017	0.157 0.892 0.1222 0.9002 1.1817 0.3264	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4245	211 97 57 36 94 36	1036 63 53 71 172 89	56.3% 10.1% 12.0% 6.7% 7.9% 7.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31]		1				-
	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI)	0.157 0.892 0.1222 0.9002 1.1817 0.3264	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4204 0.4445	211 97 57 36 94 36 531	1036 63 53 71 172 89 1484 1	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82]						_
	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: Chi ² = §	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09);	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4204 0.4245 1 ² = 47%	211 97 57 36 94 36 36	1036 63 53 71 172 89 1484 1	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82]	L	2 0				-
	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: Chi ² = 5 Test for overall effect: 1	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002)	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4204 0.42445 1 ² = 47%	211 97 57 36 94 36 531	1036 63 53 71 172 89 1484 1	56.3% 10.1% 12.0% 6.7% 7.9% 7.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82]	⊢ 0.1 0.:	.2 0 N	0.5 1 lon-RVI R		5	-
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: Chi ^a = Test for overall effect :	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002)	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4445 1 ² = 47%	211 97 57 36 94 36 531	1036 63 53 71 172 89 1484 1	56.3% 10.1% 12.0% 6.7% 7.9% 7.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82]	i <u> </u>	2 0 N	0.5 1 lon-RVI R	← ↓ 2 WI Ratio		
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Park 2017 Total (95% CI) Heterogeneity: Chi ² = { Test for overall effect : Study or Subgroup	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002)	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4204 0.4445 1 ² = 47%	211 97 57 36 94 36 531 FFI R' Total	1036 63 53 71 172 89 1484 1 VI or FI Total	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0%	1.17 [0.8.6, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV. Fixed, 95% (H + + 0.1	2 0 N	D.5 1 lon-RVI R Hazard IV. Fixed.	← 2 :∨I Ratio 95% CI	5	10
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: Chi ² = Test for overall effect : Study or Subgroup Baccos 2013	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) log[Hazard Ratio] 0.6382	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4445 1 ² = 47%	211 97 57 36 94 36 531 I+FI R' <u>fotal</u> 41	1036 63 53 71 172 89 1484 1 VI or FI <u>Total</u> 81	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 1.13 [0.58, 2.20] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54]	↓ 0.1 0.3 CI	2 0 N	0.5 1 lon-RVI R Hazard	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2		-
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: Chi ² = § Test for overall effect: : Study or Subgroup Baccos 2013 da Costa 2012 Oceana	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) log[Hazard Ratio] 0.6382 0.9847 (0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4445 1 ² = 47% RV SE 1 0.32 0.32	211 97 57 36 94 36 531 531 FFI R' fotal 41 11	1036 63 53 71 172 89 1484 1 VI or FI <u>Total</u> 81 35	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV. Fixed, 95% 1.89 [1.01, 3.54 2.86 [1.07, 6.72]	1	2 0 N	J.5 1 Ion-RVI R Hazard	2 VI Ratio 95% Cl		- 10
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Park 2017 Total (95% CI) Heterogeneity: Ch [™] = { Study or Subgroup Baccos 2013 da Costa 2012 Ch 2018 Park 2017	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.09); Z = 3.14 (P = 0.09); 0.6382 0.9847 (0.6382 0.9847 (0.64871) 0.9847 (0.64871)	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4445 ² = 47% RV (<u>SE 1</u> 0.32 .4698 0.2769 0.3907	211 97 57 36 94 36 531 I+FI R' <u>Fotal</u> 41 11 47 69	1036 63 53 71 172 89 1484 1 VI or FI <u>Total</u> 81 35 164 197	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4% 38.5% 19.3%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% 4.268 [1.07, 6.72] 1.91 [1.11, 3.29] 2.71 [1.26, 5.83]	+ + 0.1 0.3 C1	2 0 N	J.5 1 Ion-RVI R Hazard	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	5	-
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Park 2017 Total (95% Cl) Heterogeneity: Ch ^p = 5 <u>Study or Subgroup</u> Baccos 2013 da Costa 2012 Oh 2018 Park 2017	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) 10g[Hazard Ratio] 0.6382 0.9847 (0.9847) 0.6471 (0.9969 (0.9969)	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4204 0.4204 0.4445 1 ² = 47% RV SE 1 0.32 0.32 0.4698 0.3907	211 97 57 36 94 36 531 531 +FI R' 531 41 11 47 69	1036 63 53 71 172 89 1484 1 1484 1 1000 FI Total 81 35 164 197	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4% 38.5% 19.3%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 3.26 [1.10, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72] 2.71 [1.26, 5.83]		2 0 N	J.5 1 Hazard IV. Fixed.	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2		- 10
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% Cl) Heterogeneity: Chi ² = Study or Subgroup Baccos 2013 da Costa 2012 Oh 2018 Park 2017 Total (95% Cl)	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) log[Hazard Ratio] 0.6382 0.9847 (0.9969 (0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4204 0.4204 0.4445 1 ² = 47% RV SE 1 0.32 0.32 0.4698 0.3907	211 97 57 36 94 36 531 I+FI R' Fotal 41 11 47 69 168	1036 63 53 71 172 89 1484 1 1484 1 VI or FI <u>Total</u> 81 35 164 197 477	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4% 38.5% 19.3%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72] 2.71 [1.26, 5.83] 2.13 [1.52, 2.99]		2 0 N	J.5 1 Hazard IV. Fixed.	2 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	5	-
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (85% CI) Heterogeneity: ChiP = 5 Study or Subgroup Baccos 2013 Baccos 2012 Oh 2018 Park 2017 Total (85% CI) Heterogeneity: ChiP = 4 Total (95% CI)	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) 10g[Hazard Ratio] 0.6382 0.9847 (0.9847 (0.9969 (0.9847 (0.9847 (0.9847 (0.9847 (0.9847 (0.9847 (0.9847 (0.9847 (0.9847 (0.9969 (0.9847 (0.9847 (0.9847 (0.9969 (0.9847 (0.984	0.1571 2 0.3707 0.3403 0.4542 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32	211 97 57 36 94 36 531 531 41 41 11 47 69 168	1036 63 53 71 172 89 1484 1 <u>Total</u> 81 35 164 197 477	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4% 38.5% 19.3% 100.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72] 1.91 [1.11, 3.29] 2.71 [1.26, 5.83] 2.13 [1.52, 2.99]		2 0 N	0.5 1 N. Fixed	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2		1010
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Park 2017 Total (95% CI) Heterogeneity: Ch [™] = { Study or Subgroup Baccos 2013 da Costa 2012 Ch 2018 Park 2017 Total (95% CI) Heterogeneity: Ch [™] = { Test for overall effect: :	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) log[Hazard Ratio] 0.6382 0.9847 (0.9847 (0.9847 (0.9969 (0.991, df = 3 (P = 0.82); Z = 4.41 (P < 0.0001)	0.1571 2 0.3407 0.3403 0.4542 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.32 0.32 0.32 0.4698 0.3207 1 ² = 0%	211 97 57 36 94 36 531 531 I+FI R' Total 41 11 47 69 168	1036 63 53 172 89 1484 1 <u>Total</u> 81 35 164 197 477	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4% 38.5% 19.3% 100.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72 1.91 [1.11, 3.29 2.71 [1.26, 5.83] 2.13 [1.52, 2.99]		2 0 N 0.2 F	J.5 1 Ion-RVI R Hazard IV. Fixed.			10
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Total (95% Cl) Heterogeneity: Ch ^p = \pm Study or Subgroup Baccos 2013 da Costa 2012 Oh 2018 Park 2017 Total (95% Cl) Heterogeneity: Ch ^p = \pm Test for overall effect :	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); z = 3.14 (P = 0.002) 10g[Hazard Ratio] 0.6382 0.9847 (0.6471 (0.9969 (0.991, df = 3 (P = 0.82); z = 4.41 (P < 0.0001)	0.1571 2 0.3707 0.3403 0.4542 0.4542 0.4542 0.4542 0.4542 0.4204 0.4445 2 = 47% RVI <u>SE 1</u> 0.32 (.4698 0.2769 3.3907 2 = 0%	211 97 57 36 94 36 531 i+FI R' 531 41 11 41 47 69 168	1036 63 53 71 172 89 1484 1 1484 1 VI or FI <u>Total</u> 81 35 5164 197 477 Single p	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4% 38.5% 19.3% 100.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 3.26 [1.10, 5.99] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72] 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ra	0.1 0.3	2 0 N 0.2 F	D.5 1 Ion-RVI R Hazard IV. Fixed.	2 VI Ratio 95% Cl 2 VI Ratio 95% Cl 2 VI Ratio	5	- 10 10
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Total (95% Cl) Heterogeneity: Chi ² = (Study or Subgroup Baccos 2013 da Costa 2012 Oh 2018 Park 2017 Total (95% Cl) Heterogeneity: Chi ² = (Total (95% Cl) Heterogeneity: Chi ² = (Study or Subgroup L	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) 109[Hazard Ratio] 0.6382 0.9847 (0.9847 (0.9867 (0.9847 (0.9867 (0.9867 (0.9867 (0.9867 (0.996 (0.996 (0.996 (0.996 (0.996 (0.000)) (0.996 (0.000) (0.996 (0.000) (0.996 (0.000) (0.996 (0.000) (0.996 (0.000) (0.00	0.1571 2 0.3403 0.3403 0.4542 0.4204 0.4445 2 1 ² = 47% RV RV SE 1 0.32 0.4698 0.3907 1 ² = 0% Multiple p	211 97 57 36 94 36 531 **FI R' 531 ** ** 41 11 47 69 168 ** ** ** ** ** ** **	1036 63 53 71 172 89 1484 1 1484 1 1484 1 81 35 164 197 477 \$ingle p	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4% 13.4% 19.3% 100.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72] 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ra	0.1 0.1 0.1 0.1 1 1 1 1 1 1 1 1 1 1 1 1 1	1 0.2 N	J.5 1 Joon-RVI R Hazard IV. Fixed.	2 2 Ratio 95% Cl 2 2 2 V/I+Fl d Ratio dd 95% Cl		- 10
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Park 2017 Total (95% CI) Heterogeneity: ChiP = { Study or Subgroup Baccos 2013 da Costa 2012 Ch 2018 Park 2017 Total (95% CI) Heterogeneity: ChiP = { Total (95% CI) Heterogeneity: ChiP = { Study or Subgroup I Baccos 2013 Baccos 2013 Baccos 2013 Study or Subgroup I Baccos 2013 Baccos 2013 Study or Subgroup I Baccos 2013 Baccos 2013 Study or Subgroup I Baccos 2013 Study or Subgroup I Baccos 2013	0.157 0.852 0.1222 0.222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002); 10g[Hazard Ratio] 0.6382 0.9847 (0.6471 (0.9969 (0.9969 (0.91, df = 3 (P = 0.82); Z = 4.41 (P < 0.0001) 0.6382 0.33 10116 0.375	0.1571 2 0.3707 0.3403 0.4542 0.4542 0.4542 0.4542 0.4542 0.4542 1 ² = 47% RV SE 1 0.32 0.4698 0.2769 0.3907 1 ² = 0% Multiple p 2	211 97 57 36 94 36 531 531 1+FI R ¹ 41 11 47 69 168 41 11 47 69	1036 63 53 71 172 89 1484 1 1484 1 1484 1 1484 1 81 35 164 197 477 \$ingle p	56.3% 10.1% 12.0% 6.7% 7.9% 7.0% 00.0% Weight 28.8% 13.4% 38.5% 19.3% 100.0% attern Total 1 81	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, <u>95%</u> (1.89 [1.07, 6.72 1.91 [1.11, 3.29 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ratio IV, Fixed, <u>95%</u> (1.89 [1.07, 6.72 1.91 [1.11, 3.29 2.71 [1.26, 5.83] 2.13 [1.52, 2.99]	0.1 0.1 0.1 0.1 1 1 0.1 0 1 1 1 1 1 1 1 5 5 741	2 0 N 0.2 F	J.5 1 lon-RVI R Hazard IV. Fixed.	2 2 2 2 2 2 2 2 2 2 2 2 2 1 4 4 2 2 2 2		-
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Park 2017 Total (95% CI) Heterogeneity: ChP = ≤ Study or Subgroup Baccos 2013 da Costa 2012 Ch 2017 Total (95% CI) Heterogeneity: ChP = ≤ Study or Subgroup Baccos 2013 Becke 2009 Capitanio 2018	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) 109[Hazard Ratio] 0.6382 0.9847 (0.6387 0.6382 0.9969 (0.9969 (0.991, df = 3 (P = 0.82); Z = 4.41 (P < 0.0001) 0.6382 0.33 1.0116 0.375 -0.1054 0.413	0.1571 2 0.3707 0.3403 0.3403 0.4542 0.4204 0.4445 1 ² = 47% SE 1 0.32 0.4698 0.2769 0.3907 1 ² = 0% Multiple p 2 1 7	211 97 57 36 94 36 531 41 531 41 41 47 69 168 41 47 69 168 44 47 69 168 8	1036 63 53 71 172 89 1484 1 172 89 1484 1 172 81 35 164 197 477 \$\$ingle p	56.3% 10.1% 12.0% 6.7% 7.9% 7.9% 7.0% 00.0% Weight 13.4% 38.5% 19.3% 100.0% attern Total 1 81 58 161	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.77 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ra Veloht IV, Fixed, 95% (7.2% 1.89 [1.01, 3.54] 7.2% 1.89 [1.01, 3.54]	↓ ↓ ↓ 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1	2 0 N	0.5 1 N. Fixed.	2 2 VI 95% Cl 2 2 VI+FI d Ratio d, 95% Cl		- 10 10
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Total (95% Cl) Heterogeneity: Chi ² = 1 Test for overall effect: 3 Study or Subgroup Baccos 2013 da Costa 2012 Oh 2018 Park 2017 Total (95% Cl) Heterogeneity: Chi ² = (Test for overall effect: 3 Study or Subgroup IB Baccos 2013 Baccos 2013 Bedaccos 2013 Baccos 2013 Bedaccos 2014	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); z = 3.14 (P = 0.002) log[Hazard Ratio] 0.6382 0.9847 (0.6471 (0.9969 (0.9471 (0.9969 (0.947 (0.946 (0.964 (0.1571 2 0.3707 0.3403 0.3403 0.4542 0.4204 0.4445 1 ² = 47% RV (SE 1 0.32 0.4698 0.32 0.4698 0.32 0.4698 1.2769 0.32 0.4698 1.2769 1.3907 1 ² = 0% Multiple p	211 97 57 36 94 36 531 531 41 11 41 41 41 47 69 168 41 47 69 168	1036 63 71 712 89 1484 1 81 81 81 81 81 81 85 5 5 7 7 477 477	56.3% 10.1% 6.7% 7.9% 7.9% 00.0% Weight 28.8% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 10.1%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72] 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ra Veluht IV, Fixed, 3.54 3.23 [1.52, 2.99] Hazard Ra Veluht IV, Fixed, 3.54 3.24 [1.52, 2.99] Hazard Ra Veluht IV, Fixed, 3.54 3.25 [1.52, 2.99] Hazard Ra Veluht IV, Fixed, 3.54 3.25 [1.52, 2.99] Hazard Ra Veluht IV, Fixed, 3.54 3.25 [1.52, 2.99] Hazard Ra Veluht IV, Fixed, 3.55 3.25 [1.52, 2.99] Hazard Ra Veluht IV, Fixed, 3.55 [1.52, 2.99]	← + + + + + + + + + + + + + + + + + + +	1 0 N	0.5 1 N. Fixed. 0.5 1 N. Fixed. N. Fixed. N. Fixed. N. Fixed.	2 2 2 2 2 2 2 2 2 2 2 1 2 2 2 1 2 2 2 1 1 2 2 2 2 1 1 2 2 2 2 1 1 1 2 2 2 1 1 1 2 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1		- 10
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: Chi ² = 5 Study or Subgroup Baccos 2013 da Costa 2012 Ch 2018 Park 2017 Total (95% CI) Heterogeneity: Chi ² = (Test for overall effect : Study or Subgroup Baccos 2013 Baccos 2013 Study or Subgroup Baccos 2013 Baccos 2013 Capitanio 2018 Capitanio 2018 Capitanio 2018 Capitanio 2018 Capitanio 2018 Capitanio 2018	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) 100[Hazard Ratio] 0.6382 0.9847 (0.6471 (0.9969 (0.9969 (0.391, df = 3 (P = 0.82); Z = 4.41 (P < 0.0001) 10.6382 0.382 0.33 1.0116 0.375 0.0474 0.456 0.6471 0.276 0.6471 0.456 0.647 0.456 0.557 0.5	0.1571 2 0.3707 0.3403 0.3403 0.4542 0.4204 0.4405 0.4204 0.4405 0.4204 0.4405 0.4204 0.4405 0.4204 0.4405 0.4204 0.4405 0.4204 0.4405 0.4204 0.4405 0.327 0.32769 0.33007 0.32769 0.33007 0.32769 0.3307 0.32769 0.3307 0.32769 0.3307 0.32769 0.3307 0.32769 0.3307 0.3307 0.32769 0.3307 0.33907 0.33907 0.4045 0.4045 0.4045 0.4045 0.4045 0.32769 0.33907 0.33907 0.33907 0.33907 0.405 0.405 0.405 0.405 0.405 0.405 0.32769 0.33907 0.33907 0.405 0.	211 97 57 36 94 36 53 33 1 +FI R [*] 53 33 1 +FI R [*] 69 168 11 41 41 11 47 69 168 168 11 27 88 81 11 69 168	1036 63 71 172 89 1484 1 1 1 1 1 1 1 1 1 1 	56.3% 10.1% 20.% 6.7% 7.9% 000.0% Weight 28.8% 19.3% 100.0% attern 104.0% 104.0% 105.0	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% C 1.89 [1.01, 3.54] 2.68 [1.07, 6.72] 1.91 [1.11, 3.29 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ratio IV, Fixed, 95% C 1.89 [1.01, 3.54] 2.73 [1.52, 2.99] Hazard Ratio IV, Fixed, 95% C 1.89 [1.01, 3.54] 2.73 [1.52, 2.99] Hazard Ratio IV, Fixed, 95% C 2.75 [1.32, 4.98] 1.03, 3.98 [1.07, 9.56] 1.92% C 2.75 [1.32, 4.98] 1.93% C 2.88 [1.07, 9.56] 1.92% C 2.75 [1.32, 4.98] 1.93% C 2.88 [1.07, 9.56] 1.93% C 2.88 [1.07, 9.56] 1.93% C 2.93%	0.1 0. 1 1 1 1 1 1 1 1 1 1 1 1 1	2 0 N N				-
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Park 2017 Total (95% CI) Heterogeneity: Ch [™] = { Study or Subgroup Baccos 2013 da Costa 2012 Ch 2018 Park 2017 Total (95% CI) Heterogeneity: Ch [™] = { Study or Subgroup Heterogeneity: Ch [™] = { Study or Subgroup Heterogeneity: Ch [™] = { Study or Subgroup Baccos 2013 Becke 2009 Capitanio 2018 da Costa 2012 Oh 2018 Park 2017 Study or Subgroup Data 2017 Study or Subgroup Data 2018 Data 2019 Data 2019 Data 2019 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2019 Data 2019 Data 2019 Data 2018 Data 2019 Data 2019 Data 2019 Data 2019 Data 2019 Data 2019 Data 2019 Data 2018 Data 2019 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2018 Data 2018 Data 2018 Data 2018 Data 2019 Data 2018 Data 2018 Data 2018 Data 2018 Data 2019 Data 2018 Data 2019 Data 2018 Data 2019 Data 2018 Data 2018	0.157 0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002); log[Hazard Ratio] 0.6382 0.9847 (0.9847 (0.9969 (0.9969 (0.991, df = 3 (P = 0.82); Z = 4.41 (P < 0.0001) 0.882 0.33 1.0116 0.323 0.9847 0.493 0.8842 0.33 1.0164 0.413 0.9847 0.496 0.4947 0.496 0.4947 0.130	0.1571 2 0.3403 0.3403 0.3404 0.3404 0.4542 0.4204 0.4204 0.4204 0.4445 (2 1 ² = 47% RV (SE 1 0.32 0.4698 0.3907 1 ² = 0% Multiple p 2 7 3 3 7 5	211 97 57 36 94 36 53 33 1 +FI R' 10 41 11 47 69 168 11 41 41 41 41 41 41 41 41 41 41 41 41	1036 63 53 71 172 89 1484 1 172 1484 1 197 477 477 5 164 197 477	56.3% 10.1% 20.% 6.7% 7.9% 00.0% Weightt 28.8% 19.3% 19.3% 100.0% attern Total 13.4% 81 55 164 197 355	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72 1.91 [1.11, 3.29 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.75 [1.32] 2.75 [1.32] 2.75 [1.32] 2.75 [1.32] 2.75 [1.32] 2.75 [1.32] 2.75 [1.32] 2.75 [1.32] 3.3% [1.64 [1.27, 1.75]] 3.3% [1.64 [1.27, 1.75]]	L 1 0.1 0. Cl 1 0	2 0 N		2 VI 2 VI 95% Cl 2 2 VI+FI d Ratio d; 95% Cl 		-
F	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: ChP = 5 Heterogeneity: ChP = 5 Study or Subgroup Baccos 2013 Gada Costa 2012 Oh 2018 Park 2017 Total (95% CI) Heterogeneity: ChP = 5 Heterogeneity: ChP = 4 Total (95% CI) Heterogeneity: ChP = 4 Test for overall effect: 3 Study or Subgroup In Baccos 2013 Bedea 2009 Capitania 2018 da Costa 2012 Oh 2018 Park 2017 Study or Subgroup In Study or Subgroup In Sharb 2019 Sharb 2019 Wang 2020 Vang 2020	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002) 109[Hazard Ratio] 0.6382 0.9847 (0.6382 0.9847 (0.0847) 0.6471 (0.9969 (0.300) 2 = 4.41 (P < 0.0001) 1.016 0.375 -0.1054 0.413 0.9847 0.489 0.6471 0.276 0.9969 (0.300) 0.4947 0.498 0.4947 0.4988 0.4947 0.4988 0.4947 0.4988 0.4947 0.4988 0.494	0.1571 2 0.3707 2 0.3703 2 0.4542 0.4542 0.4544 0.4204 0.3207 0.3207 0.3307 7 7 7 7 7 7 7 7 7 7 7 7 7	211 97 57 57 36 94 36 531 41 41 41 47 669 168 41 47 47 69 41 47 47 69 41 47 47 69 47 47 69 47 47 69 47 47 68 47 47 47 68 47 47 47 47 47 47 47 47 47 47 47 47 47	1036 63 71 172 89 1484 1 70tal 81 35 164 197 477 477	56.3% 10.1% 12.0% 6.7% 7.9% 7.9% 00.0% 00.0% 00.0% 13.4% 38.5% 13.4% 38.5% 100.0% 100.0%	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] C.86 [1.07, 6.72 1.91 [1.11, 3.29] 2.77 [1.26, 5.43] 2.13 [1.52, 2.99] Hazard Ra Velght IV, Fixed, 95% (3.3% 2.68 [1.07, 6.72] 7.2% 1.89 [1.01, 3.54] 7.2% 1.89 [1.54] 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2% 7.2%	0.1 0. Cl 1 1 1 1 1 1 1 1 1 1 1 1 1		J.5 1 J.5 1 Hazard IIV. Fixed	2 2 2 2 2 2 2 2 2 2 2 2 2 2		-
G	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Total (95% CI) Heterogeneity: ChP = 1 Study or Subgroup Baccos 2013 da Costa 2012 Oh 2018 Park 2017 Total (95% CI) Heterogeneity: ChP = 1 Baccos 2013 Baccos 2013 Baccos 2013 Backer 2012 Total (95% CI) Heterogeneity: ChP = 1 Study or Subgroup IB Baccos 2013 Baccos 2013 Backer 2013 Mac Casta 2012 Oh 2018 Park 2017 Shah 2019 Mark 2017 Shah 2019 Vang 2020 Total (95% CI)	0.157 0.892 0.1222 0.9002 1.1817 0.3264 9.45, df = 5 (P = 0.09); z = 3.14 (P = 0.002) 10g[Hazard Ratio] 0.6382 0.9847 (0.6382 0.9847 (0.984	0.1571 2 0.3707 2 0.3707 3.3403 0.4542 0.4204 0.4204 0.4204 0.4204 0.4204 0.4204 0.4245 0.425	211 97 57 36 94 36 33 36 331 41 41 47 69 168 44 47 69 168 44 47 22 80 41 11 47 69 44 41 22 80 41 47 69 44 41 28 60 44 41 28 60 44 41 41 41 28 60 44 41 41 41 41 41 41 41 41 41 41 41 41	1036 63 71 172 89 1484 1 81 35 164 197 477 \$Single p	56.3% 10.1% 12.0% 6.7% 7.9% 00.0% 13.4% 38.5% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 19.3% 10.1% 10	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72] 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ra Veight IV, Fixed, 5.43 2.13 [1.52, 2.99] Hazard Ra Veight IV, Fixed, 5.43 2.13 [1.52, 2.99] Hazard Ra Veight IV, Fixed, 5.43 3.43% 0.90 [0.40] 3.3% 2.68 [1.07] 9.6% 1.97 [1.26] 4.3% 0.90 [0.40] 3.3% 2.68 [1.07] 9.6% 1.97 [1.26] 4.2% 1.70 [1.19] 0.0% 1.77 [1.49]	0.1 0. 0.1 0. 0.1 0. 0.1 0. 0.1 0. 0.1 0. 0. 0.1 0. 0. 0. 0. 0. 0. 0. 0. 0. 0.		0.5 1 N. Fixed. 0.5 1 N. Fixed. N. Fixed. N. Fixed. N. Fixed.			-
G	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: Chi ² = 4 Study or Subgroup Baccos 2013 da Costa 2012 Ch 2018 Park 2017 Total (95% CI) Heterogeneity: Chi ² = 4 Study or Subgroup Baccos 2013 da Costa 2012 Ch 2018 Park 2017 Total (95% CI) Heterogeneity: Chi ² = 4 Study or Subgroup Baccos 2013 Gaptianio 2018 Baccos 2013 Baccos 2013 Capitanio 2018 Capitanio 2017 Shah 2019 Viang 2020 Total (95% CI) Heterogeneity: Chi ² = 6,5	0.157 0.892 0.1222 0.0002 1.1817 0.3264 9.45, df = 5 (P = 0.09); Z = 3.14 (P = 0.002); 109[Hazard Ratio] 0.6382 0.9847 (0.6471 (0.9969 (C 0.9969 (C 0.991, df = 3 (P = 0.82); Z = 4.41 (P < 0.0001) 0.6382 0.33 1.0116 0.375 0.05382 0.33 1.0116 0.375 0.0530 (C 0.4947 0.2001) 0.6382 0.33 0.0417 0.276 0.9969 (C 0.4947 0.2001) 0.6300 0.360 0.4947 0.458 0.9447 0.130 0.5306 0.180 3. df = 7 (P = 0.48); P = 0 0.570 (C = 0.570); P = 0 0.570 (C = 0	0.1571 2 3.3707 3.3707 3.3403 3.4632 4.46445 { 1 ² = 47% RV (RV (SE] 0.32 1 ² = 0% Multiple p 2 1 ³ = 0% Multiple p 5 2 2 3 3 3 3 3 4 4 4 4 4 4 5 5 2 2 3 3 4 5 5 2 2 3 3 4 5 5 5 2 5 5 5 5 5 5 5 5 5 5 5 5 5	211 97 57 36 94 36 331 +FI R ¹ 531 41 11 47 69 168 41 200 8 41 21 8 41 47 69 168 41 220 746	1036 63 53 71 172 89 1484 1 172 89 170 170 170 184 197 477 55 5 5	56.3% 10.1% 12.0% 6.7% 7.0% 7.0% 00.0% Weight 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.4% 13.5% 16.1 55 164 155 161 155 164 1197 358 746	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 1.39 [0.58, 3.31] 1.45 [1.15, 1.82] Hazard Ratio [IV, Fixed, <u>95%</u> C 1.99 [1.01, 3.54] 2.68 [1.07, 6.72 1.91 [1.11, 3.29 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ratio [I.15, 2.29] Hazard Ratio [I.15, 2.29] Hazar	L	L 02	0.5 1 0.5 1 Hazard N.Fixed. 0.5 1 Hazard 0.5 1 Hazard 0.5 1			- 10
G	Brookman-May 2015 Flood 2020 Kresowik 2010 Lai 2021 Park 2017 Peng 2017 Total (95% CI) Heterogeneity: Chi ^p = { Heterogeneity: Chi ^p = { Study or Subgroup Baccos 2013 Baccos 2013 da Costa 2012 Ch 2018 Park 2017 Total (95% CI) Heterogeneity: Chi ^p = { Heterogeneity: Chi ^p = { Total (95% CI) Heterogeneity: Chi ^p = { Study or Subgroup Baccos 2013 Beckes 2009 Capitanio 2018 Park 2017 Study or Subgroup Heterogeneity: Chi ^p = { Heterogeneity: Chi ^p = { Heterogeneity: Chi ^p = { Park 2017 Shah 2019 Wang 2020 Total (95% CI) Heterogeneity: Chi ^p = 6.5 Test for overall effect: 2 =	$\begin{array}{c} 0.157\\ 0.157\\ 0.892\\ 0.1222\\ 0.9002\\ 1.1817\\ 0.3264\\ 9.45, df=5 (P=0.09);\\ Z=3.14 (P=0.09);\\ Z=3.14 (P=0.002)\\ \hline \mbox{log[Hazard Ratio]}\\ 0.6382\\ 0.9847 (0.6387\\ 0.9969 (0.001)\\ 0.9969 (0.001)\\ 0.991, df=3 (P=0.82);\\ Z=4.41 (P<0.0001)\\ 0.9969 (0.001)\\ 0.0812 (0.3382\\ 0.33\\ 1.0116 (0.375\\ 0.03647 (0.4043)\\ 0.0969 (0.306)\\ 0.0497 (0.4043)\\ 0.0969 (0.306)\\ 0.0497 (0.406)\\ 0.$	0.1571 2 0.3707 3.3403 0.4542 0.4542 0.4204 0.320 0	211 97 57 36 94 33 33 33 1 +FI R' 57 33 33 1 +FI R' 69 11 11 47 69 168 41 11 11 47 69 41 11 11 47 69 41 11 11 47 69 4 41 11 11 47 69 4 41 41 11 11 47 69 4 41 41 11 11 47 69 4 4 41 11 11 47 69 4 4 41 11 11 47 69 4 4 41 11 11 47 69 4 4 41 11 11 47 69 4 4 41 11 11 47 69 4 4 41 11 11 47 69 4 4 41 11 11 47 69 4 4 41 11 11 47 69 4 4 11 11 11 47 69 4 4 11 11 11 47 69 4 11 11 11 11 11 47 69 11 11 11 11 11 11 11 11 11 11 11 11 11	1036 63 53 711 172 89 11484 1 777 81 1484 197 477 \$ingle p	56.3% 10.1% 12.0% 6.7% 7.0% 7.0% 00.0% Weight 28.8% 7.0% 00.0% 13.4% 38.5% 19.3% 100.0% 81 50 51 51 51 51 51 51 51 51 51 51 51 51 51	1.17 [0.86, 1.59] 2.44 [1.18, 5.05] 2.46 [1.01, 5.99] 3.26 [1.43, 7.43] 3.26 [1.43, 7.43] 1.45 [1.15, 1.82] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.68 [1.07, 6.72 1.91 [1.11, 3.29 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.71 [1.26, 5.83] 2.13 [1.52, 2.99] Hazard Ratio IV, Fixed, 95% (1.89 [1.01, 3.54] 2.72% 1.89 [1.01, 5.2% 2.75 [1.32] 3.3% 1.64 [1.27, 2.2% 1.70 [1.19, 0.0% 1.77 [1.49,	0.1 0. 0.1 0. 0.1 0. 0.1 0. 10 10 10 10 10 10 10 10 10 10	2 00 N 1 0.2 F	0.5 1 N.5 1 Hazard IV. Fixed 0.5 1 Hazard NV. Fixed 0.5 1 Hazard	2 VI 2 VI 5 5 5 VI+FI 4 4 4 5 5 CI 1 2 VI+FI 4 4 5 5 CI 1 2 VI+FI 4 Multipe pe		- 10

