REVIEW ARTICLE

Vol. 48 (3): 406-455, May - June, 2022
doi: 10.1590/S1677-5538.IBJU.2020.1032

Impact of pathological factors on survival in patients with upper tract urothelial carcinoma: a systematic review and meta-analysis

Gopal Sharma [1], Anuj Kumar Yadav [1], Tarun Pareek [1], Pawan Kaundal [1], Shantanu Tyagi [1], Sudheer Kumar Devana [1], Shrawan Kumar Singh [1]

[1] *Department of Urology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

ABSTRACT

Introduction: There is an ongoing need to identify various pathological factors that can predict various survival parameters in patients with upper tract urothelial carcinoma (UTUC). With this review, we aim to scrutinize the impact of several pathological factors on recurrence free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) in patients with UTUC.

Materials and Methods: Systematic electronic literature search of various databases was conducted for this review. Studies providing multivariate hazard ratios (HR) for various pathological factors such as tumor margin, necrosis, stage, grade, location, architecture, lymph node status, lymphovascular invasion (LVI), carcinoma in situ (CIS), multifocality and variant histology as predictor of survival parameters were included and pooled analysis of HR was performed.

Results: In this review, 63 studies with 35.714 patients were included. For RFS, all except tumor location (HR 0.94, p=0.60) and necrosis (HR 1.00, p=0.98) were associated with worst survival. All the pathological variables except tumor location (HR 0.95, p=0.66) were associated with worst CSS. For OS, only presence of CIS (HR 1.03, p=0.73) and tumor location (HR 1.05, p=0.74) were not predictor of survival.

Conclusions: We noted tumor grade, stage, presence of LVI, lymph node metastasis, hydronephrosis, variant histology, sessile architecture, margin positivity and multifocality were associated with poor RFS, CSS and OS. Presence of CIS was associated with poor RFS and CSS but not OS. Tumor necrosis was associated with worst CSS and OS but not RFS. Tumor location was not a predictor of any of the survival parameters.

ARTICLE INFO


Shantanu Tyagi
http://orcid.org/0000-0001-6621-7120

Keywords:
Carcinoma, Transitional Cell; Pathology; Prognosis

Int Braz J Urol. 2022; 48: 406-55

Submitted for publication:
November 20, 2020

Accepted after revision:
March 29, 2021

Published as Ahead of Print:
April 20, 2021

INTRODUCTION

Upper tract urothelial carcinomas (UTUCs) are rare but aggressive malignancies, accounting for about 5-10% of all urothelial cancers (1). They have an estimated incidence of around 2 cases per 100.000 person-year in the United States (1, 2). Radical nephroureterectomy with bladder cuff excision with or without lymph node dissection is the cornerstone for the management of these cases (3). Until recently, data on the use of systemic chemotherapy either in the adjuvant or neoadjuvant setting was based on small retrospective studies (4). Only in a recently reported phase III randomi-

zed controlled trial (RCT), definite survival advantage with adjuvant chemotherapy has been shown (5). Multiple prognostic factors have been implicated with survival outcomes in patients with UTUCs. These prognostic factors have been conveniently divided into clinical, surgical and pathological factors (3, 6). Besides, several molecular markers have been associated with prognosis in UTUCs in various single or multicenter studies (6, 7). The purpose of these prognostic markers is to identify patients with aggressive disease and institute prompt adjuvant therapy.

Some of the pathological factors such as tumor stage, lymph node metastasis, tumor grade, lymphovascular invasion (LVI) have been consistently reported as predictors of all the survival outcomes i.e. recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) (6). The literature on the other pathological factors such as the presence of tumor necrosis (8, 9), carcinoma in situ (CIS) (10-12), variant histology (13-19) and multifocality (20-22) as prognostic factors for survival in UTUC is still conflicting concerning for different survival outcomes. Data for these pathological factors have been mostly derived from retrospective observational studies. Some of these pathological variables have been individually evaluated in systematic reviews as a predictor of survival parameters (23-25). However, these studies had multiple limitations (including data from overlapping patient population studies, limited search) and were not methodologically adequate (24, 25). Furthermore, there has been only one review that assessed various clinical-pathological factors associated with intravesical recurrence in patients with UTUC (26). To the best of our knowledge, there hasn't been a systematic review examining all the pathological variables for all the clinically essential survival outcomes i.e. CSS, RFS and OS following surgical management for patients with UTUC. Thus, this systematic review aimed to scrutinize the survival predictability of various pathological variables (such as tumor necrosis) for which literature is still conflicting and generate pooled hazard ratios (HR) for other pathological factors for all the relevant survival parameters (OS, CSS and RFS) in a single study.

MATERIALS AND METHODS

Study Design

With this study, we comprehensively explored all the available literature regarding various pathological factors implicated in the survival of patients with UTUCs. We included all the studies where data on multivariable analysis predicting various survival outcomes such as CSS, OS and RFS were available. From each of these studies, HR for different pathological variables was extracted for quantitative analysis. While conducting this review standard preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (27) were followed. The study protocol was registered with PROSPERO (CRD42020184885).

Search Strategy and selection criteria

The literature search for this review was conducted by two review authors independently (GS & TP). Multiple electronic databases such as Pubmed/Medline, Scopus, Embase, CENTRAL and Web of Science were used for conducting the literature search. The literature search was conducted from the date of inception of these databases till the last search on 29th March 2020. Following filters were applied [Species--Humans] and [Language-English]. Additional articles were sought from the articles selected for the full-text review.

We followed the PICO (patient/population, intervention, control, outcome) methodology to design our search strategy.

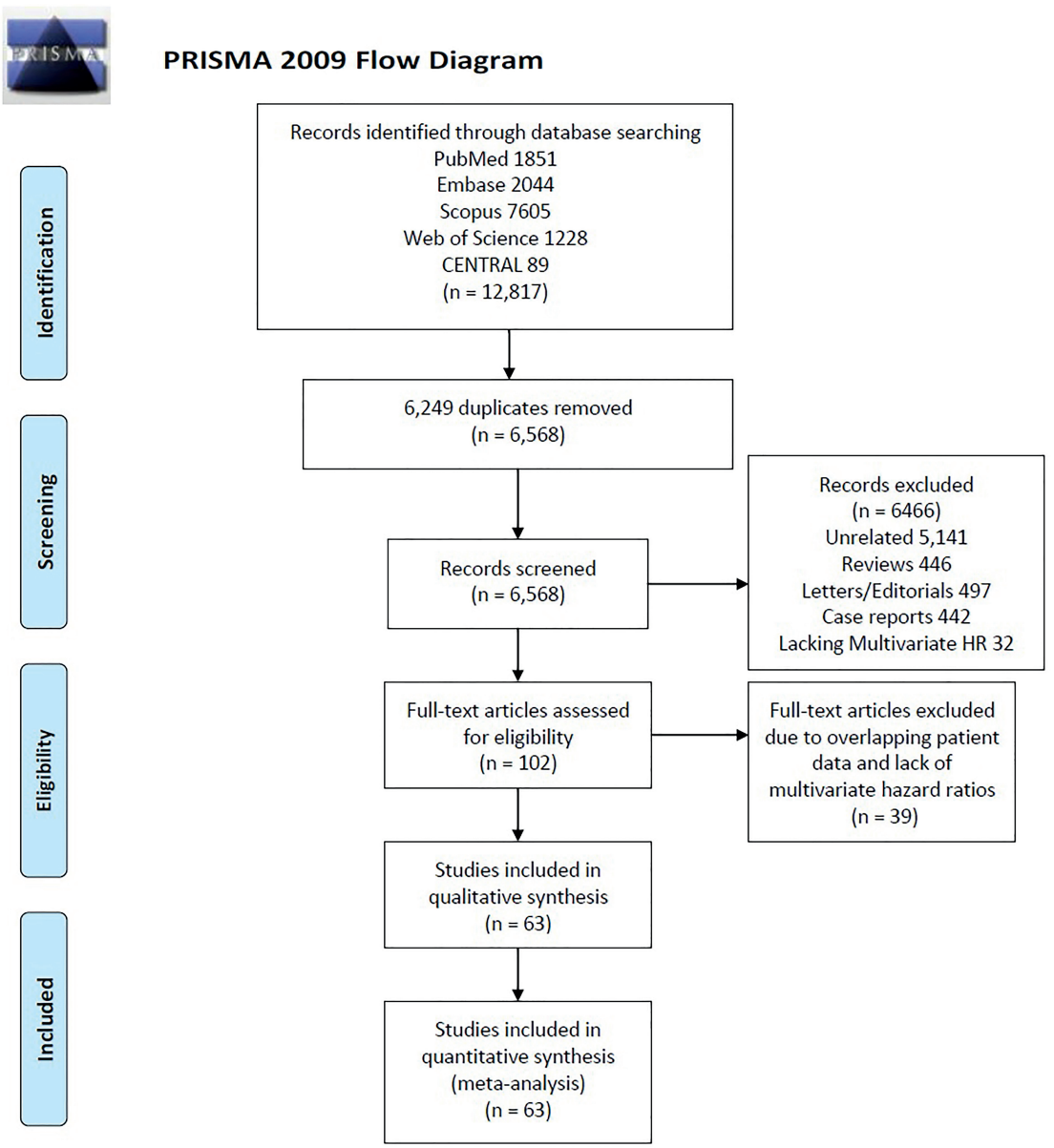
Patient/population: Upper tract urothelial carcinoma, upper tract urothelial cancer, UTUC

Control/Intervention: stage, grade, lymphovascular invasion, LVI, tumor necrosis, margin, tumor margin, carcinoma in situ, CIS, multifocality, architecture, sessile, pathology, pathological, variant histology, tumor location.

Outcome: prognosis, prognostic, survival.

Both key words and meshed terms were used to develop the search strategy. Key words used for this study were "upper tract urothelial carcinoma" OR "upper tract urothelial cancer" OR "UTUC" AND "stage" OR "grade" OR "lymphovascular invasion" OR "LVI OR "tumor

Figure 1 - PRISMA flow-chart depicting search strategy used for conducting this review.



necrosis" OR "margin" OR "tumor margin" OR "carcinoma in situ" OR "CIS" OR "multifocality" OR "architecture" OR "sessile" OR "pathology" OR "pathological" OR "variant histology" OR "location" AND "prognosis" OR "prognostic" OR "survival" OR "outcome".

The search strategy used for PubMed has been provided in supplementary file S1 (Appendix-1).

Statistical Analysis

Forest plots were used to perform quantitative analysis of multivariate HR and generate pooled HR to describe relation between a particular pathological variable and survival parameters (CSS, OS and RFS). For T- stage of the tumor we performed a pooled analysis of HR of those studies that only compared stage T_3 and T_4 stages against

T_{is}, T_1 and T_2. For assessment of grade, we used HR describing the relation between high grade and low-grade tumor for survival outcomes. Similarly, pooled HRs was generated for variant histology (absence or presence), tumor necrosis (absence or presence), LVI (absence or presence), multifocality (absence or presence), CIS (absence or presence), margin status (negative or positive), tumor architecture (papillary or sessile), tumor location (ureter vs. renal pelvis), and lymph node metastasis (absence or presence) in relation to various survival parameters (CSS, OS and RFS). Statistical analysis was performed using the Cochrane Collaboration review manager software RevMan 5.2™ (the Cochrane Collaboration, Copenhagen, Denmark). Chi^2 and I^2 tests were used to assess heterogeneity across each variable in the quantitative analysis. A p-value <0.10 was used to indicate significant heterogeneity and in such a case Random effect model was used. Whereas, p-value was >0.10 signifies absence of statistical heterogeneity and in such a case fixed-effects model (Mantel-Haenszel method) was used. A p-value of <0.05 was considered statistically significant.

Outcomes

Survival parameters (CSS, OS & RFS) were assessed according to various pathological factors such as stage (T_{is}, T_A, T_1 & T_2 vs. T_3 & T_4), tumor grade (low versus high), variant histology (absence vs. presence), tumor necrosis (absence vs. presence), LVI (absence vs. presence), multifocality (absence vs. presence), tumor location (ureter vs. renal pelvis), CIS (absence vs. presence) and margin status (negative vs. positive), tumor architecture (papillary vs. sessile) and lymph node metastasis (absence vs. presence). Recurrence-free survival was defined as the absence of extraluminal metastasis (local surgical site recurrence, distant metastasis, local and distant metastatic lymph nodes). Studies including only bladder or contralateral upper urinary tract were not included in recurrences free survival calculations. We initially also planned to study tumor size variable, however pooled analysis was not possible due to lack of consistent data for this parameter. Some studies had reported tumor size as a continuous variable and others as a categorical variable with variable cut-offs. Impact of other clinical parameters such as mode of surgery (open or minimally invasive) or chemotherapy (adjuvant and neoadjuvant) were not a part of this study.

Quality assessment

We used the Newcastle-Ottawa quality assessment scale (NOS) for the quality assessment of the studies included in this review. Using this scale quality assessment of non-randomized studies was done based upon selection and comparability of study groups and ascertainment of the primary outcome in the two groups. A study can be awarded a maximum of 9 stars, studies with >5 stars are considered to be of good quality. Quality assessment was performed by two review authors (GS & TP) independently and the help of other authors was sought in case of discrepancy of results (AKR & PMK).

RESULTS

Search strategy and study selection

Using various electronic databases mentioned above, a total of 12.817 articles were extracted of which 6.249 duplicate citations were removed. A total of 6.568 articles underwent initial title and abstract screening of which 6.466 articles were excluded for not meeting the inclusion criteria. Full-text reviews of 102 articles were performed of which 39 articles were removed due to overlapping patient data and lack of multivariate HR. For the final analysis, 63 studies were included in this meta-analysis (supplementary file S2 – Appendix-1).

Study characteristics and quality assessment

A total of 63 studies were included in the final analysis with 35.714 patients. All the included studies were retrospective in nature and 30 were multicenter. The duration of follow-up and variables adjusted in multivariate analysis were variable in all the studies (Supplementary Table-2). Further details on age, stage, LVI, tumor necrosis, factors controlled in multivariate analysis and survival parameters studies across the studies have been provided in supplementary Table-S3 (Appendix-1). Quality assessment as performed

using NOS revealed stars ranging from 6-8, with 26, 34 and 3 studies being awarded 6, 7 and 8 stars respectively.

Pooled analysis

Tumor location (Ureter versus renal pelvis)

Multivariate HRs for tumor location concerning to RFS, CSS and OS were available from 3, 5 and 3 studies respectively. Pooled HR for the RFS, CSS and OS were 0.94 (0.75, 1.18), 0.95 (0.78, 1.17) and 1.05 (0.80, 1.36) respectively. There was no statistically significant difference for the pooled HR for any of the survival outcomes.

Stage of the tumor

Of all the studies, data comparing T3 and T4 to lower stages of the tumor was available from 14, 22 and 16 studies for RFS, CSS and OS respectively. Higher tumor stage was significant predictor of recurrence (HR 2.43, 95% CI (1.86, 3.17), p <0.00001), poor CSS (HR 2.69, 95% CI (2.28, 3.18), p <0.00001) and poor OS (HR 2.45, 95% CI (2.19, 2.73), p <0.00001).

Grade of the tumor

Data on comparison for the high-grade to the low-grade tumor was available for RFS, CSS and OS from 22, 38 and 23 studies respectively. Higher tumor grade was associated with poor survival outcomes with significantly higher HRs i.e. RFS (HR 1.39, 95% CI (1.17, 1.65), p <0.00001), CSS (HR 1.69, 95% CI (1.45, 1.98), p <0.00001) and OS (HR 1.60, 95% CI (1.44, 1.77), p <0.00001) (Appendix-2).

LVI and positive lymph nodes

The presence or absence of LVI for RFS, CSS and OS were noted in 27, 36 and 21 studies respectively, whereas data on the positivity of lymph nodes was available from 23, 36 and 21 studies for RFS, CSS and OS respectively. Both presence of LVI and lymph node positivity were associated with significantly higher HRs for all three survival parameters. Pooled HRs for LVI and positive lymph nodes were 1.73 (95% CI (1.47, 2.03) and 2.22 (95% CI (1.88, 2.62) respectively for RFS. Pooled HRs for CSS was 2.03 (95% CI (1.74, 2.36) and 2.24 (95% CI (1.99, 2.52) for LVI and lymph node positivity. For OS pooled HRs were 1.60 (95% CI (1.37, 1.87) for LVI and 2.02 (95% CI (1.72, 2.39) for positive lymph nodes (Appendix-2).

Architecture of the tumor (papillary versus sessile)

Quantitative data on multivariate HR for tumor architecture was available from 12, 12 and 8 studies for RFS, CSS and OS respectively. Sessile tumor architecture was associated with significantly higher HR for RFS (1.48 (95% CI (1.20, 1.83)), CSS (1.47 (95% CI (1.22, 1.76)) and OS (1.58 (95% CI (1.26, 1.99)) (Appendix-2).

Multifocality and presence of CIS

The presence of multiple tumors and CIS were associated with significantly higher HR for all the survival parameters except for one (CIS for OS). For RFS pooled HR was 1.14 (95% CI (1.02, 1.29) for CIS and 1.52 (95% CI (1.13, 2.04) for multifocality, for CSS pooled HR were 1.21 (95% CI (1.06, 1.38) for CIS and 1.33 (95% CI (1.12, 1.59) for multifocality, for OS pooled HR were 1.05 (95% CI (0.87, 1.25) for CIS and 1.50 (95% CI (1.28, 1.76) for multifocality (Appendix-2).

Tumor margin positivity and necrosis

From the pooled analysis of all the studies with available data on surgical margin status, we noted positive surgical margin was associated with the worst RFS (HR 1.38, 95%CI (1.20, 1.59), p <0.00001), CSS (HR 1.59, 95% CI (1.36, 1.87), p <0.00001) and OS (HR 1.71, 95% CI (1.34, 2.19), p <0.0001). Presence of tumor necrosis was significant predictor of poor CSS (HR 1.47, 95% CI (1.08, 1.99), p=0.01) and OS (HR 1.77, 95% CI (1.05, 2.95), p=0.03) but not RFS (HR 1.00, 95% CI (0.86, 1.16), p=0.98).

Variant histology

As previously mentioned, some studies have described specifically the subtype of variant histology whereas others have not. The presence of variant histology was associated with significantly worst survival parameters i.e. RFS (HR 1.48, 95% CI (1.31, 1.66), p <0.00001), CSS (HR 1.86, 95% CI (1.51, 2.30), p <0.00001) and OS (HR 1.74, 95% CI (1.47-2.05), p <0.00001) (Appendix-2).

DISCUSSION

UTUCs are considered to be one of the most aggressive urological malignancies, around 60% of cases have muscle invasion compared to 15-25% of the bladder tumors at diagnosis (28, 29). One of the vexing issues associated with their management is the high rates of the bladder (22-47%) and contralateral upper tract (2-6%) recurrences following treatment (30-32). To prognosticate and intensify the treatment regimens according to the patient-specific risk factors, a risk-adapted classification has been provided in the European Association of Urology (EAU) guidelines (3). Many pathological factors are considered important prognostic factors and guidelines recommend explicit reporting of such elements in the final pathology. As previously noted, the role of some of the pathological factors as an independent predictor is not clear as the data are conflicting. In a previous meta-analysis by Seisen et al. (26), assessing risk for intravesical recurrence for various clinic-pathological factors; the authors noted ureter tumor location, multifocality, pathological T stage, tumor necrosis and positive surgical margin were independent predictors of intravesical recurrence and, LVI, concomitant CIS, tumor grade, and positive lymph node status were not identified as independent predictors of intravesical recurrence. The above mentioned-review despite being exhaustive and methodologically sound was limited by the fact that they only studied the risk factors for intravesical recurrence. Thus, the clinical relevance of this review becomes more as no previously conducted review has examined all the pathological factors at the same time for all the survival outcomes.

In this large systematic review, a total of 63 studies with 35.714 patients were included. Most of the studies included in this review were multicenter and retrospective case series. Quality assessment performed using NOS and all the studies scored more than 6 on this scale implying that all the studies were of adequate quality. However, caution should be exerted while interpreting the results of this review as the results have been pooled from retrospective case series which are inherently at risk of bias. With the paucity of properly conducted prospective studies, this study remains the best evidence available so far in the literature.

In this study, pooled analysis for survival outcomes (RFS, CSS and OS) for 11 pathological variables was performed (Table-1). For RFS, all the pathological variables except tumor location and necrosis were associated with significantly higher pooled HRs. Thus, for RFS tumor location and necrosis were not predictors of survival. For CSS, all the variables except tumor location were identified as independent predictors and for OS all but tumor location and presence of CIS were independent predictors. In a previous meta-analysis by Ku et al. (33), authors noted LVI to be a predictor of RFS and CSS but not OS, on the contrary, we noted LVI to be a predictor of all the survival parameters (CSS, OS, RFS). Compared to the study by Ku et al. (33) our study is much larger and most updated. In another meta-analysis, Fan et al. (24) noted sessile tumor architecture to be associated with worst the RFS and CSS, however, authors did not include OS in the analysis. Regarding presence of CIS, our findings are similar to a previous meta--analysis by Gao et al. (25), who also noted CIS to be associated with poor RFS and CSS but not OS. These two previously mentioned meta-analysis by Fan et al. (24) and Gao et al. (25) were of limited methodological quality as they contained studies with overlapping patient populations. For the presence of variant histology (23), our findings are similar to a previously reported meta-analysis on the topic by Mori et al. Another important point noted in our study is that tumor location is not an independent predictor of survival which is contrary to few individual studies (34, 35) in which ureter location was identified as an independent predictor of poor survival outcomes. However, we acknowledge that the pooled analysis for the location was derived from a handful number of studies which can be its limitation. Literature regarding tumor necrosis as an independent prognostic factor is controversial (8, 9). From our pooled analysis, we noted tumor necrosis to be associated with the worst CSS and OS but not RFS. Even after an exhaustive literature search, we could not find any systematic review reporting data on grade,

Table 1 - Survival analysis for various pathological factors with their pooled analysis.

