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

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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.

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.

PRISMA 2009 Flow Diagram

Records identified through database searching
PubMed 1851
Embase 2044
Scopus 7605
Web of Science 1228
CENTRAL 89
(n = 12,817)

6,249 duplicates removed
(n = 6,568)

Records screened
(n = 6,568)

Full-text articles assessed for eligibility
(n = 102)

Studies included in qualitative synthesis
(n = 63)

Studies included in quantitative synthesis
(meta-analysis)
(n = 63)

Records excluded
(n = 6466)
Unrelated 5,141
Reviews 446
Letters/Editorials 497
Case reports 442
Lacking Multivariate HR 32

Full-text articles excluded due to overlapping patient data and lack of multivariate hazard ratios
(n = 39)

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 T3 and T4 stages against
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). Chi² and I² 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 (T₁, T₂, T₃, T₄ vs. T₅, T₆), 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 | Chi² | I² | 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 | Chi² | I² | 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, 1.38 | 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    | 18.73 | 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 | <0.00001 |
|                          | 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.

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### 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 in situ)) OR (tumor margin) OR (margin) OR (tumor necrosis)) OR (LVII) 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 ("(cancer"[All Fields]) AND ("cancerated"[All Fields]) OR ("canceration"[All Fields]) OR ("cancerization"[All Fields])) OR ("cancerized"[All Fields]) OR ("cancerous"[All Fields]) OR ("neoplasms"[MeSH Terms]) OR ("neoplasm"[All Fields]) OR ("neoplasm s"[All Fields]) OR ("tumor s"[All Fields]) OR ("tumoral"[All Fields]) OR ("tumour s"[All Fields]) OR ("tumorous"[All Fields]) OR ("tumours"[All Fields]) OR ("tumor"[All Fields]) OR ("tumoral"[All Fields]) OR ("tumoural"[All Fields])) | 1,851 |
| outcome | "outcome"[All Fields] OR "outcome"[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 "survives"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "surviving"[All Fields] | 2,086,664 |
| prognostic | "prognostic"[All Fields] OR "prognostically"[All Fields] OR "prognosticate"[All Fields] OR "prognostication"[All Fields] OR "prognostications"[All Fields] OR "prognosticators"[All Fields] OR "prognosticator"[All Fields] OR "prognostic"[All Fields] OR "prognostic"[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 "locato"[All Fields] OR "locating"[All Fields] OR "location"[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"[MeSH Terms]) OR "histology"[All Fields]) OR "histology"[MeSH Terms] OR "histologic"[All Fields]) | 74,389 |
| pathological | "pathologic"[All Fields] OR "pathologically"[All Fields] OR "pathology"[MeSH Terms] OR "pathology"[All Fields] OR "pathologic"[All Fields] OR "pathological"[All Fields] | 3,795,533 |
| pathology | "pathology"[MeSH Terms] OR "pathology"[All Fields] OR "pathologic"[All Fields] OR "pathological"[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 "architectural"[All Fields] OR "architecture"[All Fields] | 171,372 |
| CIS | "CIS"[All Fields] | 123,073 |
| carcinoma in situ | (("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) OR "carcinomas"[All Fields] OR "cancer"[All Fields]) AND "in situ"[All Fields] | 1,315 |
| tumor margin | (((((("cyts"[MeSH Terms] OR "cyts"[All Fields]) OR "cyt"[All Fields]) OR "neoplasms"[All Fields]) OR "neoplasia"[All Fields]) OR "neoplastic"[All Fields]) OR "neoplasticity"[All Fields]) OR "neoplastic"[All Fields]) OR "neoplasticism"[All Fields]) OR "neoplastic"[All Fields]) OR "tumorous"[All Fields]) OR "tumour"[All Fields]) OR "tumoural"[All Fields]) OR "tumoral"[All Fields]) OR "tumours"[All Fields]) | 63,557 |
| Margin | ((((("margin s"[All Fields] OR "margin"[All Fields]) OR "margins"[All Fields]) OR "marginal"[All Fields]) OR "margins of excision"[MeSH Terms]) OR ("margin"[All Fields] AND "excision"[All Fields])) OR ("margins of excision"[All Fields]) OR ("margin"[All Fields]) OR ("margins"[All Fields])) | 159,818 |
| Term                                                                 | Count |
|----------------------------------------------------------------------|-------|
| tumor necrosis                                                      | 254,227 |
| LVI                                                                | 1,509 |
| lymphovascular invasion                                             | 5,770 |
| Grade                                                              | 451,054 |
| Stage                                                              | 1,203,520 |
| UTUC                                                               | 869 |
| Upper tract urothelial cancer                                      | 2,345 |
| Upper tract urothelial carcinoma                                   | 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.

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### Supplementary File S3 - Characteristics of included studies.

| S. no | Author Year | Country | Number of patients | Stud type | Multi variate analysis | Age (Median) | Male% | Cancer Site | Tumor Grade | Tumor Site | Parameter controlled in multivariate analysis | Follow up | NOS |
|-------|-------------|---------|-------------------|-----------|------------------------|-------------|-------|-------------|-------------|-----------|--------------------------------------------|-----------|-----|
| 1     | Hayakawa 2017 | Japan   | 371               | N         | 54.7 (5-75)            | 140.6        | 46.8  | Urinary tract | Is/pT1/a | Is/1      | Node positive STSM | 72.4 (56.7-87.6) | 18 |
| 2     | Ichimura 2015 | Taiwan  | 206               | N         | 64.7 (5-91)            | 138.6        | 53.9  | Upper urinary tract | Ta/Tis | C2-3/T2     | Histopathological Variant | 72.3 (56.7-87.6) | 18 |
| 3     | Izumiya 2014 | Japan   | 171               | N         | 70.8 (16-76.4)         | 115.2        | 42.9  | Bladder | G1/2 | Both       | - | 68.7 (56.7-87.6) | 18 |
| 4     | Kido 2010    | Korea   | 258               | N         | 54.1 (5-75)            | 147.4        | 47.8  | Upper urinary tract | T2-81 | C3-6/5     | Histopathological Variant | 72.4 (56.7-87.6) | 18 |
| 5     | Kim 2016     | Korea   | 236               | N         | 61.5 (5-75)            | 131.4        | 40.3  | Upper urinary tract | Ta/Tis | C2-3/T2     | - | 72.4 (56.7-87.6) | 18 |

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**Notes:**
- **S. no:** Study number.
- **Author Year:** Author and year of publication.
- **Country:** Country of study.
- **Number of patients:** Total number of patients in the study.
- **Stud type:** Type of study.
- **Multi variate analysis:** Type of analysis.
- **Age (Median):** Median age of patients.
- **Male%:** Percentage of male patients.
- **Cancer Site:** Site of cancer.
- **Tumor Grade:** Grade of tumor.
- **Tumor Site:** Site of tumor.
- **Parameter controlled in multivariate analysis:** Parameters controlled in multivariate analysis.
- **Follow up:** Follow-up period.
- **NOS:** Quality assessment score.

**Quality Assessment:**
- **Quality:** Based on predefined criteria.

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**References:**
- [Hayakawa et al. (2017)]
- [Ichimura et al. (2015)]
- [Izumiya et al. (2014)]
- [Kido et al. (2010)]
- [Kim et al. (2016)]
| Study | Authors | Year | Country | Patients | pT2/pT3a | pT3b/pT4 | ISUP | Grade | Factors |
|-------|---------|------|---------|----------|----------|----------|------|-------|---------|
| 15    | Lee Yoon | 2006 | Korea   | 114      | T4       | T3b-T4a  | NA   | T4   | 1 | T stage > pT3, - Invasion, - Tumor necrosis |
| 16    | Lee Young | 2014 | Korea   | 295      | T4       | T3b-T4a  | NA   | T4   | 1 | T stage > pT3, - Invasion, - Tumor necrosis |
| 17    | Lee Young | 2014 | Taiwan  | 354      | T4       | T3b-T4a  | NA   | T4   | 1 | T stage > pT3, - Invasion, - Tumor necrosis |
| 23    | Li Fei  | 2019 | China   | 302      | T4       | T3b-T4a  | NA   | T4   | 1 | T stage > pT3, - Invasion, - Tumor necrosis |
| 24    | Li Yifan | 2019 | China   | 602      | T4       | T3b-T4a  | NA   | T4   | 1 | T stage > pT3, - Invasion, - Tumor necrosis |
| No. | Year | Country | Study Design | Follow-up | n | Sex | Age | Stage | Grade | Histology | LVI | Adjuvant Chemotherapy | Recurrence | CSS | OS | RFS | MFS | IVRFS |
|-----|------|---------|--------------|-----------|---|-----|-----|------|-------|----------|-----|----------------------|------------|-----|----|-----|-----|-------|
| 14  | 2013 | South Korea | retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 15  | 2013 | South Korea | retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 16  | 2011 | Japan | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 17  | 2011 | Japan | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 18  | 2011 | Japan | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 19  | 2012 | France | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 20  | 2011 | France | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 21  | 2011 | China | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 22  | 2009 | Japan | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 23  | 2010 | Japan | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |
| 24  | 2010 | South Korea | Retrospective | 60 months | 150 | Male | 65±10 | pT1 | G3 | - | - | - | - | - | - | - | - | - |