TNM system (26, 27, 29–31). Palapattu et al. reported a strong relationship between PSI, lymph node invasion and distant metastases (32). Third, high-certainty evidence suggests that the concomitance of RVI and FI significantly increased the risk of deterioration of CSS as compared to RVI or FI supported the finding that multiple invasion patterns translated into moderate-certainty evidence of significantly decreased CSS. However, most contemporary studies that reported the prognostic heterogeneity

of T3a RCC failed to comprehensively explore the survival difference among the various combinations. A precise-risk grade of CSS for different invasion patterns, including comprehensive combinations, may be useful for further refinements of the TNM system. Finally, high-certainty evidence indicates that distant metastases, sarcomatoid differentiation, high Fuhrman grade and positive margin were the predictors of inferior CSS. Tumor size >7cm and necrosis

patterns vs Single pattern. SFI, sinus fat invasion; PFI< perinephric fat invasion; PSI, pelvicaliceal system invasion; RVI, renal vein invasion; FI, fat invasion.

TABLE 3 | The overall quality of evidence according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach.

Comparison			Certainty as	sessment			No. of	f patients		Effect	Certainty	Importance
	No. of Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Large effect	Case	Control	HRs	95% CI		
SFI only vs PFI only	6	not serious	not serious	not serious	serious	No	631	903	0.92	0.69-1.23	⊕⊕OO LOW	IMPORTANT
SFI+PFI vs SFI only	2	not serious	not serious	not serious	not serious	No	138	422	1.97	1.13–3.42	⊕⊕⊕⊖MODERATE	IMPORTANT
SFI \pm PFI vs PFI only	3	not serious	not serious	not serious	not serious	No	126	290	1.81	1.33-2.47	⊕⊕⊕⊖ MODERATE	IMPORTANT
PSI vs non-PSI	3	not serious	not serious	not serious	not serious	No	102	676	1.91	1.33-2.75	⊕⊕⊕⊖ MODERATE	IMPORTANT
RVI vs non-RVI	6	not serious	not serious	not serious	not serious	No	531	1484	1.45	1.15-1.82	⊕⊕⊕⊖ MODERATE	IMPORTANT
RVI+FI vs RVI or FI	4	not serious	not serious	not serious	not serious	Yes	168	477	2.13	1.52-2.99	⊕⊕⊕⊕ НІGН	IMPORTANT
Multiple vs Single pattern	8	not serious	not serious	not serious	not serious	No	1226	1800	1.77	1.49-2.09	⊕⊕⊕⊖ MODERATE	IMPORTANT
Node	6	not serious	serious	not serious	not serious	No	398	1912	1.71	1.17-2.5	⊕⊕OO LOW	IMPORTANT
N1 vs N0/x												
Metastases	8	not serious	not serious	not serious	not serious	Yes	726	1844	3.36	2.88–3.91	⊕⊕⊕⊕ нідн	IMPORTANT
M1 vs M0												
Sarcomatoid	10	not serious	not serious	not serious	not serious	Yes	436	3185	2.09	1.78-2.46	⊕⊕⊕⊕ НІGН	IMPORTANT
Yes vs No												
Fuhrman grade	8	not serious	not serious	not serious	not serious	Yes	1737	1065	2.7	2.18–3.34	⊕⊕⊕⊕ НІGН	IMPORTANT
III or IV vs II or I												
Necrosis	6	not serious	not serious	not serious	not serious	No	640	699	1.96	1.54-2.49	⊕⊕⊕⊖ MODERATE	IMPORTANT
Yes vs No												
Size	5	not serious	not serious	not serious	not serious	No	1571	1811	1.77	1.46–2.15	⊕⊕⊕⊖ MODERATE	IMPORTANT
>7cm vs ≤ 7cm												
Margin status	6	not serious	not serious	not serious	not serious	Yes	28	1154	7.61	4.12-14.04	⊕⊕⊕⊕ НІGН	IMPORTANT
positive vs negative												
LVI vs non-LVI	3	not serious	not serious	not serious	not serious	No	159	290	1.11	0.69-1.8	⊕⊕OO LOW	IMPORTANT

Guo et al.