Recurrence free survival								
S.no.	Variable	Number of studies	Chi^2	I^2	Model	Pooled HR	95% CI	p-value
1	Tumor location (ureter vs. pelvic)	3	2.99	33%	IV Fixed	0.94	0.75,1.18	0.60
2	T stage	14	60.11	78%	Random	2.43	1.86-3.17	<0.00001
3	Grade	22	46.86	55%	IV, Random	1.39	1.17, 1.65	0.0002
4	LVI	27	121.1	79%	IV, Random	1.73	1.47, 2.03	<0.00001
5	LN positivity	23	62.29	65%	IV, Random	2.22	1.88, 2.62	<0.00001
6	Architecture	12	43.27	75%	IV, Random	1.48	1.20, 1.83	0.0002
7	CIS	9	6.24	0%	IV Fixed	1.14	1.02, 1.29	0.02
8	Multifocality	7	22.39	73%	IV, Random	1.52	1.13, 2.04	0.006
9	Margin	9	7.93	0%	IV Fixed	1.38	1.20, 1.59	<0.00001
10	Necrosis	4	5.35	44%	IV, Random	1.00	0.86, 1.16	0.98
11	Variant Histology	11	16.27	26%	Fixed	1.48	1.31-1.66	<0.00001
Cancer specific survival								
S.no.	Variable	Number of studies	Chi^2	I^2	Model	Pooled HR	95% CI	p-value
1	Tumor location (ureter vs. pelvic)	5	3.66	0%	IV, Fixed	0.95	0.78,1.17	0.66
2	T stage	22	34.07	38%	Random	2.69	2.28-3.18	<0.00001
3	Grade	38	81.55	55%	IV, Random	1.69	1.45, 1.98	<0.00001
4	LVI	36	117.1	70%	IV, Random	2.03	1.74, 2.36	<0.00001
5	LN positivity	36	52.69	35%	IV, Random	2.24	1.99, 2.52	<0.00001
6	Architecture	12	22.9	52%	IV, Random	1.47	1.22, 1.76	<0.0001
7	CIS	17	14.31	0%	IV, Fixed	1.21	1.06, 1.38	0.004
8	Multifocality	14	27.7	53%	IV, Random	1.33	1.12, 1.59	0.001
9	Margin	12	13.53	19%	IV, Fixed	1.59	1.36, 1.87	<0.00001
10	Necrosis	8	20.14	65%	IV, Random	1.47	1.08, 1.99	0.01
11	Variant Histology	20	60.66	64%	IV, Random	1.86	1.51-2.30	<0.00001
Overall survival								
S.no.	Variable	Number of studies	Chi2	I2	Model	Pooled HR	95% CI	p-value
1	Tumor location (ureter vs. pelvic)	3	2.63	24%	IV, Fixed	1.05	0.80,1.36	0.74
2	T stage	16	10.86	0%	IV, Fixed	2.45	2.19-2.73	<0.00001
3	Grade	23	14.28	0%	IV, Fixed	1.60	1.44, 1.77	<0.00001
4	LVI	21	60.48	67%	IV, Random	1.60	1.37, 1.87	<0.00001
5	LN positivity	21	38.46	48%	IV, Random	2.02	1.72, 2.39	<0.00001
6	Architecture	8	19.73	65%	IV, Random	1.58	1.26, 1.99	<0.0001
7	CIS	8	2.8	0%	IV, Fixed	1.05	0.87, 1.25	0.63
8	Multifocality	10	8.75	0%	IV, Fixed	1.50	1.28, 1.76	<0.00001
9	Margin	10	21.07	57%	IV, Random	1.71	1.34, 2.19	<0.0001
10	Necrosis	5	8.5	53%	IV, Random	1.77	1.05, 2.95	0.03
11	Variant Histology	13	21.01	43%	IV, Random	1.74	1.47-2.05	<0.00001

HR= Hazard ratio; **CIS**= carcinoma in situ, **LN** = lymph node; **LVI**= lymphovascular invasion; **IV**= Inverse variance

stage, lymph node status, tumor location, tumor necrosis and margin status as predictors of survival in patients with UTUCs. Thus, our study is the first systematic review to provide pooled analysis for the above-mentioned pathological variables.

LIMITATIONS

There are multiple limitations of this study that needs to be highlighted. We acknowledge that the studies included in this study were observational studies that have inherent selection bias. Furthermore, the likelihood of reporting bias cannot be completely ruled out as negative trials have lower chances of publication. We also noted significant heterogeneity in the analysis of some pathological factors for survival parameters. For accounting for heterogeneity in the model we used the random-effects model. Since our review focused only on the impact of various pathological factors on oncological outcomes, we were not able to control for other multiple confounding factors. Firstly, different types of surgical methods have been employed for the treatment (open or laparoscopic or segmental ureterectomy). Secondly, lymph node dissection was performed in some and not in others. Thirdly, some studies had included patients with prior history of bladder cancer, a group associated with the poor prognosis. Lastly, the use of chemotherapy in an adjuvant or neoadjuvant setting could also influence the outcomes. Subgroup analysis, according to a number of adverse pathological factors was also not possible due to lack of data. We were also not able to perform pooled analyses for tumor size as it was reported differently in different studies. Some studies had reported it as a continuous variable and others had reported it as a dichotomous variable with different cut-offs. Most of the studies in this review lack a central review of pathological specimens and have been based on the interpretation of a single pathologist. Furthermore, many of the studies did not properly define various pathological characteristics such as LVI, site of margin positivity, percentage of tumor necrosis and percentage of variant histology in the tumor.

CONCLUSION

From this review, we noted tumor grade, stage, presence of LVI, lymph node metastasis, hydronephrosis, variant histology, sessile tumors, margin positivity and multifocality were associated with poor RFS, CSS and OS. The presence of CIS was associated with poor RFS and CSS but not OS. Tumor necrosis was associated with the worst CSS and OS but not RFS. Tumor location was not a predictor of any of the survival parameters.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. J Urol. 2000; 164:1523-5.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66:7-30.
3. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. Eur Urol. 2018; 73:111-22.
4. Leow JJ, Martin-Doyle W, Fay AP, Choueiri TK, Chang SL, Bellmunt J. A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. Eur Urol. 2014; 66:529-41.
5. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet. 2020; 395:1268-77.
6. Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol. 2012; 62:100-14.
7. Suyama T, Kanbe S, Maegawa M, Shimizu H, Nakajima K. Prognostic significance of inflammation-based prognostic scoring in patients with upper urinary tract urothelial carcinoma. Int Braz J Urol. 2019; 45:541-8.

8. Seitz C, Gupta A, Shariat SF, Matsumoto K, Kassouf W, Walton TJ, et al. Association of tumor necrosis with pathological features and clinical outcome in 754 patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma: an international validation study. J Urol. 2010; 184:1895-900.
9. Zigeuner R, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Weizer A, et al. Tumour necrosis is an indicator of aggressive biology in patients with urothelial carcinoma of the upper urinary tract. Eur Urol. 2010; 57:575-81.
10. Aydin AM, Singla N, Panwar V, Woldu SL, Freifeld Y, Wood CG, et al. Prognostic significance of BAP1 expression in high-grade upper tract urothelial carcinoma: a multi-institutional study. World J Urol. 2019; 37:2419-27.
11. Fairey AS, Kassouf W, Estey E, Tanguay S, Rendon R, Bell D, et al. Comparison of oncological outcomes for open and laparoscopic radical nephroureterectomy: results from the Canadian Upper Tract Collaboration. BJU Int. 2013; 112:791-7.
12. Kim TH, Hong B, Seo HK, Kang SH, Ku JH, Jeong BC. The Comparison of Oncologic Outcomes between Open and Laparoscopic Radical Nephroureterectomy for the Treatment of Upper Tract Urothelial Carcinoma: A Korean Multicenter Collaborative Study. Cancer Res Treat. 2019; 51:240-51.
13. Abe T, Kondo T, Harabayashi T, Takada N, Matsumoto R, Osawa T, et al. Comparative study of lymph node dissection, and oncological outcomes of laparoscopic and open radical nephroureterectomy for patients with urothelial carcinoma of the upper urinary tract undergoing regional lymph node dissection. Jpn J Clin Oncol. 2018; 48:1001-11.
14. Chung HS, Hwang EC, Kim MS, Yu SH, Jung SI, Kang TW, et al. Effects of Variant Histology on the Oncologic Outcomes of Patients With Upper Urinary Tract Carcinoma After Radical Nephroureterectomy: A Propensity Score-Matched Analysis. Clin Genitourin Cancer. 2019; 17:e394-e407.
15. Fang D, He S, Xiong G, Singla N, Cao Z, Zhang L, et al. Comparison of clinicopathologic characteristics, epigenetic biomarkers and prognosis between renal pelvic and ureteral tumors in upper tract urothelial carcinoma. BMC Urol. 2018; 18:22.
16. Hsieh MC, Sung MT, Chiang PH, Huang CH, Tang Y, Su YL. The Prognostic Impact of Histopathological Variants in Patients with Advanced Urothelial Carcinoma. PLoS One. 2015; 10:e0129268.
17. Kim JK, Moon KC, Jeong CW, Kwak C, Kim HH, Ku JH. Variant histology as a significant predictor of survival after radical nephroureterectomy in patients with upper urinary tract urothelial carcinoma. Urol Oncol. 2017; 35:458.e9-458.e15.
18. Lee YJ, Moon KC, Jeong CW, Kwak C, Kim HH, Ku JH. Impact of squamous and glandular differentiation on oncologic outcomes in upper and lower tract urothelial carcinoma. PLoS One. 2014; 9:e107027.
19. Masson-Lecomte A, Colin P, Bozzini G, Nison L, de La Taille A, Comperat E, et al. Impact of micropapillary histological variant on survival after radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol. 2014; 32:531-7.
20. Tang Q, Xiong G, Li X, Fang D, Xi C, Zhang L, et al. The prognostic impact of squamous and glandular differentiation for upper tract urothelial carcinoma patients after radical nephroureterectomy. World J Urol. 2016; 34:871-7.
21. Vartolomei MD, Mathieu R, Margulis V, Karam JA, Rouprêt M, Lucca I, et al. Promising role of preoperative neutrophil-to-lymphocyte ratio in patients treated with radical nephroureterectomy. World J Urol. 2017; 35:121-30.
22. Ichimura T, Morikawa T, Kawai T, Nakagawa T, Matsushita H, Kakimi K, et al. Prognostic significance of CD204-positive macrophages in upper urinary tract cancer. Ann Surg Oncol. 2014; 21:2105-12.
23. Mori K, Janisch F, Parizi MK, Mostafaei H, Lysenko I, Kimura S, et al. Prognostic Value of Variant Histology in Upper Tract Urothelial Carcinoma Treated with Nephroureterectomy: A Systematic Review and Meta-Analysis. J Urol. 2020; 203:1075-84.
24. Fan B, Hu B, Yuan Q, Wen S, Liu T, Bai S, et al. Impact of tumor architecture on disease recurrence and cancer-specific mortality of upper tract urothelial carcinoma treated with radical nephroureterectomy. Tumour Biol. 2017l; 39:1010428317710822.
25. Gao X, Ma Y, Chen G, Chen J, Li H, Li H, et al. Concomitant carcinoma in situ as a prognostic factor in the upper tract urothelial carcinoma after radical nephroureterectomy: A systematic review and meta-analysis. Urol Oncol. 2020; 38:574-81.
26. Seisen T, Granger B, Colin P, Léon P, Utard G, Renard-Penna R, et al. A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol. 2015; 67:1122-33.
27. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339:b2535.
28. Xylinas E, Rink M, Margulis V, Karakiewicz P, Novara G, Shariat SF; et al. Multifocal carcinoma in situ of the upper tract is associated with high risk of bladder cancer recurrence. Eur Urol. 2012; 61:1069-70.

29. Li WM, Shen JT, Li CC, Ke HL, Wei YC, Wu WJ, et al. Oncologic outcomes following three different approaches to the distal ureter and bladder cuff in nephroureterectomy for primary upper urinary tract urothelial carcinoma. Eur Urol. 2010; 57:963-9.
30. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009; 115:1224-33.
31. Qian S, Liang C, Ding Y, Wang C, Shen H. Preoperative hydronephrosis predicts adverse pathological features and postoperative survival in patients with high-grade upper tract urothelial carcinoma. Int Braz J Urol. 2021; 47:159-68.
32. Ko YH, Song PH, Park T, Choi JY. Retrograde pyelography before radical nephroureterectomy for upper tract urothelial carcinoma is associated with intravesical tumor recurrence. Int Braz J Urol. 2020; 46:778-85.
33. Ku JH, Byun SS, Jeong H, Kwak C, Kim HH, Lee SE. Lymphovascular invasion as a prognostic factor in the upper urinary tract urothelial carcinoma: a systematic review and meta-analysis. Eur J Cancer. 2013; 49:2665-80.
34. Ouzzane A, Colin P, Xylinas E, Pignot G, Ariane MM, Saint F, et al. Ureteral and multifocal tumours have worse prognosis than renal pelvic tumours in urothelial carcinoma of the upper urinary tract treated by nephroureterectomy. Eur Urol. 2011; 60:1258-65.
35. Yafi FA, Novara G, Shariat SF, Gupta A, Matsumoto K, Walton TJ, et al. Impact of tumour location versus multifocality in patients with upper tract urothelial carcinoma treated with nephroureterectomy and bladder cuff excision: a homogeneous series without perioperative chemotherapy. BJU Int. 2012; 110 (2 Pt 2) :E7-13.

Correspondence address:
Shantanu Tyagi, MS
Department of Urology,
Postgraduate Institute of
Medical Education and Research
Level II B Block, Advanced Urology Center,
PGIMER, Sector 12, Chandigarh 160012, India
Telephone: + 91 98183--02207
E-mail: metyagishantanu@gmail.com

APPENDIX 1

Supplementary Table 1 - Pubmed search with search query, search details and results

Query	Search Details	Results
((((Upper tract urothelial carcinoma) OR (Upper tract urothelial cancer)) OR (UTUC)) AND (((((((((((((location)) OR (variant histology)) OR (pathological)) OR (pathology)) OR (multifocality)) OR (sessile)) OR (architecture)) OR (CIS)) OR (carcinoma insitu)) OR (tumor margin)) OR (margin)) OR (tumor necrosis)) OR (LVI)) OR (lymphovascular invasion)) OR (grade)) OR (stage))) AND ((((outcome) OR (survival)) OR (prognostic)) OR (prognosis))	(((((("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND ((((("carcinoma, transitional cell"[MeSH Terms] OR (("carcinoma"[All Fields] AND "transitional"[All Fields]) AND "cell"[All Fields])) OR "transitional cell carcinoma"[All Fields]) OR ("urothelial"[All Fields] AND "carcinoma"[All Fields])) OR "urothelial carcinoma"[All Fields])) OR (("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND "urothelial"[All Fields] AND (((((((((("cancer s"[All Fields] OR "cancerated"[All Fields]) OR "canceration"[All Fields]) OR "cancerization"[All Fields]) OR "cancerized"[All Fields]) OR "cancerous"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "cancer"[All Fields]) OR "cancers"[All Fields])))) OR "UTUC"[All Fields]) AND (((((((((("locate"[All Fields] OR "located"[All Fields]) OR "locater"[All Fields]) OR "locates"[All Fields]) OR "locating"[All Fields]) OR "location"[All Fields]) OR "locational"[All Fields]) OR "locations"[All Fields]) OR "locator"[All Fields]) OR "locators"[All Fields])) OR ((("variant"[All Fields] OR "variant s"[All Fields]) OR "variants"[All Fields]) AND (((((("anatomy and histology"[MeSH Subheading] OR ("anatomy"[All Fields] AND "histology"[All Fields])) OR "anatomy and histology"[All Fields]) OR "histology"[All Fields]) OR "histology"[MeSH Terms]) OR "histologies"[All Fields])))) OR (((((("pathologic"[All Fields] OR "pathologically"[All Fields]) OR "pathologics"[All Fields]) OR "pathology"[MeSH Terms]) OR "pathology"[All Fields]) OR "pathological"[All Fields])) OR ((("pathology"[MeSH Terms] OR "pathology"[All Fields]) OR "pathologies"[All Fields]) OR "pathology"[MeSH Subheading])) OR ((("multifocal"[All Fields] OR "multifocality"[All Fields]) OR "multifocally"[All Fields]) OR "multifocals"[All Fields])) OR "sessile"[All Fields]) OR ((((((("architectural"[All Fields] OR "architecturally"[All Fields]) OR "architecture"[MeSH Terms]) OR "architecture"[All Fields]) OR "architecture s"[All Fields]) OR "architectured"[All Fields]) OR "architectures"[All Fields])) OR "CIS"[All Fields]) OR ((((("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR "carcinomas"[All Fields]) OR "carcinoma s"[All Fields]) AND "insitu"[All Fields])) OR ((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND (((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields])))) OR (((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All	1,851

	Fields])) OR ((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasms"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumors"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND ((((((("necrose"[All Fields] OR "necrosed"[All Fields]) OR "necrosi"[All Fields]) OR "necrosing"[All Fields]) OR "necrosis"[MeSH Terms]) OR "necrosis"[All Fields]) OR "necroses"[All Fields])))) OR "LVI"[All Fields]) OR ("lymphovascular"[All Fields] AND (((((((("invasibility"[All Fields] OR "invasible"[All Fields]) OR "invasion"[All Fields]) OR "invasions"[All Fields]) OR "invasive"[All Fields]) OR "invasively"[All Fields]) OR "invasiveness"[All Fields]) OR "invasives"[All Fields]) OR "invasivity"[All Fields]))) OR ((((("grade"[All Fields] OR "graded"[All Fields]) OR "grades"[All Fields]) OR "grading"[All Fields]) OR "gradings"[All Fields])) OR ((((("stage"[All Fields] OR "staged"[All Fields]) OR "stages"[All Fields]) OR "staging"[All Fields]) OR "stagings"[All Fields])))) AND ((((("outcome"[All Fields] OR "outcomes"[All Fields]) OR ((((((((("mortality"[MeSH Subheading] OR "mortality"[All Fields]) OR "survival"[All Fields]) OR "survival"[MeSH Terms]) OR "survivability"[All Fields]) OR "survivable"[All Fields]) OR "survivals"[All Fields]) OR "survive"[All Fields]) OR "survived"[All Fields]) OR "survives"[All Fields]) OR "surviving"[All Fields])))) OR ((((((((((("prognostic"[All Fields] OR "prognostical"[All Fields]) OR "prognostically"[All Fields]) OR "prognosticate"[All Fields]) OR "prognosticated"[All Fields]) OR "prognosticates"[All Fields]) OR "prognosticating"[All Fields]) OR "prognostication"[All Fields]) OR "prognostications"[All Fields]) OR "prognosticator"[All Fields]) OR "prognosticators"[All Fields]) OR "prognostics"[All Fields])))) OR (("prognosis"[MeSH Terms] OR "prognosis"[All Fields]) OR "prognoses"[All Fields]))	
((Upper tract urothelial carcinoma) OR (Upper tract urothelial cancer)) OR (UTUC)	((("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND ((((("carcinoma, transitional cell"[MeSH Terms] OR (("carcinoma"[All Fields] AND "transitional"[All Fields]) AND "cell"[All Fields])) OR "transitional cell carcinoma"[All Fields]) OR ("urothelial"[All Fields] AND "carcinoma"[All Fields])) OR "urothelial carcinoma"[All Fields])) OR ((("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND "urothelial"[All Fields] AND (((((((((("cancer s"[All Fields] OR "cancerated"[All Fields]) OR "canceration"[All Fields]) OR "cancerization"[All Fields]) OR "cancerized"[All Fields]) OR "cancerous"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "cancer"[All Fields]) OR "cancers"[All Fields]))) OR "UTUC"[All Fields]	3,368
((((((((((((((((location)) OR (variant histology)) OR (pathological)) OR (pathology)) OR (multifocality)) OR (sessile)) OR (architecture)) OR (CIS)) OR (carcinoma insitu)) OR (tumor margin)) OR (margin)) OR (tumor necrosis)) OR (LVI)) OR (lymphovascular invasion)) OR (grade)) OR (stage)	(((((((((("locate"[All Fields] OR "located"[All Fields]) OR "locater"[All Fields]) OR "locates"[All Fields]) OR "locating"[All Fields]) OR "location"[All Fields]) OR "locational"[All Fields]) OR "locations"[All Fields]) OR "locator"[All Fields]) OR "locators"[All Fields])) OR ((("variant"[All Fields] OR "variant s"[All Fields]) OR "variants"[All Fields]) AND (((((("anatomy and histology"[MeSH Subheading] OR ("anatomy"[All Fields] AND "histology"[All Fields])) OR "anatomy and histology"[All Fields]) OR "histology"[All Fields]) OR "histology"[MeSH Terms]) OR "histologies"[All Fields])))) OR (((((("pathologic"[All Fields] OR "pathologically"[All Fields]) OR "pathologics"[All Fields]) OR "pathology"[MeSH Terms]) OR "pathology"[All Fields]) OR "pathological"[All Fields])) OR ((("pathology"[MeSH Terms] OR "pathology"[All Fields]) OR	6,005,790