**Note:** The table includes various factors such as study design, follow-up duration, number of patients (n), sex distribution, age distribution, stage, grade, histology, lymphovascular invasion (LVI), adjuvant chemotherapy, recurrence, and survival outcomes (CSS, OS, RFS, MFS, IVRFS).
| Study | Authors | Year | Country | T stage | N stage | Age | Tumor grade | LVI | Concomitant CIS | N stage | MFS | CSS | OS |
|-------|---------|------|---------|---------|---------|-----|-------------|-----|----------------|---------|-----|-----|-----|
| 25    | Kohada 2016 Japan | 148 | R | N | T1/2 (70) | 77-90 | NA | Y | T2b-2c | T4 | 0-66 | U-89 | G1-2 | G3-88 | 25 | 65 | 69 | 86 |
| 26    | Morizane 2015 Japan | 345 | R | Y | T4 (50) | 70-90 | 11 | Y | T3a-2b | T3-4 | 112/3 | NA | Y | T3a | U-66 | G1 | G3-109 | NA | 50 | (61.1 | 100) |
| 27    | Makise 2015 Japan | 140 | N | N | NA | 10-50 | 8 | NA | Y | T2a | T3-4 | 51 | NA | G1/2 | G3-77 | 52 | 63 | NA |
| 28    | Zhang 2016 China | 184 | R | N | T2 (37) | 70-74 | 84-10 | 6 | O | T2 (15) | L-59 | Y | T2a | T3-4 | 111 | 28 | 30 | 79 | 80 |
| 29    | Xu 2016 China | 687 | N | N | <3 cm (20) | <3 cm (80) | <3 cm (29) | 80-85 | 3 | 230 | L-017 | Y | T2a | T2a | T3-19 | 0-8 | NA | NA | 78 | 65 |

- T stage
- Tumor grade
- LVI
- Concomitant CIS
- N stage
- MFS
- CSS
- OS
| Study          | Year | Country     | Subjects | Follow-Up | Stage | Grade | Tumor Number | Multifocality | LN Status | CIS | LVI | Adjuvant therapy | Complications | Sites | CSS | OS | RFS | CSF | PLR Score | ECOG | PLR | LVI | Architecture | LN involvement | Adjacent tumor grade | Age > 65 | Multifocality | LVI | Grade | Multifocality | LN involvement | Adjacent tumor grade | Age > 65 | Multifocality | LVI | Grade | Multifocality | LN involvement | Adjacent tumor grade | Age > 65 | Multifocality | LVI | Grade | Multifocality | LN involvement | Adjacent tumor grade | Age > 65 |
|----------------|------|-------------|----------|-----------|-------|-------|-------------|---------------|------------|-----|-----|-----------------|----------------|-------|-----|----|-----|-----|----------|------|-----|-----|----------|----------------|----------------|----------------|---------|------------|-----|-------|------------|----------------|----------------|----------------|---------|------------|-----|-------|------------|----------------|----------------|----------------|---------|------------|-----|-------|------------|----------------|----------------|----------------|---------|------------|-----|-------|------------|----------------|----------------|----------------|---------|
| Huang et al.   | 2018 | China       | 368      | 236       | NS    | NS    | NS          | NS             | NS         | NS | NS | NS               | NS             | NS    | NS | NS | NS | NS | NS       | 239  | NS | NS | NS       | NS             | NS             | NS         | NS      | NS       | NS             | NS             | NS         | NS         | NS     |
| Chung et al.   | 2019 | South Korea | 357      | 188       | NS    | NS    | NS          | NS             | NS         | NS | NS | NS               | NS             | NS    | NS | NS | NS | NS | NS       | 540  | NS | NS | NS       | NS             | NS             | NS         | NS      | NS       | NS             | NS             | NS         | NS         | NS     |
| Akao et al.    | 2012 | Japan       | 352      | 174       | NS    | NS    | NS          | NS             | NS         | NS | NS | NS               | NS             | NS    | NS | NS | NS | NS | NS       | 42   | NS | NS | NS       | NS             | NS             | NS         | NS      | NS       | NS             | NS             | NS         | NS         | NS     |
| Bolenz et al.  | 2016 | USA         | 300      | 150       | NS    | NS    | NS          | NS             | NS         | NS | NS | NS               | NS             | NS    | NS | NS | NS | NS | NS       | 348  | NS | NS | NS       | NS             | NS             | NS         | NS      | NS       | NS             | NS             | NS         | NS         | NS     |
| Garcia et al.  | 2011 | USA         | 224      | 112       | NS    | NS    | NS          | NS             | NS         | NS | NS | NS               | NS             | NS    | NS | NS | NS | NS | NS       | 500  | NS | NS | NS       | NS             | NS             | NS         | NS      | NS       | NS             | NS             | NS         | NS         | NS     |
| Aydin et al.   | 2013 | Turkey      | 200      | 100       | NS    | NS    | NS          | NS             | NS         | NS | NS | NS               | NS             | NS    | NS | NS | NS | NS | NS       | 360  | NS | NS | NS       | NS             | NS             | NS         | NS      | NS       | NS             | NS             | NS         | NS         | NS     | | | | | | |
| Year | Country | Study Type | N | T-stage | Disease-free survival | Overall survival | Cause of death | p-stage | Tumor necrosis | Lymph node metastasis | Infiltrative growth | Grade | Histology | Focality | Differentiation | Nuclear grade | Other factors |
|------|---------|------------|---|---------|----------------------|-----------------|----------------|---------|---------------|----------------------|-------------------|--------|-----------|---------|----------------|-------------|--------------|
| 2012 | Canada  | Canada     | 100 | pT2-3   | 5-year OS 90%        | 5-year OS 90%    | Stage 4        | pT4     | No            | No                   | Yes               | No     | No        | No      | No             | No          | No           |
| 2012 | USA     | USA        | 200 | pT2-3   | 5-year OS 90%        | 5-year OS 90%    | Stage 4        | pT4     | No            | No                   | Yes               | No     | No        | No      | No             | No          | No           |
| Year | Authors   | Country  | Tumor Type | Tumor Size | T-Stage | L-Stage | pT | pN | pStage | Gender | Age | BMI | HTN | HDN | Plasma LDH | Fibrinogen | LVI | LVI | Location | L.Venous Invasion | L.Node | HDN | ACM | MFS | CSS | RFS | OS | CSS |
|------|-----------|----------|-------------|------------|---------|---------|----|----|--------|--------|-----|-----|------|-----|-------------|------------|-----|-----|----------|------------------|--------|-----|-----|-----|-----|-----|-----|-----|
| 2015 | Sakono    | Japan    | UCUT       | (30-40)    | 149.7   | 39.3   | T3 | N0 | 3-1    | Female | 60-  | 21.1 | 42   | 11.0 | -10.5       | 11.0        | 2.1 | 2.1 | 15-20    | -                | 2       | 2.1 | 2   | 2.1 | 2  | 7   | 7   | 7   |
| 2015 | Sakono    | Japan    | UCUT       | (26-38)    | 232.1   | 20.1   | T1  | N1 | 0-1    | Female | 60-  | 20.6 | 38   | 6.2  | -15.2       | 15.2        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
| 2015 | Song      | Korea    | UCUT       | (22-40)    | 180.3   | 21.0   | T3  | N2 | 0-1    | Female | 60-  | 21.0 | 42   | 6.0  | -15.0       | 15.0        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
| 2015 | Tang      | Taiwan   | UCUT       | (26.11)    | 250.0   | 31.0   | T3  | N2 | 0-1    | Female | 60-  | 21.0 | 42   | 6.0  | -15.0       | 15.0        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
| 2015 | Tai       | Taiwan   | UCUT       | (4-5)      | 245.0   | 34.0   | T1  | N1 | 0-1    | Female | 60-  | 21.0 | 42   | 6.0  | -15.0       | 15.0        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
| 2015 | Tan       | China    | UCUT       | (64.4-77.2)| 280.8   | 34.0   | T1  | N1 | 0-1    | Female | 60-  | 21.0 | 42   | 6.0  | -15.0       | 15.0        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
| 2015 | Tanaka    | Japan    | UCUT       | (26.52)    | 160.8   | 35.0   | T3  | N0 | 0-1    | Female | 60-  | 21.0 | 42   | 6.0  | -15.0       | 15.0        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
| 2015 | Tanaka    | Japan    | UCUT       | (63-75)    | 285.0   | 35.0   | T3  | N0 | 0-1    | Female | 60-  | 21.0 | 42   | 6.0  | -15.0       | 15.0        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
| 2015 | Tong      | China    | UCUT       | (20-30)    | 360.0   | 31.0   | T3  | N0 | 0-1    | Female | 60-  | 21.0 | 42   | 6.0  | -15.0       | 15.0        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
| 2015 | Vorherr   | India    | UCUT       | (61-75)    | 152.7   | 54.0   | T1  | N1 | 0-1    | Female | 60-  | 21.0 | 42   | 6.0  | -15.0       | 15.0        | 0   | 0   | 0-20     | -                | 1       | 1   | 1   | 1   | 1  | 7   | 7   | 7   |
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 transaminase, 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.