	Subaroun loalH	lazard Ratio] S	Positive nor	tal Negative	e node Total	Weight	Hazard Ratio	CI	Hazan	d Ratio
Bedke 200)9	-0.2614 0.402	3	22	84	13.0%	0.77 [0.35, 1.6	59]		
Bertini 200	09	0.2398 0.227	1	13	92	21.0%	1.27 [0.81, 1.9	98]	_	-
da Costa 2 Margulis 2	2012	1.581 0.523	8	8	38	9.4%	4.86 [1.74, 13.5	57]		
Poon 2009	9	-0.0171 0.597	1	8	222	7.8%	0.98 [0.31, 3.1	7] -		
Wang 2020	0	0.5766 0.111	7 2	98	1160	27.0%	1.78 [1.43, 2.2	22]		-
Total (95%	% CI)		3	98	1912	100.0%	1.71 [1.17, 2.5	01		+
Heterogen	neity: Tau ² = 0.13; C	hi² = 15.11, df = 5 (F	P = 0.010); l ² = 6	57%				01 02	0.5	1 2 5
Test for ov	verall effect: Z = 2.7	7 (P = 0.006)						Neg	ative node	Positive node
			Metastases	Non-meta:	stases		Hazard Ratio		Hazard	Ratio
Study or S	Subgroup log[h	azard Ratio]	SE Tota	1	Total \	Weight	IV. Fixed. 95% C		IV. Fixed	95% CI
Baccos 20	013	0.9966 0.19	21 1	3	108	16.2%	2.71 [1.86, 3.95]			_
Bertini 200	09	0.9995 0.45	78 10)	95	2.9%	2.72 [1.11, 6.66]			
da Costa 2	2012	1.1969 0.58	15 1	9	37	1.8%	3.31 [1.06, 10.35]		-	
Kresowik 3	2010	1.1569 0.34	11 31 70 101	3	72	5.1%	3.18 [1.62, 6.24]			
Poon 2009	9	2.2783 0.41	54 2	í	209	3.5%	9.76 [4.32, 22.07]			
Wang 202	:0	1.1119 0.1	08 47:	2	1020	51.4%	3.04 [2.46, 3.76]			-
Total (95%	% CI)		720	5	1844	100.0%	3.36 [2.88, 3.91]			•
Heterogen	neity: Chi ² = 12.16, c	df = 7 (P = 0.10); l ² =	42%					0.05 0.2	1	5
Test for ov	verall effect: Z = 15.	64 (P < 0.00001)						Non-met	astases	Metastases
~			Sarcomatoio	Non-sarc	omatoid		Hazard Ratio		Hazard	Ratio
Study or S	Subgroup log[H	lazard Ratio] S	E Tot	al	Total	Weight	IV. Fixed. 95% 0		IV. Fixed	I. 95% CI
Bedke 200	013 09	1.0127 0.501	o 1 5	7	112	2.7%	2.75 [1.03, 7.36	1	-	
Bertini 200	09	1.6656 0.506	2 1	0	95	2.7%	5.29 [1.96, 14.26			
Capitanio 2	2018	1.5476 0.903	4	5	304	0.8%	4.70 [0.80, 27.61	1		
Chen 2017 Marculic 2	007	0.3577 0.676	2 0 9	9	154	1.5%	1.43 [0.38, 5.38	1		
Oh 2018		0.4574 0.66	4 2	6	185	1.5%	1.58 [0.43, 5.81	1		
Schiavina :	2015	0.9594 0.186	8 1	6	169	19.5%	2.61 [1.81, 3.76]		
Shah 2019 Wapo 2029	9	1.1184 0.305	9 2	6	537	7.3%	3.06 [1.68, 5.57	1		-
						400				•
Total (95%	% CI) weity: Chi² = 10.26 d	f = 0 (P = 0 33) 2 =	43	6	3185	100.0%	2.09 [1.78, 2.46]	¹		—
Test for ov	verall effect: Z = 8.93	3 (P < 0.00001)	12.70					0.1 0.2 Non-car	0.5 1	2 5 Sarcomatoid
_								Non our	U	-41-
Study or	Subaroup	log[Hazard Rati	0] SE	Total Tota	al Weig	ht_IV	Fixed, 95% CI		V. Fixed	95% C
Capitanio	2018	0.587	8 0.4137	133 17	6 6.9	% 1.8	0 [0.80, 4.05]			
Chen 201	17	0.896	9 0.357	55 8	3 9.3	% 2.4	5 [1.22, 4.94]			
da Costa	2012	0.067	7 0.7026	22 2	4 2.4	% 1.0	7 [0.27, 4.24]		_	
Garcia Ma	archinena 2019	0.797	5 0.3583	175 11	8 9.2	% 2.2 % 1.0	2 [1.10, 4.48]		_	
Poon 200)9	1.147	4 0.382	78 13	3 4.7 8 8.1	% 3.1	5 [1.49, 6.66]			
Schiavina	a 2015	1.466	4 0.2702	139 4	4 16.2	% 4.3	3 [2.55, 7.36]			
Wang 202	20	1.00	8 0.1657	1100 00	0 40 44					
				1123 30	9 45.1	% 2.7	4 [1.98, 3.79]			
Total (95	% CI)			1737 106	9 43.1 5 100.0	% 2.7	4 [1.98, 3.79] 0 [2.18, 3.34]			٠
Total (95 Heteroge	% CI) neity: Chi² = 6.85,	df = 7 (P = 0.44);	l² = 0%	1737 106	5 100.0	% 2.7 1% 2.7	4 [1.98, 3.79] 0 [2.18, 3.34] ⊢			•
Total (95 Heteroger Test for o	% CI) eneity: Chi² = 6.85, overall effect: Z = 9	df = 7 (P = 0.44); 9.14 (P < 0.00001)	¹² = 0%	1737 106	5 100.0	% 2.7 1% 2.7	4 [1.98, 3.79] 0 [2.18, 3.34] 	1 0.2 0. Grad	5 1 elorli G	2 5
Total (95 Heteroge Test for o	% CI) eneity: Chi² = 6.85, overall effect: Z = 9	df = 7 (P = 0.44); 9.14 (P < 0.00001)	1² = 0%	1737 106	9 43.1 5 100.0	% 2.7 1% 2.7	4 [1.98, 3.79] 0 [2.18, 3.34] 	1 0.2 0. Grade	5 1 e I or II G Hazard I	2 irade III or IV
Total (95 Heteroger Test for o	% CI) meity: Chi ² = 6.85, overall effect: Z = 9 Subgroup log	df = 7 (P = 0.44); 9.14 (P < 0.00001) [Hazard Ratio]	I ² = 0% Necrosis SE Tota	1737 106 No necro	9 43.1 5 100.0 sis <u>otal We</u>	% 2.7 % 2.7 	4 [1.98, 3.79] 0 [2.18, 3.34] 	1 0.2 0. Grade	5 1 e I or II G Hazard I IV. Fixed.	2 5 irade III or IV Ratio 95% CI
Total (95 Heteroger Test for o	% CI) neity: Chi ² = 6.85, overall effect: Z = 9 <u>Subgroup log</u> 09	df = 7 (P = 0.44); 9.14 (P < 0.00001) [Hazard Ratio] 0.5247 0.3	I ² = 0% Necrosis SE Tota 3447 6	1737 106 No necro al T 0	9 43.1 5 100.0 sis <u>total We</u> 46 12	% 2.7 1% 2.7 F <u>eight IV</u> 2.5% 1	4 [1.98, 3.79] 0 [2.18, 3.34] 	1 0.2 0. Grade	5 1 e I or II G Hazard F IV. Fixed.	2 5 irade III or IV Ratio 95% Cl
Total (95 Heteroger Test for o <u>Study or</u> Bedke 200 Bertini 200	% CI) meity: Chi ² = 6.85, overall effect: Z = 9 <u>Subgroup log</u> 09	df = 7 (P = 0.44); 9.14 (P < 0.00001) [Hazard Ratio] 0.5247 0.: 0.4953 0.:	¹² = 0% Necrosis <u>SE Tot</u> 3447 6 3344 8	1737 106 No necro No necro	sis <u>otal We</u> 46 12 25 5	% 2.7 % 2.7 F F F F F F F F F F F F F	4 [1.98, 3.79] 0 [2.18, 3.34] 0 [2.18, 3.34] 0 [2.18, 3.34] 0 [0.86, 3.32] .64 [0.58, 4.68] .69 [0.86, 3.32]	1 0.2 0. Grade	5 1 elor II G Hazard I IV. Fixed.	2 5 irade III or IV Ratio 95% Cl
Total (95' Heteroger Test for o Study or : Bedke 200 Bertini 200 Capitanio	% CI) neity: Chi ² = 6.85, vverall effect: Z = 9 Subgroup log 09 09 2018 2012	df = 7 (P = 0.44);).14 (P < 0.00001) [Hazard Ratio] 0.5247 0.: 0.4953 0.: 0.1823 0.: 1.0328 0.0	¹² = 0% Necrosis <u>SE Toti</u> 3447 6 3344 8 1467 10 1684 2	1737 106 No necro al T 0 0 8 8	sis <u>otal We</u> 46 12 25 5 201 7 18 1	% 2.7 % 2.7 Height IN 2.5% 1 5.2% 1 7.4% 1	4 [1.98, 3.79] 0 [2.18, 3.34] 0 [2.18, 3.34] 0 [2.18, 3.34] 0 [0.60, 3.32] .64 [0.58, 4.68] .20 [0.50, 2.88] 10.42 [4.74]	1 0.2 0. Grade	5 1 e I or II G Hazard F IV. Fixed.	2 5 irade III or IV Ratio 95% Cl
Total (95' Heteroger Test for o Study or Bedke 200 Bertini 200 Capitanio da Costa : Oh 2018	% CI) neity: Chi ² = 6.85, vverall effect: Z = 9 <u>Subgroup log</u> 09 09 2018 2012	df = 7 (P = 0.44);).14 (P < 0.00001) [Hazard Ratio] 0.5247 0.3 0.4953 0.4 0.1823 0.4 1.0328 0.4 1.4446 0	¹² = 0% <u>SE Totr</u> 3447 6 3344 8 1467 10 3684 2 3684 10	No necro No necro	sis otal We 46 12 25 5 201 7 18 1 108 3	% 2.7 % 2.7 Fight IV 2.5% 1 5.2% 1 5.2% 1 1.6% 2. 3.6% 4.	4 [1.98, 3.79] 0 [2.18, 3.34] 	1 0.2 0. Grade	5 1 e I or II G Hazard F IV. Fixed.	2 5 rrade III or IV Ratio 95% Cl
Total (95' Heteroger Test for o Bedke 200 Bertini 200 Capitanio da Costa : Oh 2018 Shah 2019	% CI) neity: Chi ² = 6.85, verall effect: Z = 5 <u>Subgroup log</u> 09 09 2018 2012 9	df = 7 (P = 0.44); 9.14 (P < 0.00001) [Hazard Ratio] 0.5247 0.; 0.4953 0.4 0.1823 0.4 1.0328 0.3 1.4446 0 0.7178 0	Necrosis SE Totr 3447 6 3344 8 1467 10 3684 2 6684 20 6644 10 .146 26	No necro No necro	sis <u>otal We</u> 46 12 25 5 201 7 18 1 108 3 301 69	% 2.7 % 2.7 Fight IN 2.5% 1 5.2% 1 5.2% 1 1.6% 2. 3.6% 4. 9.7% 2	4 [1.98, 3.79] 0 [2.18, 3.34] 	1 0.2 0. Gradi	5 1 elor II G Hazard F IV. Fixed.	2 5 Frade III or IV 95% CI
Total (95' Heteroger Test for o Bedke 200 Bertini 200 Capitanio da Costa : Oh 2018 Shah 2019	% CI) neity: Chi ² = 6.85, vverall effect: Z = 5 <u>Subgroup log</u> 09 09 09 2018 2018 2012 9 % CD	df = 7 (P = 0.44); 9.14 (P < 0.00001) (Hazard Ratio) 0.5247 0.: 0.4953 0.4 0.1623 0.4 1.0328 0.5 1.4446 0 0.7178 0	Necrosis SE Tot: 3447 6 5344 8 1467 10 9684 2 6644 10 .146 26	No recro No recro	sis <u>total We</u> 46 12 25 5 201 7 18 1 108 3 301 69 699 100	% 2.7 % 2.7 kight IN 2.5% 1 5.2% 1 5.2% 1 1.6% 2. 3.6% 4. 9.7% 2 0.0% 1	4 [1.98, 3.79] 0 [2.18, 3.34] 0 1 [2.18, 3.34] 0 1 [2.18, 3.34] 0 1 [2.18, 3.34] 0 1 [2.18, 3.34] 1 [2.18, 3.34] 1 [2.18, 4.86] 1 [0.42, 18, 74] 24 [1.20, 14.98] 1 [0.42, 18, 2.49] 1 [1.96, 3.79] 1 [2.18, 3	1 0.2 0. Gradi	5 1 e l or II G Hazard I IV. Fixed.	2 5 rrade III or IV Ratio 95% Cl
Total (95' Heteroger Test for o E Study or : Bedke 200 Bertini 200 Capitanio da Costa : Oh 2018 Shah 2019 Total (95' Heteroger	% CI) neity: Chi ² = 6.85, vverall effect: Z = 5 <u>Subgroup log</u> 09 09 2018 2012 9 % CI) neity: Chi ² = 3.17.4	df = 7 (P = 0.44); 9.14 (P < 0.00001) (Hazard Ratio) 0.5247 0: 0.4953 0: 0.4953 0: 0.1823 0: 1.4246 0 0.7178 0 df = 5 (P = 0.67); P	Necrosis SE Totr 3447 6 43447 10 4684 2 .644 10 .146 26 64 = 0%	No recro No rec	sis 5 100.0 5 100.0 5 100.0 611 5 5 5 201 7 18 1 108 3 301 69 699 100	% 2.7 % 2.7 hight N 2.5% 1 5.2% 1 5.2% 1 1.6% 2. 3.6% 4. 9.7% 2 0.0% 1	4 [1.98, 3.79] 0 [2.18, 3.34] 0 1 [2.18, 3.34] 1 [2.18, 3.34]	1 0.2 0. Grad	5 1 e l or II G Hazard I IV. Fixed.	2 5 5 State III or IV Ratio 95% CI
Total (95' Heteroger Test for o Bedke 200 Bertini 200 Capitanio da Costa : Oh 2018 Shah 2011 Total (95' Heteroger Test for o	% CI) neity: Chi ² = 6.85, vverall effect: Z = 5 <u>Subgroup log</u> 09 09 2018 2012 9 % CI) neity: Chi ² = 3.17, (vverall effect: Z = 5.	df = 7 (P = 0.44); 9.14 (P < 0.00001) (Hazard Ratio) 0.5247 0: 0.4953 0: 0.4953 0: 0.4953 0: 1.428 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001)	P = 0% Necrosis <u>SE Totr</u> 3447 6 3344 8 3344 8 4467 10 0684 2 .644 10 .146 26 64 = 0%	No recro No recro No recro No recro T 0 0 8 8 3 1 0	sis <u>total We</u> 46 12 25 5 201 7 18 1 108 3 301 69 699 100	% 2.7 % 2.7 + +ight IV 2.5% 1 5.2% 1 5.2% 1 1.6% 2. 3.6% 4. 9.7% 2 0.0% 1	4 [1.98, 3.79] 0 [2.18, 3.34]	1 0.2 0. Grad	5 1 Hazard F W. Fixed.	Action State
Total (95' Heterogen Test for o Study or: Bedke 200 Bertini 200 Capitanio da Costa : Oh 2018 Shah 2011 Total (95' Heterogen Test for o	% CI) neity: Ch ² = 6.85, vverall effect: Z = 5 <u>Subgroup</u> log 09 09 2018 2012 9 % CI) neity: Ch ² = 3.17, vverall effect: Z = 5.	df = 7 (P = 0.44); .14 (P < 0.00001) [Hazard Ratio] 0.5247 0: 0.4953 0: 1.0328 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); I ² 52 (P < 0.00001)	Necrosis SE Toti 1447 6 3344 8 1467 10 1664 2 644 10 146 26 64 20 64 50 64 50 64 64 = 0% 64	No necro No nec	sis <u>total We</u> 46 12 25 5 201 7 18 1 108 3 301 69 699 100	% 2.7 % 2.7 Height N 2.5% 1 7.4% 1 1.6% 2. 3.6% 4. 9.7% 2 0.0% 1	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0. Gradi	5 1 Hazard F W. Fixed.	2 5 rade III or IV Ratio 95% CI 95% CI
Total (95' Heteroge Test for o <u>Study or</u> Bedke 200 Bertini 200 Capitanio da Costa : Oh 2018 Shah 201! Total (95' Heteroger Test for or	% CI) neity: Chi ² = 6.85, vverall effect: Z = 6 <u>Subgroup</u> log 09 09 2018 2012 9 % CI) neity: Chi ² = 3.17, verall effect: Z = 5.	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio) 0.5247 0: 0.4953 0: 0.4953 0: 0.4953 0: 0.4923 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); I ² 52 (P < 0.00001)	P = 0% Necrosis SE Tots 1447 6 1447 6 1447 6 1447 10 1668 2 644 10 146 26 644 = 0% > 7 cr	1737 106 1737 106 No recro 1 0 0 8 8 3 1 0 1 2 7 cm	sis <u>fotal We</u> 46 12 25 5 201 7 18 1 108 3 301 69 699 100	% 2.7 % 2.7 Height N 2.5% 1 7.4% 1 1.6% 2. 3.6% 4. 9.7% 2 0.0% 1 Haz	4 (1.98, 3.79) 0 (2.18, 3.34) azard Ratio <i>L</i> .Fixed, 95% C1 64 (0.58, 4.68) 10 (0.2, 0.2, 88) 10 (0.42, 18.74) 24 (1.20, 14.98) 	1 0.2 0. Gradi	5 1 Belor II G Hazard F IV. Fixed.	2 5 rrade III or IV Ratio 95% CI 95% CI 2 5 Vecrosis atio
Total (95' Heteroge Test for o E <u>Study or:</u> Bedke 200 Bertini 200 Capitanio da Costa 3 Oh 2018 Shah 2011 Total (95' Heteroger Test for o	% C1) neity: Chi ² = 6.85, verall effect: Z = 6 <u>Subgroup</u> log 09 09 2018 2012 9 % C1) neity: Chi ² = 3.17, verall effect: Z = 5. <u>Subgroup</u> lo	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.4953 0: 0.4953 0: 0.4823 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) bg[Hazard Ratio]	P = 0% <u>SE</u> Totr <u>3447</u> 66 <u>3444</u> 8 <u>1467</u> 10 <u>1467</u> 10 <u>1464</u> 26 <u>644</u> = 0% <u>> 7 cr</u> <u>SE</u> Tot	1723 30 1737 106 No recro 1 0 0 8 8 3 1 0 1 0 1 0 1 0 1 1 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1	sis <u>otal We</u> 46 12 25 5 201 7 18 1 108 3 301 69 699 100 <u>I Weigh</u>	% 2.7 % 2.7 % 2.7 % 2.7 % 2.5% 1 5.2% 1	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0. Gradi 0.1 0.2 (No m	5 1 Hazard F IV. Fixed. 	2 5 rade III or IV Ratio 95% CI
Total (95' Heteroger Test for o Study or: Bedke 200 Bertin 200 Capitanio da Costa : Oh 2018 Shah 2011 Total (95' Heteroger Test for or Bedke 20	% CI) neity: Chi² = 6.85, neity: Chi² = 6.85, yverall effect: Z = 5 Subgroup log 09 2018 2012 9 % CI) neity: Chi² = 3.17, verall effect: Z = 5. 5 Subgroup log Subgroup log	df = 7 (P = 0.44); .14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.4953 0.1 0.1823 0. 1.0328 0.1 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.0001) 20 (Hazard Ratio] 0.0953 0.5257	P = 0% Necrosis <u>SE</u> Tot <u>3447</u> 6 <u>3447</u> 6 <u>3444</u> 8 <u>1467</u> 10 <u>16644</u> 2 <u>644</u> = 0% > 7 cm <u>SE</u> Tot <u>0.3178</u> 4 0.138	1123 30 1737 106 No necro 1 T 0 0 8 8 8 3 1 0 1 0 1 5 7 7 7 7 7	sis <u>otal We</u> 46 12 25 5 201 7 18 1 108 3 301 69 699 100 <u>I Weigh</u> 7 9.6% 5269	% 2.7 % 2.7 kight N 2.5% 1 5.2% 1 1.6% 2. 3.8% 4. 9.7% 2 0.0% 1 Haz t IV. F % 1.11 % 4.	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0. Gradi	5 1 Hazard F IV. Fixed.).5 1 ecrosis N Hazard R /, Fixed. 9	