	"pathologies"[All Fields]) OR "pathology"[MeSH Subheading])) OR ((("multifocal"[All Fields] OR "multifocality"[All Fields]) OR "multifocally"[All Fields]) OR "multifocals"[All Fields])) OR "sessile"[All Fields]) OR ((((((("architectural"[All Fields] OR "architecturally"[All Fields]) OR "architecture"[MeSH Terms]) OR "architecture"[All Fields]) OR "architecture s"[All Fields]) OR "architectured"[All Fields]) OR "architectures"[All Fields])) OR "CIS"[All Fields]) OR ((((("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR "carcinomas"[All Fields]) OR "carcinoma s"[All Fields]) AND "insitu"[All Fields])) OR ((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND (((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields]))) OR (((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields])) OR ((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND ((((((("necrose"[All Fields] OR "necrosed"[All Fields]) OR "necrosi"[All Fields]) OR "necrosing"[All Fields]) OR "necrosis"[MeSH Terms]) OR "necrosis"[All Fields]) OR "necroses"[All Fields]))) OR "LVI"[All Fields]) OR ("lymphovascular"[All Fields] AND (((((((("invasibility"[All Fields] OR "invasible"[All Fields]) OR "invasion"[All Fields]) OR "invasions"[All Fields]) OR "invasive"[All Fields]) OR "invasively"[All Fields]) OR "invasiveness"[All Fields]) OR "invasives"[All Fields]) OR "invasivity"[All Fields]))) OR ((((("grade"[All Fields] OR "graded"[All Fields]) OR "grades"[All Fields]) OR "grading"[All Fields]) OR "gradings"[All Fields])) OR ((((("stage"[All Fields] OR "staged"[All Fields]) OR "stages"[All Fields]) OR "staging"[All Fields]) OR "stagings"[All Fields])	
(((outcome) OR (survival)) OR (prognostic)) OR (prognosis)	"outcome"[All Fields] OR "outcomes"[All Fields] OR "mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields] OR "prognostic"[All Fields] OR "prognostical"[All Fields] OR "prognostically"[All Fields] OR "prognosticate"[All Fields] OR "prognosticated"[All Fields] OR "prognosticates"[All Fields] OR "prognosticating"[All Fields] OR "prognostication"[All Fields] OR "prognostications"[All Fields] OR "prognosticator"[All Fields] OR "prognosticators"[All Fields] OR "prognostics"[All Fields] OR "prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]	4,432,884

outcome	"outcome"[All Fields] OR "outcomes"[All Fields]	2,461,422
survival	"mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields]	2,086,064
prognostic	"prognostic"[All Fields] OR "prognostical"[All Fields] OR "prognostically"[All Fields] OR "prognosticate"[All Fields] OR "prognosticated"[All Fields] OR "prognosticates"[All Fields] OR "prognosticating"[All Fields] OR "prognostication"[All Fields] OR "prognostications"[All Fields] OR "prognosticator"[All Fields] OR "prognosticators"[All Fields] OR "prognostics"[All Fields]	301,748
prognosis	"prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]	1,823,869
location	"locate"[All Fields] OR "located"[All Fields] OR "locater"[All Fields] OR "locates"[All Fields] OR "locating"[All Fields] OR "location"[All Fields] OR "locational"[All Fields] OR "locations"[All Fields] OR "locator"[All Fields] OR "locators"[All Fields]	771,575
variant histology	(("variant"[All Fields] OR "variant s"[All Fields]) OR "variants"[All Fields]) AND (((((("anatomy and histology"[MeSH Subheading] OR ("anatomy"[All Fields] AND "histology"[All Fields])) OR "anatomy and histology"[All Fields]) OR "histology"[All Fields]) OR "histology"[MeSH Terms]) OR "histologies"[All Fields])	74,389
pathological	"pathologic"[All Fields] OR "pathologically"[All Fields] OR "pathologics"[All Fields] OR "pathology"[MeSH Terms] OR "pathology"[All Fields] OR "pathological"[All Fields]	3,795,533
pathology	"pathology"[MeSH Terms] OR "pathology"[All Fields] OR "pathologies"[All Fields] OR "pathology"[MeSH Subheading]	3,554,131
multifocality	"multifocal"[All Fields] OR "multifocality"[All Fields] OR "multifocally"[All Fields] OR "multifocals"[All Fields]	33,181
Sessile	"sessile"[All Fields]	7,165
architecture	"architectural"[All Fields] OR "architecturally"[All Fields] OR "architecture"[MeSH Terms] OR "architecture"[All Fields] OR "architecture s"[All Fields] OR "architectured"[All Fields] OR "architectures"[All Fields]	171,172
CIS	"CIS"[All Fields]	123,073
carcinoma insitu	((("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR "carcinomas"[All Fields]) OR "carcinoma s"[All Fields]) AND "insitu"[All Fields]	1,315
tumor margin	((((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND ((((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields])	63,557
Margin	(((((("margin s"[All Fields] OR "marginal"[All Fields]) OR "marginals"[All Fields]) OR "margined"[All Fields])	159,816

	OR "margins of excision"[MeSH Terms]) OR ("margins"[All Fields] AND "excision"[All Fields])) OR "margins of excision"[All Fields]) OR "margin"[All Fields]) OR "margins"[All Fields]	
tumor necrosis	((((((((((((((((("cysts"[MeSH Terms] OR "cysts"[All Fields]) OR "cyst"[All Fields]) OR "neoplasm s"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "neoplasm"[All Fields]) OR "neurofibroma"[MeSH Terms]) OR "neurofibroma"[All Fields]) OR "neurofibromas"[All Fields]) OR "tumor s"[All Fields]) OR "tumoral"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumor"[All Fields]) OR "tumour s"[All Fields]) OR "tumoural"[All Fields]) OR "tumourous"[All Fields]) OR "tumours"[All Fields]) OR "tumors"[All Fields]) AND ((((((("necrose"[All Fields] OR "necrosed"[All Fields]) OR "necrosi"[All Fields]) OR "necrosing"[All Fields]) OR "necrosis"[MeSH Terms]) OR "necrosis"[All Fields]) OR "necroses"[All Fields])	254,227
LVI	"LVI"[All Fields]	1,509
lymphovascular invasion	"lymphovascular"[All Fields] AND (((((((("invasibility"[All Fields] OR "invasible"[All Fields]) OR "invasion"[All Fields]) OR "invasions"[All Fields]) OR "invasive"[All Fields]) OR "invasively"[All Fields]) OR "invasiveness"[All Fields]) OR "invasives"[All Fields]) OR "invasivity"[All Fields])	5,770
Grade	"grade"[All Fields] OR "graded"[All Fields] OR "grades"[All Fields] OR "grading"[All Fields] OR "gradings"[All Fields]	451,054
Stage	"stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]	1,203,520
UTUC	"UTUC"[All Fields]	869
Upper tract urothelial cancer	("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND "urothelial"[All Fields] AND (((((((("cancer s"[All Fields] OR "cancerated"[All Fields]) OR "canceration"[All Fields]) OR "cancerization"[All Fields]) OR "cancerized"[All Fields]) OR "cancerous"[All Fields]) OR "neoplasms"[MeSH Terms]) OR "neoplasms"[All Fields]) OR "cancer"[All Fields]) OR "cancers"[All Fields])	2,343
Upper tract urothelial carcinoma	("upper"[All Fields] OR "uppers"[All Fields]) AND (("tract"[All Fields] OR "tract s"[All Fields]) OR "tracts"[All Fields]) AND ((("carcinoma, transitional cell"[MeSH Terms] OR (("carcinoma"[All Fields] AND "transitional"[All Fields]) AND "cell"[All Fields])) OR "transitional cell carcinoma"[All Fields]) OR ("urothelial"[All Fields] AND "carcinoma"[All Fields])) OR "urothelial carcinoma"[All Fields])	3,098

Supplementary File S2: List of studies included in the review.

1. Abe T, Kondo T, Harabayashi T, Takada N, Matsumoto R, Osawa T, et al. Comparative study of lymph node dissection, and oncological outcomes of laparoscopic and open radical nephroureterectomy for patients with urothelial carcinoma of the upper urinary tract undergoing regional lymph node dissection. Jpn J Clin Oncol. 2018;48:1001-11. Epub 2018/10/03.

2. Akao J, Matsuyama H, Yamamoto Y, Hara T, Kawai Y, Sakano S, et al. Clinical significance of lymphovascular invasion in upper urinary tract urothelial cancer. BJU Int. 2008;102:572-5. Epub 2008/05/20.

3. Aydin AM, Singla N, Panwar V, Woldu SL, Freifeld Y, Wood CG, et al. Prognostic significance of BAP1 expression in high-grade upper tract urothelial carcinoma: a multi-institutional study. World J Urol. 2019;37:2419-27. Epub 2019/02/14.

4. Aziz A, Rink M, Gakis G, Kluth LA, Dechet C, Miller F, et al. Preoperative C-reactive protein in the serum: a prognostic biomarker for upper urinary tract urothelial carcinoma treated with radical nephroureterectomy. Urol Int. 2014;93:352-60. Epub 2014/08/21.

5. Bolenz C, Shariat SF, Fernandez MI, Margulis V, Lotan Y, Karakiewicz P, et al. Risk stratification of patients with nodal involvement in upper tract urothelial carcinoma: value of lymph-node density. BJU Int. 2009;103:302-6. Epub 2008/11/08.

6. Cha EK, Shariat SF, Kormaksson M, Novara G, Chromecki TF, Scherr DS, et al. Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol. 2012;61:818-25. Epub 2012/01/31.

7. Cho YH, Hwang JE, Chung HS, Kim MS, Hwang EC, Jung SI, et al. The De Ritis (aspartate transaminase/alanine transaminase) ratio as a predictor of oncological outcomes in patients after surgery for upper urinary tract urothelial carcinoma. Int Urol Nephrol. 2017;49:1383-90. Epub 2017/05/10.

8. Chromecki TF, Cha EK, Fajkovic H, Margulis V, Novara G, Scherr DS, et al. The impact of tumor multifocality on outcomes in patients treated with radical nephroureterectomy. Eur Urol. 2012;61:245-53. Epub 2011/10/07.

9. Chung HS, Hwang EC, Kim MS, Yu SH, Jung SI, Kang TW, et al. Effects of Variant Histology on the Oncologic Outcomes of Patients With Upper Urinary Tract Carcinoma After Radical Nephroureterectomy: A Propensity Score-Matched Analysis. Clin Genitourin Cancer. 2019;17:e394-e407. Epub 2019/02/21.

10. Dalpiaz O, Pichler M, Mannweiler S, Martin Hernandez JM, Stojakovic T, Pummer K, et al. Validation of the pretreatment derived neutrophil-lymphocyte ratio as a prognostic factor in a European cohort of patients with upper tract urothelial carcinoma. Br J Cancer. 2014;110:2531-6. Epub 2014/04/03.

11. Ekmekci S, Kucuk U, Dere Y, Cakir E, Sayar HC, Ergani B, et al. 8-armed octopus: Evaluation of clinicopathologic prognostic factors of urothelial carcinoma of the upper urinary system. Turk J Med Sci. 2019;49:153-61. Epub 2019/02/16.

12. Elawdy MM, Taha DE, Elbaset MA, Abouelkheir RT, Osman Y. Histopathologic Characteristics of Upper Tract Urothelial Carcinoma With an Emphasis on Their Effect on Cancer Survival: A Single-Institute Experience With 305 Patients With Long-Term Follow-Up. Clin Genitourin Cancer. 2016;14:e609-e15. Epub 2016/06/06.

13. Fairey AS, Kassouf W, Estey E, Tanguay S, Rendon R, Bell D, et al. Comparison of oncological outcomes for open and laparoscopic radical nephroureterectomy: results from the Canadian Upper Tract Collaboration. BJU Int. 2013;112:791-7. Epub 2012/11/15.

14. Fang D, He S, Xiong G, Singla N, Cao Z, Zhang L, et al. Comparison of clinicopathologic characteristics, epigenetic biomarkers and prognosis between renal pelvic and ureteral tumors in upper tract urothelial carcinoma. BMC Urol. 2018;18:22. Epub 2018/03/29.

15. Gao X, Chen W, Zhang R, Wu C, Li Y, Zhu H, et al. Preoperative AST/ALT ratio predicts long-term survival after radical nephroureterectomy in patients with upper tract urothelial carcinoma. Internaional Journal of Clinical and Experimental Medicine. 2017;10:8.

16. Godfrey MS, Badalato GM, Hruby GW, Razmjoo M, McKiernan JM. Prognostic indicators for upper tract urothelial carcinoma after radical nephroureterectomy: the impact of lymphovascular invasion. BJU Int. 2012;110:798-803. Epub 2012/02/09.

17. Hara T, Fujimoto H, Sakura M, Inokuchi J, Nishiyama H, Miyazaki J, et al. Prognostic factors of recurrent disease in upper urinary tract urothelial cancer after radical nephroureterectomy: Subanalysis of the multi-institutional national database of the Japanese Urological Association. Int J Urol. 2015;22:1013-20. Epub 2015/08/06.

18. Hayakawa N, Kikuchi E, Mikami S, Fukumoto K, Oya M. The Role of PD-1 Positivity in the Tumour Nest on Clinical Outcome in Upper Tract Urothelial Carcinoma Patients Treated with Radical Nephroureterectomy. Clin Oncol (R Coll Radiol). 2018;30:e1-e8. Epub 2017/11/21.

19. Hong B, Park S, Hong JH, Kim CS, Ro JY, Ahn H. Prognostic value of lymphovascular invasion in transitional cell carcinoma of upper urinary tract. Urology. 2005;65:692-6. Epub 2005/04/19.

20. Hsieh MC, Sung MT, Chiang PH, Huang CH, Tang Y, Su YL. The Prognostic Impact of Histopathological Variants in Patients with Advanced Urothelial Carcinoma. PLoS One. 2015;10:e0129268. Epub 2015/06/27.

21. Huang J, Yuan Y, Wang Y, Zhang J, Kong W, Chen H, et al. Prognostic value of preoperative plasma fibrinogen level and platelet-to-lymphocyte ratio (F-PLR) in patients with localized upper tract urothelial carcinoma. Oncotarget. 2017;8:36761-71. Epub 2016/12/03.

22. Hurel S, Roupret M, Ouzzane A, Rozet F, Xylinas E, Zerbib M, et al. Impact of lymphovascular invasion on oncological outcomes in patients with upper tract urothelial carcinoma after radical nephroureterectomy. BJU Int. 2013;111:1199-207. Epub 2013/05/09.

23. Ichimura T, Morikawa T, Kawai T, Nakagawa T, Matsushita H, Kakimi K, et al. Prognostic significance of CD204-positive macrophages in upper urinary tract cancer. Ann Surg Oncol. 2014;21:2105-12. Epub 2014/02/05.

24. Ikeda M, Matsumoto K, Hirayama T, Koguchi D, Murakami Y, Matsuda D, et al. Selected High-Risk Patients With Upper Tract Urothelial Carcinoma Treated With Radical Nephroureterectomy for Adjuvant Chemotherapy: A Multi-Institutional Retrospective Study. Clin Genitourin Cancer. 2018;16:e669-e75. Epub 2017/12/15.

25. Inamoto T, Komura K, Watsuji T, Azuma H. Specific body mass index cut-off value in relation to survival of patients with upper urinary tract urothelial carcinomas. Int J Clin Oncol. 2012;17:256-62. Epub 2011/07/09.

26. Kang HW, Jung HD, Ha YS, Kim TH, Kwon TG, Byun SS, et al. Preoperative Underweight Patients with Upper Tract Urothelial Carcinoma Survive Less after Radical Nephroureterectomy. J Korean Med Sci. 2015;30:1483-9. Epub 2015/10/02.

27. Kawashima A, Nakai Y, Nakayama M, Ujike T, Tanigawa G, Ono Y, et al. The result of adjuvant chemotherapy for localized pT3 upper urinary tract carcinoma in a multi-institutional study. World J Urol. 2012;30:701-6. Epub 2011/10/11.

28. Kikuchi E, Margulis V, Karakiewicz PI, Roscigno M, Mikami S, Lotan Y, et al. Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. J Clin Oncol. 2009;27:612-8. Epub 2008/12/17.

29. Kim DS, Lee YH, Cho KS, Cho NH, Chung BH, Hong SJ. Lymphovascular invasion and pT stage are prognostic factors in patients treated with radical nephroureterectomy for localized upper urinary tract transitional cell carcinoma. Urology. 2010;75:328-32. Epub 2009/12/19.

30. Kim HS, Ku JH, Jeong CW, Kwak C, Kim HH. Laparoscopic radical nephroureterectomy is associated with worse survival outcomes than open radical nephroureterectomy in patients with locally advanced upper tract urothelial carcinoma. World J Urol. 2016;34:859-69. Epub 2015/10/27.

31. Kim JK, Moon KC, Jeong CW, Kwak C, Kim HH, Ku JH. Variant histology as a significant predictor of survival after radical nephroureterectomy in patients with upper urinary tract urothelial carcinoma. Urol Oncol. 2017;35:458 e9- e15. Epub 2017/03/30.

32. Kim TH, Hong B, Seo HK, Kang SH, Ku JH, Jeong BC. The Comparison of Oncologic Outcomes between Open and Laparoscopic Radical Nephroureterectomy for the Treatment of Upper Tract Urothelial Carcinoma: A Korean Multicenter Collaborative Study. Cancer Res Treat. 2019;51:240-51. Epub 2018/04/25.

33. Kohada Y, Hayashi T, Goto K, Kobatake K, Abdi H, Honda Y, et al. Preoperative risk classification using neutrophil-lymphocyte ratio and hydronephrosis for upper tract urothelial carcinoma. Jpn J Clin Oncol. 2018;48:841-50. Epub 2018/08/08.

34. Lee HY, Li CC, Huang CN, Ke HL, Li WM, Liang PI, et al. Prognostic significance of lymphovascular invasion in upper urinary tract urothelial carcinoma is influenced by tumor location. Ann Surg Oncol. 2015;22:1392-400. Epub 2014/09/23.

35. Lee SE, Hong SK, Han BK, Yu JH, Han JH, Jeong SJ, et al. Prognostic significance of tumor necrosis in primary transitional cell carcinoma of upper urinary tract. Jpn J Clin Oncol. 2007;37:49-55. Epub 2007/01/06.

36. Lee YJ, Moon KC, Jeong CW, Kwak C, Kim HH, Ku JH. Impact of squamous and glandular differentiation on oncologic outcomes in upper and lower tract urothelial carcinoma. PLoS One. 2014;9:e107027. Epub 2014/09/06.

37. Li T, Xu H, Yang L, Tan P, Wei Q. Predictive value of preoperative lymphocyte-to-monocyte ratio for patients with upper tract urothelial carcinoma. Clin Chim Acta. 2019;492:50-6. Epub 2019/02/15.

38. Li Y, Fang D, Bao Z, He A, Guan B, He S, et al. High aspartate transaminase/alanine transaminase ratio predicts poor prognosis in patients with localized upper tract urothelial cancer: a propensity score-matched study in a large Chinese center. Onco Targets Ther. 2019;12:2635-48. Epub 2019/05/23.

39. Liu JY, Li YH, Zhang ZL, Ye YL, Liu ZW, Yao K, et al. Age-specific effect of gender on upper tract urothelial carcinoma outcomes. Med Oncol. 2013;30:640. Epub 2013/06/20.

40. Makise N, Morikawa T, Kawai T, Nakagawa T, Kume H, Homma Y, et al. Squamous differentiation and prognosis in upper urinary tract urothelial carcinoma. Int J Clin Exp Pathol. 2015;8:7203-9. Epub 2015/08/12.

41. Masson-Lecomte A, Colin P, Bozzini G, Nison L, de La Taille A, Comperat E, et al. Impact of micropapillary histological variant on survival after radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol. 2014;32:531-7. Epub 2013/08/03.

42. Matsumoto K, Novara G, Gupta A, Margulis V, Walton TJ, Roscigno M, et al. Racial differences in the outcome of patients with urothelial carcinoma of the upper urinary tract: an international study. BJU Int. 2011;108:E304-9. Epub 2011/04/22.

43. Morizane S, Iwamoto H, Masago T, Yao A, Isoyama T, Sejima T, et al. Preoperative prognostic factors after radical nephroureterectomy in patients with upper urinary tract urothelial carcinoma. Int Urol Nephrol. 2013;45:99-106. Epub 2012/12/12.

44. Nakagawa T, Komemushi Y, Kawai T, Otsuka M, Miyakawa J, Uemura Y, et al. Efficacy of post-nephroureterectomy cisplatin-based adjuvant chemotherapy for locally advanced upper tract urothelial carcinoma: a multi-institutional retrospective study. World J Urol. 2017;35:1569-75. Epub 2017/04/12.

45. Ouzzane A, Colin P, Ghoneim TP, Zerbib M, De La Taille A, Audenet F, et al. The impact of lymph node status and features on oncological outcomes in urothelial carcinoma of the upper urinary tract (UTUC) treated by nephroureterectomy. World J Urol. 2013;31:189-97. Epub 2012/12/12.

46. Qin C, Liang EL, Du ZY, Qiu XY, Tang G, Chen FR, et al. Prognostic significance of urothelial carcinoma with divergent differentiation in upper urinary tract after radical nephroureterectomy without metastatic diseases: A retrospective cohort study. Medicine (Baltimore). 2017;96:e6945. Epub 2017/05/26.

47. Saito K, Kawakami S, Fujii Y, Sakura M, Masuda H, Kihara K. Lymphovascular invasion is independently associated with poor prognosis in patients with localized upper urinary tract urothelial carcinoma treated surgically. J Urol. 2007;178:2291-6; discussion 6. Epub 2007/10/16.