| Study | Year | Country | Sample Size | R | U | P | Open | L | Gender | Age (Mean) | LVI | STSM | T Stage | INF | Grade | OS | CSS | RFS | MFS | Location | Age | Study (Year) |
|-------|------|---------|-------------|---|---|---|------|---|--------|------------|-----|-------|----------|-----|--------|---|-----|-----|------|-----------|-----|-------------|
| Waseda 2015 | Japan | 1088 | R | Y | 35 (50-70) | 10 | NA | Y | T2-441 | T3-671 | T4-66 | 448 | NA | NA | 196/18 | 6 | LG | HG | 317 | NIL | Gender | 17 | Waseda 2015 Japan |
| Xu 2018 | China | 862 | R | N | 37 (39-74) | 86 | NA | Y | T2-65 | T3-324 | T4-342 | 102 | NA | NA | 166/2 | 6 | LG | HG | 410 | CORT | - | RY | 70 (62-76) | Xu 2018 China |
| Zhang 2016 | China | 186 | R | Y | 64 (60-72) | 33 | NA | Y | T2-441 | T3-46 | T4-62 | 109 | NA | NA | 72/18 | 6 | LG | HG | 410 | - | - | RY | 70 (62-76) | Zhang 2016 China |
| Zamboni 2019 | Multicentre | 1610 | R | Y | 69 (61-76) | 1096/512 | O | Y | T0/Ta/Tis-401 | T1-330 | T2-227 | 110 | NA | NA | 344/23 | 6 | LG | HG | 230 | micropapillary variant | T3-4 stage | Sarcomatoid variant | RFS | CSS | 42 | Zamboni 2019 Multicentre |
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.

| Study or Subgroup | log(Hazard Ratio) | SE | Weight | Hazard Ratio IV, Fixed, 95% CI | Hazard Ratio IV, Fixed, 95% CI |
|-------------------|------------------|----|--------|------------------------------|------------------------------|
| Cha 2012          | 0.27             | 0.1511 | 19.5% | 1.31 [0.97, 1.78]               |                               |
| Chung 2019        | 0.3507           | 0.4311 | 2.4%  | 1.42 [0.61, 3.31]               |                               |
| Elawdy 2017       | 0.1023           | 0.5605 | 1.4%  | 1.20 [0.40, 3.60]               |                               |
| Fahey 2012        | -0.0439          | 0.2231 | 9.1%  | 0.96 [0.62, 1.49]               |                               |
| Fang 2018         | 0.0296           | 0.3881 | 3.0%  | 1.03 [0.48, 2.20]               |                               |
| HS Kim 2016       | 0.3993           | 0.3392 | 4.2%  | 1.49 [0.79, 2.85]               |                               |
| Hurel 2013        | -0.2357          | 0.5687 | 1.3%  | 0.79 [0.25, 2.50]               |                               |
| Ichimura 2014     | 1.1939           | 0.4912 | 1.5%  | 3.30 [1.28, 8.64]               |                               |
| Ikeda 2017        | -0.1508          | 0.3159 | 4.8%  | 0.86 [0.46, 1.60]               |                               |
| JK Kim 2017       | 0.1231           | 0.2929 | 5.5%  | 1.13 [0.64, 2.01]               |                               |
| Kang 2015         | -0.3481          | 0.5949 | 1.3%  | 0.71 [0.22, 2.27]               |                               |
| Kuhada 2018       | 0.8005           | 0.4160 | 2.6%  | 2.24 [0.99, 5.07]               |                               |
| Lee 2014          | -0.0834          | 0.2267 | 8.8%  | 0.92 [0.59, 1.43]               |                               |
| Wessou 2013       | -0.0043          | 0.2854 | Not testable |                               |                               |
| Motsumoto 2011    | 0.1139           | 0.1139 | Not testable |                               |                               |
| Sakamoto 2014     | 0.4318           | 0.3342 | 4.1%  | 1.54 [0.80, 2.96]               |                               |
| Du 2016           | 0.5145           | 0.3095 | 4.7%  | 1.67 [0.91, 3.10]               |                               |
| Tang 2015         | 0.3001           | 0.2137 | 4.6%  | 1.35 [0.73, 2.50]               |                               |
| TH Kim 2019       | 0.1338           | 0.1483 | 20.7% | 1.15 [0.66, 2.04]               |                               |
| Varolbasi 2016    | 0.077            | 0.1103 | Not testable |                               |                               |
| Zanunori 2013     | -0.2231          | 0.4368 | Not testable |                               |                               |

Total (95% CI) 100.0% 1.21 [1.06, 1.38]

Heterogeneity: Ch² = 14.31, df = 15 (P = 0.50); I² = 0%
Test for overall effect Z = 2.84 (P = 0.0004)

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

| Study or Subgroup | log(Hazard Ratio) | SE | Weight | Hazard Ratio IV, Fixed, 95% CI | Hazard Ratio IV, Fixed, 95% CI |
|-------------------|------------------|----|--------|------------------------------|------------------------------|
| Chung 2013        | 0.1655           | 0.2095 | 7.0%  | 1.13 [0.55, 2.33]               |                               |
| Fahey 2012        | -0.0232          | 0.1865 | 30.8% | 0.98 [0.68, 1.41]               |                               |
| HS Kim 2016       | 0.3577           | 0.2037 | 13.2% | 1.43 [0.82, 2.49]               |                               |
| JK Kim 2017       | 0.2374           | 0.2618 | 16.5% | 1.27 [0.75, 2.12]               |                               |
| Kang 2015         | -0.2784          | 0.5160 | 4.0%  | 0.79 [0.38, 2.08]               |                               |
| Lee 2014          | 0.1893           | 0.1893 | 29.7% | 1.00 [0.69, 1.45]               |                               |
| TH Kim 2019       | 0.0000           | 0.0000 | Not testable |                               |                               |

Total (95% CI) 100.0% 1.08 [0.88, 1.32]

Heterogeneity: Ch² = 2.32, df = 5 (P = 0.60); I² = 0%
Test for overall effect Z = 0.76 (P = 0.45)
Supplementary Figure 7: Forest plot depicting RFS for grade.

| Study or Subgroup | log(Hazard Ratio) | SE | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|-------------------|------------------|----|--------|--------------------------------|--------------------------------|
| Abe 2018          | -0.1177          | 0.3286 | 4.1%   | 0.69 [0.47, 1.69]              |                                |
| Aziz 2014         | 0.3143           | 0.2684 | 4.6%   | 1.37 [0.77, 2.44]              |                                |
| Che 2012          | 0.3221           | 0.5339 | 2.1%   | 1.38 [0.49, 3.83]              |                                |
| Chen et al. 2011  | 0.2311           | 0.4317 | 3.1%   | 1.26 [0.56, 2.83]              |                                |
| Chung 2013        | 0.5565           | 0.7316 | 1.3%   | 2.60 [0.62, 10.90]             |                                |
| D’Silva 2010      | 0.705            | 0.3286 | 4.1%   | 2.03 [1.57, 2.64]              |                                |
| Farey 2012        | 0.1132           | 0.1407 | 7.7%   | 1.12 [0.56, 1.98]              |                                |
| Fang 2016         | -0.8162          | 0.2892 | 4.8%   | 0.54 [0.31, 0.94]              |                                |
| Gao 2017          | 1.0023           | 0.4943 | 2.4%   | 2.73 [1.96, 3.70]              |                                |
| Hara 2016         | 1.6001           | 1.0220 | 0.7%   | 5.42 [0.73, 40.24]             |                                |
| Hong 2005         | 0                | 0     |        | Not estimable                  |                                |
| Hurel 2013        | 0.077            | 0.3172 | 4.3%   | 1.08 [0.58, 2.01]              |                                |
| Ikeda 2017        | 0.6152           | 0.2221 | 5.9%   | 1.85 [1.20, 2.86]              |                                |
| Kawaihara 2012    | 0.7768           | 0.436  | 2.8%   | 2.66 [1.13, 6.24]              |                                |
| Li Tao 2019       | 0.3801           | 0.1739 | 7.0%   | 1.55 [0.96, 2.49]              |                                |
| Matsunuma 2011    | 0.5873           | 0.1282 |        | Not estimable                  |                                |
| Nakagawa 2017     | 0.8043           | 0.3736 | 5.5%   | 1.83 [0.88, 3.81]              |                                |
| Shihing 2015      | 0.7844           | 0.3271 | 4.1%   | 2.19 [1.16, 4.16]              |                                |
| Shihing 2016      | 0.3133           | 0.192  | 6.6%   | 1.37 [0.84, 2.30]              |                                |
| Sung 2013         | -0.4005          | 0.2303 | 5.6%   | 0.67 [0.42, 1.07]              |                                |
| Tai 2016          | 0.27             | 0.3108 | 4.2%   | 1.31 [0.70, 2.46]              |                                |
| Tan 2018          | 0.3577           | 0.1774 | 9.9%   | 1.43 [1.01, 2.02]              |                                |
| Th Kim 2019       | 0.8195           | 0.1613 | 7.3%   | 2.25 [1.64, 3.10]              |                                |
| Vanotome 2016     | 0.0352           | 0.1231 |        | Not estimable                  |                                |
| Xu 2018           | 0.2231           | 0.1791 | 5.9%   | 1.26 [0.58, 2.81]              |                                |
| Zamboni 2018      | -0.2231          | 0.3268 |        | Not estimable                  |                                |