Total (95' Heteroger Test for o E Study or: Bedke 20 Berlini 20 Capitanio da Costa : Oh 2018 Shah 2011 Total (95' Heteroger Test for o E Study or: Bedke 20 Brookma Chen 20'	% CI) neity: Chi ² = 6.85, vverall effect: Z = 6 <u>Subgroup</u> logi 09 09 2018 2012 9 % CI) neity: Chi ² = 3.17, vverall effect: Z = 5. <u>r Subgroup</u> log 09 17	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio) 0.5247 0: 0.4953 0: 0.4953 0: 0.4953 0: 0.4953 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 29([Hazard Ratio] 0.5953 0.5965 0.9187	P = 0% Necrosis SE Tot: 447 6 5344 8 4467 10 644 10 644 2 644 = 0% 544 10 64 = 0% > 7 cr SE Tot 0.3178 4 0.3891	1737 106 No necro 1737 106 No necro 1 0 0 8 8 8 3 1 0 1 1 0 1 5 7 6 5 7 7 6 5 7 7 6 5 7 7 6 5 7 6 5 7 6 5 7 6 5 7 6 5 7 6 5 7 6 6 7 6 7 6 7 6 7 6 7 6 7 6 7 6 7 6 7 7 6 7 7 7 6 7 7 7 7 7 7 7 7 7 7 7 7 7	sis <u>otal We</u> <u>46</u> 12 25 5 201 7 18 1 108 3 301 69 699 100 <u>1 Weight</u> 7 9.6% 0 52.6% 0 64.00	% 2.7 iight N 2.5% 1 5.2% 1 1.6% 2. 3.8% 4. 3.7% 2 3.0% 1 Haz 1.11 % 1.11 % 1.7 % 2.57	4 (1.98, 3.79) 0 (2.18, 3.34) 0 (2.18, 3.34) 6 (2.18, 3.34) 6 (0.66, 3.32) 6 4 (0.58, 4.68) 10 (0.58, 4.68) 10 (0.42, 18.74) 10 (1.54, 2.73) 96 (1.54, 2.73) 96 (1.54, 2.43) 6 (1.54, 2.43) 9 (0.59, 2.05) 1 (1.31, 2.23) 1 (1.17, 2.37)	1 0.2 0. Gradi	5 1 Hazard I IV. Fixed. J.5 1 ecrosis N Hazard R Y. Fixed. 9	2 5 rade III or IV Ratio 95% Cq 95% Cq 2 5 Necrosis atio
Total (95' Heteroge Test for o Study or : Bedke 200 Berlini 200 Capitanio da Costa : Oh 2018 Shah 2011 Total (95' Heteroger Test for o Bedke 20 Brookma Chen 201 da Costa :	 % CI) neity: Chi² = 6.85, yverall effect: Z = 5 <u>Subgroup</u> log 09 2018 2012 9 % CI) neity: Chi² = 3.17, verall effect: Z = 5. rsubgroup log D09 n-May 2015 17 12012 	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio) 0.5247 0: 0.4953 0: 0.4953 0: 0.4953 0: 0.4466 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) df = 5 (P = 0.67); P 52 (P < 0.00001) 0.9953 0.5365 0.9187 0.2852	P = 0% Necrosis SE Toto 1447 10 1467 10 1467 10 1468 25 644 2 644 2 644 = 0% > 7 cr SE Tot 0.3178 4 0.3378 5 0.136 44 0.3391 5 0.3891 5 0.3991 5 0.3	1737 106 No recro 1 T 37 106 No recro 1 T 0 0 8 8 3 1 0 1 5 7 7 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	sis <u>otal We</u> <u>46</u> 12 25 5 201 7 18 1 108 3 301 69 699 100 <u>1 Weight</u> 7 9.6%) 52.6%) 6.4%) 1.5%	% 2.7 % 2.7 % 2.7 % 2.7 % 2.7 % 2.7 % 1 % 1 % 2.7 % 1 % 1.6% % 2.3 % 1.41 % 1.77 % 2.55 % 1.41 % 1.77 % 2.55	4 (1.98, 3.79) 0 (2.18, 3.34) azard Ratio (, Fixed, 95% CI 69 (0.86, 3.32) 64 (0.58, 4.68) 210 (5.0, 2.68) 210 (5.0, 2.68) 20 (5.1, 2.48) 20 (5.1, 2.48) 20 (5.1, 2.48) 20 (1.54, 2.73) 96 (1.54, 2.73) 96 (1.54, 2.49) 20 (1.54, 2.54) 20 (1.54, 2.54	1 0.2 0. Gradi	5 1 Hazard F IV. Fixed.	2 5 rade III or IV Ratio 95% CI
Total (95' Heterogen Test for o E Study or . Bedke 200 Bertini 200 Capitanio da Costa i Oh 2018 Shah 2011 Total (95' Heterogen Test for or Bedke 20 Brookma Chen 201 da Costa i Guo 2015	% CI) neity: Chi² = 6.85, neity: Chi² = 6.85, Subgroup log Subgroup log 2012 9 % CI) neity: Chi² = 3.17, Ywerall effect: Z = 5. Subgroup log Subgroup Ico 100 n-May 2015 17 12012 9 9 12012	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Jazard Ratio] 0.5247 0; 1.0328 0; 1.0328 0; 1.4446 0 0.7178 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.0001) 20[Hazard Ratio] 0.0853 0.5385 0.9187 0.2852 0.7324	P = 0% Necrosis SE Toto 1447 6 1344 8 1467 10 1466 26 644 2 644 10 1466 26 64 = 0% > 7 cm SE Tot 0.3178 4 0.3891 3 0.795 5 0.795 9 0.806 9	1123 36 1737 106 10 1 0 8 8 3 1 0	sis otal We 46 12 25 5 201 7 18 1 108 3 301 69 699 100 I Weight 7 9.6% 0 52.6% 0 52.6% 0 6.4% 0 1.5% 4 29.8%	% 2.7 % 2.7 % 2.7 % 2.7 % 2.7 % 2.5% % 1.11 % 1.11 % 1.27 % 1.27 % 2.0% % 1.33 % 2.00%	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0. Gradi	5 1 Hazard F W. Fixed. 9	
Total (95' Heteroger Test for o E Study or: Bedke 200 Bertini 200 Capitanio da Costa : Oh 2018 Shah 2011 Total (95' Heteroger Test for o F Study or costa Brookma Chen 201 da Costa Brookma Chen 201 da Costa Guo 2015	% CI) metry: Chi ² = 6.85, wverall effect: Z = 6 <u>Subgroup</u> log 09 09 2018 2012 9 % CI) metry: Chi ² = 3.17, vverall effect: Z = 5. <u>r Subgroup</u> loc 009 m-May 2015 17 2012 9 % CI)	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 1.0328 0: 1.0328 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 0.0953 0.5365 0.9187 0.2852 0.7324	P = 0% Necrosis <u>SE</u> Toti <u>344</u> 7 6 344 8 1467 10 064 2 64 = 0% > 7 cm <u>SE</u> Tot 0.3178 4 0.136 4 0.3391 3 0.795 9 0.1806 9 151	1737 106 No recro 1 T T 106 No recro 1 T T 0 0 8 8 3 1 0 1 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	sis otal Wei 46 12 25 5 201 7 18 1 108 3 301 69 699 100 1 Weight 7 9.69 0 52.69 0 6.49 0 1.59 4 29.89 100 09	% 2.7 ** 2.7 ** 1 ** 1 ** 1 ** 1.1	4 (1.98, 3.79) 0 (2.18, 3.34) 0 (2.18, 3.34) 6 (2.18, 3.34) 6 (0.86, 3.32) 6.69 (0.86, 3.32) 6.40 (0.88, 4.68) 120 (0.50, 2.68) 81 (0.42, 18.74) 120 (1.54, 2.73) 9.65 (1.54, 2.73) 9.65 (1.54, 2.43) (1.54, 2.43) 10 (0.59, 2.05) [1.31, 2.23] [1.31, 2.23] 10.59, 2.05] [1.31, 2.23] 11.46, 2.96] 11.46, 2.96]	1 0.2 0 Gradi	5 1 Hazard I W. Fixed, 9 	2 5 rade III or IV Ratio 95% Cq 95% Cq 2 5 Necrosis atio 15% Cl
Total (95' Heterogen Test for o E Study or: Bedke 200 Bertini 200 Capitanio da Costa: Oh 2018 Shah 2011 Total (95' Heteroger Test for o F Study or Bedke 22 Brookma Guo 2011 Total (95 Heteroger	% CI) metry: Ch ² = 6.85, vverall effect: Z = 6 <u>Subgroup</u> log 09 09 2018 2012 9 % CI) netry: Ch ² = 3.17, vverall effect: Z = 5. <u>Subgroup</u> log 09 n-May 2015 17 12 2012 9 5% CI) netry: Ch ² = 4.03	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.04953 0: 0.04953 0: 0.04953 0: 0.04953 0: 0.04953 0: 0.04953 0: 0.04953 0: 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) cg[Hazard Ratio] 0.0953 0.5385 0.9187 0.2852 0.7324 df = 4 (P = 0.40);	P = 0% Necrosis SE Toti 447 6 334 8 1467 10 1664 2 644 10 146 26 644 10 146 26 644 = 0% > 7 cr SE Toti 0.3178 4 0.3378 1 0.3378 1 0.3378 1 5 7 cr 16 3 16 4 0.3378 1 17 5 17 5 18 7 19 7	1737 106 1737 106 No necro 1 1 1 1 1 1 1 1 1 1 1 1 1	sis total We 46 12 25 5 201 7 18 1 108 3 301 69 699 100 108 3 301 69 699 100 108 3 301 69 108 3 301 69 108 3 108 3 109 3 10	% 2.7 * 2.7 * 1.7 * 2.7 * 1.1 * 1.6% * 1.1 * 1.7 * 2.5 % 1.3 % 2.0 % 1.77	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0 Gradi	5 1 e I or II G Hazard F IV. Fixed. 	tecrosis
Total (95' Heterogen Test for o Estudy or: Bedke 200 Bedke 200 Bedke 200 Capitanio da Costa : Shah 201' Total (95' Heterogen Test for o Brookma Chen 201' da Costa : Brookma Chen 201' Total (95' Heterogen Total (95' Heterogen Total (95' Heterogen Total (95' Heterogen Total (95' Heterogen Total (95' Heterogen Total (95' Heterogen Total (95' Heterogen Total (95')	% CI) neity: Chi² = 6.85, vvvrall effect: Z = 5 Stubgroup logi 90 2018 2018 2017 9 % CI) neity: Chi² = 3.17, vverall effect: Z = 5. Stubgroup 100 009 00 009 00 009 00 009 10 9 \$2012 9 \$2012 9 \$2012 9 \$2012 9 \$2012 9 \$2015 17 12012 9 \$5% CI) 9 \$5% CI) 9 \$5% CI)	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0.: 0.4853 0.: 0.4853 0.: 0.4823 0.: 1.4346 0. 0.7178 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.0001) 20[Hazard Ratio] 0.0953 0.5365 0.5365 0.5365 0.7324 df = 4 (P = 0.40); 5.81 (P < 0.00001)	P = 0% Necrosis <u>SE</u> Tot 1447 6 1344 8 1467 10 1664 2 64 = 0% > 7 cr <u>SE</u> Tot 0.3178 4 0.3891 5 0.136 44 0.3891 5 0.136 9 [P = 1%	No necro No necro 1737 106 0 0 8 8 31 0 11 0 11 0 11 0 12 13 14 15 16 16 16 16 16 16 15 90 11 11 12 13 14 14	sis <u>otal</u> We <u>otal</u> We <u>46</u> 12 <u>25</u> 5 201 7 18 1 108 3 301 69 100 699 100 <u>1 Weight</u> 9.699 100 <u>699 100</u> 1.55 5.64 1.55	% 2.7 + + + + + + + + + + + + +	4 (1.98, 3.79) 0 (2.18, 3.34) azard Ratio 1. Fixed, 95% CI .69 (0.86, 3.32) .64 (0.58, 4.68) .20 (5.50, 2.68) .20 (5.50, 2.68) .20 (5.1, 2.4, 8.74) .20 (5.50, 2.68) .20 (5.1, 2.4, 8.74) .20 (5.1, 2.4, 8.74) .20 (5.1, 2.4, 8.74) .20 (5.1, 2.4, 9.74) .20 (5.1, 2.4, 9.74)	1 0.2 0. Gradi	5 1 Hazard H H. Fixed. 	
Total (95' Heterogen Test for o Study or: Bedke 200 Bertini 200 Capitanio da Costa Shah 2011 Total (95' Heterogen Test for on Bedke 20 Brokima Capitanio da Costa Guo 2011 Total (95' Heterogen Test for on Chen 200 da Costa Guo 2011 Total (95' Heterogen Test for on Chen 200 da Costa Guo 2011 Total (95'	% CI) neity: Chi² = 6.85, vvvrall effect: Z = 9 Subgroup logi 09 2018 2012 9 % CI) neity: Chi² = 3.17, vverall effect: Z = 5. Subgroup Ice Subgroup Ice	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.4953 0. 0.4953 0. 0.4953 0. 1.0328 0. 1.4346 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 0.5953 0.5965 0.9187 0.2852 0.7324 , df = 4 (P = 0.40); 5.81 (P < 0.00001)	P = 0% Necrosis <u>SE</u> Toti <u>5447</u> 6 344 8 4467 10 0664 2 64 = 0% > 7 cr <u>SE</u> Tot 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.139 1 157 P = 1%	No recro 1737 106 No recro 1737 106 No recro 1 0 0 8 8 8 3 1 0 1 1 0 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	sis <u>otal We</u> <u>otal We</u> <u>46</u> 12 <u>25</u> 5 201 7 18 1 108 3 301 69 699 100 <u>108</u> 3 301 69 699 100 <u>108</u> 3 301 69 699 100 <u>108</u> 4 <u>108</u> 4 <u>100</u> 4 <u>109</u> 4 <u>100</u> 4	% 2.7 F - sight N 2.7 1.1 - 2.5% 1 1.2% 1 1.6% 2.1 1.6% 2.6% 1.6% 2.0 2.0 % 2.0 % 1.77	4 (1.98, 3.79) 0 (2.18, 3.34) azard Ratio (-, Fixed, 95% CI 20 (0.50, 2.88) 31 (0.48, 4.68) 31 (0.48, 4.68) 31 (0.42, 10.74) 30 (1.54, 2.73) 36 (1.54, 2.73) 36 (1.54, 2.73) 36 (1.54, 2.73) 30 (2.58, 2.05) [1.31, 2.23] [1.37, 5.37] 3 (0.28, 6.32) 3 (1.46, 2.96) [1.46, 2.96] (1.46, 2.96]	1 0.2 0 Gradi	5 1 Hazard I Horli G Hazard I Hazard R Hazard R Hazard R Hazard R 	
Total (95' Heterogen Test for o Study or: Bedike 200 Bertini 200 Capitanio da Costa Shah 2011 Total (95' Heteroger Test for o Bedke 22 Brookma Chen 20' da Costa Guarda Study or 1 Study or 1	% C1) metry: Chi ² = 6.85, wverall effect: Z = 6 Subgroup logi 09 09 2018 2012 9 % C1) metry: Chi ² = 3.17, vverall effect: Z = 5. CSubgroup logi 17 12012 9 5% C1) metry: Chi ² = 4.03 sverall effect: Z = 1 Subgroup logit	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio) 0.5247 0: 0.4953 0: 0.4953 0: 0.4953 0: 0.4953 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 25(Hazard Ratio) 0.9853 0.9187 0.2852 0.7324 , df = 4 (P = 0.40); 5.81 (P < 0.00001) 10222	P ² = 0% Necrosis <u>SE</u> Toti <u>544</u> 1447 6 1544 7 10 146 26 146 26 147 26 147 26 147 26 147 26 147 26 147 26 157 26 15	No recro No re	sis sis vial We 46 12 25 5 201 7 18 1 108 3 301 69 699 100 1 Weight 699 100 1 Sp 52.69 1 00.09 1 100.09 H Waight 1 00.09 H Waigh	% 2.7 F F F C S S S S S S S S S S S S S	4 (1.98, 3.79) 0 (2.18, 3.34) . (.18, 2.18) . (.	1 0.2 0. Gradi	5 1 b lorll G Hazard I V. Fixed. 4. Fixed. 93 5. 1 7. m > 5. 1 7. m > 5. 1 7. m > 5. 1	2 5 rrade III or IV Ratio 95% Cq 2 5 Necrosis atio 15% Cl 5
Total (95' Heterogen Test for o Estudy or: Bedke 20' Capitanio da Costa : Shah 20' Total (95' Heterogen Test for o Estudy or: Bedke 20 Brookma Chen 20' da Costa : Brookma Chen 20' da Costa : Brookma Costa : Bro	% CI) neity: Chi² = 6.85, viverall effect: Z = 5 Subgroup logi 09 0218 2018 2018 2018 2017 9 % CI) relive: Chi² = 3.17, verall effect: Z = 5. rsubgroup log 009 neity: Chi² = 3.17, verall effect: Z = 5. rsubgroup log 9 % CI) rsubgroup log 90 % CI) 90 % CI) 90 % CI) 90 % CI) 91 % CI) 92 % CI) 93% CI) e4.03 90 % CI) 90 % CI) 90 % CI) 90 % CI) 913 % CI)	df = 7 (P = 0.44); 0.14 (P < 0.00001) (b.5247 0.: 0.4553 0.: 0.4853 0.: 0.4823 0.: 1.4446 0. 0.7178 0 0.7178 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.0001) 2g[Hazard Ratio] 0.9852 0.7324 0.7324 0.4852 0.7324 0.7	P = 0% Necrosis <u>SE</u> Toti <u>5447</u> 6 <u>5447</u> 6 <u>5444</u> 8 <u>1467</u> 10 <u>6684</u> 2 <u>648</u> = 0% > 7 cr <u>SE</u> Toti <u>0.3178</u> 6 <u>0.3178</u> 6 <u>0.3178</u> 6 <u>0.3178</u> 6 <u>0.3178</u> 6 <u>0.3178</u> 6 <u>0.3178</u> 6 <u>0.3178</u> 7 <u>0.3178</u> 7 <u>0.3186</u> 7 <u>0.3178</u> 7 <u>0.3178</u> 7 <u>0.3186</u> 7 <u>0.3178</u> 7 <u>0.3178</u> 7 <u>0.3178</u> 7 <u>0.3186</u> 7 <u>0.3178</u> 7 <u>0.3178</u> 7 <u>0.3186</u> 7 <u>0.3178</u> 7 <u>0.3178</u> 7 <u>0.3186</u> 7 <u>0.3178</u> 7 <u>0.3186</u> 7 <u></u>	I1737 106 No rescrond I II III	sis <u>ctal We</u> <u>ctal Stal We</u> <u>ctal Stal We</u> <u>ctal Stal Stal Stal Stal Stal Stal Stal S</u>	% 2.7 + F + C + C + C + C + C + C + C + C	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0 Grad 0.1 0.2 (No m 1 0.2 0 1 0.2 0 Htt IV.1	5 1 Hazard I Hitter (1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	2 5 rade III or IV Ratio 95% CI 2 5 Vecrosis atio 15% CI 15% CI
Total (95' Heterogen Test for o E Study or: Bedke 200 Bertini 200 Capitanio da Costa Shah 2011 Total (95' Heterogen Test for on Bedke 20 Brokima Capitanio da Costa Garcata Chen 201 Brokima Chen 201 Backe 20 Brokima Capitanio da Costa Gastado Chen 201 Capitanio Chen 201 Backe 20 Brokima Capitanio Chen 201 Backe 20 Brokima Chen 201 Backe 20 Brokima Chen 201 Backe 20 Backe 20 Brokima Chen 201 Backe 20 Backe	% CI) neity: Chi² = 6.85, vverall effect: Z = 9 Subgroup logi 09 2018 2012 9 % CI) neity: Chi² = 3.17, vverall effect: Z = 5. rsubgroup log 009 100 % CI) neity: Chi² = 3.17, verall effect: Z = 5. rsubgroup log 9 % CI) 9 17 12012 9 9 S% CI) 9 9 5% CI) neiby: Chi² = 4.03 0verall effect: Z = 1 13 Subgroup log[H: 113 2018 2018	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.4953 0: 0.4953 0: 0.4953 0: 0.4953 0: 1.4446 0 0.7178 0 0.7178 0 0.7178 0 0.7178 0 0.7178 0 0.9187 0.2953 0.7324 df = 4 (P = 0.40); 5.81 (P < 0.0001) 1.553 0.76 0.9187 0.2852 0.7324 df = 4 (P = 0.40); 5.81 (P < 0.0001) 1.553 0.576 0.9183 0.5853 0.75 0.583 0.576 0.9833 0.576 0.9853 0.576 0.9833 0.576 0.9855 0.9833 0.576 0.9855 0.9855 0.9855 0.9853 0.576 0.9855 0.98	P² = 0% Necrosis SE Totu V447 6 344 8 4467 10 064 2 64 64 = 0% 57 cr SE Total 0.136 40 0.3891 157 0.795 90 157 157 Positive Ne E Total 3 3 3 3 3 6 157	11737 106 No rectro 1 1 1 0 0 8 8 3 1 1 1 1 1 1 1 1 1 5 904 1 1811 19 118 119 119	sis ctal We ctal We ctal We ctal We 225 5 201 7 18 1 108 3 301 69 699 100 1 Weight 699 100 1 Sp 4 29.89 1 100.09 H 100.09 1 4 29.89 1 30.15 1 4 29.89 1 4 29.89 1 4 29.89 1 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5	% 2.7 ight N ight N 1.6% 2.7 ight N 1.77 ight N 1.6% 2.7 ight N 1.77 ight N 1.77 i	4 (1.98, 3.79) 0 (2.18, 3.34) 0 (2.18, 3.34) 6 (2.18, 3.34) 6 (0.86, 3.32) 6 (0.86, 3.32) 6 (0.86, 3.32) 6 (0.86, 3.32) 6 (0.86, 4.38) 10.02, 10.39, 2.88) 8 (0.42, 18.74) 9 (1.54, 2.73) 9 (1.54, 2.75) 1 (1.37, 13, 2.23) 1 (1.46, 2.96) 1 (1.46, 2.96) 1 (1.42, 2.96) 1 (1.42, 2.96) 1 (1.42, 2.96) 1 (1.42, 2.96) 1 (1.43, 2.96) 1 (1.44, 2.96) 1 (1.45, 2.96) 1 (1	1 0.2 0 Gradi 0.1 0.2 0 No m No m No m No m No m No m No m No m	5 1 bloril G Hazard I Hazard I Hazard R Fixed, 9 5 1 7 cm - 5 1 2 cm - 5 cm -	