48. Sakano S, Matsuyama H, Kamiryo Y, Hayashida S, Yamamoto N, Kaneda Y, et al. Impact of variant histology on disease aggressiveness and outcome after nephroureterectomy in Japanese patients with upper tract urothelial carcinoma. Int J Clin Oncol. 2015;20:362-8. Epub 2014/06/27.

49. Shibing Y, Liangren L, Qiang W, Hong L, Turun S, Junhao L, et al. Impact of tumour size on prognosis of upper urinary tract urothelial carcinoma after radical nephroureterectomy: a multi-institutional analysis of 795 cases. BJU Int. 2016;118:902-10. Epub 2016/03/05.

50. Shibing Y, Turun S, Qiang W, Junhao L, Haichao Y, Shengqiang Q, et al. Effect of concomitant variant histology on the prognosis of patients with upper urinary tract urothelial carcinoma after radical nephroureterectomy. Urol Oncol. 2015;33:204 e9-16. Epub 2015/03/25.

51. Song SH, Ye CH, Lee S, Hong SK, Byun SS, Lee SE, et al. Association between lymphovascular invasion and oncologic outcomes among upper urinary tract urothelial carcinoma patients who underwent radical nephroureterectomy. J Cancer Res Clin Oncol. 2019;145:2863-70. Epub 2019/09/11.

52. Su X, Fang D, Li X, Xiong G, Zhang L, Hao H, et al. The Influence of Tumor Size on Oncologic Outcomes for Patients with Upper Tract Urothelial Carcinoma after Radical Nephroureterectomy. Biomed Res Int. 2016;2016:4368943. Epub 2017/01/11.

53. Sung HH, Cho J, Kwon GY, Jeon HG, Jeong BC, Seo SI, et al. Clinical significance of micropapillary urothelial carcinoma of the upper urinary tract. J Clin Pathol. 2014;67:49-54. Epub 2013/08/14.

54. Tai YS, Chen CH, Huang CY, Tai HC, Wang SM, Pu YS. The effect of tumor location on oncologic outcomes in patients with upper urinary tract urothelial carcinoma stratified by pathologic stage. Urol Oncol. 2016;34:4 e19-25. Epub 2015/09/10.

55. Tan P, Chen J, Xie N, Xu H, Ai J, Xu H, et al. Is preoperative serum lactate dehydrogenase useful in predicting the outcomes of patients with upper tract urothelial carcinoma? Cancer Med. 2018;7:5096-106. Epub 2018/08/29.

56. Tanaka N, Kikuchi E, Kanao K, Matsumoto K, Shirotake S, Miyazaki Y, et al. Impact of Combined Use of Blood-based Inflammatory Markers on Patients with Upper Tract Urothelial Carcinoma Following Radical Nephroureterectomy: Proposal of a Cumulative Marker Score as a Novel Predictive Tool for Prognosis. Eur Urol Focus. 2015;1:54-63. Epub 2015/08/01.

57. Tanaka N, Kikuchi E, Matsumoto K, Hayakawa N, Ide H, Miyajima A, et al. Prognostic value of plasma fibrinogen levels in patients with localized upper tract urothelial carcinoma. BJU Int. 2013;111:857-64. Epub 2012/07/05.

58. Tang Q, Xiong G, Li X, Fang D, Xi C, Zhang L, et al. The prognostic impact of squamous and glandular differentiation for upper tract urothelial carcinoma patients after radical nephroureterectomy. World J Urol. 2016;34:871-7. Epub 2015/10/27.

59. Vartolomei MD, Mathieu R, Margulis V, Karam JA, Roupret M, Lucca I, et al. Promising role of preoperative neutrophil-to-lymphocyte ratio in patients treated with radical nephroureterectomy. World J Urol. 2017;35:121-30. Epub 2016/05/23.

60. Waseda Y, Saito K, Ishioka J, Matsuoka Y, Numao N, Fujii Y, et al. Ureteral Involvement Is Associated with Poor Prognosis in Upper Urinary Tract Urothelial Carcinoma Patients Treated by Nephroureterectomy: A Multicenter Database Study. Eur Urol Focus. 2016;2:296-302. Epub 2017/07/21.

61. Xu H, Tan P, Jin X, Ai J, Lin T, Lei H, et al. Validation of the preoperative controlling nutritional status score as an independent predictor in a large Chinese cohort of patients with upper tract urothelial carcinoma. Cancer Med. 2018;7:6112-23. Epub 2018/11/30.

62. Zamboni S, Foerster B, Abufaraj M, Seisen T, Roupret M, Colin P, et al. Incidence and survival outcomes in patients with upper urinary tract urothelial carcinoma diagnosed with variant histology and treated with nephroureterectomy. BJU Int. 2019;124:738-45. Epub 2019/03/26.

63. Zhang B, Song Y, Jin J, Zhou LQ, He ZS, Shen C, et al. Preoperative Plasma Fibrinogen Level Represents an Independent Prognostic Factor in a Chinese Cohort of Patients with Upper Tract Urothelial Carcinoma. PLoS One. 2016;11:e0150193. Epub 2016/03/02.

Supplementary File S3 - Characteristics of included studies.

S. no	Author Year Country	Number of patients	Study type	Multi-centre (Yes/No)	Age (Mean/Median (range)	Male/Female	Surgery (O/L)	L. Node Dissection	Pathological Stage (pTa-is/pT1/pT2/pT3/pT4)	LVI (PRESENT)	No. of Patient with Necrosis	Definition of necrosis	Tumor Site	Tumor Grade (1,2/3/unknown)	Adjuvant Chemotherapy (Yes/No)	Variant Histology (%)	Duration of Follow up	Parameters controlled in multivariate analysis	Survival outcomes assessed	NOS
1.	Hayakawa 2017 Japan	181	R	N	73(36-93)	140/41	NA	N	<T2-78 >T2-103	79	NA	NA	P-101 U-70 Both-10	LG-52 HG-129	NA	30	53(1-253)	-LVI -PD-1 expression in tumor nest	CSS PFS	6
2.	Hong 2005 Korea	73	R	N	59.1	NA	NA	Y-37	Ta-15 T1-18 T2-9 T3-27 T4-4	18	NA	NA	P-40 U-33	G1-6 G2-35 G3-32	13	NA	42.3	-LVI - grade -stage	DSS RFS	6
3.	Hsieh 2015 Taiwan	206	R	N	63(22-84)	138/68	NA	NA	NA	NA	NA	NA	Upper urinary tract-119 Bladder-84 Both-3		206	53	134.5	-Histopathological Variant -Renal function -Visceral metastasis	OS PFS OS	6
4.	Hurel 2013 France	551	R	Y	69.4(61.8-76.4)	365/186	O-551	Y	Ta/Tis-142 T1-124 T2-53 T3-193 T4-39	163	NA	NA	P-302 U-169 Both-80	G1-80 G2-251 G3-415	79	NA	26.8(10.3-48.7)	-Multifocal -pT3 stage -LVI -positive surgical margin(MFS)	CSS RFS MFS	6
5.	Ichimura 2014 Japan	171	R	N	70	119/52	NA	Y	Ta/Tis-44 T1-31 T2-18 T3-69 T4-9	74	NA	NA	P-103 U-68	LG-19 HG-152	NA	NA	56	-High CD204^{+} -LVI -LN Mets	RFS MFS CSS	6
6.	Ikeda 2017 Japan	441	R	Y	69(62-75)	319/122	O-247 L-194	Y	Ta/Tis-86 T1-92 T2-81 T3-158 T4-24	156	NA	NA	P-245 U-196	G1/2-305 G3-130	100	37	35.7	-T stage - Lymph node status -Grade3 -LVI -positive STSM	DFS CSS	7
7.	Kang 2015 Korea	440	R	Y	NA	305/135	NA	Y	Ta/Tis-31 T1-135 T2-101 T3-155 T4-8	76	NA	NA	P-159 U-219 Both-62	LG-110 HG-330	78	NA	31(15-57)	-Locally advanced stage -Node positive status -LVI -Margin status	OS DSS	8
8.	Kim DS 2010 Korea	238	R	N	64.1(25-91)	164/74	NA	Y	Ta-T2-131 T3-107	31	NA	NA	P-134 U-104	LG-95 HG-143	NA	24	53.4(3-240)	-Tumor architecture -squamous differentiation -LVI -Tumor grade	RFS CSS	7
9.	Kim JK 2017 Korea	452	R	N	64±10.2	347/105	O-332 L-120	Y	T0/a/is/1-187 T2-75 T3/4-188	99	NA	NA	P-223 U-165 Both-64	LG-59 HG-81	110	41	67.8(0-254)	-Age -T stage - multifocality -Positive STSM -tumor location -variant histology -LVI	OS CSS	7
10.	Kim SH 2015	371	R	N	64.7(57.7)	287/84	O-271	Y	pT0/a/is/1-162	71	NA	NA	P-183 U-140	LG-125 HG-246	85	28	50.8	-LRUN - stage	OS CSS	7

	Korea						L-100		pT2-63 pT3/4- 146				Both-48					-grade		
11.	Lee Sang 2006 Korea	119	R	N	62(36- 90)	92/27	NA	Y	Ta/T1-38 pT2-4-81	30	19	>1 0% ma cro sc opi c ne cro sis	P-54 U-65	G1/2-76 G3-43	40	NA	41(2- 164)	-T stage -LVI -Tumor necrosis	DSS	7
12.	Lee Young 2014 Korea	341	R	N	63.1(5 6.4- 70.5)	301/4 0	NA	Y	Ta/Tis-54 T1-81 T2-58 T3-144 T4-4	70	NA	NA	NA	G1-39 G2-206 G3-96	86	27	66.8(30- 95.3)	-Age -T stage -LVI -positive STSM -Nodal metastasis -Histological variant	CSS OS	7
13.	Lee Hsiang 2014 Taiwan	250	R	N	68	108/1 42	O- 166 L-84	Y	Ta/Tis-40 T1-53 T2-73 T3-70 T4-14	60	NA	NA	P-128 U-122	LG-55 HG-195	42	NA	41	-T stage - Lymph node involvement -LVI -Concomitant bladder tumor(RFS)	CSS MFS RFS	7
14.	Li Tao 2019 China	704	R	N	66±11. 4	401/3 03	O- 474 L-230	Y	</=T2- 359 >/=T3- 345	107	NA	NA	P-375 U-202 Both- 127	LG-185 HG-519	286	162	39(3 4-43)	-Low lymphocyte to monocyte ratio -Tumor size >/=3cm -High tumor grade -Advance tumor stage(>/=T3) -Lymph node invasion -Tumor architecture -Concomitant variant histology -Albumin to globulin ratio	CSS RFS OS	7
15.	Li Yifan 2019 China	602	R	N	66.77± 9.90	285/3 17	NA	Y	Ta-6 T1-322 T2- 2956T3- 238 T4-24	46	114	NA	P-310 U-292	G1-15 G2-342 G3-245	NA	105	6138 -102)	-High AST/ALT -T stage -N stage -Age -Gender -Tumor location -Tumor size -Glandular	CSS OS RFS	7

																		differentiation		
16.	Liu 2013 China	421	R	Y	62(51-70)	285/136	O-364 L-57	Y	Ta/Tis/T1-157 T2-91 T3-144 T4-29	101	NA	NA	P-225 U-196	G1-87 G2-128 G3-206	88	NA	NA	-Female gender -LVI -Tumor grade -Tumor stage - N stage	CSS	6
17.	Masson 2013 France	519	R	Y	68.4(61.2-76.5)	342/177	O-519	Y	Ta/is/1-246 pT2/3/4-273	361	NA	NA	P-289 U-154 Both-76	G1-46 G2-167 G3-306	80	39	27(10.2-48.7)	-T stage -LVI -margin status -Adjuvant chemotherapy	CSS MFS	6
18.	Matsumoto 2011 Japan	2163	R	Y	69(61-76)	1478/685	O-1790 L-373	Y	T0-10 Ta-450 Tis-36 T1-488 T2-401 T3-667 T4-111	481	496	NA	NA	LG-655 HG-1508	224	NA	36(15.3-71.1)	-Age - T stage -Tumor grade -LVI -Tumor architecture - N stage	RFS CSS	7
19.	Nakagawa 2017 Japan	109	R	Y	71(64-77)	67/42	NA	Y	T3-104 T4-5	78	NA	NA	P-50 U-23 Both-36	G1-0 G2-40 G3-69	43	NA	46.5(23.2-76.7)	-Adjuvant chemotherapy -lower nuclear grade -absence of hydronephrosis	RFS CSS	8
20.	Ouzzane 2012 France	714	R	Y	70(60-75)	484/228	NA	Y	Ta/Tis-131 T1-216 T2-124 T3-205 T4-40	157	NA	NA	P-388 U-236 Both-90	G1-71 G2-244 G3-399	NA	NA	27(10-50)	-Age -T stage - surgical margin	CSS MFS OS	6
21.	Qin 2017 China	346	R	N	66.61±9.897	206/140	NA	N	Ta/is/1-258 pT2/3/4-88	NA	18	NA	P-175 U-171	LG-59 HG-287	169	50	21(10-36)	-T stage -Tumor grade -variant histology -adjuvant chemotherapy	RFS CSS OS	6
22.	Kikuchi 2009 japan	1453	R	Y	69.7(27-97)	986/467	NA	Y	Ta-295 Tis-28 T1-317 T2-269 T3-475 T4-69	349	387	NA	P-958 U-495	LG-516 HG-937	169	NA	NA	-T stage -Tumor grade -N stage -LVI	CSS RFS	6
23.	Kawashima 2011 Japan	93	R	Y	NA	68/25	NA	Y	>T3-93	54	NA	NA	P-55 U-38	G1-6 G2-31 G3-56	38	11	NA	-Adjuvant chemotherapy -Tumor grade -LVI -Sex -Histology	CSS RFS	6
24.	Kim TH 2019 South Korea	1521	R	Y	65(57-72)	1127/394	O-906 L-615	Y	Ta/Tis-235 T1-404 T2-255	332	NA	NA	P-682 U-565 Both-274	LG-485 HG-993 Missing-43	340	NA	54.9(32.7-89.7)	-Previous bladder Tumor -Concomitant bladder tumor	IVRFS PFS CSS OS	6

									T3-592 T4-35									-Age -T stage -Tumor grade -LVI -Concomitant CIS -N stage		
25.	Kohada 2018 Japan	148	R	N	71(64-78)	112/36	NA	Y	Ta/1/2-82 T3/4-66	55	NA	NA	P-82 U-66	G1/2-60 G3-88	25	NA	35.5(12-66)	-Elevated pre-op Neutrophil-lymphocytes ratio -Hydronephrosis -LVI	CSS RFS	7
26.	Morizane 2015 Japan	345	R	Y	74(38-95)	234/111	O-244 L-101	Y	<T3-188 >/=T3-152	102	NA	NA	P-140 U-205	Non G3-222 G3-109	80(23.2%)	29	39.9(6.1-160)	-ECOG performance status -Number of tumor foci -Serum HB -eGFR -T stage -Histological variant -Tumor grade -Positive LN -INF -LVI -Positive margin	CSS	6
27.	Makise 2015 Japan	140	R	N	NA	101/39	NA	Y	Ta/Tis-36 T1-25 T2-11 T3-60 T4-8	61	NA	NA	P-89 U-51	G1/2-63 G3-77	42	23	NA	5 -T stage -N stage -LVI -Tumor grade -Age	MFS CSS OS	7
28.	Zhang 2016 China	184	R	N	70(60-74)	84/100	O-125 L-59	Y	Ta/1-73 T2/3/4-111	28	30	NA	P-99 U-85	G1/2-117 G3-67	NA	NA	78(34-92)	-preoperative plasma fibrinogen level -Gender -T stage -Age>70 -Preoperative CKD4/5	OS CSS	7
29.	Su 2016 China	687	R	N	<3cm-69(20-90) >3cm-68(29-86)	306/381	O-220 L-467	Y	Ta/is/1-129 T2-242 T3-197 T4-19	NA	79	NA	P-380 U-307	G1-21 G2-368 G3-298	NA	81	65(3-144)	-Older age -Male -presence of hydronephrosis -Advance T stage -Positive LN -preoperative ureteroscopy -Lower tumor grade -N0 status -Tumor multifocality	CSS RFS	7

30.	Huang 2016 China	481	R	N	65.8±11.1	311/170	O-318 L-163	Y	Ta/1-248 T2/3/4-233	76	NA	NA	P-232 U-160 Multifocal-89	LG-163 HG-318	96	NA	40(24-64)	-F-PLR score -Age >65 -Tumor multifocality -T stage -Higher grade -LVI Higher pN stage	OS CSS	6
31.	Abe 2018 Japan	214	R	Y	70.5 (35-93)	151/63	0-100 L-114	Y 214	42/48/41/75/8	96	NA	NA	P-127 U-82 Both-5	100/113/1	14/200	NA	15	-T stage -LVI -- Tumor number	RFS CSF OS	7
32.	Akao 2008 Japan	90	R	N	NA	57/33	NA	NA	0/3/24/14/43/6	34	NA	NA	P-51 U-39	4/56/29	24/61	NA	42(2-179)	-LVI - pT - pN - Tumor grade -Adjuvant therpy	DSS	6
33.	Aydin 2019 USA	348	R	Y	70(64-77)	163/185	NA	Yes (n=86)	31/103/57/129/28	98	62	NA	P-267 U-81	NA	NA	NA	36	-T stage - LVI -Necrosis- Architecture	RFS CSS OS	7
34.	Aziz 2014 Germany	265	R	Y	67.7 ± 9.85; 69.8 ± 8.85	169/96	NA	Yes (n=59)	106(Ta-T1)/49/102/8	52	NA	NA	P- 57 U- 33 Both-26	43/60/162	46/219	NA	37(9-48)	-ECOG -Tumor multifocality -LN involvement -LVI	RFS DSS ACS	6
35.	Bolenz 2008 Germany	116	R	N	NA	80/36	0-107 L-09	Y 27	9/3/23/28/42/11/20	36	17	10 %	P-84 U-32	12/58/46	NA	NA	38	-LVI -Pathological stage	DSS	7
36.	Cha 2012 USA	2244	R	Y	69 (61.6-76.0)	1502/742	NA	Y-129 N-540 X-1575	516/46/537/444/606/80	484	NA	NA	P- 1449 U- 795	HG-1838 LG- 406	NA	NA	45	-T stage -LN status -LVI -Architecture -CIS	RFS CSM CSS	7
37.	Cho 2017 Korea	1049	R	Y	68.5 (60.5-74.3)	759/290	NA	505	106/316/201/403/23	202	NA	NA	P-489 U-306 Both-92	HG- 745 LG- 304	Y-300	NA	40 (18.4 - 64.8)	-T stage -N1 disease -Hydronephrosis -De Retis Ratio	RFS CSS OS	8
38.	Chromecki 2011 USA	1169	R	Y	69 (30-92)	785/384	O-1014 L-155	Y 398	285/20/274/231/318/53	259	287	NA	P-742 U-427	LG-179 HG- 982	Y- 78	NA	37 (1-197)	-Age -Stage -Grade -Architecture -Necrosis -LVI	CSD OS	7
39.	Chung 2019 Korea	1173	R	Y	68.8 (61-74.6)	849/324	NA	540	Tis/Ta/T1-460 T2-230 T3/T4-483	236	NA	NA	P-542 U-537 Both-94	LG-343 HG-830	Y-357	93 (7.9%)	NA	-Preoperative anemia -HDN -LVI -VH	RFS CSS OS	7

40.	Dalpiaz 2014 Austria	171	R	N	69 +/- 10.1	107/ 64	NA	NA	T1-79 T2-4=92	NA	21	NA	P-95 U-76	G1-2=92 G3-4=79	NA	NA	31 (13-69)	-p stage -Grade pHistological - Tumor necrosis	CSS OS	7
41.	Ekmekci 2019 Turkey	74	R	Y	63.3 (40-84)	60/ 14	NA	64	pTa-16 13/ 04/ 28/ 13	25	29	NA	P-38 U-7 Both-29	NA	NA	22 (39.2 %)	43.5 +/- 48.7	-Tumor necrosis -Tumor differentiation -LN metastasis	DFS OS	7
42.	Elawddy 2016 Osman	305	R	N	59+/- 11	262/ 43	O-268 L-24 Renal sparing-13	NA	T0-3 Ta,is.1-196 T2-44 T3-61 T4-1	NA	NA	NA	P-183 U-182	G0-3 G1-16 G2-195 G3-100	NA	NA	34 (6-300)	-Tumor stage -Micropapillary variant	CSS OS	7
43.	Fairey 2012 Canada	849	R	Y	70.5		O-403 L-446	245	<=T1-186 T2-66 T3-89 T4-22	NA	NA	NA	NA	HG-274 LG-123	Y-94	NA	2.2 (0.6-5.0)	-T stage -Surgical approach -LN stage -Grade -Surgical margin	OS DSS RFS	6
44.	Fang 2018 China	612	R	N	Pelvis-65.29 +/- 11.11 Ureter-68.07+/ -10.20	340/ 272	NA	41	pTa-1=206 pT2-4= 406	NA	75	NA	P-341 U-271	G1-19 G2-334 G3-259	NA	NA	64	-Necrosis -LN status -Architecture -Grade -CIS	OS CSS	7
45.	Gao 2017 China	259	R	N	67.53	187/ 179	O-80 L-179	24	<=pT2-171 >=pT3-88	212	NA	NA	NA	G1-59 G2-3= 200	NA	23(8.8%)	33.3 (15.5-64.2)	-AST/ALT -Stage -Grade -HIstology -Sarcomatoid differentiation	OS PFS CSS Bladder recurrence free survival	7
46.	Godfrey 2012 USA	211	R	N	70 (11.4)	124/ 87	O-121 L-90	59	Ta-Tis=78 T1-41 T2-18 T3-71 T4-3	68	NA	NA	P-170 U-41	HG-134 LG-77	NA	NA	27 (11-65.5)	-Race -LVI -High nuclear grade	OS OSS	6
47.	Hara 2015 Japan	1172	R	Y	NA	806/ 366	O-750 L-421 Missing data-1	1138	Ta-125 Tis-29 T1-344 T2-302 T3-240 T4-21 Tx-111	423	NA	NA	P-593 U-546 Both-32 Missing data-1	G0-1 G1-71 G2-528 G3-558 Missing data-14	179	NA	55.8	-Age -Stage -LN -Metastasis -LVI -Infiltrative growth pattern	OS RFS	7
48.	Inamoto 2011 Japan	103	R	N	68.6 ±10.05	71/32	NA	Y	Tis/Ta/T1 - 43 T2- 13 T3/T4- 47	32	Nil	NA	-	G1-20 G2-28 G3-55	-	11	29 (14-63)	-C reactive protein -BMI -Focality -Lymph.Node	OS CSS RFS	6
49.	Saito	189	R	N	NA	94/41	NA	Y	≤T2 –	57	Nil	NA	59/76	LG-81	30	-	55	-Age	CSS	6