Total (95% CI) 100.0% 1.39 [1.17, 1.65]

Heterogeneity: Tau² = 0.08, Chi² = 46.76, df = 21 (P = 0.0010), I² = 56%
Test for overall effect Z = 3.77 (P = 0.0002)
Supplementary Figure 8: Forest plot depicting CSS for grade.

| Study or Subgroup     | log(Hazard Ratio) | SE   | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|-----------------------|-------------------|------|--------|---------------------------------|---------------------------------|
| Abe 2016              | 0.3812            | 0.408 | 2.0%   | 1.46 [0.86, 2.50]               |                                 |
| Akao 2008             | -0.0619           | 0.220 | 3.5%   | 0.94 [0.60, 1.47]               |                                 |
| Aza 2014              | 0.4511            | 0.319 | 3.0%   | 1.57 [0.84, 2.93]               |                                 |
| Cha 2012              | 0.5247            | 0.583 | 1.5%   | 1.69 [0.50, 5.10]               |                                 |
| Cho 2017              | 0.5596            | 0.204 | 3.3%   | 1.75 [0.81, 3.73]               |                                 |
| Chrennek 2011         | 0.7372            | 0.506 | 1.7%   | 2.00 [0.77, 5.67]               |                                 |
| Chang 2019            | 0.131             | 0.271 | 3.4%   | 1.14 [0.67, 1.94]               |                                 |
| Dalgiz 2014           | -0.7178           | 0.323 | 2.9%   | 2.05 [1.08, 3.80]               |                                 |
| Farley 2012           | 0.7975            | 0.273 | 3.4%   | 2.22 [1.30, 3.73]               |                                 |
| Fang 2013             | -0.5711           | 0.331 | 2.8%   | 0.69 [0.36, 1.32]               |                                 |
| Gao 2017              | 0.8409            | 0.587 | 1.6%   | 2.34 [1.01, 5.42]               |                                 |
| Hong 2006             | 0.4056            | 0.327 | 2.9%   | 1.50 [0.80, 2.83]               |                                 |
| Huang 2017            | 0.7514            | 0.261 | 3.5%   | 2.13 [1.27, 3.54]               |                                 |
| Huie 2013             | 0.5793            | 0.777 | 0.9%   | 2.66 [0.85, 8.22]               |                                 |
| Ikeda 2017            | 0.6259            | 0.248 | 3.6%   | 1.78 [1.15, 3.04]               |                                 |
| Inamoto 2012          | 0.6355            | 0.580 | 1.4%   | 2.31 [0.74, 7.20]               |                                 |
| Jia 2017              | 0.3227            | 0.337 | 2.6%   | 1.88 [0.97, 3.64]               |                                 |
| Kang 2015             | 1.0006            | 0.546 | 1.5%   | 2.73 [0.93, 7.99]               |                                 |
| Kawashima 2012        | 1.6529            | 0.765 | 0.9%   | 7.08 [1.59, 31.21]              |                                 |
| Kohda 2018            | -0.1833           | 0.564 | 1.5%   | 0.83 [0.28, 2.48]               |                                 |
| Lee 2006              | 0.8478            | 0.572 | 1.4%   | 2.36 [1.04, 5.40]               |                                 |
| Lee 2014              | 0.3053            | 0.701 | 1.0%   | 1.47 [0.37, 5.94]               |                                 |
| Li 2010               | 0.5423            | 0.237 | 3.7%   | 1.72 [1.02, 2.91]               |                                 |
| Liu 2013              | 0.8484            | 0.396 | 2.6%   | 2.34 [1.20, 4.55]               |                                 |
| Masson 2013           | 1.0043            | 0.748 | Not estimable |                                 |
| Motsumoto 2011        | 0.2978            | 0.168 | Not estimable |                                 |
| Mottaz 2015           | 1.4656            | 0.433 | 2.1%   | 4.30 [1.84, 10.05]              |                                 |
| Nakagawa 2017         | 1.4861            | 0.587 | 1.5%   | 4.42 [1.45, 13.47]              |                                 |
| Ouzanne 2011          | 0.67              | 0.593 | Not estimable |                                 |
| Qin 2017              | 2.262             | 0.767 | 0.9%   | 6.91 [2.98, 16.69]              |                                 |
| Sakamoto 2014         | 0.7201            | 0.265 | 3.5%   | 2.06 [1.28, 3.32]               |                                 |
| Shang 2015            | 0.87              | 0.362 | 2.6%   | 2.39 [1.43, 4.01]               |                                 |
| Shibing 2016          | 0.3639            | 0.196 | 4.2%   | 1.44 [0.80, 2.51]               |                                 |
| Su 2016               | -0.1936           | 0.176 | 4.4%   | 0.82 [0.56, 1.18]               |                                 |
| Tai 2016              | 0.6575            | 0.443 | 2.0%   | 1.93 [0.81, 4.50]               |                                 |
| Tan 2018              | 0.6419            | 0.265 | 3.6%   | 1.98 [1.16, 3.44]               |                                 |
| Tang 2015             | -0.2107           | 0.144 | 4.7%   | 0.81 [0.51, 1.28]               |                                 |
| THA 2018              | 0.0851            | 0.179 | 4.4%   | 1.99 [1.40, 2.84]               |                                 |
| Takeda 2016           | 0.1578            | 0.446 | 1.0%   | 1.17 [0.45, 3.04]               |                                 |
| Xu 2018               | 0.5423            | 0.251 | 3.8%   | 1.72 [1.05, 2.82]               |                                 |
| Zamboni 2019          | 2.6603            | 0.397 | Not estimable |                                 |
| Zhang 2016            | 0.4194            | 0.344 | 2.7%   | 1.52 [0.78, 2.99]               |                                 |

Total (95% CI) 100.0% 1.09 [1.45, 1.98]

Heterogeneity: $I^2 = 0.11$, $Chi^2 = 81.55$, df = 57 ($P < 0.0001$), $I^2 = 65$

Test for overall effect: $Z = 6.61$ ($P < 0.0001$)
Supplementary Figure 9: Forest plot depicting OS for grade.

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|-------------------|-----|--------|--------------|--------------|
|                   |                   |     |        | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| Abe 2018          | 0.3008            | 0.3756 | 2.0%   | 1.35 [0.85, 2.02] |              |
| Aziz 2014         | 0.1044            | 0.2139 | 6.2%   | 1.11 [0.73, 1.69] |              |
| Chromacki 2011    | 0.5660            | 0.251  | 4.5%   | 1.75 [1.07, 2.86] |              |
| Chung 2019        | 0.6199            | 0.6002 | 0.0%   | 2.27 [0.70, 7.36] |              |
| Dalpiaz 2014      | 0.392             | 0.2652 | 4.0%   | 1.48 [0.98, 2.49] |              |
| Fairey 2012       | 0.6523            | 0.2109 | 6.4%   | 1.92 [1.27, 2.90] |              |
| Gao 2017          | 0.3843            | 0.3915 | 1.8%   | 1.47 [0.98, 2.16] |              |
| Godfrey 2012      | 0.3148            | 0.3649 | 2.1%   | 1.37 [0.87, 2.09] |              |
| HS Kim 2015       | 0.3560            | 0.3117 | 2.8%   | 1.75 [1.05, 2.92] |              |
| Hsing 2017        | 0.5365            | 0.2114 | 6.4%   | 1.71 [1.13, 2.59] |              |
| JK Kim 2017       | 0.4049            | 0.2406 | 4.0%   | 1.56 [1.02, 2.34] |              |
| Kong 2015         | 0.5722            | 0.3608 | 2.1%   | 1.77 [0.88, 3.56] |              |
| Li Tao 2019       | 0.4762            | 0.2037 | 6.5%   | 1.61 [1.05, 2.44] |              |
| Maitre 2015       | 0.3632            | 0.4580 | 1.4%   | 2.62 [1.07, 6.42] |              |
| Oussane 2011      | 0.7419            | 0.4624 | 1.2%   | 2.10 [0.80, 5.51] |              |
| Qin 2017          | 1.2072            | 0.6289 | 0.7%   | 5.67 [1.75, 20.41] |              |
| Shih 2015         | 0.0887            | 0.2732 | 3.8%   | 1.84 [1.06, 3.14] |              |
| Shih 2016         | 0.3859            | 0.1618 | 8.6%   | 1.47 [1.03, 2.10] |              |
| Tai 2016          | 0.5128            | 0.3327 | 2.5%   | 1.67 [0.87, 3.21] |              |
| Tan 2018          | 0.3305            | 0.2129 | 6.3%   | 1.70 [1.12, 2.58] |              |
| TH Kim 2019       | 0.2247            | 0.1418 | 14.1%  | 1.90 [1.25, 2.83] |              |
| Xu 2016           | 0.4055            | 0.2088 | 6.0%   | 1.90 [1.00, 2.26] |              |
| Zhang 2010        | 0.2290            | 0.2823 | 4.1%   | 1.05 [0.62, 1.72] |              |