Total (95' Heterogen Test for o Estudy or: Berlini 200 Capitanio da Costa: Oh 2018 Shah 2011 Total (95' Heterogen Test for o Bedke 22 Brookma Chen 20' da Costa: Guadata Total (95' Heterogen Test for o Gstudy or 1 Baccos 20 Capitanio Oh 2018 Total (95' Heterogen Test for o	% CI) metty: Chi ² = 6.85, vverall effect: Z = 6 Subgroup log 09 09 2018 2012 9 % CI) metty: Chi ² = 3.17, vverall effect: Z = 5. Cubgroup log 09 m-May 2015 17 2012 9 3% CI) metty: Chi ² = 4.03 vverall effect: Z = 1. Subgroup log[P 13 2018 7	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio) 0.5247 0: 1.0328 0: 1.0328 0: 1.0328 0: 1.0328 0: 1.0328 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 0.5365 0.9187 0.2852 0.7324 , df = 4 (P = 0.40); 5.81 (P < 0.00001) 1.5593 0.76 0.9333 0.974 2.9868 0.643 3.7213 0.025 2.713 0.025 3.7213 0.025 3.7215 3.72	P = 0% Necrosis <u>SE</u> Toti <u>344</u> 7 6 <u>344</u> 8 <u>4467</u> 10 <u>1664</u> 2 <u>644</u> 10 <u>146</u> 26 <u>64</u> = 0% > 7 cm <u>SE</u> Tot 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 157 Positive Nt <u>E</u> Total <u>3 3</u> 3 6 4 4 2 2	I1737 106 No rescription In I I 0 I 0 I 0 I 0 I 0 I 0 I 0 I 0 I 0 I 0 I 0 I 1119 I 1120 I 1130 I 1140 I 1150 I	isis isis otal Wee otal Wee otal Wee otal Wee isis isis isis 29.83 isis 29.83 isis 100.07 isis 100.07 isis 100.07 isis 29.83 isis 29.83 isis 29.83	% 2.7 H H H H H H H H H H H H H	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0. Gradi	5 1 Hazard R J.5 1 N Hazard R Hazard R Hazard R S 1 S 1 S 1 S 1 S 1 S 2 S 1 S 1 S 1 S 1 S 1 S 1 S 1 S 1 S 1 S 1	2 5 rade III or IV Ratio 95% CQ
Total (95' Heterogen Test for o Estudy or: Bedke 200 Capitanio da Costa : Shah 201' Total (95' Heterogen Test for o F Study or: Bedke 20 Brookma Chen 20' da Costa : Brookma Chen 20' da Costa : Costa : C	% CI) neity: Chi² = 6.85, neity: Chi² = 6.85, Subgroup logi 9 2018 2018 2018 2017 9 % CI) neity: Chi² = 3.17, verall effect: Z = 5. rsubgroup logi 2012 9 % CI) neity: Chi² = 3.17, rsubgroup logi 2019 90 100 rsubgroup logi 2012 9 12012 9 2015 7 9 Subgroup logity: 103 2018 7 9 9	df = 7 (P = 0.44); 0.14 (P < 0.00001) (b.5247 0.: 0.4553 0.: 0.4853 0.: 0.4853 0.: 0.4823 0.: 1.4446 0. 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 2g[Hazard Ratio] 0.9853 0.5365 0.9187 0.2852 0.7324 df = 4 (P = 0.40); 5.81 (P < 0.00001) 4azard Ratio] 1.5953 0.766 0.9933 0.742 0.7324 3.7213 0.922 2.1883 0.674	P = 0% Necrosis <u>SE</u> Toti 1447 6 1344 8 1467 10 1664 2 644 = 0% > 7 cr <u>SE</u> Toti 146 26 64 = 0% > 7 cr <u>SE</u> Toti 0.136 4 0.3891 5 0.136 9 Positive Nr <u>E</u> Total 3 3 3 6 4 4 4 2 2 1 9	11737 106 No rescro 10 1 1 0 1 0 6 6 6 7 7 0 1 1 1 0 2 8 3 1 1 0 2 7 7 60 5 90/ 1 1811 19 900 11 119 11 303 11 304 119 305 207 123 119	sis ctal We ctal We	% 2.7 H 2.5% 1 2.5%	4 (1.98, 3.79) 0 (2.18, 3.34) azard Ratio (. Fixed, 95% CI (. 69 (0.86, 3.32) .64 (0.58, 4.68) 20 (0.50, 2.68) 20 (0.50, 2.68) 20 (0.50, 2.68) 20 (1.54, 2.73) .05 (1.54, 2.74) .05 (1 0.2 0 Grad 0.1 0.2 (No m 1 0.2 0 1 0.2 0 Ht WJ	5 1 3 1 0 1 1 G Hazard R 1, <u>Fixed</u> , <u>1</u> Hazard R <u>4</u> <u>5</u> 1	2 5 rade III or IV Ratio 95% Cq 2 5 kecrosis atio 15% Cl 2 5
Total (95' Heterogen Test for o E Study or: Bedrini 200 Capitanio da Costa Shah 201' Total (95' Heterogen Test for or F Study or f Bedke 20 Brookma Chen 20' da Costa Guo 2011 Total (95 Heterogen Test for o Chen 20' da Costa Guo 2011 Total (95 Heterogen Test for o Capitanio da Costa Study or f Bedco 20 Capitanio da Costa Study or f Baccos 20 Capitanio no 2018	% CI) neity: Chi² = 6.85, vverall effect: Z = 5 Subgroup log 09 2018 2012 9 % CI) neity: Chi² = 3.17, vverall effect: Z = 5. Subgroup log Newrall effect: Z = 5. 1009 Subgroup log 9 % CI) neity: Chi² = 3.17, vverall effect: Z = 5. Subgroup log 9 % CI) 12012 9 5% CI) neity: Chi² = 4.03 soverall effect: Z = 1. 13 2018 2018 7 9 2015 2015	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Jazard Ratio] 0.5247 0: 0.4653 0.0 0.10328 0.0 1.0328 0.0 1.0328 0.0 1.4446 0 0.7178 0 0.7178 0 0.6536 0.0 0.0475 0.0001) 20[Hazard Ratio] 0.7324	Necrosis SE Toti 5447 6 5447 6 5448 10 146 26 64 64 = 0% 57 cr 0.136 40 0.376 7 cr 0.136 40 0.3891 157 10.1806 9 0.1806 157 Positive Nr. Nr. 2 20 3 6 4 2 2 2 1 9 5 4	No recro No recro No recro No recro No Total Total G Total G Total G Total G Total G Total G Total Corr Total Corr Corr S G Total Corr S G Total S G S G S G S S S S S S S S S S S S S S S <td< td=""><td>Image: square Squar S</td><td>% 2.7 % 2.7 F F 1011 D 122% 1 12.8% 4 1.22% 1 1.6% 2. 1.6% 2. 1.6% 2. 1.6% 2. 1.6% 2. 1.0% 1 Haz 1.1% 1.77 4.2.57 % 1.33 % 2.00 % 1.77 4.2.57 % 1.33 % 2.01 % 1.77 4.2.57 % 1.33 % 2.01 % 1.77 4.2.57 % 1.33 % 2.01 % 2</td><td>4 (1.98, 3.79) 0 (2.18, 3.34) 1 (2.18, 3.34) 1 (2.18, 3.34) 1 (2.18, 3.34) 1 (2.18, 3.34) 1 (2.18, 3.34) 1 (0.48, 3.22) 1.64 (0.58, 4.68) 1 (0.42, 10.74) 1 (1.02, 10.34) 1 (1.02, 10.34) 1 (1.04, 2.13) 1 (1.17, 5.37) 3 (0.28, 6.32) 3 (1.46, 2.96) [(1.46, 2.15) 1 (1.46, 2.96) [(1.46, 2.15] 1 (1.46, 2.96) [(1.46, 2.15] 1 (1.46, 2.96)] (1.46, 2.96) [(1.46, 2.15] 1 (1.46, 2.96)] (1.47, 2.96)] (1.47,</td><td>1 0.2 0 Gradi 0.1 0.2 0 No n No n No n No n No n No n No n No n</td><td>5 1 Hazard R J. Eixed. J. Eixed. S 1 L. Eixe</td><td></td></td<>	Image: square Squar S	% 2.7 % 2.7 F F 1011 D 122% 1 12.8% 4 1.22% 1 1.6% 2. 1.6% 2. 1.6% 2. 1.6% 2. 1.6% 2. 1.0% 1 Haz 1.1% 1.77 4.2.57 % 1.33 % 2.00 % 1.77 4.2.57 % 1.33 % 2.01 % 1.77 4.2.57 % 1.33 % 2.01 % 1.77 4.2.57 % 1.33 % 2.01 % 2	4 (1.98, 3.79) 0 (2.18, 3.34) 1 (2.18, 3.34) 1 (2.18, 3.34) 1 (2.18, 3.34) 1 (2.18, 3.34) 1 (2.18, 3.34) 1 (0.48, 3.22) 1.64 (0.58, 4.68) 1 (0.42, 10.74) 1 (1.02, 10.34) 1 (1.02, 10.34) 1 (1.04, 2.13) 1 (1.17, 5.37) 3 (0.28, 6.32) 3 (1.46, 2.96) [(1.46, 2.15) 1 (1.46, 2.96) [(1.46, 2.15] 1 (1.46, 2.96) [(1.46, 2.15] 1 (1.46, 2.96)] (1.46, 2.96) [(1.46, 2.15] 1 (1.46, 2.96)] (1.47,	1 0.2 0 Gradi 0.1 0.2 0 No n No n No n No n No n No n No n No n	5 1 Hazard R J. Eixed. J. Eixed. S 1 L. Eixe	
Total (95' Heterogen Test for o E Study or / Bedke 200 Bertini 200 Capitanio da Costa Oh 2018 Shah 2011 Total (95' Heterogen Test for o Bedke 22 Brookma Chen 201 da Costa Guo 2015 Heterogen Test for c G Study or 1 Baccos 20 Capitanio Oh 2018 Heterogen Total (95' Heterogen Total (95'	% C1) metry: Chi ² = 6.85, vverall effect: Z = 6 Subgroup log 09 09 2018 2012 9 % C1) metry: Chi ² = 3.17, vverall effect: Z = 5. r Subgroup log 09 17 2012 9 % C1) metry: Chi ² = 4.03 vverall effect: Z = 1. Subgroup log 17 2012 9 Subgroup log 17 2012 9 Subgroup log 17 2012 9 Subgroup log 17 2012 9 Subgroup log 17 17 2012 9 Subgroup log 17 17 2012 9 Subgroup log 17 17 17 17 17 17 17 17 17 17	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.4953 0: 0.4953 0: 0.4953 0: 0.4953 0: 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 0.5965 0.9187 0.2852 0.7324 , df = 4 (P = 0.40); 5.81 (P < 0.00001 1.553 0.76 0.933 0.974 2.9880 0.43 3.7213 0.922 2.1883 0.674 1.3514 0.666	P = 0% Necrosis <u>SE</u> Toti <u>344</u> 7 6 344 8 1467 10 064 2 64 = 0% > 7 cm <u>SE</u> Toti 0.3178 4 0.136 4 0.1378 4 0.136 4 0.3391 1 157 Positive Nr E <u>E</u> Total 3 3 4 4 2 2 1 9 5 4 28	Initial Total Monopole 1 Tata Total Monopole 1 Tata Monopole Monopole 1 Tata Tata Tata	sis total We total We t	% 2.7 % 2.7 F 10 10 10 10 10 10 10 10 10 10	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0. Gradi	5 1 Hazard R J.5 1 N Hazard R Hazard R Hazard R Hazard R 1 7 cm >	2 5 rrade III or IV Ratio 95% Cq 2 5 kecrosis atio 15% Cl 5 ccl
Total (95' Heterogen Test for o Estudy or: Bedke 200 Capitanio da Costa : Shah 201' Total (95' Heterogen Test for o Estudy or: Bedke 20 Brookma Chen 20' da Costa : Brookma Chen 20' da Costa : Costa : Co	% C1) neity: Chi² = 6.85, vvorall effect: Z = 5 Subgroup logi 90 2018 2018 2018 2018 2017 9 % C1) neity: Chi² = 3.17, vvorall effect: Z = 5. rsubgroup logi 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 0010 001 0011 001 00218 7 0215 % C1) vc15 % C1) vc15 % C1)	df = 7 (P = 0.44); 0.14 (P < 0.00001) 0.5247 0.: 0.4553 0.: 0.4853 0.: 0.4853 0.: 0.4823 0.: 1.4446 0. 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 2g[Hazard Ratio] 0.0853 0.5365 0.9187 0.2852 0.7324 .5.81 (P < 0.00001) 4azard Ratio] 1.5953 0.765 0.9333 0.767 0.2852 0.7324 3.7213 0.922 2.1883 0.674 1.5953 0.765 0.9933 0.771 2.9888 0.843 3.7213 0.922 2.1883 0.674 1.3514 0.692 2.1883 0.674 1.3514 0.692 2.1883 0.674 1.3514 0.692 2.1883 0.674 0.933 0.757 0.2852 0.7324 0.745 0.7	P = 0% Necrosis <u>SE</u> Toti 1447 6 344 8 1467 10 1664 2 64 = 0% > 7 cr <u>SE</u> Toti 146 26 64 = 0% > 7 cr <u>SE</u> Toti 0.136 4 0.3891 1 0.136 4 0.3891 1 0.136 4 2 5 4 4 2 2 1 9 5 4 28	No rescription 1737 106 No rescription 10 1 0 1 1 1 0 2 8 8 8 6 3 1 0 1 1 10 1 0 8 6 3 1 0 1 1 10 1 0 0 1 1 11 0 0 1 1 11 0 1 1 1 1 0 1 1 1 1 0 1 1 1 1 0 1 1 1 1	Image: square Square Square sis State Square Square state 46 12 Square Square 46 12 25 S Square Square 46 12 25 S Square Square Square 108 3 301 69 9 69 100 Square Squar Squa	% 2.7 % 2.7 F 10.5 1	4 (1.98, 3.79) 0 (2.18, 3.34) azard Ratio (. Fixed, 95% CI . 20 (0.50, 3.32) .64 (0.58, 4.68) .20 (0.50, 2.468) .20 (0.568) .20 (0.568)	0.1 0.2 0 Grad 0.1 0.2 0 No m No m	5 1 3 1 or 11 G Hazard R Hazard R Hazard R Hazard R 1 7 cm > 5 1 7 cm > 5 1 7 cm >	
Total (95' Heterogen Test for o E Study or: Bedrini 20(Capitanio da Costa Shah 201' Total (95' Heterogen Test for or F Study or f Bedke 20 Brookma Chen 20' da Costa Guo 2011 Total (95' Heterogen Test for c Capitanio da Costa Guo 2011 Total (95 Heterogen Test for c Capitanio da Costa Guo 2011 Total (95 Heterogen Test for c Capitanio Capitanio Schiavani Poon 2000 Schiavina Total (95) Heterogen Test for c	% C1) neity: Chi² = 6.85, vverall effect: Z = 5 Subgroup log 09 2018 2012 9 % C1) neity: Chi² = 3.17, vverall effect: Z = 5. Subgroup log 000 10 001 3.17, vverall effect: Z = 5. Subgroup log 12012 9 % C1) neity: Chi² = 4.03 0xverall effect: Z = 4.03 0xverall effect: Z = 5. 2018 2018 7 9 2015 % C1) 103 2015 % C1 = 7.36, df	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.4953 0.0 0.10328 0.0 1.0328 0.0 1.0328 0.0 1.0328 0.0 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 20[Hazard Ratio] 0.5365 0.9187 0.2852 0.7324 df = 4 (P = 0.40); 5.81 (P < 0.0001) 1.5935 0.765 0.9933 0.974 2.9890 0.843 3.7930 0.2852 2.1863 0.773 2.9890 0.843 3.7913 0.025 2.1853 0.771 0.6933 0.974 1.3514 0.600 = 5 (P = 0.20); P = 5 9 (P < 0.0001)	P = 0% Necrosis <u>SE</u> Toti 447 6 344 8 4467 10 6664 2 64 = 0% > 7 cr <u>SE</u> Toti 0.136 41 0.136 41 0.136 41 0.3891 1 0.795 9 157 P = 1% Positive Ne <u>E</u> Total 2 4 2 2 1 9 5 4 2 8	11737 106 No rectro 1 1 1 0 0 8 3 1 1 1 1 1 1 1 1 1 1 1 1 20 1 119 11 119 12 207 11 207 11 119 11 119 11 111 1811 207 11 1151 10	sis otal We otal We	% 2.7.	4 (1.98, 3.79) 0 (2.18, 3.34) 0 (2.18, 3.34) 6 (0.68, 3.32) 6.69 (0.86, 3.32) 6.69 (0.86, 3.68) 10.42, 10.74) 10.06, 2.863 10.42, 10.74) 10.059, 2.05] (1.34, 2.43) 9.6 (1.54, 2.43) 9.6 (1.54, 2.43) 10.59, 2.05] (1.31, 2.23) (1.32, 2.32) 10.59, 2.05] (1.31, 2.23) (1.32, 2.32) 10.59, 2.05] (1.31, 2.23) (1.32, 2.32) 10.59, 2.05] (1.34, 2.43) 10.59, 2.05] (1.34, 2.43) 10.59, 2.05] (1.34, 2.43) 10.59, 2.05] (1.34, 2.23) 11.40, 2.15] (1.46, 2.15] (1.46, 2.15] (1.46, 2.15] 11.62,3] 13.23] 14.04] 0.01 Neg	1 0.2 0 Gradi 0.1 0.2 0 No n No n No n No n No n No n No n No n	5 1 5 1 1 Arazerd P 1 Jos 1 1 Jos 1	trade III or IV Ratio 95% Cq trade III or IV Ratio 95% Cq trade III or IV Ratio 95% Cq trade
Total (95' Heterogen Test for o E Study or: Bedke 200 Bertini 200 Capitanio da Costa Shah 2011 Total (95' Heterogen Test for o Bedke 20 Brookma Chen 201 da Costa G Study or 1 Becke 20 Brookma Chen 201 da Costa G Study or 1 Becke 20 Brookma Chen 201 da Costa G Study or 1 Beccos 20 Capitanio Oh 2018 Beca 201 Becos 20 Brookma Chen 201 Di da Costa Beccos 20 Capitanio Oh 2018 Berng 2017 Pon 2005 Schiavina Total (95' Heterogen Total (95')	% CI) nneity: Chi² = 6.85, ivverall effect: Z = 6 Subgroup logi 09 .2018 2012 9 % CI) neity: Chi² = 3.17, ivverall effect: Z = 5. rsubgroup log 009	df = 7 (P = 0.44); $0.14 (P < 0.00001)$ $(Hazard Ratio]$ $0.5247 0;$ $0.4953 0;$ $0.4953 0;$ $0.1823 0;$ $1.4446 0;$ $0.7178 0;$ $df = 5 (P = 0.67); P = 5,$ $0.9853 0;$ $0.5365 0;$ $0.9187 0;$ $0.2852 0;$ $0.7324 ;$ $df = 4 (P = 0.40);$ $5.81 (P < 0.00001;$ $1.5853 0$	P = 0% Necrosis <u>SE</u> Toti <u>344</u> 7 6 344 8 1467 10 0664 2 64 = 0% > 7 cm SE Toti 0.3178 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 157 Positive Ne E Total 3 3 4 4 2 2 1 9 5 4 28	Initial 30 11737 106 No record 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 161 0 0 0 0 0 0 0 0 0 0 1 164 119 11 120 123 1221 122 1154 10 // 1154	sis total We total We t	% 2.7 % 2.7 iah 2.5% 1 2.5% 1 2.2% 1 1.22% 1 1.25% 1 1.25% 1 1.25% 1 1.25% 1 1.25% 1 1.27% 1	4 (1.98, 3.79) 0 (2.18, 3.34) . (-) . (-)	1 0.2 0. Gradi	5 1 Hazard R Hazard R 10 5 1 1 5 1 7 cm > 5 5 1 7 cm > 5 1 7 cm > 5 1 1 7 cm > 1 1 7 cm > 1 1 7 cm > 1 1 7 cm > 1 1 7 cm > 1 1 7 cm > 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	trade III or IV Ratio 95% Cq 95% Cq 10 ve margin status tatio