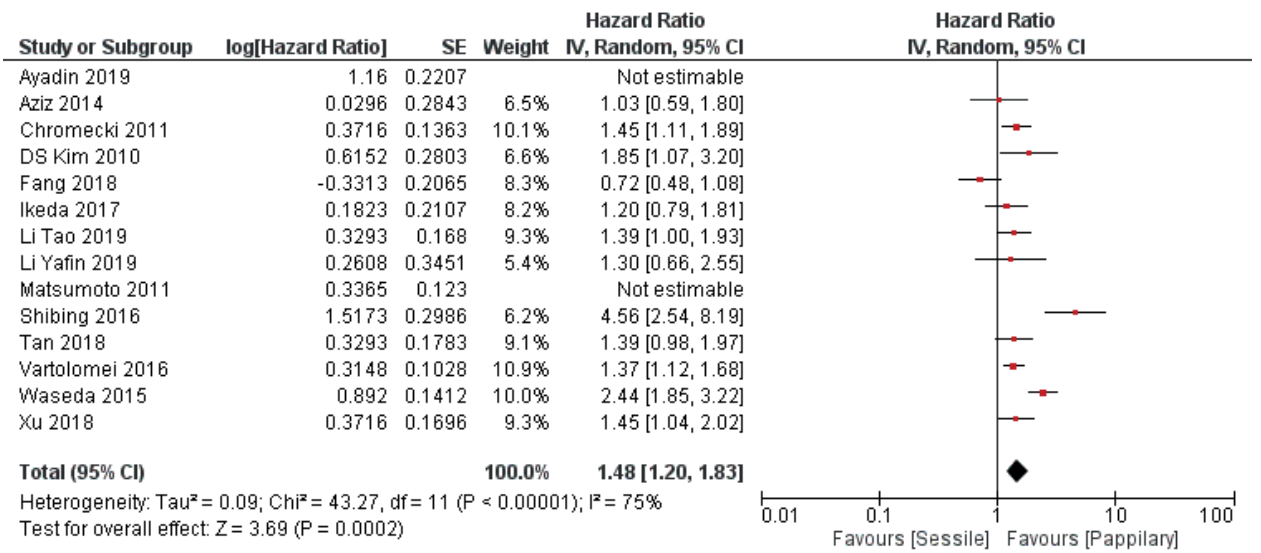
	2007 Japan								73 T3 – 62					HG- 54			(3-232)	-pT -LVI	RFS	
50.	Sakano 2014 Japan	502	R	Y	72 (32-93)	344/158	NA	Y	<3 – 290 ≥3-212	166	Nil	NA	221/232	LG-257 HG-233	144	60	41.4 (3-200)	-pT -Grade -LVI -Variant Histology	CSS	7
51.	Shibing 2015 China	417	R	N	67 (26-86)	246/171	NA	Y	Tis/Ta/T1 - 118 T2-79 T3-168 T4-52	74	Nil	NA	271/110	LG-100 HG-317	78	90	26 (12-54)	-pT -Grade -L.Nodes -Tumor Size -SurgicalMargins	OS CSS RFS	7
52.	Song 2019 Korea	453	R	N	69 (52-80)	320/133	O-164 L-143 Robotic-146	Y	Ta-6 T1-127 T2-147 T3-145 T4-23	132	Nil	NA	161/201	G1-2 G2-225 G3-222	-	-	23.2 (0-172)	-BMI -pT -LVI -L.Node -HDN -HTN	OS CSS RFS	7
53.	Sung 2014 Korea	386	R	N	64 (56-71)	293/93	NA	Y	Ta/Tis-78 T1-85 T2-56 T3/T4-167	-	Nil	NA	175/166	G1-20 G2-193 G3-161	-	7	39 (21.1 - 70.6)	-Age -Gender -Location -Grade -pT	RFS CSS	7
54.	Tai 2015 Taiwan	503	R	N	68 (60-74.8)	249/254	NA	Y	Ta/Tis/T1 -144 T2-31 T3-101 T4-4	49	Nil	NA	280/184	LG-135 HG-142	8	-	52 (23-77)	-Grade -pT -LVI -Location	OS RFS CSS	6
55.	Tan 2018 China	668	R	Y	65.8 (54.4-77.2)	380/288	NA	Y	≤ pT2-338 ≥pT3-330	99	Nil	NA	353/196	LG-173 HG-495	281	-	45 (21-74)	-Focality -pT -L.Nodes -LVI -LDH	CSS OS RFS MFS	7
56.	Tanaka 2012 Japan	218	R	Y	69 (38-92)	160/58	O-155 L-63	Y	Ta-T1-75 T2-27 T3-107 T4-9	84	Nil	NA	130/88	LG-59 HG-159	42	-	38 (3-187)	-Plasma Fibrinogen -pT -LVI	CSS RFS	7
57.	Tanaka 2015 Japan	394	R	Y	70 (63-77)	289/105	NA	Y	Ta/T1-125 T2-57 T3-201 T4-11	170	Nil	NA	232/162	LG-128 HG-266	88	-	30 (15-63)	-pT -LVI -Plasma Fibrinogen	CSS RFS ACM	7
58.	Tang 2015 China	687	R	N	68 (20-90)	306/381	NA	Y	T1-216 T2-217 T3-160 T4-13		Nil	NA	339/267	G1-20 G2-354 G3-232	-	81	65 (3-144)	-Gender -pT -Variant Histology -Pre op -HDN	RFS CSS	7
59.	Vartolomei 2015 Multicentre	2274	R	Y	69 (61-76)	1527/747	NA	Y	Ta-497 Tis-48 T1-532	499	516	-	1448/826	LG- 367 HG-1907	-	-	40 (20-76)	-pT -Grade -LVI	RFS CSS	7

									T2-441 T3-671 T4-85									-NLR -L.Node -Gender		
60.	Waseda 2015 Japan	1068	R	Y	70 (62-76)	758/310	NA	Y	Ta-127 Tis-34 T1-186 T2-164 T3-518 T4-39	446	Nil	NA	198/181	LG-751 HG-317	-	-	40 (17-77)	-Age -LVI -pT -pN -Location	RFS CSS	6
61.	Xu 2018 China	662	R	N	67 (59-74)	376/286	O-430 L-232	Y	≤pT2-338 ≥pT3-324	100	Nil	NA	349/193	LG-169 HG-493	279	149	42 (19-72)	-Grade -pT -L.Node -Variant Histology -CONUT score	OS RFS CSS	6
62.	Shibing 2016 China	795	R	Y	NA	462/333	O-588 L-207	Y	Tls/Ta/T1-149 T2-241 T3-313 T4-92	169	Nil	NA	497/187	LG-212 HG-583	202	162	32 (17-60)	-Grade -pT -LVI -Variant Histology -Size -Lymph.Node	OS CSS RFS	7
63.	Zamboni 2019 Multicentre	1610	R	Y	69 (61-76)	1096/512	O-999 L-489	Y	T0/Ta/Tis-401 T1-330 T2—227 T3-521 T4-110	344	235	NA	NA	HG-1058	233	150	42	-micropapillary variant -T3-4 stage -Sarcomatoid variant	RFS CSM	6
		35714																		

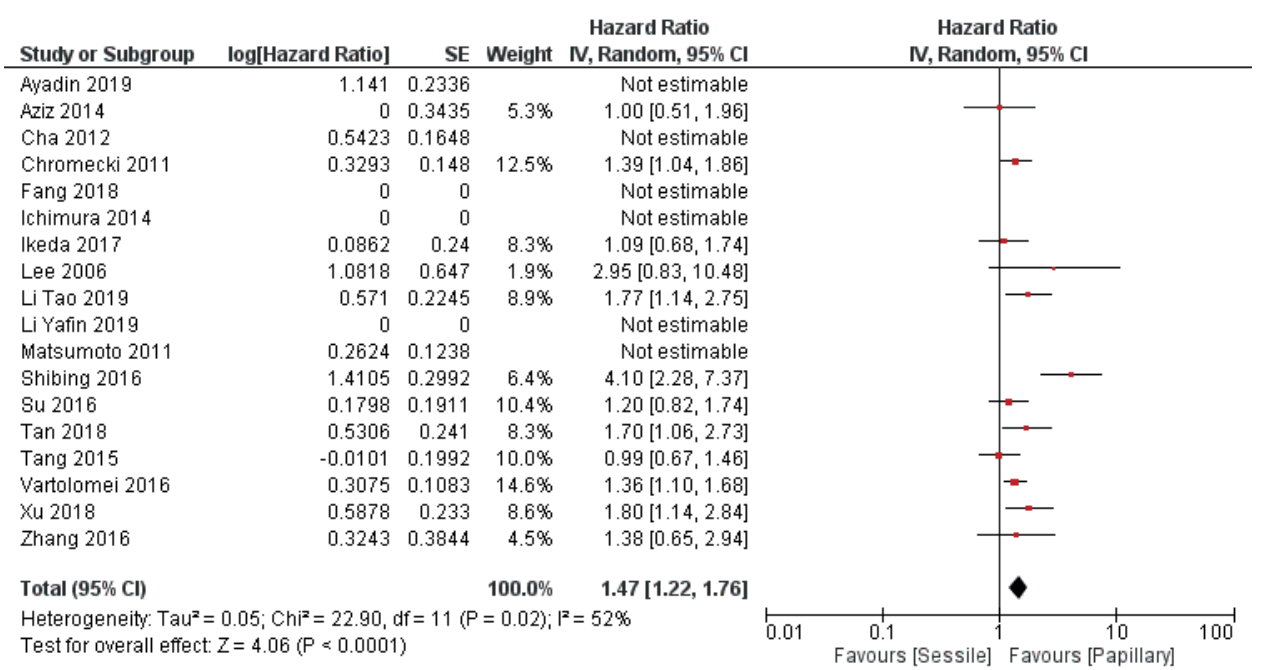
R-Retrospective, U- ureter, P-Renal Pelvis, O- Open, L- Laparoscopic, R- retrospective , LG- low grade, HG- high Grade, G-grade , LVI-Lymphovascular invasion, STSM- soft tissue surgical margin, T stage- pathological T stage, INF- interferon, O –Open, L= Laparoscopic, X= not known, LN- Lymph node, AST- aspartate transaminase, ALT-alanine transminase, CSS- cancer specific survival, RFS- Recurrence free survival, OS- overall survival, MFS-metastasis free survival, ECOG- Eastern co-operative oncology group, HB- hemoglobin, GFR- Glomerular filtration rate, CIS- carcinoma in situ.

APPENDIX 2

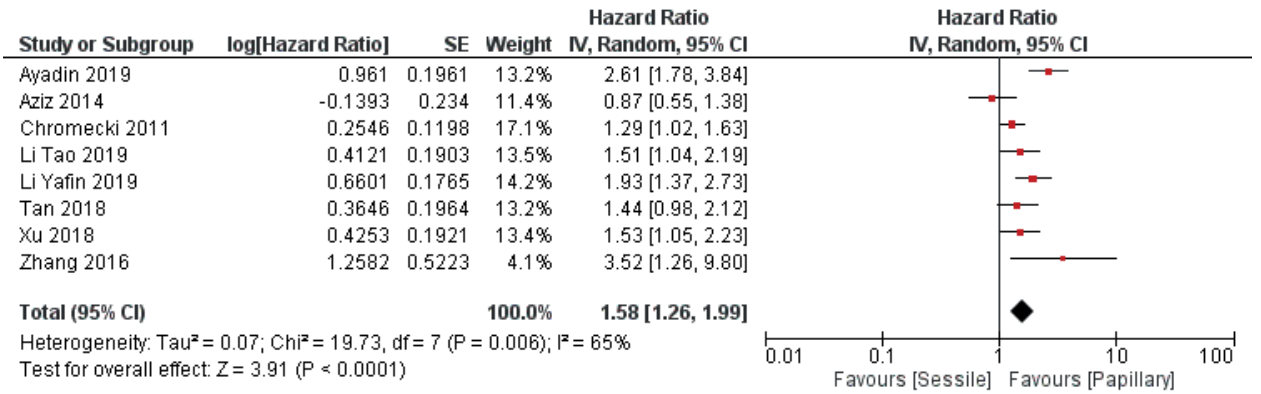
Supplementary Figure 1 - Forest plot depicting RFS for architecture



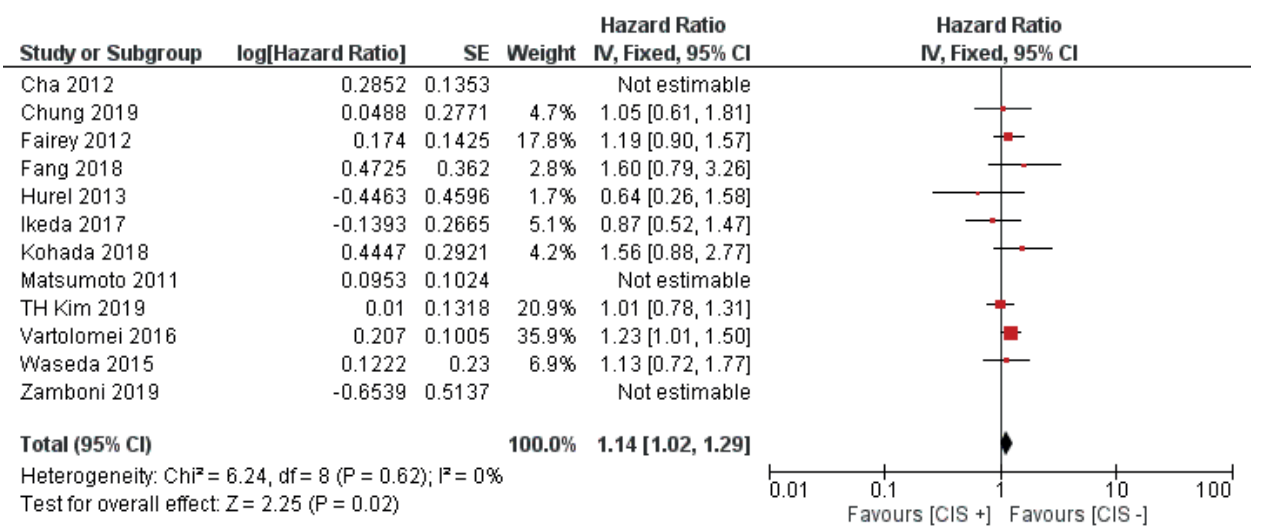
Supplementary Figure 2: Forest plot depicting CSS for architecture.



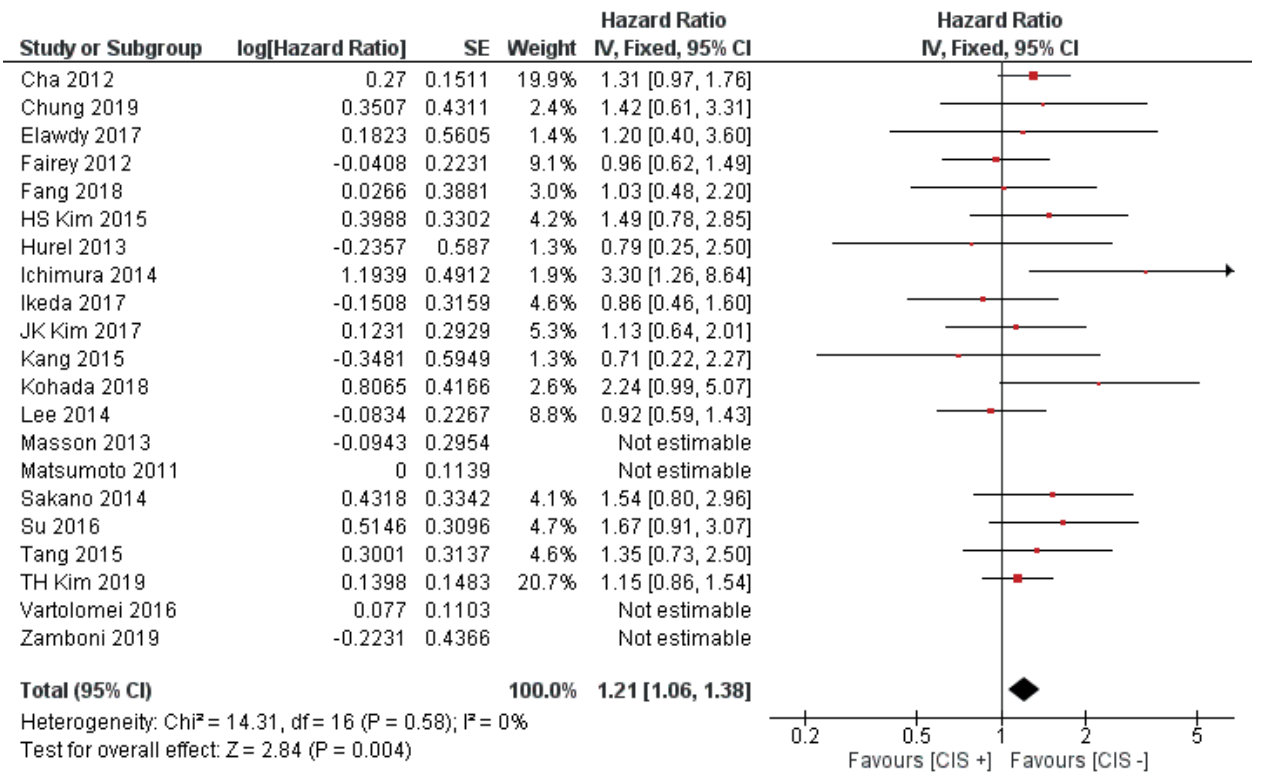
Supplementary Figure 3: Forest plot depicting OS for architecture.



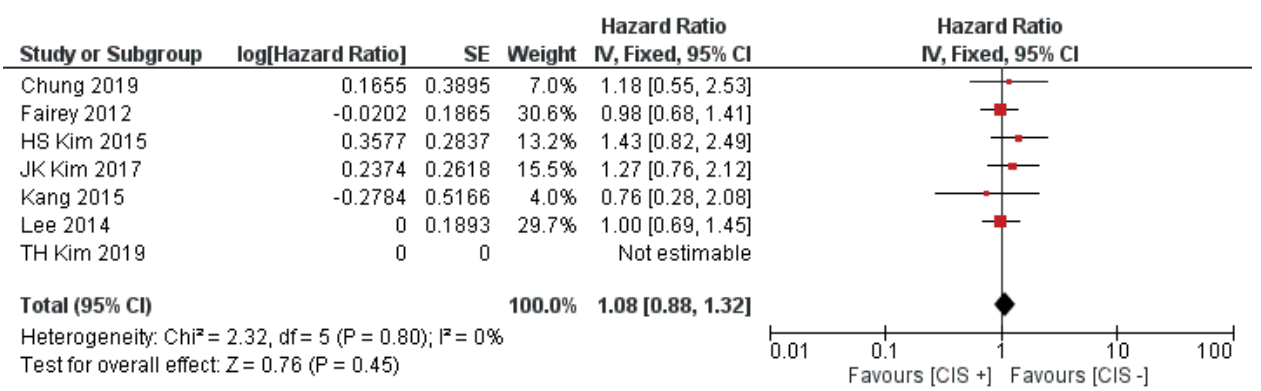
Supplementary Figure 4: Forest plot depicting RFS for carcinoma in situ.