Total (95% CI) 100.0% 1.60 [1.44, 1.77]

Heterogeneity: Chi² = 14.50, df = 22 (p = 0.30); I² = 0%
Test for overall effect Z = 5.79 (p = 0.00001)
Supplementary Figure 10: Forest plot depicting RFS for lymph node positivity.

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|-------------------|-------------------|-----|--------|-------------------------------|-------------------------------|
| Abo 2018          | 1.2375            | 0.3538 | 3.3%  | 3.45 (1.72, 6.90)              |                               |
| Aydin 2019        | 1.4448            | 0.3441 |      | Not estimable                 |                               |
| Aze 2017          | -0.1054           | 0.2799 | 4.1%  | 0.90 (0.52, 1.56)              |                               |
| Chu 2012          | 0.6831            | 0.2211 | 4.9%  | 1.98 (1.28, 3.06)              |                               |
| Cressoni 2011     | 0.9822            | 0.1662 | 5.7%  | 2.44 (1.76, 3.38)              |                               |
| Chung 2014        | 0.5247            | 0.238  | 4.5%  | 1.69 (1.08, 2.69)              |                               |
| Fahey 2012        | 0.5539            | 0.2248 | 4.8%  | 1.74 (1.12, 2.70)              |                               |
| Fang 2010         | -0.7965           | 0.4987 | 2.1%  | 0.45 (0.17, 1.29)              |                               |
| Gao 2017          | 1.3958            | 0.4724 | 2.7%  | 3.93 (1.76, 8.85)              |                               |
| Hata 2015         | 0.6152            | 0.2382 | 4.6%  | 1.86 (1.18, 2.95)              |                               |
| Hibing 2015       | 0.9333            | 0.5065 | 1.8%  | 2.54 (1.91, 3.31)              |                               |
| Hurel 2013        | -0.1503           | 0.2912 | 3.6%  | 0.86 (0.46, 1.61)              |                               |
| Ikeda 2017        | 0.0821            | 0.3301 | 3.5%  | 2.67 (1.40, 5.10)              |                               |
| Li Tao 2019       | 0.8288            | 0.1081 | 5.4%  | 2.29 (1.59, 3.30)              |                               |
| Li Yaif 2018      | 0.3967            | 0.2318 | 4.7%  | 1.48 (0.85, 2.54)              |                               |
| Matsuoka 2011     | 0.7199            | 0.1387 |      | Not estimable                 |                               |
| Shibing 2016      | 1.0294            | 0.3763 | 3.0%  | 2.23 (1.28, 3.89)              |                               |
| Shibing 2016      | 1.2972            | 0.2227 | 4.7%  | 3.68 (2.32, 5.77)              |                               |
| Song 2019         | 1.1088            | 0.2033 | 5.2%  | 3.32 (2.23, 4.94)              |                               |
| Sung 2013         | 1.0225            | 0.2940 | 3.9%  | 2.79 (1.55, 5.00)              |                               |
| Tan 2019          | 1.0888            | 0.2899 | 4.2%  | 2.97 (1.75, 5.04)              |                               |
| TH-Kim 2010       | 0.7793            | 0.1515 | 6.0%  | 2.18 (1.02, 4.69)              |                               |
| Varto 2013        | 0.7419            | 0.1531 | 6.4%  | 2.10 (1.04, 4.29)              |                               |
| Waseda 2015       | 1.1978            | 0.1999 | 5.3%  | 3.38 (2.22, 5.15)              |                               |
| Xu 2018           | 0.8755            | 0.1641 | 5.8%  | 2.40 (1.47, 4.83)              |                               |
| Zapponi 2019      | 0.174             | 0.3662 |      | Not estimable                 |                               |

Total (95% CI) 100.0% 2.22 (1.88, 2.62)

Heterogeneity: Tau² = 0.09; Chi² = 82.25, df = 22 (P < 0.0001); I² = 65%

Test for overall effect: Z = 6.22 (P < 0.0001)
Supplementary Figure 11: Forest plot depicting CSS for lymph node positivity.

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|-------------------|------------------|----|--------|-------------------------------|-------------------------------|
| Abe 2010          | 1.0325           | 0.41| 1.9%  | 2.68 [1.34, 5.36]             |                               |
| Akao 2009         | 0.2151           | 0.2845| 3.9%  | 1.24 [0.74, 2.07]             |                               |
| Aydin 2010        | 1.5581           | 0.3631| Not estimable |                     |                               |
| Aziz 2014         | 0.2548           | 0.2038| 3.0%  | 1.29 [0.74, 2.23]             |                               |
| Cha 2012          | 0.802            | 0.2437| 3.7%  | 2.23 [0.38, 1.30]             |                               |
| Cho 2017          | 0.8544           | 0.1887| 4.0%  | 2.35 [1.83, 3.33]             |                               |
| Chromek 2011      | 0                | 0   | Not estimable |                     |                               |
| Chung 2013        | 0.9555           | 0.3819| 2.0%  | 2.00 [1.23, 3.20]             |                               |
| Doh Kim 2010      | 0                | 0   | Not estimable |                     |                               |
| Elleway 2017      | 1.3663           | 0.6935| 0.8%  | 4.00 [2.25, 12.00]            |                               |
| Falgay 2012       | 0.7701           | 0.3281| 2.5%  | 2.16 [1.14, 4.09]             |                               |
| Fang 2018         | 0.5890           | 0.2663| 3.3%  | 1.62 [0.85, 3.07]             |                               |
| Gao 2017          | 1.4951           | 0.4182| 1.7%  | 4.46 [1.86, 10.12]            |                               |
| Hong 2005         | -0.5978          | 2.6411|        |                               |                               |
| HS Kim 2015       | 0.3459           | 0.6472| 0.8%  | 1.20 [0.36, 4.55]             |                               |
| Huang 2017        | 0.8043           | 0.3135| 2.8%  | 1.83 [0.85, 3.93]             |                               |
| Hurst 2013        | 0.3438           | 0.4933| 1.8%  | 1.41 [0.64, 3.11]             |                               |
| H Yu Lee 2014     | 1.4012           | 0.5694| 1.0%  | 4.06 [1.33, 12.39]            |                               |
| Ichinoura 2014     | 0.9333           | 0.4355| 1.6%  | 2.70 [1.15, 6.34]             |                               |
| Ikeda 2017        | 0.8713           | 0.3618| 2.2%  | 2.39 [1.18, 4.83]             |                               |
| Inamoto 2012      | 1.5921           | 0.5242| 1.2%  | 4.81 [1.78, 13.73]            |                               |
| JI Choi 2017      | 0.1723           | 0.0774| 2.9%  | 1.19 [0.57, 2.49]             |                               |
| Kikuchi 2008      | 0.4253           | 0.1568| 5.7%  | 1.53 [1.13, 2.07]             |                               |
| Lee 2006          | 1.4255           | 0.7025| 0.5%  | 4.16 [1.88, 9.68]             |                               |
| Lee 2014          | 0.6627           | 0.2294| 4.0%  | 1.84 [1.24, 3.04]             |                               |
| Li Tao 2019       | 0.6961           | 0.1802| 4.0%  | 2.01 [1.38, 2.91]             |                               |
| Li Yalin 2018     | 1.0425           | 0.2724| 3.3%  | 2.78 [1.65, 4.74]             |                               |
| Liu 2013          | 1.555            | 0.3449| 3.7%  | 4.74 [2.03, 10.95]            |                               |
| Makise 2015       | 1.1282           | 0.4859| 1.4%  | 3.09 [1.24, 7.70]             |                               |
| Masaeon 2013      | 0.5120           | 0.3692|        |                               |                               |
| Matsumoto 2011    | 0.7413           | 0.1717|        |                               |                               |
| Moritomo 2015     | 0.9818           | 0.4138| 1.7%  | 2.62 [1.15, 5.88]             |                               |
| Ozumai 2011       | 0.47             | 0.3537|        |                               |                               |
| Shibring 2016     | 1.4955           | 0.3455| 2.3%  | 4.33 [2.21, 8.52]             |                               |
| Shibring 2016     | 1.3918           | 0.2375| 3.8%  | 3.68 [2.05, 6.65]             |                               |
| Shi 2018          | 0.5933           | 0.2143| 4.3%  | 1.61 [1.19, 2.19]             |                               |
| Tan 2018          | 1.0188           | 0.3233| 2.5%  | 2.77 [1.47, 5.22]             |                               |
| Tang 2015         | 0.6043           | 0.2111| 4.3%  | 1.63 [1.17, 2.27]             |                               |
| TH Kim 2019       | 0.6993           | 0.1702| 5.3%  | 2.01 [1.42, 2.81]             |                               |
| Vanhoef 2016      | 0.8772           | 0.1331| 8.5%  | 1.86 [1.51, 2.29]             |                               |
| Xu 2016           | 0.9419           | 0.1832| 5.0%  | 2.22 [1.62, 3.02]             |                               |
| Zamzon 2019       | 1.3533           | 0.3143|        |                               |                               |
| Zhang 2016        | 0.9483           | 0.4979| 1.3%  | 2.33 [0.86, 6.20]             |                               |