Total (95' Heterogen Test for o Estudy or: Bedke 20(Capitanio da Costa: Shah 201' Total (95' Heterogen Test for o Estudy or: Bedke 20 Brookma Chen 20' da Costa: Brookma Chen 20' da Costa: Chen	"% C1) neity: Chi² = 6.85, vverall effect: Z = 5 Subgroup logi 09 09 2018 2018 2019 2018 2012 9 % C1) neity: Chi² = 3.17, vverall effect: Z = 5. rsubgroup log 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 009 9 3% C1) 001 009 003 2015 % C1) 004 005 301 007 9 2015 % C1) % C1) 004 005 015 % C1) 014 015 5.4 subgroup 5.4	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0. 1.0328 0. 1.0328 0. 1.0328 0. 1.0328 0. 1.0328 0. 1.0328 0. 1.0328 0. 1.0328 0. 0.7178 0 0.7178 0 0.07178 0 0.07178 0 0.0353 0.0365 0.9187 0.2852 0.7324 0	P = 0% Necrosis <u>SE</u> Tot 1447 6 1344 8 1467 10 1664 2 2.644 100 1.146 266 64 = 0% > 7 cr <u>SE</u> Total 0.136 4 0.3891 5 0.136 4 0.3891 5 0.136 4 Positive Nr <u>E</u> Total 3 3 3 6 4 4 4 2 2 1 9 5 4 28 28 1 9 5 4 28 1 9 5 4 1 9 5 5 4 1 9 5 5 1 9 5 1 1 9 5 1 1 9 5 5 1 9 5 1 1 9 5 1 1 9 5 5 1 9 5 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	No recro 11737 106 No recro 1 1 1 0 1 0 0	sis total Week 46 12 25 5 2017 18 1 108 3 301 69 6699 100 1 Weight 6699 100 6699 100 6699 100 1.599 1.29,89 1.59,8	% 2.7 % 2.7 ight D D.5% 1 1.5% 1 1.5% 1 1.5% 1 1.6% 2.7 Mazard R. 1.71 % 2.5.3 % 2.00 % 1.77 4azard R. 2.13 % 2.00 % 1.77 4azard R. 1.77 % 2.5.3 % 2.00 % 2.00 % 2.13 % 2.00 % 2.13 % 2.00 % 2.13 % 2.00 % 2.13 % 2.00 % 2.13 % 2.00 % 2.13 % 2.00 % 2.00 % 2.13 % 2.00 % 2.13 % 2.00 % 2.13 % 2.00 % 2.13 % 2.00 % 2.00 % 2.13 % 2.00 %	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0. Gradi	5 1 1 Hazard R J. Eixed. 9 5 1 7 Cm > 5 1 7	trade III or IV Ratio 95% Cl
Total (95' Heterogen Test for o Estudy or: Bedke 200 Berrini 200 Capitanio da Costa i Shah 2011 Total (95' Heterogen Test for or F <u>Study or</u> Bedke 20 Brookma Chen 201 da Costa i Guo 2011 Total (95' Heterogen Total (95 Heterogen Total (95 Heterogen Total (95 Heterogen Total (95 Heterogen Total (95 Heterogen Total (95 Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Test for o	% C1) neity: Chi² = 6.85, vverall effect: Z = 5 Subgroup log 09 2018 2012 9 % C1) neity: Chi² = 3.17, vverall effect: Z = 5. Subgroup log 000 100 n=May 2015 17 17 2012 9 5% C1) n=neity: Chi² = 4.03 soverall effect: Z = 1: Subgroup log(1) 2018 2018 7 9 2015 % C1) 13 2015 % C1) 10, 10, 10, 10, 10, 10, 10, 10, 10, 10,	df = 7 (P = 0.44); 0.14 (P < 0.00001) (b.5247 0: 0.65247 0: 1.0228 0: 1.0228 0: 1.0228 0: 1.0228 0: 1.0228 0: 1.0228 0: 1.0228 0: 1.0228 0: 0.7178 0: 0.0353 0.527 (P = 0.67); P 52 (P < 0.00001) 20[Hazard Ratio] 1.5953 0.765 0.9187 0.2852 0.7324 0.7324 0.4f = 4 (P = 0.40); 5.81 (P < 0.00001) 1.5953 0.765 0.9933 0.974 1.5953 0.765 0.9933 0.974 1.5954 0.00001 1.5954 0.0001	P² = 0% Necrosis SE Toti V447 6 344 8 V47 6 344 8 4467 10 0664 2 64 64 = 0% 5 > 7 cr 5 0.136 44 0.378 7 0.735 9 0.1369 9 0.1306 9 0.1806 9 157 10 19 9 5 4 28 22% 28 19 0 325 0 0	No rectro No rectro No rectro No rectro No Tota Tota Tota Tota Tota Tota Tota Tota So Tota Tota So Tota Tota Tota So Tota So Tota So So Tota	sis sis <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>stat</u> <u>sta</u>	% 2.7. % 2.7. inht 2.5% 1.6% 2.5% 1.6% 2.5% 1.6% 2.5% 1.6% 2.6% 4.8% 1.11 % 1.77 4.8% 2.5% 4.33 1.10 4.25% 4.33 1.10% 4.25% 4.33 1.11% 4.33 1.11% 4.33 1.11% 4.25% 4.33 1.11% 4.32% 4.	4 (1.98, 3.79) 0 (2.18, 3.34) 10 (2.18, 3.34) 10 (2.18, 3.34) 10 (2.18, 3.34) 10 (2.18, 3.34) 10 (2.18, 3.21) 1.69 (10.86, 3.32) 1.64 (10.86, 3.62) 13 (1.02, 10.74) 13 (1.02, 10.74) 13 (1.02, 10.74) 14 (1.02, 10.74) 14.04] 14.04] 10 (1.17, 5.37) 14.04] 14.04] 14.04] 127.3] 14.04] 10.059, 2.05) 14.04] 10.059 10.059, 2.05] 14.04 10.059 11.05, 2.05] 11.05, 2.05] 11.	1 0.2 0. Gradi 0.1 0.2 0. No n No n N	5 1 Hazard R J. Fixed. J 5 1 L Fixed. S Hazard R Hazard R K. Fixed. S	
Total (95' Heterogen Test for o E Study or: Bedke 200 Bertini 200 Capitanio da Costa Shah 2011 Total (95' Heterogen Test for on Bedke 20 Brookma Costa Garcata Chen 201 Brookma Chen 201 Backe 20 Brookma Chen 201 Chen	% C1) neity: Chi² = 6.85, vverall effect: Z = 9 Subgroup logi 09 2018 2012 9 % C1) neity: Chi² = 3.17, vverall effect: Z = 5. rsubgroup log 9 % C1) neity: Chi² = 3.17, vverall effect: Z = 5. rsubgroup log 9 % C1) n-May 2015 17 12 2012 9 9% C1) subgroup log(H) 12 2012 9 9% C1) 9 5% C1) 9 2018 7 9 2015 % C1) neity: Chi² = 7.36, df rsubgroup log(H) 12012 larchinena 2019 2012 2012	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.4953 0.0 0.1823 0.0 1.0328 0.1 1.4446 0 0.7178 0 df = 5 (P = 0.67); P 52 (P < 0.00001) 0.538 0 0.9187 0.2852 0.7324 df = 4 (P = 0.40); 5.81 (P < 0.00001) 1.563 0.76 0.9187 0.2852 0.7324 df = 4 (P = 0.40); 5.81 (P < 0.00001) 1.563 0.76 0.983 0.974 2.8880 0.843 3.7213 0.925 2.1833 0.674 2.8880 0.843 3.7213 0.925 2.1833 0.674 2.9880 0.843 3.7213 0.925 2.1833 0.674 2.9880 0.843 3.7213 0.925 2.1833 0.674 2.9880 0.843 3.7213 0.925 2.1833 0.674 3.7213 0.925 2.1833 0.674 3.7213 0.925 2.1833 0.674 3.7213 0.925 3.7213 0.925 3.7214 3.7214 0.925 3.7214 3.7214 0.925 3.7214 3.7214 0.925 3.7214 0.925 3.721	P = 0% Necrosis <u>SE</u> Toto <u>344</u> 7 6 344 8 1467 10 1664 2 64 = 0% > 7 cr <u>SE</u> Toto 0.3178 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 0.136 4 10.785 9 157 Positive Net <u>E</u> Total 3 3 4 4 2 2 2 8 4 4 2 2 1 9 5 4 1 0.785 0 0.378 1 1 0.785 0 0.378 1 1 0.785 0 0.378 1 1 0.785 1	11737 106 No recro 1 1 1 0 0 8 8 3 1 0 0 8 8 3 1 0 0 1 1 0 0 1 16 57 766 73 90 0 0 155 90.0 119 11 207 118 123 1 2030 11 2131 123 1154 10 // Non-L'1 1154 // Non-L'1 1154 // Non-L'1 22 22 22 239 22	sis total Weight 7 9.69 1 Weight 7 9.69 1 00.0 1 Weight 7 9.69 1 00.0 1 00.0	% 2.7 % 2.7 iahi D. 2.5% 1 1.2.5% 1 1.2.2% 1 1.2.2% 1 1.3.2% 1 1.3.2% 1 Haz t. <u>IV.Fixed</u> % 1.11 % 1.71 % 1.3.0% 1 1.3.0% 1	4 (1.98, 3.79) 0 (2.18, 3.34) 0 (2.18, 3.34) 6 (2.18, 3.34) 0 (2.18, 3.34) 6 (0.66, 3.32) 6 (0.68, 4.68) 1 (0.42, 18.74) 1 (1.20, 14.98) 2 (1.20, 14.9	1 0.2 0 Gradi	5 1 Hazard R J.5 1 Hazard R Fixed. 95%	trade III or IV Ratio 95% Cq 95% Cq 10 ve margin status Ratio
Total (95' Heterogen Total (95' Heterogen Total (95' Berkle 20) Capitanio da Costa Shah 201' Total (95' Heterogen Test for o Bedke 20 Brookma Chen 20' da Costa Guo 2019 Total (95' Heterogen Total (95' Schiavina	"% CI) neity: Chi² = 6.85, vvvrail effect: Z = 5 Subgroup log: 09 2018 2018 2017 9 % CI) neity: Chi² = 3.17, vverall effect: Z = 5. rsubgroup log: 009 009 009 009 n-May 2015 17 17 2012 9 % 90 Sworall effect: Z = 1. 90 soverall effect: Z = 1. 91 2012 92 9 % CI) neity: Chi² = 4.03 vorall effect: Z = 1. 5. Subgroup log:16 7 9 2015 % CI) % CI) neity: Chi² = 7.36, df reverall effect: Z = 6.4! * Subgroup 12012 12012 Iarchinena 2019 12012 *	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0. 1.0328 0. 1.0453 0. 0.1823 0. 1.0423 0. 1.0328 0. 1.0328 0. 1.0328 0. 1.0328 0. 1.0328 0. 1.0328 0. 0.7178 0 0.07178 0 0.07178 0 0.07178 0 0.0953 0.5365 0.5365 0.5365 0.5365 0.5372 0.5365 0.5365 0.5365 0.5372 0.5365 0.5365 0.5365 0.5372 0.5365 0.5365 0.5365 0.5372 0.5365 0.5372 0.5365 0.5372 0.5375 0.5365 0.546 0.5372 0.5675 0.567 0.5675 0.567 0.5675	P = 0% Necrosis SE Tot Vacrosis Tot Vacrosis Tot Vacrosis Tot Vacrosis Galaxia Status Tot Vacrosis Total 3 3 6 4 4 2 2 1 9 28 Tot Vacrosis 4 4 2 28 Col SE Tot 28 Col SE Tot 28 Col SE Tot 29 O.3537 Pace Se Tot	No recro 11737 106 No recro 1 1 0 1 1 1 0 1 1 1 0 3 1 1 0 3 1 1 0 1 1 10 1 0 3 1 1 10 0 1 1 10 1 0 0 (1 1 11 0 1 1 111 12 1 119 1 2207 12 1 11 2207 1 18 12 1 11 221 12 1 11 11 11 11 1 1154 10 1 11 11 10 // Non-L1 1 1 1 1 1 1 1 14 1 1 1 1 </td <td>isis isis total Wee 46 12 25 5 12 25 5 201 7 18 1 108 3 301 69 9 69 100 1 Weight 1 0 6,49 1 0 0 1 1 1 1 1 0 0 1 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 1</td> <td>% 2.7 % 2.7 <u>ight P</u> 8.5% 1 1.5.% 1 1.5.% 1 1.6.% 2.5 1.6.% 2.5 % 2.01 Mazard R. 1.71 % 1.71 % 1.71 % 2.53 % 2.01 % 1.71 issue 1.77 issue 1.77 is</td> <td>4 (1.98, 3.79) 0 (2.18, 3.34) </td> <td>1 0.2 0. Gradi</td> <td>5 1 1 Hazard R 5 1 5 1 Hazard R 5 1 7 cm > zard Ratio 1 7 cm > zard Ratio 1 7 cm ></td> <td>2 5 rade III or IV Ratio 95% Cl 2 5 Necrosis atio 15% Cl </td>	isis isis total Wee 46 12 25 5 12 25 5 201 7 18 1 108 3 301 69 9 69 100 1 Weight 1 0 6,49 1 0 0 1 1 1 1 1 0 0 1 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 1	% 2.7 % 2.7 <u>ight P</u> 8.5% 1 1.5.% 1 1.5.% 1 1.6.% 2.5 1.6.% 2.5 % 2.01 Mazard R. 1.71 % 1.71 % 1.71 % 2.53 % 2.01 % 1.71 issue 1.77 issue 1.77 is	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0. Gradi	5 1 1 Hazard R 5 1 5 1 Hazard R 5 1 7 cm > zard Ratio 1 7 cm > zard Ratio 1 7 cm >	2 5 rade III or IV Ratio 95% Cl 2 5 Necrosis atio 15% Cl
Total (95' Heterogen Test for o Bedike 200 Bedike 200 Bedike 200 Bedike 200 Capitanio da Costa 1 Total (95' Heterogen Test for o F Study or 1 Brockma 2011 Total (95' Heterogen Total (95' Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Total (95) Heterogen Test for o	% C1) neity: Chi ² = 6.85, vverall effect: Z = 5 <u>Subgroup log</u> 09 09 2018 2012 9 % C1) neity: Chi ² = 3.17, vverall effect: Z = 5. <u>Subgroup log</u> 09 % C1) neity: Chi ² = 4.03 vverall effect: Z = 1. <u>Subgroup log</u> 17 2012 9 5% C1) neity: Chi ² = 4.03 vverall effect: Z = 1. <u>Subgroup log</u> 17 2015 7 9 2015 % C1) archinenaz 019 2016 <u>Subgroup log</u> 10 2018 2018 2018 2018 2018 2019 2010 2019 2010 2010 2010 2010 2010	df = 7 (P = 0.44); $0.14 (P < 0.00001)$ $(Hazard Ratio]$ $0.5247 0;$ $0.4953 0;$ $0.10328 0;$ $1.01823 0;$ $1.01823 0;$ $1.4446 0;$ $0.07178 0;$ $df = 5 (P = 0.67); P;$ $52 (P < 0.00001)$ $df = 5 (P = 0.67); P;$ $2g[Hazard Ratio]$ $0.0853 0;$ 0.7324 $df = 4 (P = 0.40);$ $5.81 (P < 0.00001)$ $df = 5 (P = 0.60); P;$ $1.5953 0.766$ $0.9933 0;$ 0.7324 $df = 4 (P = 0.40);$ $5.81 (P < 0.00001)$ $df = 5 (P = 0.20); P = 1;$ $g (P < 0.00001)$ $10g[Hazard Ratii]$ 0.0853 0.087 0.1962	P² = 0% Necrosis SE Toti V447 6 334 8 4467 10 0664 2 SE Toti 0.146 26 9 7 cr SE Total 0.785 Total 0.785 Total 3 6 4 2 Positive Nc 28 Total 3 6 4 2 28 20 19 2 28 2% 21 0.03785 0.0357 2	I1737 106 No rectro 1 No rectro 1 1 T 0 0 8 8 3 1 1 Tota 1 Tota 10 55 90 1 11 1811 10303 1154 1154 101 123 1154 1154 101 // Non-LL 76 2 59 21	Image: second	% 2.7, % 2.7, % 2.7 % 2.7 % 2.7 % 3.7 % 3.7 % 3.7 % 3.7 % 4.8 % 2.5 % 1.3 % 2.5 % 1.3 % 2.5 % 1.3 % 2.5 % 1.3 % 2.5 % 1.3 % 1.77 % 2.5 % 1.3 % 2.5 % 1.77 % 1.7	4 (1.98, 3.79) 0 (2.18, 3.34) 	1 0.2 0 Grad 0.1 0.2 (No m 1 0.2 0 1 0.2 0 1 0.2 0 1 0.2 0 1 0.2 0 1 0 1 0 2 1 1 0 2 1 0 1 0 1 0 2 1 0 1 0 1 0 2 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0	5 1 Hazard R J. Fixed. 5 1 S 1 Hazard R K. Fixed. V. Fixed. V. Fixed.	
Total (95' Heterogen Test for o E Study or: Bedke 200 Bertini 200 Capitanio da Costa Shah 201' Total (95' Heterogen Test for or Bedke 22 Brookma Chen 201' da Costa Guo 2018' Total (95' Heterogen Test for o Capitanio da Costa Gastador Baccos 20 Capitanio Chen 201' da Costa Gastador Deno 200 Capitanio Chen 201' da Costa Gastador Deno 200 Capitanio Chen 201' da Costa Gastador Deno 200 Schialvina Total (95' Heterogen Test for o Chen 201' Capitanio Chen 201' da Costa Gastador Deno 200 Schialvina Total (95' Heterogen Test for o Chen 201' Capitanio Chen 201' Capitani	% C1) neity: Chi² = 6.85, vverall effect: Z = 9 Subgroup log 09 2018 2012 9 % C1) neity: Chi² = 3.17, yverall effect: Z = 5. 100 mcMay 2015 17 17 2012 9 % C1) neity: Chi² = 4.03 overall effect: Z = 1. Subgroup log[1+2] 013 2016 7 9 2015 % C1) reveral effect: Z = 6.40 reveral effect: Z = 6.41 2012 12012 12012 12012 12012 12012 12012 12012 12012 12012 12012 12012 12012 12012 12012 12012 12012 13 12012 13	df = 7 (P = 0.44); 0.14 (P < 0.00001) (Hazard Ratio] 0.5247 0: 0.4953 0.0 0.1823 0.0 1.0328 0.0 1.0328 0.0 1.0328 0.0 1.0328 0.0 1.0328 0.0 1.4446 0 0.7178 0 0.0535 0.5365 0.9187 0.2852 0.7324 0.4f = 4 (P = 0.40); 5.81 (P < 0.0001) 1.5953 0.765 0.9433 0.765 0.9431 0.955 0.7324 1.3514 0.605 0.9431 0.955 0.0457 0.045	P² = 0% Necrosis SE Totu V447 6 S447 6 S44 0 146 26 0.136 64 = 0% 57 cr SE Total 0.136 40 0.3178 40 0.3391 157 * Total 3 3 4 4 2 2 1 9 5 4 4 2 2 1 9 3 6 2 2 1 9 3 6 2 2 2 1 1 0.785 0 0.3785 9 0 SE Tr 1 0.785 0 0.3785 9 0.3537 7	11737 106 No recro 1 1 1 0 0 0 0 8 8 3 1 1 1 0 0 0 0 8 8 3 1 0 0 1 16 57 766 73 90 10 100 119 1 120 121 121 122 1154 10 // Non-L'L // 1154 // 1154 // 1154 // 1154 // 1154 // 100 // 100 // 100 // 100 // 100 // 100	sis total Weight 7 9.69 1 Weight 7 9.69 1 00.0° 1 Weight 7 9.69 1 00.0° 1 0 0.0° 1 0 0.0°	% 2.7. % 2.7. % 2.7. % 2.7. % 2.5% 1 % 1.11 % 1.7. % 1.3. % 2.5% 1 % 1.4% % 1.11 % 1.7. % 1.3. % 2.5% % 1.3. % 2.5% % 1.3. % 2.5% % 1.4. % 1.77 % 2.5% % 1.3. % 1.77 % 2.5% % 1.4. % 1.77 % 2.5% % 1.11 % 1.77 % 2.5% % 1.77 %	4 (1.98, 3.79) 0 (2.18, 3.34) 0 (2.18, 3.34) 6, 50, 61, 322) 6, 69 (0.86, 3.32) 6, 69 (0.86, 3.32) 6, 69 (0.86, 3.32) 6, 40 (0.88, 4.88) 10, 22, 10, 50, 2.88] 81 (0.42, 18, 74) 10, 14, 98] 10, 14, 98] 11, 17, 5, 37] 10, 29, 20, 15] 11, 14, 2, 23] 11, 14, 2, 23] 11, 12, 23] 12, 23] 14, 04] 10, 04] 10, 04, 2, 10] 22 [0, 61, 2, 244] 10, 69, 1.80] 0, 04, 2, 10] 10, 04,	1 0.2 0 0.1 0.2 (Gradi 0.1 0.2 (No m No	5 1 5 1 6 1 or II G Hazard R 1, Fixed. 5, 1 5, 1 1 1, 7 cm > 1 5, 1 1, 7 cm > 1 1	2 5 rrade III or IV Ratio 95% CQ 2 5 Necrosis atio 15% Cl 2 5 CC 10 10 10 25% Cl 25% 25% 25% 25% 25% 25% 25% 25%