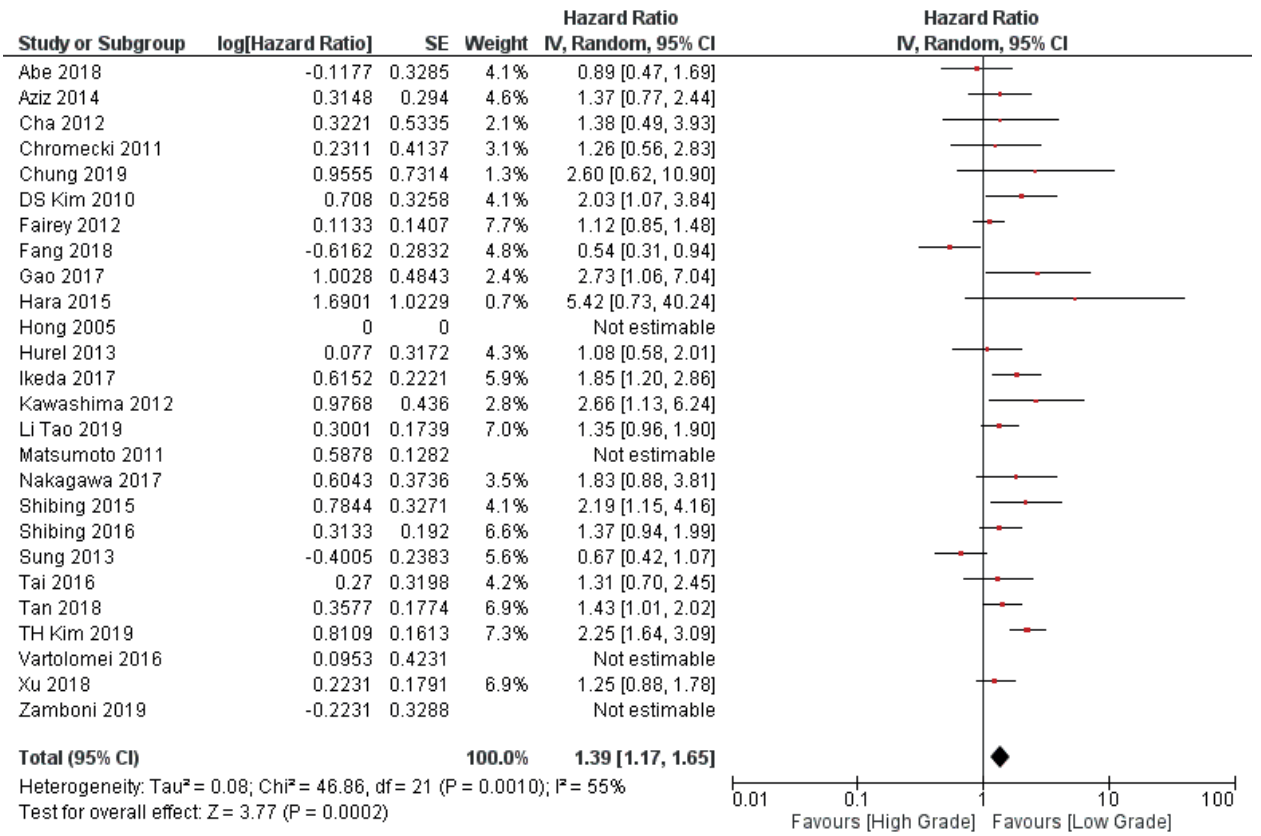
Supplementary Figure 5: Forest plot depicting CSS for carcinoma in situ.



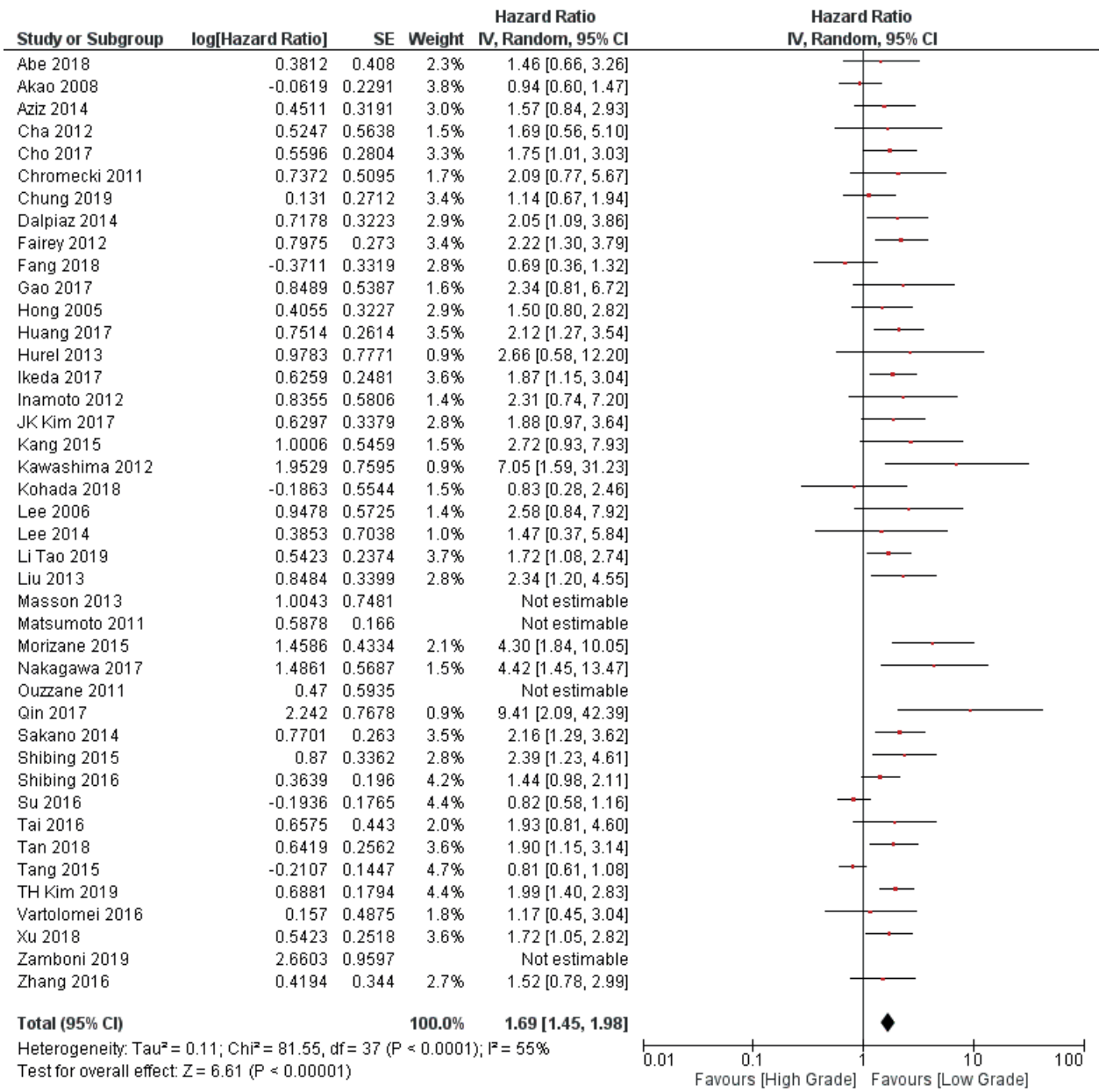
Supplementary Figure 6: Forest plot depicting OS for carcinoma in situ.



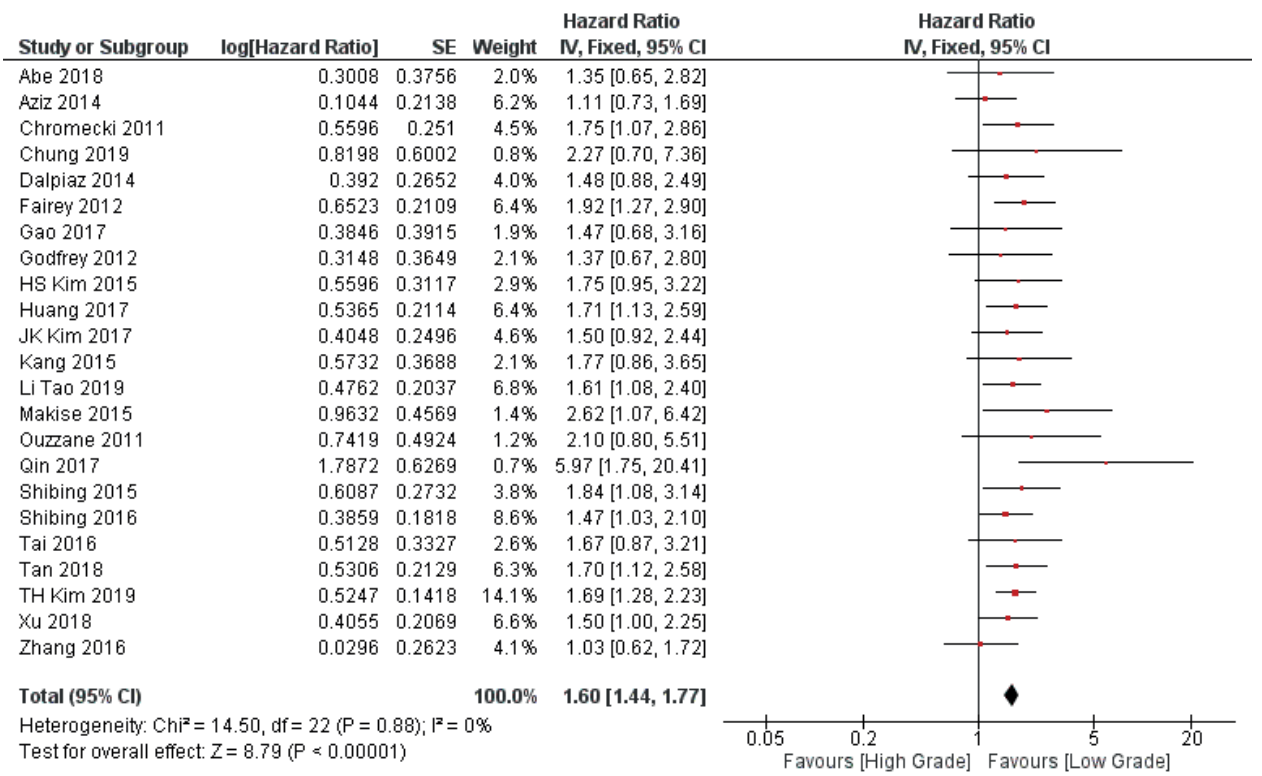
Supplementary Figure 7: Forest plot depicting RFS for grade.



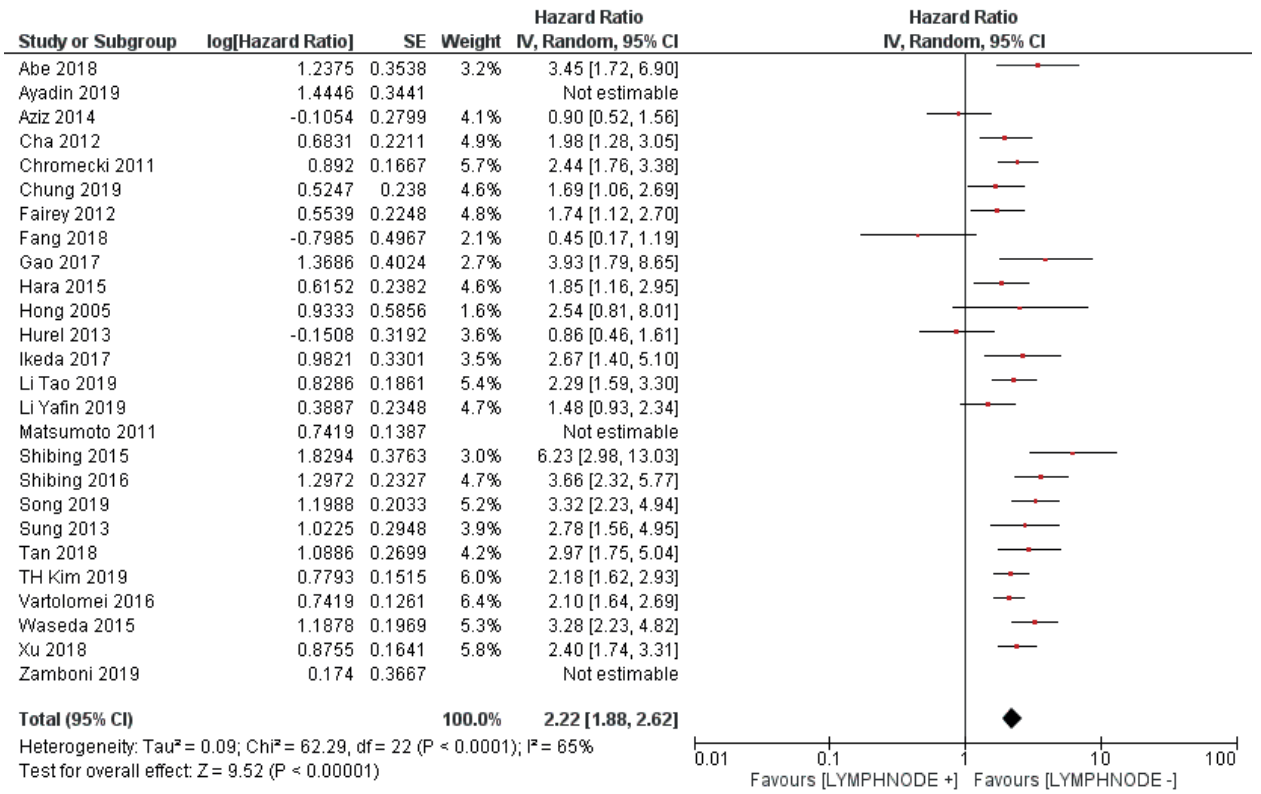
Supplementary Figure 8: Forest plot depicting CSS for grade.



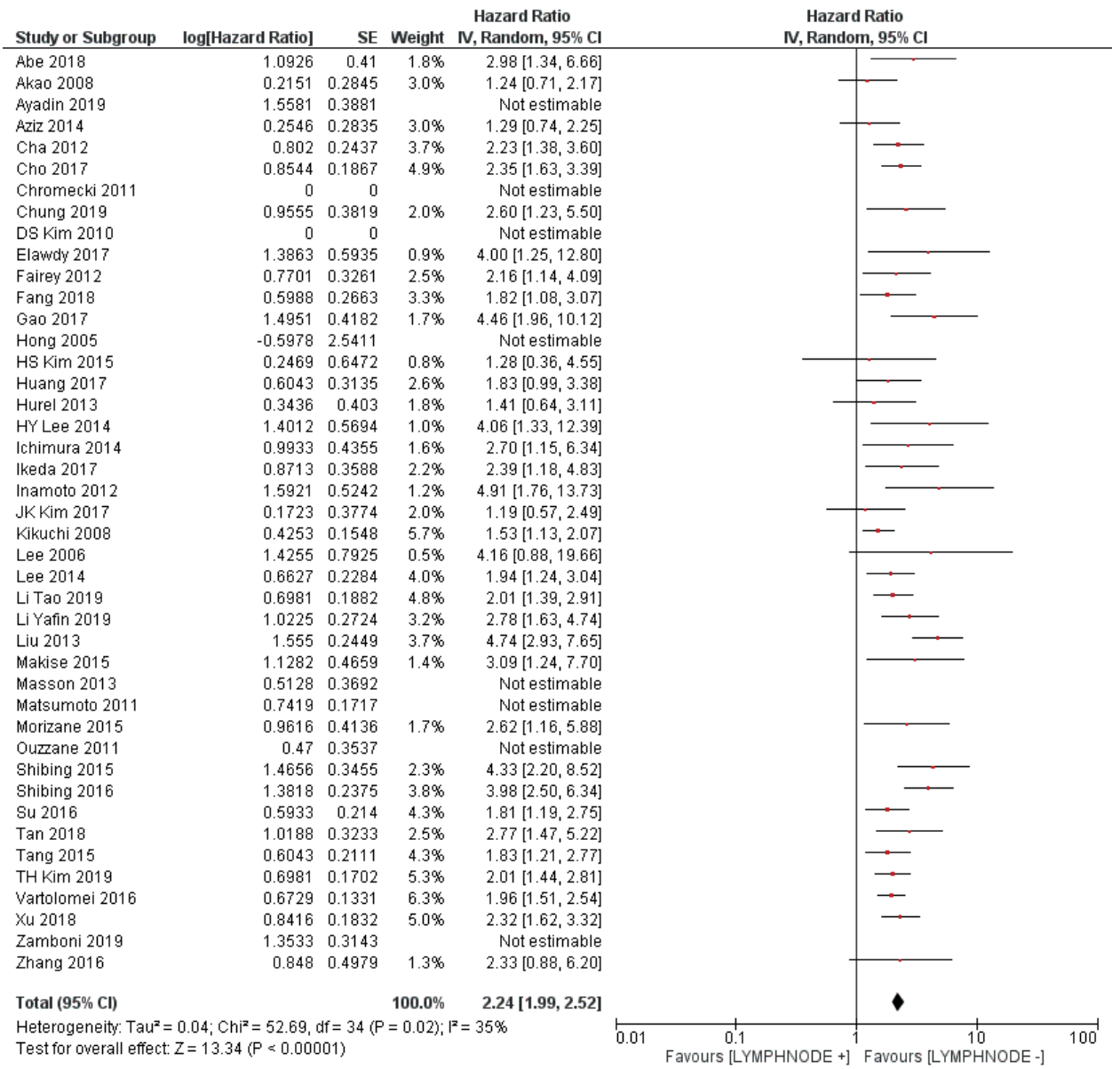
Supplementary Figure 9: Forest plot depicting OS for grade.



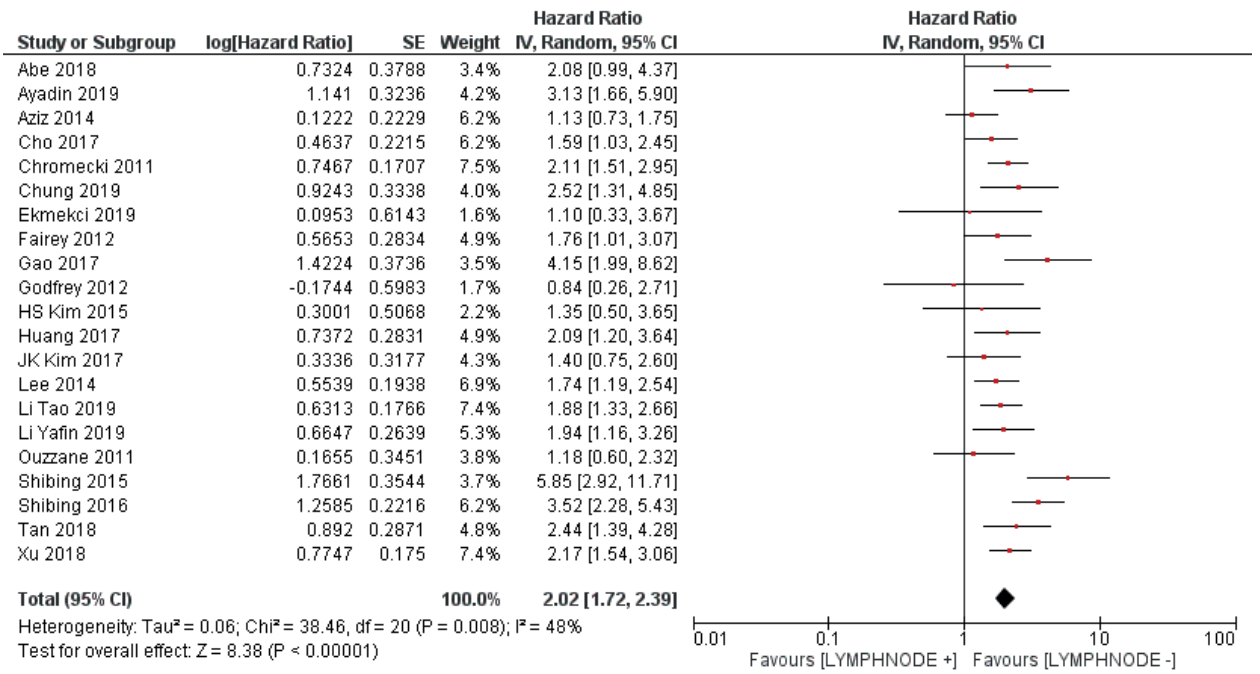
Supplementary Figure 10: Forest plot depicting RFS for lymph node positivity.



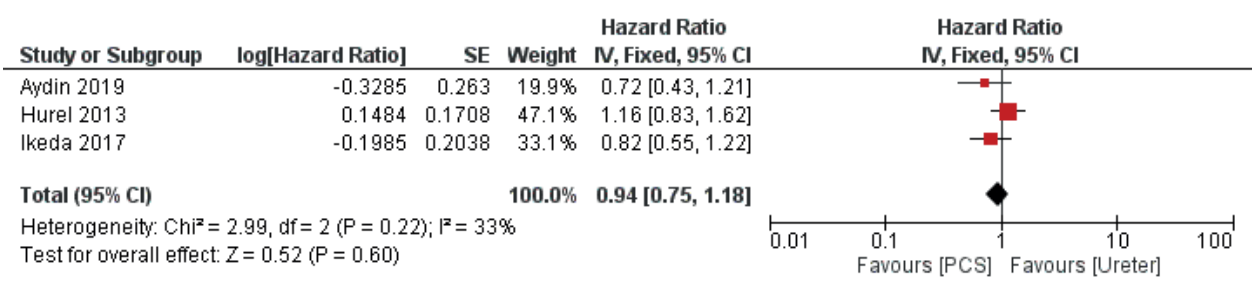
Supplementary Figure 11: Forest plot depicting CSS for lymph node positivity.



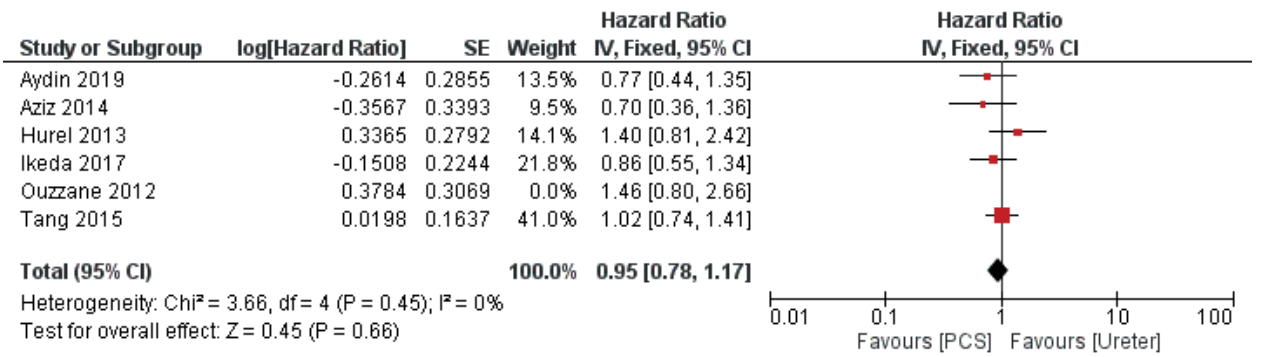
Supplementary Figure 12: Forest plot depicting OS for lymph node positivity.