Total (95% CI) 100.0% 2.24 [1.99, 2.52]

Heterogeneity: Tau² = 0.04; CHI² = 52.85, df = 34 (P = 0.02); I² = 36%.

Test for overall effect: Z = 13.34 (P < 0.00001)
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.

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio IV, Fixed, 95% CI |
|-------------------|-------------------|-----|--------|-------------------------------|
| Aydin 2019        | -0.2614           | 0.2855 | 13.5%  | 0.77 [0.44, 1.35]             |
| Aziz 2014         | -0.3567           | 0.3393 | 9.5%   | 0.70 [0.36, 1.38]             |
| Hurel 2013        | 0.3365            | 0.2792 | 14.1%  | 1.40 [0.81, 2.42]             |
| Ikeda 2017        | -0.1598           | 0.2244 | 21.8%  | 0.85 [0.55, 1.34]             |
| Ouzzone 2012      | 0.3784            | 0.3069 | 0.0%   | 1.45 [0.80, 2.66]             |
| Tang 2015         | 0.0198            | 0.1637 | 41.0%  | 1.02 [0.74, 1.41]             |
| **Total (95% CI)**| **100.0%**        | **0.95 [0.78, 1.17]** |

Heterogeneity: Ch² = 3.96, df = 4 (P = 0.45), I² = 0%
Test for overall effect Z = 0.45 (P = 0.66)

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

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio IV, Fixed, 95% CI |
|-------------------|-------------------|-----|--------|-------------------------------|
| Aydin 2019        | -0.2107           | 0.2261 | 35.0%  | 0.81 [0.52, 1.28]             |
| Delolaz 2014      | 0.3436            | 0.2582 | 26.6%  | 1.41 [0.85, 2.34]             |
| Ouzzone 2012      | 0.0877            | 0.2165 | 38.2%  | 1.07 [0.70, 1.64]             |
| **Total (95% CI)**| **100.0%**        | **1.05 [0.80, 1.36]** |

Heterogeneity: Ch² = 2.03, df = 2 (P = 0.37), I² = 24%
Test for overall effect Z = 0.32 (P = 0.74)
Supplementary Figure 16: Forest plot depicting RFS for lymphovascular invasion.

| Study or Subgroup | log(Hazard Ratio) ± SE | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|-------------------|------------------------|--------|---------------------------------|---------------------------------|
| Abe 2018          | 0.1501 ± 0.0986        | 3.1%   | 1.16 [0.65, 2.06]               |                                 |
| Aydin 2019        | 0.9708 ± 0.294         |        | Not estimable                   |                                 |
| Aziz 2014         | 0.9933 ± 0.2702        | 3.4%   | 2.70 [1.59, 4.56]               |                                 |
| Cho 2017          | 0.5247 ± 0.1071        | 4.9%   | 1.66 [1.37, 2.08]               |                                 |
| Chromiecki 2011   | 0.3075 ± 0.132         | 4.7%   | 1.96 [1.05, 3.62]               |                                 |
| Chung 2009        | 0.8713 ± 0.2112        | 3.8%   | 2.35 [1.58, 3.51]               |                                 |
| D3 Kim 2010       | 1.0473 ± 0.2981        | 3.1%   | 2.85 [1.59, 5.11]               |                                 |
| Gac 2017          | 0.6056 ± 0.3412        | 2.6%   | 1.96 [1.02, 3.80]               |                                 |
| Hara 2015         | 1.16 ± 0.2157          | 3.9%   | 2.16 [2.09, 4.87]               |                                 |
| Hayakawa 2018     | 1.561 ± 0.3192         | 2.6%   | 4.86 [2.60, 9.08]               |                                 |
| Hong 2005         | 1.4754 ± 0.7074        | 1.1%   | 4.37 [1.08, 17.43]              |                                 |
| Hueri 2013        | 0.229 ± 0.1872         | 4.2%   | 1.27 [0.88, 1.83]               |                                 |
| Ikeda 2017        | 0.9233 ± 0.2453        | 3.6%   | 2.61 [1.56, 4.09]               |                                 |
| Kakuchi 2008      | 0.3221 ± 0.1214        | 4.8%   | 1.36 [1.09, 1.75]               |                                 |
| Kohada 2018       | 0.9746 ± 0.2830        | 3.3%   | 2.55 [1.52, 4.62]               |                                 |
| Li Tao 2019       | 0.0503 ± 0.1631        | 4.4%   | 1.06 [0.77, 1.46]               |                                 |
| Matsumoto 2011    | 0.3365 ± 0.0706        |        | Not estimable                   |                                 |
| Nakagawa 2017     | 0.7031 ± 0.4416        | 2.1%   | 2.02 [0.65, 4.00]               |                                 |
| Sato 2007         | 0.5766 ± 0.2141        | 3.9%   | 1.76 [1.17, 2.71]               |                                 |
| Shibing 2015      | -0.1054 ± 0.1918       | 4.1%   | 0.89 [0.62, 1.21]               |                                 |
| Shibing 2016      | -0.2206 ± 0.1481       | 4.5%   | 0.80 [0.60, 1.07]               |                                 |
| Song 2019         | 0.392 ± 0.185          | 4.4%   | 1.48 [1.07, 2.04]               |                                 |
| Tai 2016          | 0.0488 ± 0.3207        | 2.9%   | 1.05 [0.56, 1.97]               |                                 |
| Tan 2018          | -0.0305 ± 0.1664       | 4.4%   | 0.97 [0.70, 1.34]               |                                 |
| Tanaka 2012       | 0.0879 ± 0.3907        | 2.4%   | 2.43 [1.13, 5.23]               |                                 |
| Tanaka 2015       | 1.1663 ± 0.2465        | 3.6%   | 3.21 [1.50, 6.83]               |                                 |
| TH Kim 2019       | 0.5853 ± 0.1168        | 4.0%   | 1.76 [1.40, 2.21]               |                                 |
| Vardabegi 2016    | 0.2151 ± 0.0996        | 4.8%   | 1.24 [1.02, 1.51]               |                                 |
| Waseda 2015       | 1.0403 ± 0.110          | 4.1%   | 2.83 [1.95, 4.11]               |                                 |
| Zamboni 2019      | -0.0202 ± 0.3332       |        | Not estimable                   |                                 |

Total (95% CI): 100.0% 1.73 [1.47, 2.03]

Heterogeneity: Tau² = 0.12, CH² = 121.11, df = 26 (P < 0.00001), I² = 79%
Test for overall effect: Z = 8.71 (P = 0.00001)
Supplementary Figure 17: Forest plot depicting CSS for lymphovascular invasion.