FIGURE 4 | Forrest plots of Hazards ratio (HR) evaluating the significant predictors of cancer-specific survival for different pathological features of pT3a. (A): lymph node involvement; (B): distant metastases; (C): sarcomatoid differentiation; (D): Fuhrman grade (III, IV vs I, II); (E): tumor necrosis; (F): tumor size (>7 cm vs ≤ 7 cm); (G): positive margin status; (H): lymphovascular invasion.





FIGURE 5 | Sensitive analysis of the included studies by one-removed analysis. (A): SFI only vs PFI only; (B): PFI + SFI vs SFI only; (C): SFI \pm PFI vs PFI only; (D): PSI vs non-PSI; (E): RVI vs non RVI; (F): RVI + FI vs RVI or FI; (G): multiple vs single pattern; (H): lymph node involvement; (I): distant metastases; (J): sarcomatoid differentiation; (K): Fuhrman grade (III, IV vs I, II); (L), tumor necrosis; (M): tumor size (> 7 cm vs \leq 7 cm); (N), positive margin status; (O), lymphovascular invasion; SFI, sinus fat invasion; PFI, perinephric fat invasion; PSI, pelvicaliceal system invasion; RVI, renal vein invasion; FI, fat invasion.

9

also increased the risk of deterioration of CSS, which represents the moderate-certainty evidence. The low-certainty evidence suggests that lymph node involvement might increase the risk of CSM and the lymphovascular invasion was indolent in terms of CSS. The comparable CSS between SFI only and PFI only and the indolent impact of lymphovascular invasion on the survival are inconsistent with the EAU guidelines on RCC, which underlines the prognostic value of several anatomical and histological factors (1). This may require further validation due to the low-certainty evidence.

The inevitable risk of bias caused by the type of surgery that might affect the results of the included studies should be highlighted, even though it had been adjusted in the studies, which included patients undergoing PN or RN. Several studies reported comparable CSS for upstaged pT3a PN patients compared to pT3a RN patients (33, 34). However, the significantly smaller tumor size of the PN cohort compared to the tumor size of the RN cohort indicated that organ confined tumors are susceptible to receive PN. Given the absence of the standardized pathological protocol of capsular invasion in the early years, the classification of renal capsular invasion patterns was an unreliable prognostic variable in some previous studies (2, 35). The recommended routine histopathological examination of perirenal fat was conducted on a discounted basis among patients with peripheral renal tumor since the specimens of renal sinus fat were not systematically collected during PN, especially in the context of the PN enthusiasm (36). The aforementioned factors might have led to the underreported frequency of SFI. Grignon et al. noted that pT1b and pT2 renal tumors probably represented a shrinking proportion when the renal sinus was carefully evaluated (37). In the last two decades, TNM staging classification system for renal tumors was refined three times, which may affect the accuracy and manifolds of pT3a and the heterogeneity of study designs despite minor changes.

Given the increasing PN implementation, the realistic concern is the positive margin, which occurs more frequently in patients with aggressive features, including pT2a, pT3a, and grade III-IV (38, 39). Shah et al. reported that positive margin significantly increased the rate of recurrence, especially among patients with aggressive pathological features, including pT2-T3a, high Fuhrman grade, and clear cell histology (39). In their study, recurrence was observed in almost one third of patients who were up staged to pT3a after PN (40). Bensalah et al. found that positive margin did not cause a decrease CSS; however, the fact that the mean tumor size was 3.5 ± 2 cm, and almost 90% of the positive margin cohort were patients with T1-2 RCC made their conclusions not necessarily applicable to patients with pT3a patients (41). Although several studies mentioned the controversial impact of positive margin on the oncological prognosis among patients with localized RCC, according to the current results that identified more than seven times risk of CSM in patients with pT3a RCC and postoperative positive margin compared to those with negative margin, the weak recommendation of EAU guidelines for intensive follow-up of patients with positive margin may be imprecise (1, 42, 43).

Several studies have highlighted the impact of tumor size on CSS for T3a renal tumor (3, 18, 22, 39, 44-48). In light of the

agreement of some studies in which a cutoff of 7 cm was recommended as a prognosis prediction for T3a renal tumor and the applicability of the refinement for the current TNM classification, only the results that considered tumor diameter as a binary variable by using a cutoff of 7cm were merged in the current study. We found that patients with pT3a renal tumor > 7 cm experienced an additional 77% risk of CSM, which was consistent with the findings of Brookman-May et al, reporting that tumor size was identified with the highest prediction accuracy by increasing 71% risk of CSM with a 7 cm cutoff (3). Although the tumor size did not result as a predictor of prognosis in several studies, which cannot be ignored, this is not necessarily contrary to our results and should be further analyzed in the context of the design of the studies and evaluation of patients (14, 19). Whether the impact of tumor size on prognosis can induce T3a and T1/T2 reintegration needs further validation. Chevinsky et al. reported that pT3a had significantly inferior RFS compared to pT1/T2 (45). Chen et al. found that patients with pT3a renal cell carcinoma showed poorer disease-free survival (DSS) as compared to pT1a, pT1b, pT2a, and pT2b. However, Yoo et al. reported a comparable CSS and DSS between pT2 and pT3a \leq 7cm (49).

The results of the current study may be used to guide the follow-up protocols and select patients suitable for adjuvant therapy after nephrectomy. A compact interval of surveillance may be vital for patients with aggressive factors. Although limited evidence suggested that compact postoperative imaging intervals did not result in the early detection of recurrence, which would benefit survival, the EAU guidelines on RCC recommend a risk-based approach to stratify follow-up for different patients, based on the individual aggressive anatomical, histological and clinical factors (1, 50). The S-TRAC trail exhibited superior disease-free survival (DFS) with sunitinib support. The PROTECT study also reported an improved DFS in the intention to treat pazopanib 800mg population (51). Among the highest-risk subpopulation, the ATLAS study found that axitinib translated into a 36% and 27% reduction in risk of a DFS event per investigator and by independent review committee, respectively (52). However, the recent SORCE trial results, which focused on the DFS and overall survival (OS) in patients with an intermediate or high risk of recurrence, failed to offer positive evidence of sorafenib (53). A recent meta-analysis revealed that adjuvant use of tyrosine kinase inhibitors (TKI) did not translate into improved OS, but showed a benefit in DFS in overall and high-risk populations (54). Due to the lack of sufficient evidence that adjuvant therapy with vascular endothelial growth factor receptor (VEGFR) -TKI offers survival benefits for patients with high-risk RCC, the EAU guidelines on RCC do not recommend the adjuvant therapy after nephrectomy (1). However, heterogeneity among the enrolled patients could be the main cause of the negative results (55). In light of the non-strict inclusion criteria of previous studies, supplemental randomized trials are necessary to determine whether patients with aggressive patterns or characteristics of pT3a renal tumors may benefit from adjuvant treatment.

The present study has some limitations. First, the retrospective nature of the included studies inevitably led the selection bias.

Second, the inevitable risk of bias caused by the type of surgery might affect the results. Third, most contemporary studies failed to comprehensively explore the survival difference among the various combinations. Fourth, the determination of the patterns of pT3a renal tumor invasion and pathological features were made by different pathologists, probably based on different criteria. Finally, a small sample of some included studies increased the variability of results.