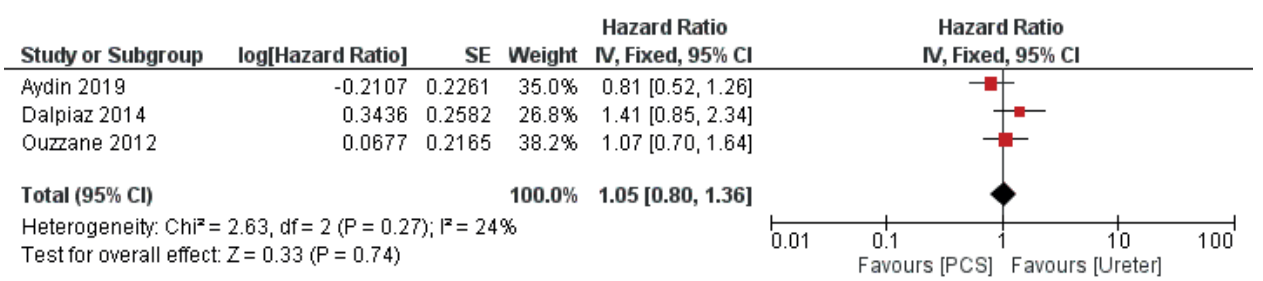
Supplementary Figure 13: Forest plot depicting RFS for location of tumor.



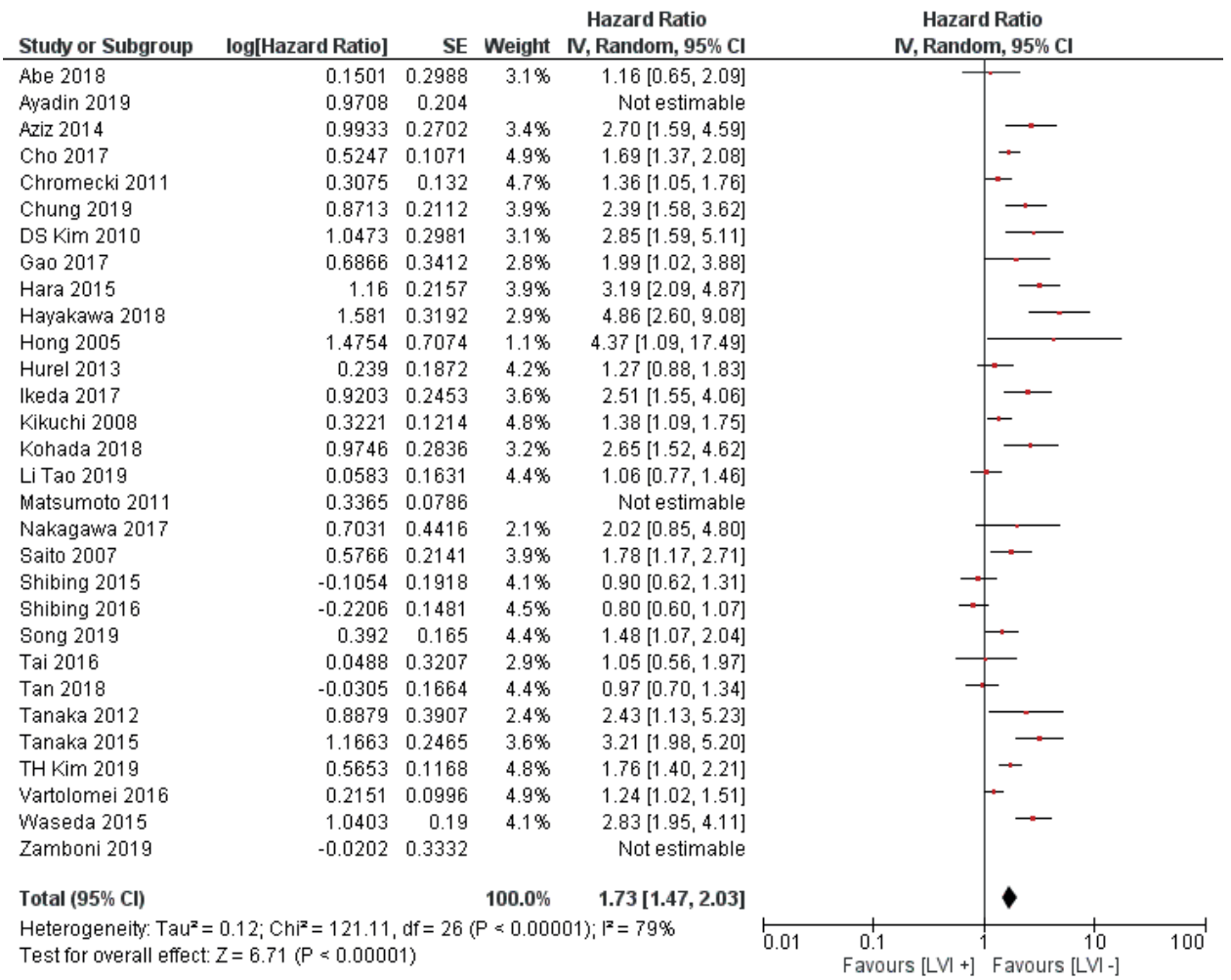
Supplementary Figure 14: Forest plot depicting CSS for location of tumor.



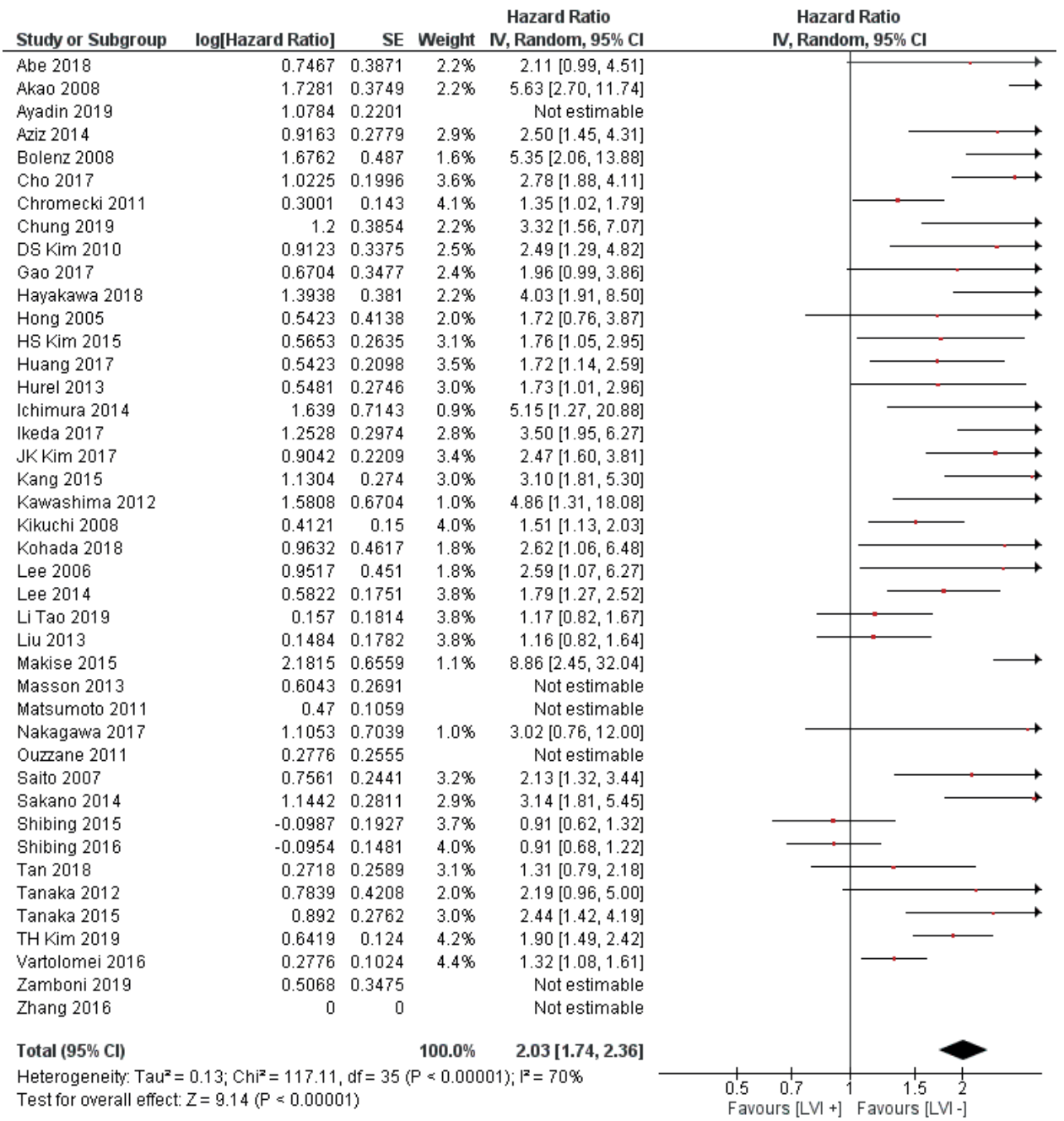
Supplementary Figure 15: Forest plot depicting OS for location of tumor.



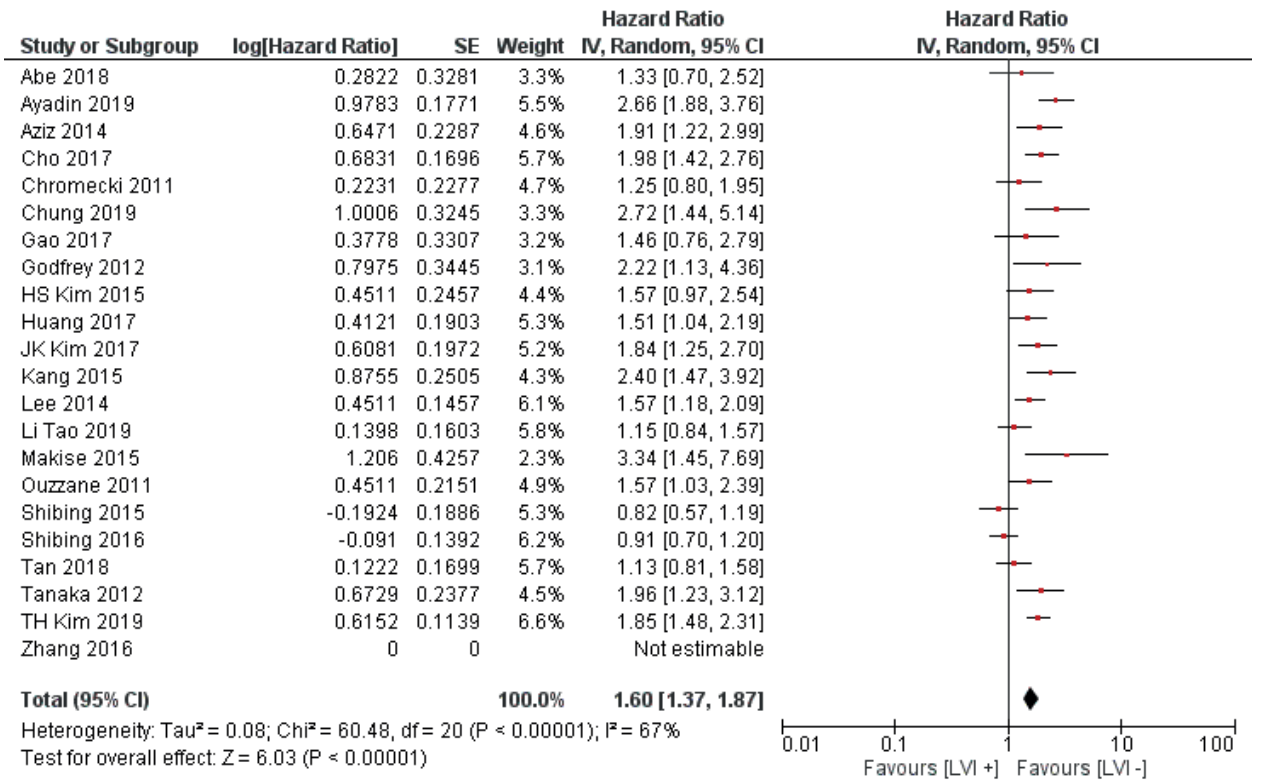
Supplementary Figure 16: Forest plot depicting RFS for lymphovascular invasion.



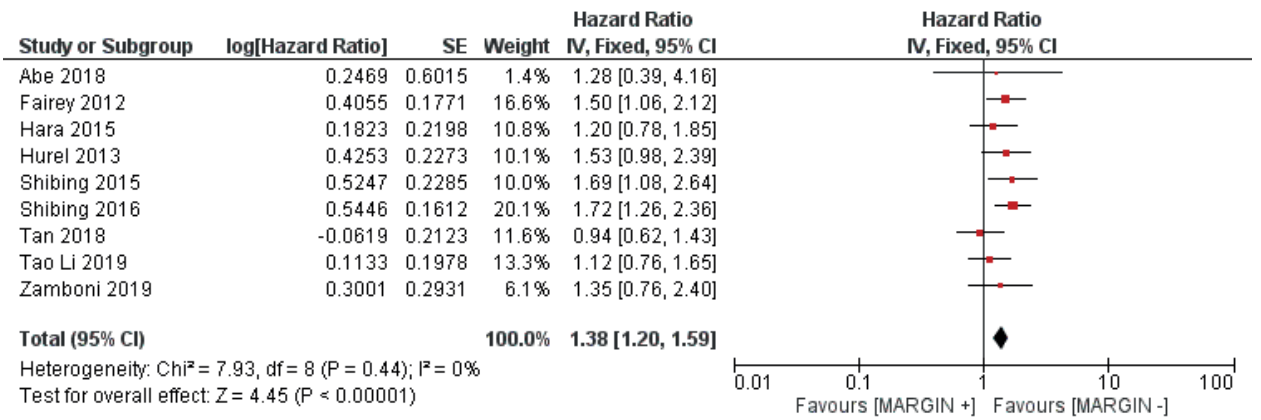
Supplementary Figure 17: Forest plot depicting CSS for lymphovascular invasion.



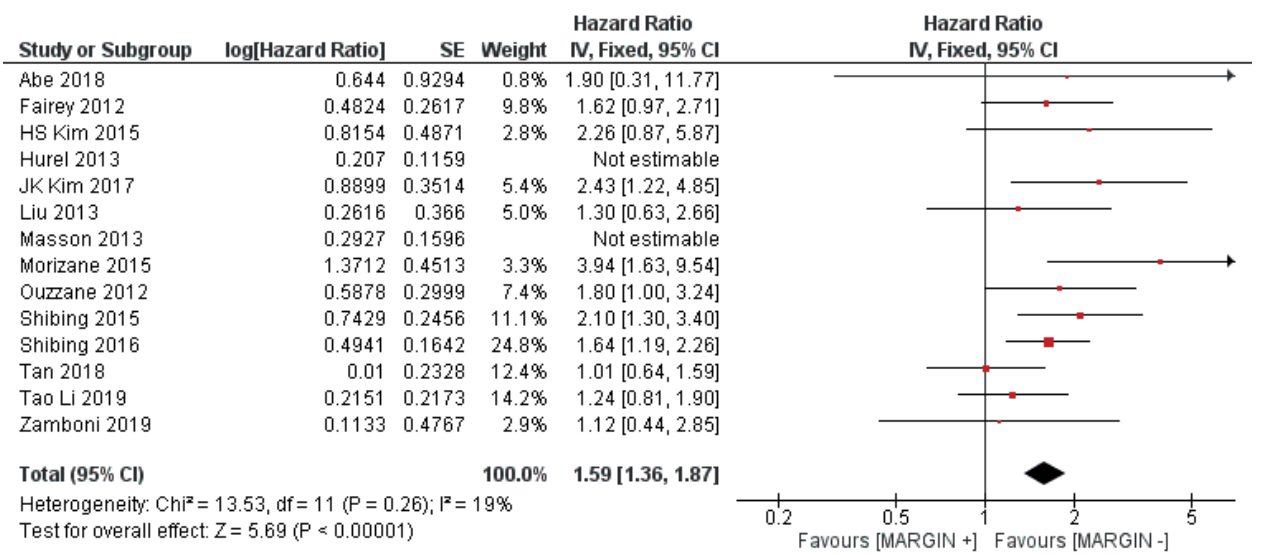
Supplementary Figure 18: Forest plot depicting OS for lymphovascular invasion.



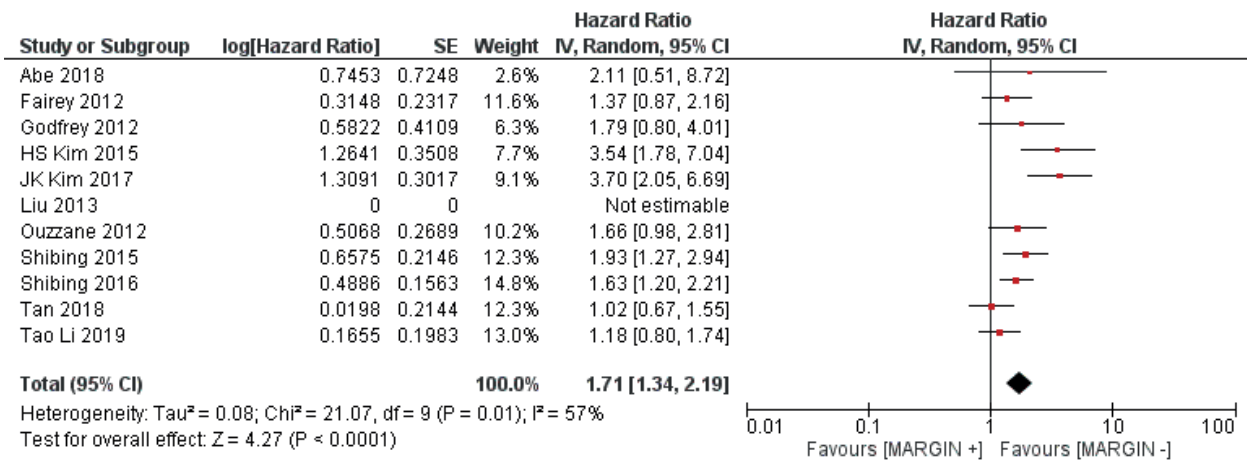
Supplementary Figure 19: Forest plot depicting RFS for margin positivity.



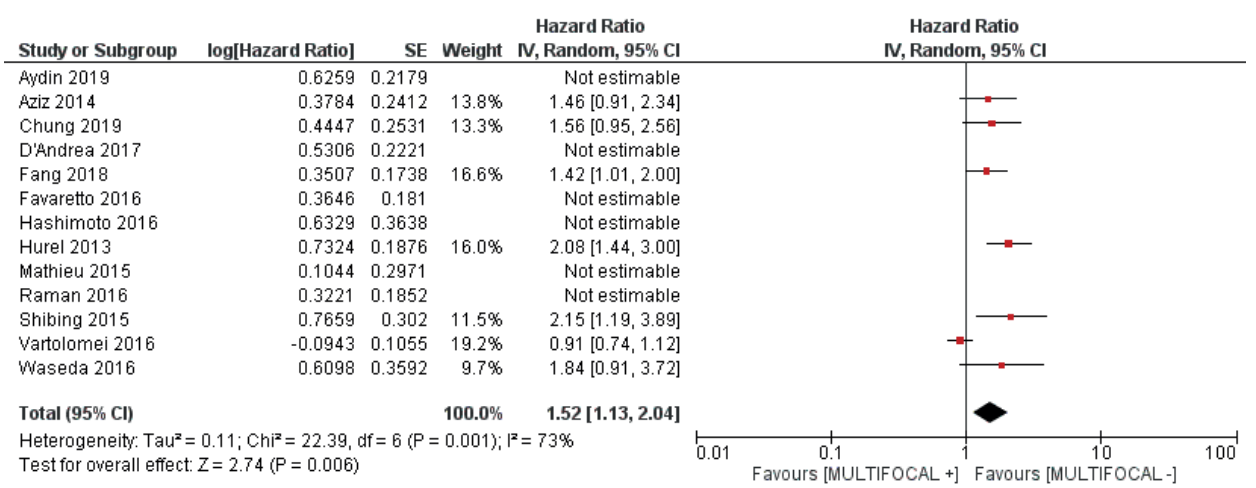
Supplementary Figure 20: Forest plot depicting CSS for margin positivity.