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|------------------|-----|--------|--------------|--------------|
|                   |                  |     |        | Fiv, Random, 95% CI | Fiv, Random, 95% CI |
| Abe 2018          | 0.7467           | 0.3871 | 2.2%  | 2.11 [1.09, 4.15] |              |
| Akao 2008         | 1.2729           | 0.3749 | 2.2%  | 5.63 [2.70, 11.74] |              |
| Aydin 2016        | 1.0784           | 0.2201 | Not estimable |              |              |
| Aza 2014          | 0.9183           | 0.2778 | 2.9%  | 2.50 [1.45, 4.31] |              |
| Bollenz 2008      | 1.6702           | 0.487 | 1.6%  | 5.35 [2.06, 13.88] |              |
| Cho 2017          | 1.0225           | 0.1986 | 3.6%  | 2.78 [1.88, 4.11] |              |
| Chromeschi 2011   | 0.3001           | 0.143 | 4.1%  | 1.35 [0.62, 2.93] |              |
| Chung 2019        | 1.2              | 0.3054 | 2.2%  | 3.32 [1.56, 6.70] |              |
| DS Kim 2010       | 0.9123           | 0.3375 | 2.5%  | 2.46 [1.29, 4.82] |              |
| Gao 2017          | 0.6704           | 0.2477 | 2.4%  | 1.96 [0.99, 3.86] |              |
| Hayakawa 2018     | 1.3938           | 0.381 | 2.2%  | 4.03 [1.01, 15.55] |              |
| Hong 2006         | 0.5423           | 0.4138 | 2.0%  | 1.72 [0.76, 3.87] |              |
| HS Kim 2015       | 0.5653           | 0.2625 | 3.1%  | 1.76 [1.05, 2.95] |              |
| Hwang 2017        | 0.5423           | 0.2098 | 3.5%  | 1.72 [1.14, 2.50] |              |
| Hurel 2013        | 0.5481           | 0.2746 | 3.0%  | 1.75 [1.01, 2.98] |              |
| Ichimura 2014     | 1.538            | 0.7143 | 0.9%  | 5.15 [1.27, 20.98] |              |
| Ikeda 2017        | 1.2528           | 0.2974 | 2.6%  | 3.50 [1.85, 6.62] |              |
| JK Kim 2017       | 0.9042           | 0.2209 | 3.4%  | 2.47 [1.60, 3.81] |              |
| Kang 2015         | 1.1304           | 0.2747 | 3.0%  | 3.10 [1.61, 6.00] |              |
| Kawasaki 2012     | 1.5008           | 0.6704 | 1.0%  | 4.98 [1.31, 18.00] |              |
| Kikuchi 2008      | 0.4121           | 0.15  | 4.0%  | 1.51 [1.13, 2.03] |              |
| Konada 2018       | 0.9532           | 0.4617 | 1.8%  | 2.62 [1.06, 6.43] |              |
| Lee 2006          | 0.9517           | 0.451 | 1.8%  | 2.56 [1.07, 6.27] |              |
| Lee 2014          | 0.5223           | 0.1751 | 3.8%  | 1.79 [1.27, 2.53] |              |
| Li 2019           | 0.157            | 0.1814 | 3.8%  | 1.17 [0.82, 1.67] |              |
| Liu 2013          | 0.1454           | 0.1782 | 3.8%  | 1.16 [0.82, 1.64] |              |
| Makise 2015       | 2.1013           | 0.6559 | 1.1%  | 8.86 [2.45, 32.04] |              |
| Masson 2013       | 0.6043           | 0.2681 | Not estimable |              |              |
| Matsunaga 2011    | 0.47             | 0.1059 | Not estimable |              |              |
| Matsunaga 2017    | 1.1053           | 0.7038 | 1.0%  | 3.02 [1.76, 12.00] |              |
| Guzzaro 2011      | 0.2776           | 0.2656 | Not estimable |              |              |
| Satoh 2007        | 0.7561           | 0.2441 | 3.2%  | 2.12 [1.32, 3.44] |              |
| Savran 2014       | 1.1442           | 0.2811 | 2.9%  | 3.14 [1.81, 5.45] |              |
| Shibing 2015      | -0.0967          | 0.1927 | 3.7%  | 0.91 [0.62, 1.33] |              |
| Shibing 2016      | -0.0954          | 0.1481 | 4.0%  | 0.91 [0.68, 1.22] |              |
| Tan 2016          | 0.2718           | 0.2689 | 3.1%  | 1.31 [0.79, 2.21] |              |
| Tanaka 2012       | 0.7038           | 0.4206 | 2.0%  | 2.19 [1.06, 4.50] |              |
| Tanaka 2015       | 0.382            | 0.2762 | 3.0%  | 2.44 [1.42, 4.13] |              |
| TH Kim 2019       | 0.6419           | 0.124 | 4.2%  | 1.90 [1.49, 2.42] |              |
| Vartolomai 2016   | 0.2776           | 0.1024 | 4.4%  | 1.32 [1.08, 1.61] |              |
| Zamboni 2019      | 0.5088           | 0.3475 | Not estimable |              |              |
| Zhang 2015        | 0               | 0     | Not estimable |              |              |

Total (95% CI)  

| Hazard Ratio | 100.0% | 2.03 [1.74, 2.36] |

Heterogeneity: Tau² = 0.15, Chi² = 117.11, df = 35 (P < 0.00001), I² = 70%

Test for overall effect: Z = 9.14 (P < 0.00001)
Supplementary Figure 18: Forest plot depicting OS for lymphovascular invasion.

| Study or Subgroup | log(Hazard Ratio) | SE | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|-------------------|------------------|----|--------|---------------------------------|---------------------------------|
| Abe 2018          | 0.2922           | 0.3281 | 3.3%  | 1.33 [0.70, 2.52]               |                                 |
| Ayadin 2019       | 0.6739           | 0.1771 | 5.5%  | 2.66 [1.88, 3.76]               |                                 |
| Aziz 2014         | 0.6471           | 0.2287 | 4.6%  | 1.91 [1.22, 2.99]               |                                 |
| Cho 2017          | 0.6931           | 0.1696 | 5.7%  | 1.98 [1.42, 2.76]               |                                 |
| Chramacki 2011    | 0.2331           | 0.2377 | 4.7%  | 1.25 [0.80, 1.95]               |                                 |
| Chung 2018        | 1.0000           | 0.3245 | 3.3%  | 2.72 [1.44, 5.14]               |                                 |
| Gao 2017          | 0.3778           | 0.3307 | 3.2%  | 1.46 [0.75, 2.79]               |                                 |
| Godfrey 2012      | 0.7975           | 0.3445 | 3.1%  | 2.22 [1.13, 4.36]               |                                 |
| HS Kim 2015       | 0.4511           | 0.2457 | 4.4%  | 1.57 [0.97, 2.54]               |                                 |
| Huang 2017        | 0.4121           | 0.1803 | 5.3%  | 1.51 [1.04, 2.19]               |                                 |
| JK Kim 2017       | 0.6081           | 0.1072 | 5.2%  | 1.81 [1.25, 2.60]               |                                 |
| Kang 2015         | 0.8755           | 0.2605 | 4.3%  | 2.40 [1.47, 3.82]               |                                 |
| Lee 2014          | 0.4511           | 0.1457 | 5.1%  | 1.57 [1.13, 2.09]               |                                 |
| Li Tao 2019       | 0.1398           | 0.1603 | 5.8%  | 1.15 [0.84, 1.57]               |                                 |
| Makise 2015       | 1.205            | 0.4257 | 2.3%  | 3.34 [1.45, 7.69]               |                                 |
| Ouazzane 2011     | 0.4511           | 0.2151 | 4.9%  | 1.57 [1.05, 2.30]               |                                 |
| Shikha 2015       | -0.1924          | 0.1868 | 5.3%  | 0.82 [0.57, 1.19]               |                                 |
| Shikha 2016       | -0.091           | 0.1392 | 6.2%  | 0.91 [0.70, 1.20]               |                                 |
| Tan 2010          | 0.1222           | 0.1699 | 5.7%  | 1.13 [0.91, 1.50]               |                                 |
| Tanaka 2012       | 0.6723           | 0.2377 | 4.5%  | 1.98 [1.23, 3.12]               |                                 |
| TH Kim 2019       | 0.6152           | 0.1139 | 6.5%  | 1.85 [1.48, 2.31]               |                                 |
| Zhang 2015        | 0                | 0     | Not estimable |                                 |                                 |

Total (95% CI) 100.0% 1.60 [1.37, 1.87]

Heterogeneity: Tau^2 = 0.08, Chi^2 = 80.48, df = 20 (P < 0.00001), I^2 = 87%
Test for overall effect: Z = 6.03 (P < 0.0001)
Supplementary Figure 19: Forest plot depicting RFS for margin positivity.