CONCLUSION

The current study identified the heterogenicity of pT3a renal tumors. Multiple invasion patterns could translate into a significantly decreased CSS, and SFI only should not be merged with the SFI + PFI group. The presence of PSI or RVI could significantly increase the risk of cancer-specific mortality. Lymph node involvement, distant metastases, sarcomatoid differentiation, necrosis, high Fuhrman grade, positive margin, and tumor size >7cm are the predictors of inferior CSS. The follow-up protocols and postoperative therapies after nephrectomy should be conducted with individuation according to a risk-based approach for stratification based on these aggressive pathological characteristics. External validation and a precise-risk grade of CSS for different invasion patterns,

REFERENCES

- Ljungberg B, Albiges L, Bedke J, Bex A, Capitanio U, Giles RH, et al. (2021). Eau Guidelines on Renal Cell Carcinoma. In: *Presented at the EAU Annual Congress Milan 2021*. Arnhem, The Netherlands: EAU Guidelines Office
- Thompson RH, Leibovich BC, Cheville JC, Webster WS, Lohse CM, Kwon ED, et al. Is Renal Sinus Fat Invasion the Same as Perinephric Fat Invasion for pT3a Renal Cell Carcinoma? *J Urol* (2005) 174(4 Pt 1):1218–21. doi: 10.1097/ 01.ju.0000173942.19990.40
- Brookman-May SD, May M, Wolff I, Zigeuner R, Hutterer GC, Cindolo L, et al. Evaluation of the Prognostic Significance of Perirenal Fat Invasion and Tumor Size in Patients With pT1-pT3a Localized Renal Cell Carcinoma in a Comprehensive Multicenter Study of the CORONA Project. Can We Improve Prognostic Discrimination for Patients With Stage pT3a Tumors? *Eur Urol* (2015) 67(5):943–51. doi: 10.1016/j.eururo.2014.11.055
- Poon SA, Gonzalez JR, Benson MC, McKiernan JM. Invasion of Renal Sinus Fat is Not an Independent Predictor of Survival in pT3a Renal Cell Carcinoma. *BJU Int* (2009) 103(12):1622–5. doi: 10.1111/j.1464-410X.2008.08239.x
- Shah PH, Lyon TD, Lohse CM, Cheville JC, Leibovich BC, Boorjian SA, et al. Prognostic Evaluation of Perinephric Fat, Renal Sinus Fat, and Renal Vein Invasion for Patients With Pathological Stage T3a Clear-Cell Renal Cell Carcinoma. *BJU Int* (2019) 123(2):270–6. doi: 10.1111/bju.14523
- 6. Wang Z, Yu K, Zhu Y, Feng C, Liu C, Liu S, et al. Multiple Patterns of Perirenal Fat Invasion are Associated With a Poorer Prognosis Compared With Isolated Invasion: A Proposal for a Revision of T3aN0M0 Tnm Staging System. *Front Oncol* (2020) 10:336. doi: 10.3389/fonc.2020.00336
- Oh JJ, Lee JK, Do Song B, Lee H, Lee S, Byun SS, et al. Accurate Risk Assessment of Patients With Pathologic T3an0m0 Renal Cell Carcinoma. *Sci Rep* (2018) 8(1):13914. doi: 10.1038/s41598-018-32362-w
- Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma After Nephrectomy. N Engl J Med (2016) 375(23):2246–54. doi: 10.1056/NEJMoa1611406
- 9. Haas NB, Manola J, Dutcher JP, Flaherty KT, Uzzo RG, Atkins MB, et al. Adjuvant Treatment for High-Risk Clear Cell Renal Cancer: Updated Results

including comprehensive combinations, may be useful for the further refinements of the TNM system.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

PG and YW contributed to the design of the study. YH and DW were responsible for literature search. PG and JZ were responsible for data extraction and analysis. PG and ML were responsible for drafting the manuscript. YJ and YL approved the submitted version. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Natural Science Foundation of Beijing Municipality (award no. 7192053).

of a High-Risk Subset of the ASSURE Randomized Trial. *JAMA Oncol* (2017) 3(9):1249–52. doi: 10.1001/jamaoncol.2017.0076

- Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing Bias in Studies of Prognostic Factors. Ann Intern Med (2013) 158 (4):280–6. doi: 10.7326/0003-4819-158-4-201302190-00009
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in Meta-Analysis Detected by a Simple, Graphical Test. *BMJ* (1997) 315(7109):629–34. doi: 10.1136/bmj.315.7109.629
- Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: An Emerging Consensus on Rating Quality of Evidence and Strength of Recommendations. *BMJ* (2008) 336(7650):924–6. doi: 10.1136/bmj.39489.470347.AD
- Margulis V, Tamboli P, Matin SF, Meisner M, Swanson DA, Wood CG. Location of Extrarenal Tumor Extension Does Not Impact Survival of Patients With pT3a Renal Cell Carcinoma. J Urol (2007) 178(5):1878–82. doi: 10.1016/j.juro.2007.07.011
- Bedke J, Buse S, Pritsch M, Macher-Goeppinger S, Schirmacher P, Haferkamp A, et al. Perinephric and Renal Sinus Fat Infiltration in pT3a Renal Cell Carcinoma: Possible Prognostic Differences. *BJU Int* (2009) 103(10):1349–54. doi: 10.1111/j.1464-410X.2008.08236.x
- Bertini R, Roscigno M, Freschi M, Strada E, Petralia G, Pasta A, et al. Renal Sinus Fat Invasion in pT3a Clear Cell Renal Cell Carcinoma Affects Outcomes of Patients Without Nodal Involvement or Distant Metastases. J Urol (2009) 181(5):2027–32. doi: 10.1016/j.juro.2009.01.048
- Kresowik TP, Johnson MT, Joudi FN. Combined Renal Sinus Fat and Perinephric Fat Renal Cell Carcinoma Invasion has a Worse Prognosis Than Either Alone. *J Urol* (2010) 184(1):48–52. doi: 10.1016/j.juro.2010.03.010
- Park M, Shim M, Kim M, Song C, Kim CS, Ahn H. Prognostic Heterogeneity in T3aN0M0 Renal Cell Carcinoma According to the Site of Invasion. Urol Oncol (2017) 35(7):458.e417–58.e422. doi: 10.1016/j.urolonc.2016.05.019
- Guo S, Liu Z, Li X, Yao K, Dong P, Chen D, et al. The Prognostic Value of the Site of Invasion in T3aN0M0 Clear Cell Renal Cell Carcinoma. *Urol Oncol* (2019) 37(5):301.e311–301.e317. doi: 10.1016/j.urolonc.2019.01.019
- da Costa WH, Moniz RR, da Cunha IW, Fonseca FP, Guimaraes GC, de Cassio Zequi S. Impact of Renal Vein Invasion and Fat Invasion in pT3a Renal Cell Carcinoma. *BJU Int* (2012) 109(4):544–8. doi: 10.1111/j.1464-410X.2011.10366.x

- Baccos A, Brunocilla E, Schiavina R, Borghesi M, Rocca GC, Chessa F, et al. Differing Risk of Cancer Death Among Patients With Pathologic T3a Renal Cell Carcinoma: Identification of Risk Categories According to Fat Infiltration and Renal Vein Thrombosis. *Clin Genitourin Cancer* (2013) 11(4):451–7. doi: 10.1016/j.clgc.2013.05.006
- Flood TA, Hogan K, Lavallee LT, Breau RH, Morash C, Belanger EC, et al. Evaluation of Individual and Cumulative Sites of Extrarenal Tumor Invasion in pT3a Clear Cell Renal Cell Carcinoma. Urol Oncol (2020) 38(2):42.e13–8. doi: 10.1016/j.urolonc.2019.09.030
- 22. Schiavina R, Borghesi M, Chessa F, Dababneh H, Bianchi L, Della Mora L, et al. The Prognostic Impact of Tumor Size on Cancer-Specific and Overall Survival Among Patients With Pathologic T3a Renal Cell Carcinoma. *Clin Genitourin Cancer* (2015) 13(4):e235–41. doi: 10.1016/j.clgc.2014.06.011
- Peng D, He ZS, Li XS, Tang Q, Zhang L, Yang KW, et al. Partial Nephrectomy for T3aN0M0 Renal Cell Carcinoma: Shall We Step Forward? *Int Braz J Urol* (2017) 43(5):849–56. doi: 10.1590/S1677-5538.IBJU.2016.0598
- 24. Chen L, Ma X, Li H, Gu L, Li X, Gao Y, et al. Influence of Tumor Size on Oncological Outcomes of Pathological T3aN0M0 Renal Cell Carcinoma Treated by Radical Nephrectomy. *PLoS One* (2017) 12(3):e0173953. doi: 10.1371/journal.pone.0173953
- 25. Capitanio U, Stewart GD, Klatte T, Akdogan B, Roscigno M, Marszalek M, et al. Does the Unexpected Presence of Non-organ-confined Disease At Final Pathology Undermine Cancer Control in Patients With Clinical T1n0m0 Renal Cell Carcinoma Who Underwent Partial Nephrectomy? *Eur Urol Focus* (2018) 4(6):972–7. doi: 10.1016/j.euf.2017.02.020
- Bailey GC, Boorjian SA, Ziegelmann MJ, Westerman ME, Lohse CM, Leibovich BC, et al. Urinary Collecting System Invasion is Associated With Poor Survival in Patients With Clear-Cell Renal Cell Carcinoma. *BJU Int* (2017) 119(4):585–90. doi: 10.1111/bju.13669
- 27. Garcia Marchinena P, Tobia I, Abreu D, de Cassio Zequi S, Jurado A, Gueglio G, et al. Prognostic Value of Perirenal and/or Sinus Fat Infiltration in Patients With pT3a Renal Cell Carcinoma: A Multicentre Cohort Study. LARCG Group. Actas Urol Esp (2019) 43(9):495–502. doi: 10.1016/j.acuro.2019.01.005
- Lai GS, Li JR, Wang SS, Chen CS, Yang CK, Hung SC, et al. Prognostic Evaluation of the Site of Invasion in Pathological Stage T3a Renal Cell Carcinoma. In Vivo (2021) 35(2):1083–9. doi: 10.21873/invivo.12353
- Verhoest G, Avakian R, Bensalah K, Thuret R, Ficarra V, Artibani W, et al. Urinary Collecting System Invasion is an Independent Prognostic Factor of Organ Confined Renal Cell Carcinoma. J Urol (2009) 182(3):854–9. doi: 10.1016/j.juro.2009.05.017
- Anderson CB, Clark PE, Morgan TM, Stratton KL, Herrell SD, Davis R, et al. Urinary Collecting System Invasion is a Predictor for Overall and Disease-Specific Survival in Locally Invasive Renal Cell Carcinoma. Urology (2011) 78 (1):99–104. doi: 10.1016/j.urology.2011.02.039
- Chen L, Ma X, Li H, Li X, Gao Y, Zhang Y, et al. Invasion of the Urinary Collecting System is an Independent Prognostic Factor in pT3 Renal Cell Carcinoma. Urol Oncol (2016) 34(7):293 e211–296. doi: 10.1016/j.urolonc.2016.02.019
- Palapattu GS, Pantuck AJ, Dorey F, Said JW, Figlin RA, Belldegrun AS. Collecting System Invasion in Renal Cell Carcinoma: Impact on Prognosis and Future Staging Strategies. J Urol (2003) 170(3):768–72; discussion 772. doi: 10.1097/01.ju.0000082580.13597.a2
- 33. Srivastava A, Patel HD, Joice GA, Semerjian A, Gorin MA, Johnson MH, et al. Incidence of T3a Up-Staging and Survival After Partial Nephrectomy: Sizestratified Rates and Implications for Prognosis. Urol Oncol (2018) 36(1):12 e17–.e13. doi: 10.1016/j.urolonc.2017.09.005
- Shvero A, Nativ O, Abu-Ghanem Y, Zilberman D, Zaher B, Levitt M, et al. Oncologic Outcomes of Partial Nephrectomy for Stage T3a Renal Cell Cancer. *Clin Genitourin Cancer* (2018) 16(3):e613–7. doi: 10.1016/j.clgc.2017.10.016
- 35. Murphy AM, Gilbert SM, Katz AE, Goluboff ET, Sawczuk IS, Olsson CA, et al. Re-Evaluation of the Tumour-Node-Metastasis Staging of Locally Advanced Renal Cortical Tumours: Absolute Size (T2) is More Significant Than Renal Capsular Invasion (T3a). *BJU Int* (2005) 95(1):27–30. doi: 10.1111/j.1464-410X.2005.05244.x
- 36. Kirkali Z, Algaba F, Scarpelli M, Trias I, Selvaggi FP, Van Poppel H. What Does the Urologist Expect From the Pathologist (and What can the Pathologists Give) in Reporting on Adult Kidney Tumour Specimens? *Eur* Urol (2007) 51(5):1194–201. doi: 10.1016/j.eururo.2006.11.024
- Grignon D, Paner GP. Renal Cell Carcinoma and the Renal Sinus. Adv Anat Pathol (2007) 14(2):63–8. doi: 10.1097/PAP.0b013e318032452e

- Wood EL, Adibi M, Qiao W, Brandt J, Zhang M, Tamboli P, et al. Local Tumor Bed Recurrence Following Partial Nephrectomy in Patients With Small Renal Masses. J Urol (2018) 199(2):393–400. doi: 10.1016/j.juro.2017.09.072
- 39. Shah PH, Moreira DM, Okhunov Z, Patel VR, Chopra S, Razmaria AA, et al. Positive Surgical Margins Increase Risk of Recurrence After Partial Nephrectomy for High Risk Renal Tumors. J Urol (2016) 196(2):327–34. doi: 10.1016/j.juro.2016.02.075
- 40. Shah PH, Moreira DM, Patel VR, Gaunay G, George AK, Alom M, et al. Partial Nephrectomy is Associated With Higher Risk of Relapse Compared With Radical Nephrectomy for Clinical Stage T1 Renal Cell Carcinoma Pathologically Up Staged to T3a. J Urol (2017) 198(2):289–96. doi: 10.1016/j.juro.2017.03.012
- Bensalah K, Pantuck AJ, Rioux-Leclercq N, Thuret R, Montorsi F, Karakiewicz PI, et al. Positive Surgical Margin Appears to Have Negligible Impact on Survival of Renal Cell Carcinomas Treated by Nephron-Sparing Surgery. *Eur Urol* (2010) 57(3):466–71. doi: 10.1016/j.eururo.2009.03.048
- 42. Tabayoyong W, Abouassaly R, Kiechle JE, Cherullo EE, Meropol NJ, Shah ND, et al. Variation in Surgical Margin Status by Surgical Approach Among Patients Undergoing Partial Nephrectomy for Small Renal Masses. J Urol (2015) 194(6):1548–53. doi: 10.1016/j.juro.2015.06.076
- 43. Tellini R, Antonelli A, Tardanico R, Fisogni S, Veccia A, Furlan MC, et al. Positive Surgical Margins Predict Progression-Free Survival After Nephronsparing Surgery for Renal Cell Carcinoma: Results From a Single Center Cohort of 459 Cases With a Minimum Follow-Up of 5 Years. *Clin Genitourin Cancer* (2019) 17(1):e26–31. doi: 10.1016/j.clgc.2018.08.004
- 44. Shimizu T, Miyake M, Hori S, Iida K, Ichikawa K, Sakamoto K, et al. Clinical Significance of Tumor Size, Pathological Invasion Sites Including Urinary Collecting System and Clinically Detected Renal Vein Thrombus as Predictors for Recurrence in Pt3a Localized Renal Cell Carcinoma. *Diagn (Basel)* (2020) 10(3):154–66. doi: 10.3390/diagnostics10030154
- Chevinsky M, Imnadze M, Sankin A, Winer A, Mano R, Jakubowski C, et al. Pathological Stage T3a Significantly Increases Disease Recurrence Across All Tumor Sizes in Renal Cell Carcinoma. J Urol (2015) 194(2):310–5. doi: 10.1016/j.juro.2015.02.013
- 46. Chen K, Lee BL, Huang HH, Tan BY, Lee LS, Ng LG, et al. Tumor Size and Fuhrman Grade Further Enhance the Prognostic Impact of Perinephric Fat Invasion and Renal Vein Extension in T3a Staging of Renal Cell Carcinoma. *Int J Urol* (2017) 24(1):51–8. doi: 10.1111/iju.13237
- Lam JS, Klatte T, Patard JJ, Goel RH, Guille F, Lobel B, et al. Prognostic Relevance of Tumour Size in T3a Renal Cell Carcinoma: A Multicentre Experience. *Eur Urol* (2007) 52(1):155–62. doi: 10.1016/j.eururo.2007.01.106
- Siddiqui SA, Frank I, Leibovich BC, Cheville JC, Lohse CM, Zincke H, et al. Impact of Tumor Size on the Predictive Ability of the pT3a Primary Tumor Classification for Renal Cell Carcinoma. J Urol (2007) 177(1):59–62. doi: 10.1016/j.juro.2006.08.069
- Yoo C, Song C, Hong JH, Kim CS, Ahn H. Prognostic Significance of Perinephric Fat Infiltration and Tumor Size in Renal Cell Carcinoma. *J Urol* (2008) 180(2):486–91; discussion 491. doi: 10.1016/j.juro.2008.04.034
- Dabestani S, Beisland C, Stewart GD, Bensalah K, Gudmundsson E, Lam TB, 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(1):14–20. doi: 10.1080/21681805.2019.1588919
- Lenis AT, Donin NM, Johnson DC, Faiena I, Salmasi A, Drakaki A, et al. Adjuvant Therapy for High Risk Localized Kidney Cancer: Emerging Evidence and Future Clinical Trials. J Urol (2018) 199(1):43–52. doi: 10.1016/j.juro.2017.04.092
- 52. Gross-Goupil M, Kwon TG, Eto M, Ye D, Miyake H, Seo SI, et al. Axitinib Versus Placebo as an Adjuvant Treatment of Renal Cell Carcinoma: Results From the Phase III, Randomized ATLAS Trial. *Ann Oncol* (2018) 29 (12):2371–8. doi: 10.1093/annonc/mdy454
- 53. Eisen T, Frangou E, Oza B, Ritchie AWS, Smith B, Kaplan R, et al. Adjuvant Sorafenib for Renal Cell Carcinoma At Intermediate or High Risk of Relapse: Results From the SORCE Randomized Phase Iii Intergroup Trial. *J Clin Oncol* (2020) 38(34):4064–75. doi: 10.1200/JCO.20.01800
- Massari F, Di Nunno V, Mollica V, Graham J, Gatto L, Heng D. Adjuvant Tyrosine Kinase Inhibitors in Treatment of Renal Cell Carcinoma: A Meta-Analysis of Available Clinical Trials. *Clin Genitourin Cancer* (2019) 17(2): e339–44. doi: 10.1016/j.clgc.2018.12.011
- 55. Gu L, Li H, Wang Z, Wang B, Huang Q, Lyu X, et al. A Systematic Review and Meta-Analysis of Clinicopathologic Factors Linked to Oncologic Outcomes for

Renal Cell Carcinoma With Tumor Thrombus Treated by Radical Nephrectomy With Thrombectomy. *Cancer Treat Rev* (2018) 69:112–20. doi: 10.1016/ j.ctrv.2018.06.014

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Guo, Wang, Han, Wei, Zhao, Li, Jiang and Luo. This is an openaccess article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.