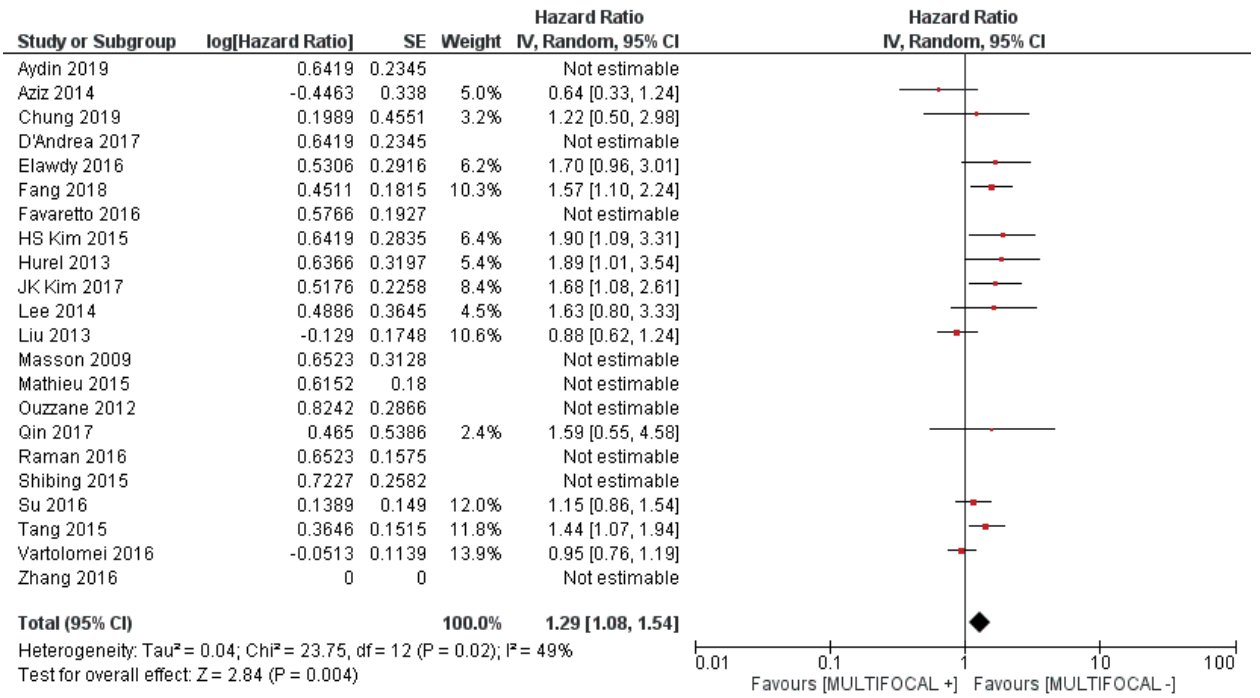
Supplementary Figure 21: Forest plot depicting OS for margin positivity.



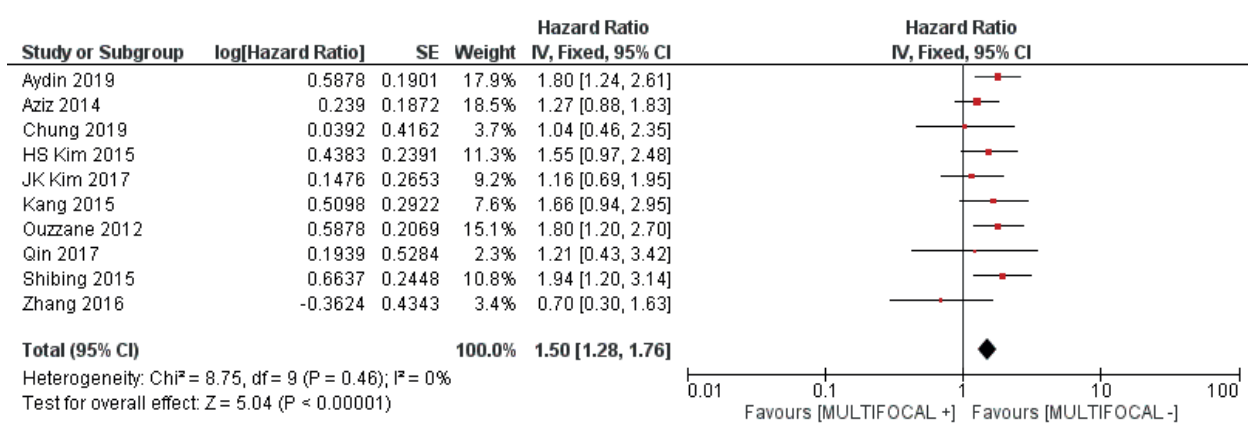
Supplementary Figure 22: Forest plot depicting RFS for multifocality.



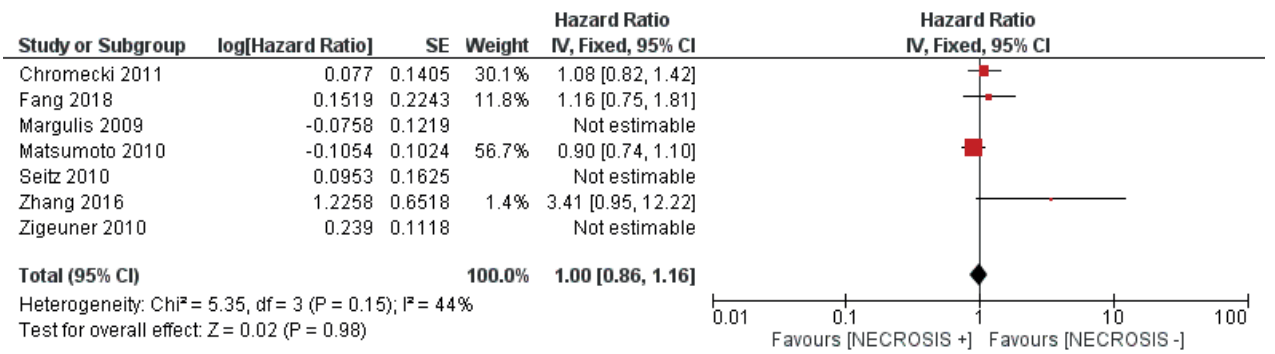
Supplementary Figure 23: Forest plot depicting CSS for multifocality.



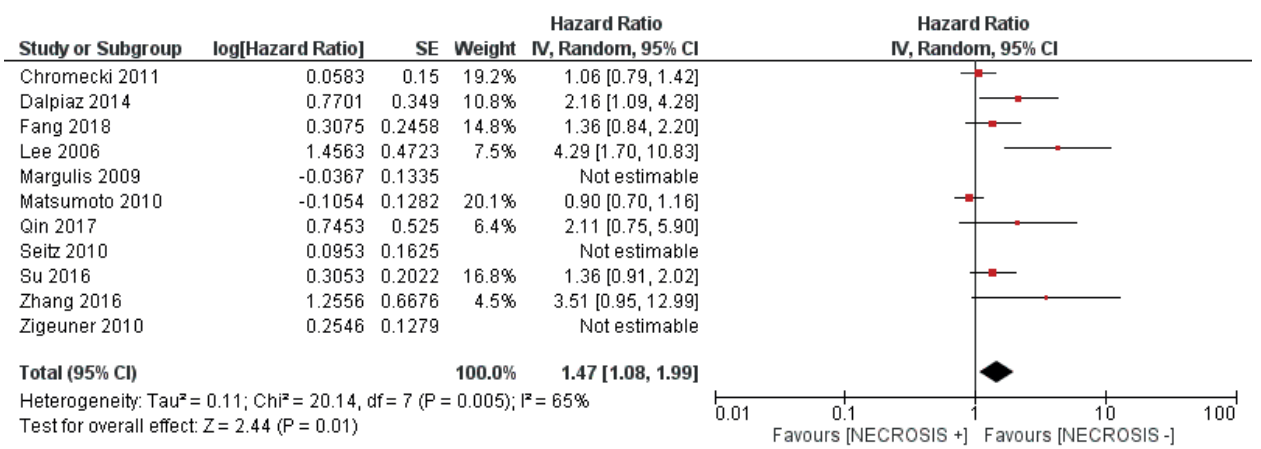
Supplementary Figure 24: Forest plot depicting OS for multifocality.



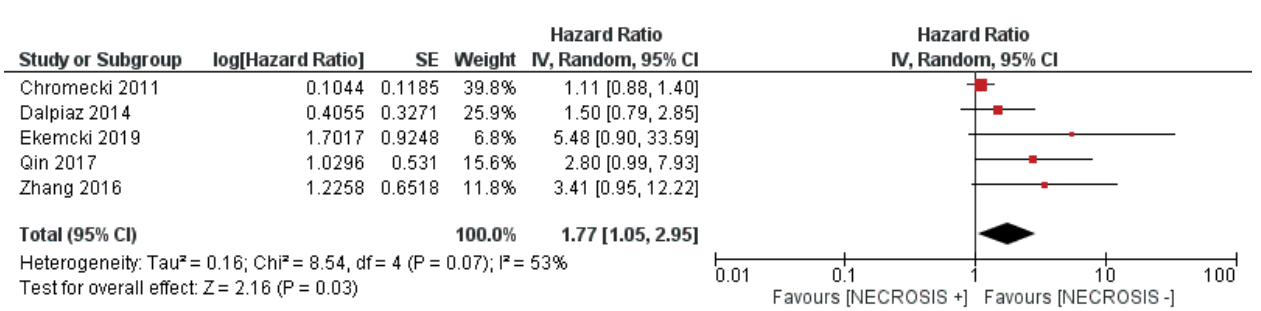
Supplementary Figure 25: Forest plot depicting RFS for necrosis.



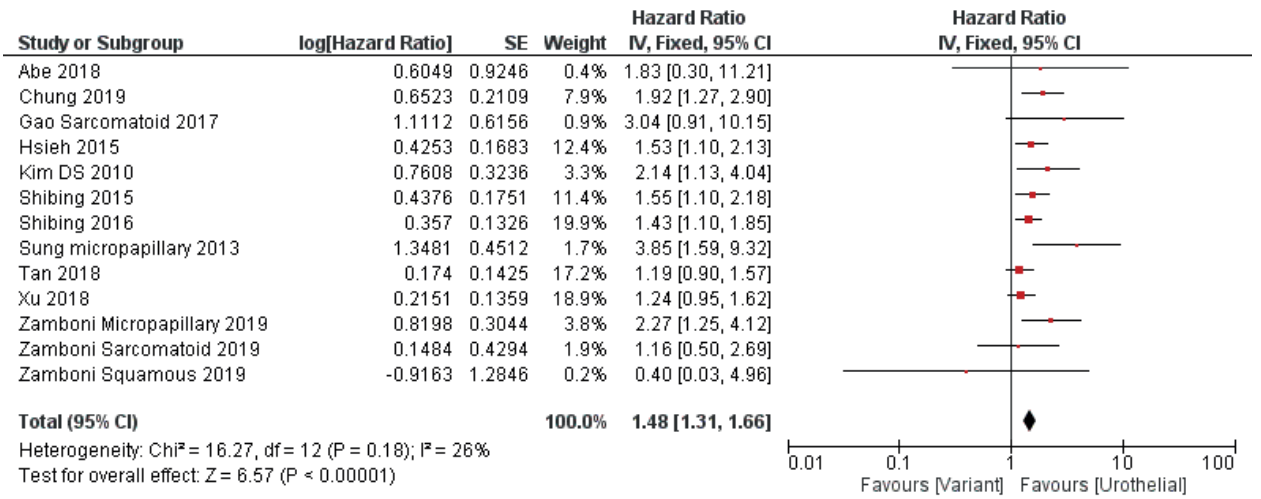
Supplementary Figure 26: Forest plot depicting CSS for necrosis.



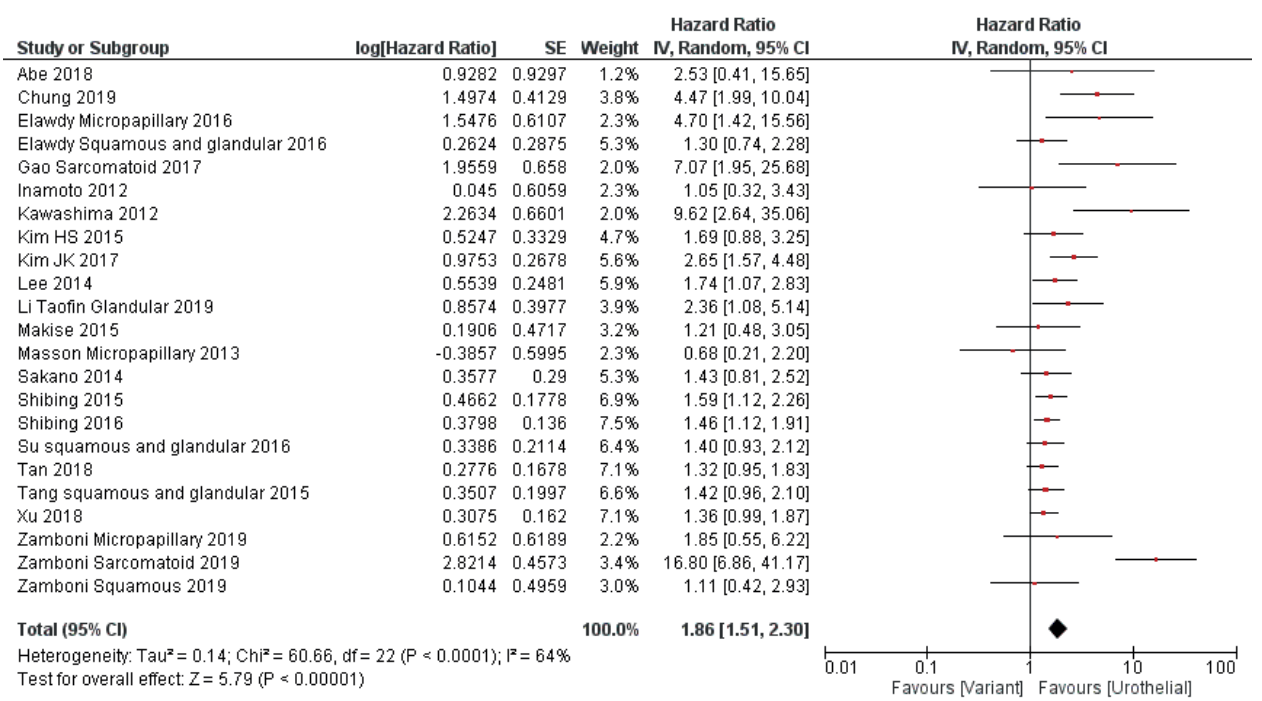
Supplementary Figure 27: Forest plot depicting OS for necrosis.



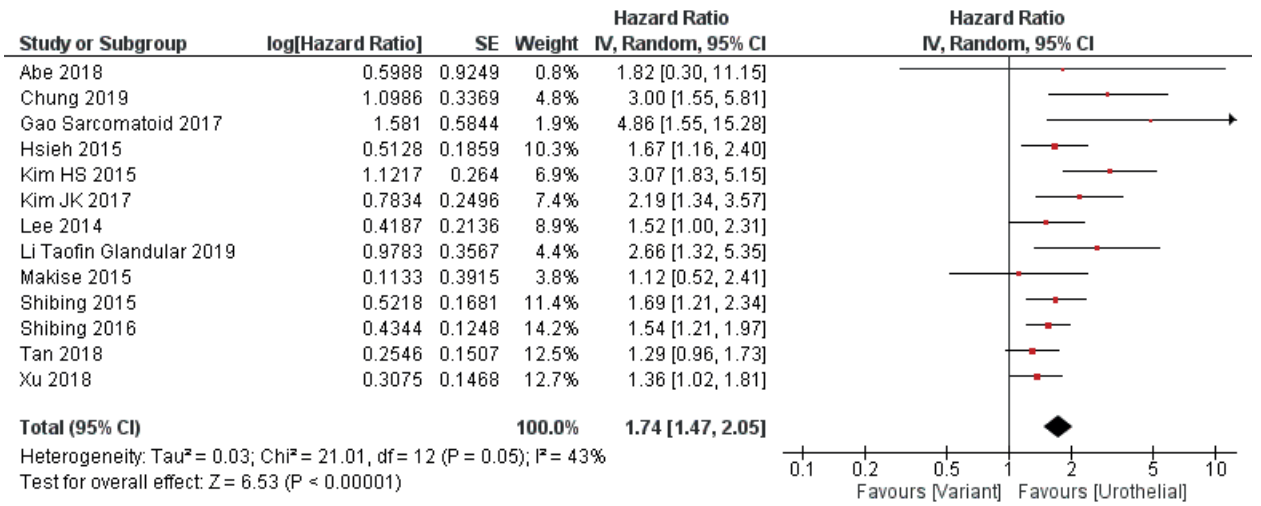
Supplementary Figure 28: Forest plot depicting RFS for variant histology.



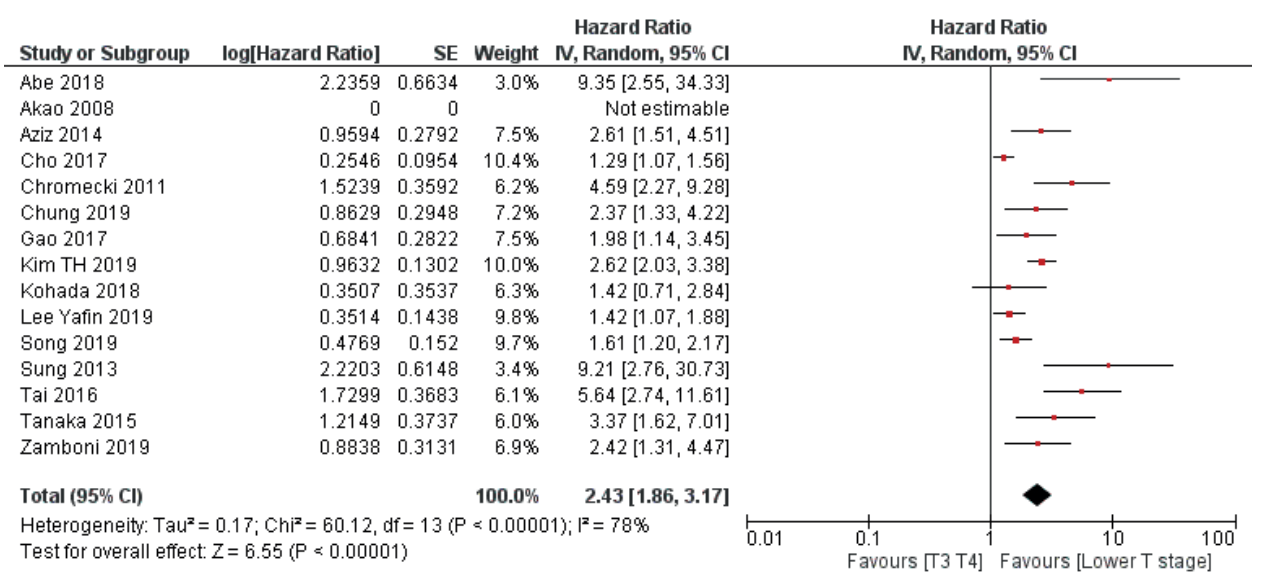
Supplementary Figure 29: Forest plot depicting CSS for variant histology.



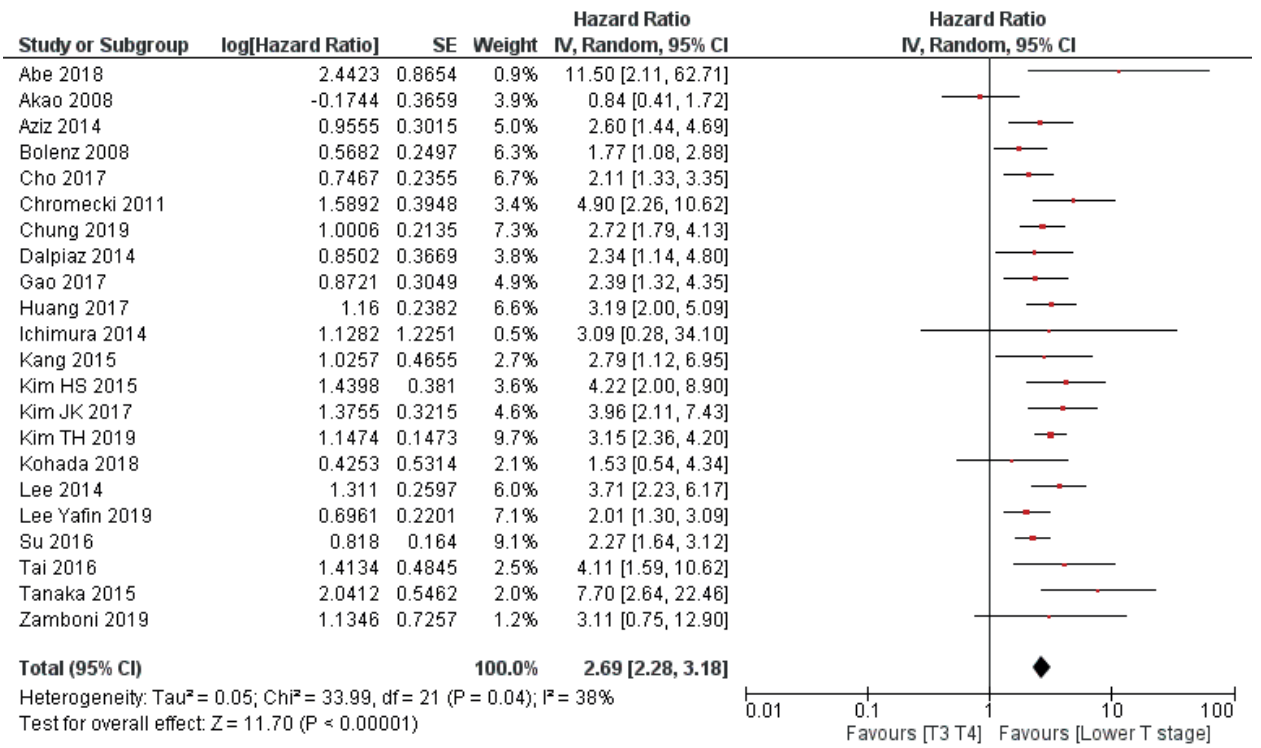
Supplementary Figure 30: Forest plot depicting OS for variant histology.



Supplementary Figure 31: Forest plot depicting RFS for stage.



Supplementary Figure 32: Forest plot depicting CSS for stage.



Supplementary Figure 33: Forest plot depicting OS for stage.