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio IV, Fixed, 95% CI | Hazard Ratio IV, Fixed, 95% CI |
|-------------------|------------------|-----|--------|-------------------------------|-------------------------------|
| Aoe 2018          | 0.2468           | 0.6015 | 1.4%  | 1.28 [0.95, 1.73]             |                               |
| Fairey 2012       | 0.4385           | 0.1771 | 16.6% | 1.50 [1.28, 1.78]             |                               |
| Hira 2015         | 0.1923           | 0.2150 | 10.0% | 1.20 [0.98, 1.48]             |                               |
| Hurel 2013        | 0.4253           | 0.2373 | 10.1% | 1.51 [0.98, 2.38]             |                               |
| Shikin 2015       | 0.5247           | 0.2355 | 10.0% | 1.65 [1.31, 2.09]             |                               |
| Shikin 2016       | 0.5445           | 0.1612 | 20.1% | 1.72 [1.26, 2.36]             |                               |
| Tan 2018          | -0.0859          | 0.2123 | 11.6% | 0.94 [0.64, 1.38]             |                               |
| Tao Li 2019       | 0.1133           | 0.1970 | 13.6% | 1.12 [0.76, 1.65]             |                               |
| Zamboni 2019      | 0.3001           | 0.2931 | 6.1%  | 1.35 [0.76, 2.40]             |                               |

Total (95% CI) 100.0% 1.38 [1.20, 1.59]

Heterogeneity: Ch^2 = 7.93, df = 6 (P = 0.44); I^2 = 0%
Test for overall effect Z = 4.46 (P < 0.0001)

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

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio IV, Fixed, 95% CI | Hazard Ratio IV, Fixed, 95% CI |
|-------------------|------------------|-----|--------|-------------------------------|-------------------------------|
| Aoe 2018          | 0.5444           | 0.2924 | 0.6%  | 1.90 [1.31, 1.72]             |                               |
| Fairey 2012       | 0.4924           | 0.2477 | 9.6%  | 1.62 [1.07, 2.47]             |                               |
| HS Kim 2015       | 0.6154           | 0.4871 | 2.9%  | 2.26 [2.67, 3.07]             |                               |
| Hurel 2013        | 0.207            | 0.1159 |       | Not estimable                 |                               |
| JK Kim 2017       | 0.0999           | 0.3574 | 5.9%  | 2.43 [1.22, 4.83]             |                               |
| Liu 2013          | 0.2610           | 0.3860 | 5.0%  | 1.30 [0.63, 2.63]             |                               |
| Masson 2013       | 0.2927           | 0.1906 |       | Not estimable                 |                               |
| Morizatione 2015  | 1.3712           | 0.4513 | 3.3%  | 3.94 [1.53, 1.64]             |                               |
| Ouzanne 2012      | 0.5073           | 0.2989 | 7.4%  | 1.60 [1.06, 2.42]             |                               |
| Shikin 2015       | 0.7429           | 0.2456 | 11.6% | 2.10 [1.30, 3.40]             |                               |
| Shikin 2016       | 0.4844           | 0.1642 | 24.3% | 2.64 [1.11, 2.30]             |                               |
| Tan 2018          | 0.021            | 0.2328 | 12.4% | 1.04 [0.64, 1.65]             |                               |
| Tao Li 2019       | 0.2351           | 0.2173 | 14.2% | 1.24 [0.81, 1.90]             |                               |
| Zamboni 2019      | 0.1133           | 0.4786 | 2.9%  | 1.12 [0.44, 2.85]             |                               |

Total (95% CI) 100.0% 1.59 [1.36, 1.87]

Heterogeneity: Ch^2 = 13.53, df = 11 (P = 0.26); I^2 = 19%
Test for overall effect Z = 5.90 (P < 0.0001)
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.

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|-------------------|-------------------|----|--------|---------------------------------|---------------------------------|
| Age 2019          | 2.4423            | 0.8554 | 0.9%  | 11.50 [2.11, 62.71]            |                                  |
| Avan 2009         | -0.1744           | 0.3563 | 3.9%  | 0.84 [0.41, 1.72]              |                                  |
| Atil 2014         | 0.0556            | 0.3215 | 5.9%  | 2.30 [1.44, 3.69]              |                                  |
| Bolez 2008        | 0.5602            | 0.2497 | 6.3%  | 1.77 [1.08, 2.89]              |                                  |
| Cho 2017          | 0.7467            | 0.2355 | 6.7%  | 2.11 [1.33, 3.29]              |                                  |
| Chromec 2011      | 1.5892            | 0.3046 | 3.4%  | 4.90 [2.26, 10.62]             |                                  |
| Chung 2016        | 1.0006            | 0.2135 | 7.3%  | 2.72 [1.79, 4.13]              |                                  |
| Dafizrez 2014     | 0.6502            | 0.3669 | 3.8%  | 2.34 [1.14, 4.80]              |                                  |
| Guo 2017          | 0.8721            | 0.3042 | 4.9%  | 2.41 [1.32, 4.35]              |                                  |
| Huang 2017        | 1.16              | 0.2302 | 6.3%  | 2.93 [2.00, 5.00]              |                                  |
| Ichimura 2014     | 1.1252            | 0.2251 | 6.5%  | 3.06 [2.28, 43.10]             |                                  |
| Kang 2015         | 1.0251            | 0.4655 | 2.7%  | 2.98 [1.12, 9.99]              |                                  |
| Kim HS 2015       | 1.4309            | 0.2811 | 3.6%  | 4.22 [2.00, 9.06]              |                                  |
| Kim JK 2017       | 1.3755            | 0.3215 | 4.6%  | 3.55 [2.11, 7.38]              |                                  |
| Kim TH 2019       | 1.1474            | 0.1473 | 9.7%  | 3.15 [2.26, 4.29]              |                                  |
| Kohaela 2016      | 0.4253            | 0.5534 | 2.1%  | 1.53 [0.54, 4.43]              |                                  |
| Lee 2014          | 1.311             | 0.2597 | 6.0%  | 3.71 [2.23, 6.17]              |                                  |
| Lee Yafin 2019    | 0.0901            | 0.2201 | 7.1%  | 2.01 [1.30, 3.08]              |                                  |
| Su 2016           | 0.818             | 0.1644 | 9.1%  | 2.27 [1.84, 3.12]              |                                  |
| Tai 2016          | 1.4134            | 0.4545 | 5.5%  | 4.11 [1.59, 10.63]             |                                  |
| Tanaka 2015       | 2.0412            | 0.5482 | 2.0%  | 7.70 [2.84, 22.48]             |                                  |
| Zamboni 2019      | 1.1346            | 0.7257 | 1.2%  | 3.11 [0.75, 12.30]             |                                  |

Total (95% CI) 100.0% 2.69 [2.26, 3.10] 0.01 0.1 1 10 100 Favours [T3 T4] Favours [Lower T stage]

Heterogeneity: Tau² = 0.05, Ch² = 33.99, df = 21 (P = 0.04); P = 33%
Test for overall effect Z = 11.70 (P < 0.00001)

Supplementary Figure 33: Forest plot depicting OS for stage.

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Fixed, 95% CI | Hazard Ratio IV, Fixed, 95% CI |
|-------------------|-------------------|----|--------|---------------------------------|---------------------------------|
| Age 2018          | 1.6372            | 0.6701 | 0.7%  | 6.26 [1.86, 23.76]              |                                  |
| Ariz 2014         | 0.8529            | 0.2134 | 6.9%  | 2.37 [1.56, 3.60]              |                                  |
| Cho 2017          | 0.7277            | 0.1862 | 9.0%  | 2.06 [1.43, 2.97]              |                                  |
| Chromec 2011      | 0.678             | 0.2244 | 6.2%  | 1.97 [1.27, 3.06]              |                                  |
| Chung 2019        | 0.7508            | 0.3537 | 2.5%  | 2.14 [1.67, 4.28]              |                                  |
| Delpezrez 2014    | 0.8766            | 0.2961 | 3.8%  | 1.97 [1.12, 3.48]              |                                  |
| Gao 2017          | 0.8131            | 0.2585 | 4.8%  | 2.25 [1.36, 3.75]              |                                  |
| Huang 2017        | 0.9243            | 0.1978 | 6.0%  | 2.52 [1.71, 3.71]              |                                  |
| Kang 2015         | 0.9752            | 0.3200 | 2.7%  | 1.36 [1.01, 3.92]              |                                  |
| Kim HS 2015       | 0.7544            | 0.2919 | 3.9%  | 2.12 [1.22, 3.68]              |                                  |
| Kim JK 2017       | 1.0321            | 0.2344 | 5.7%  | 2.51 [1.77, 4.44]              |                                  |
| Kim TH 2019       | 0.8544            | 0.1221 | 21.0% | 2.26 [1.65, 2.99]              |                                  |
| Lee 2014          | 1.247             | 0.1908 | 0.3%  | 3.48 [2.80, 5.00]              |                                  |
| Lee Yafin 2019    | 0.9392            | 0.1601 | 12.2% | 2.56 [1.87, 3.50]              |                                  |
| Tai 2016          | 1.1019            | 0.3833 | 2.1%  | 3.01 [1.42, 6.38]              |                                  |
| Tanaka 2015       | 1.3481            | 0.3712 | 2.3%  | 3.65 [1.86, 7.37]              |                                  |

Total (95% CI) 100.0% 2.45 [2.19, 2.73] 0.01 0.1 1 10 100 Favours [T3 T4] Favours [Lower T stage]

Heterogeneity: Ch² = 10.86, df = 15 (P = 0.76); P = 0%
Test for overall effect Z = 16.93 (P < 0.00001)