Long-term oncologic outcomes of laparoscopic nephroureterectomy versus open nephroureterectomy for upper tract urothelial carcinoma: a systematic review and meta-analysis

Su Zhang, You Luo, Cheng Wang, Sheng-Jun Fu, Li Yang

Background Several factors have been validated as predictors of disease recurrence in upper tract urothelial carcinoma. However, the oncological outcomes between different surgical approaches (open nephroureterectomy versus laparoscopic nephroureterectomy, ONU vs LNU) remain controversial. Therefore, we performed a meta-analysis to evaluate the oncological outcomes associated with different surgical approaches. **Methods** We conducted an electronic search of the PubMed, Embase, ISI Web of Knowledge and Cochrane Library electronic databases through November 2015, screened the retrieved references, collected and evaluated the relevant information. We extracted and synthesized the corresponding hazard ratios (HRs) and 95% confidence intervals (95% CI) using Stata 13. **Results** Twenty-one observational studies were eligible for inclusion in the meta-analysis. The results of the meta-analysis showed no differences in the intravesical recurrence-free survival (IRFS), unspecified recurrence-free survival (UnRFS) and overall survival (OS) between LNUandONU. However, improvements in the extravesical recurrence free survival (ExRFS) and cancer specific survival (CSS) were observed inLNU. The pooled hazard ratios were 1.05 (95% CI: 0.92-1.18) for IRFS, 0.80 (95% CI: 0.64-0.96) for ExRFS, 1.10 (95% CI: 0.93-1.28) for UnRFS, 0.91 (95% CI: 0.66-1.17) for OS and 0.79 (95% CI: 0.68-0.91) for CSS. **Conclusion** Based on current evidence, LNU could provide equivalent prognostic effects for upper tract urothelial carcinoma, and had better oncological control of ExRFS and CSS compared to ONU. However, considering all eligible studies with the intrinsic bias of retrospective study design, the results should be interpreted with cautions. Prospective randomized trials are needed to verify these results.

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2 **nephroureterectomy versus open nephroureterectomy for**

3 **upper tract urothelial carcinoma: a systematic review and**

4 **meta-analysis**

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Abstract

Background

27 Several factors have been validated as predictors of disease recurrence in upper tract urothelial

28 carcinoma. However, the oncological outcomes between different surgical approaches (open

29 nephroureterectomy versus laparoscopic nephroureterectomy, ONU vs LNU) remain

30 controversial. Therefore, we performed a meta-analysis to evaluate the oncological outcomes

31 associated with different surgical approaches.

Methods

33 We conducted an electronic search of the PubMed, Embase, ISI Web of Knowledge and

34 Cochrane Library electronic databases through November 2015, screened the retrieved

35 references, collected and evaluated the relevant information. We extracted and synthesized the

36 corresponding hazard ratios (HRs) and 95% confidence intervals (95% CI) using Stata 13.

Results

38 Twenty-one observational studies were eligible for inclusion in the meta-analysis. The results of

39 the meta-analysis showed no differences in the intravesical recurrence-free survival (IRFS),

40 unspecified recurrence-free survival (UnRFS) and overall survival (OS) between LNUandONU.

41 However, improvements in the extravesical recurrence free survival (ExRFS) and cancer specific

42 survival (CSS) were observed inLNU. The pooled hazard ratios were 1.05 (95% CI: 0.92-1.18)

43 for IRFS, 0.80 (95% CI: 0.64-0.96) for ExRFS, 1.10 (95% CI: 0.93-1.28) for UnRFS, 0.91 (95%

44   CI: 0.66-1.17) for OS and 0.79 (95% CI: 0.68-0.91) for CSS.

45

46   **Conclusion**

47   Based on current evidence, LNU could provide equivalent prognostic effects for upper tract

48   urothelial carcinoma, and had better oncological control of ExRFS and CSS compared to ONU.

49   However, considering all eligible studies with the intrinsic bias of retrospective study design, the

50   results should be interpreted with cautions. Prospective randomized trials are needed to verify

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Introduction

Upper tract urothelial carcinoma (UTUC), accounting for only 5% of all urothelial cancers, is a

rare malignancy with high risk for disease recurrence and mortality.(Roupret et al. 2015) Given

its high potential for recurrence and poor prognosis, assessment of the predictive factors appears

to be increasingly significant. Tumor multifocality, previous bladder cancer and concomitant

carcinoma in situ (CIS) have been validated as predictors of intravesical recurrence, which is

also associated with different surgical approaches.(Xylinas et al. 2013; Xylinas et al. 2014) The

standard treatment for UTUC is nephroureterectomy with bladder cuff excision. The treatment

approaches include open nephroureterectomy (ONU) and laparoscopic nephroureterectomy

(LNU). Compared with ONU, a traditional approach which has durable oncologic control, LNU

has shown several advantages with fewer adverse intra- and perioperative outcomes as a

minimally invasive treatment since being first introduced by Clayman in 1991.(Clayman et al.

1991; Simone et al. 2009) However, compared to ONU, whether LNU has equivalent

oncological outcomes, such as cancer-specific survival (CSS) and intravesical recurrence-free

survival (IRFS), remains controversial.(Kim et al. 2015; Xylinas et al. 2014) We aimed to

perform a meta-analysis to evaluate the oncological control associated with different surgical

approaches (ONU vs LNU).

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Methods

86 **Search and screen strategy**

87 A systematic literature search of Embase, PubMed, ISI Web of Knowledge and Cochrane

88 Library was conducted to retrieve UTUC studies comprising both surgical approaches (ONU and

89 LNU) through November 1, 2015. The search key words included *open nephroureterectomy*,

90 *laparoscopic nephroureterectomy*, *upper tract urothelial carcinoma*, and others. The detailed

91 search strategy is presented in supplement 1. We also screened the citations in the retrieved

92 articles for any relevant studies. Two independent investigators (S Zhang and Y Luo) conducted

93 the initial screening by reviewing the title and abstract. Then, the full-text articles satisfying the

94 inclusion criteria were reviewed. Clinical studies recording any evaluation of the surgical

95 approach on oncological outcomes, including intravesical recurrence-free survival (IRFS),

96 extravesical recurrence-free survival (ExRFS), unspecified recurrence-free survival (UnRFS,

97 reported as disease recurrence but not explicitly defined as IRFS or ExRFS), cancer-specific

98 survival (CSS) or overall survival (OS), were eligible. Articles were excluded if they met any of

99 the following criteria: 1) the aforementioned outcomes were not described; 2) patients were

100 treated by hand assisted laparoscopic nephroureterectomy; or 3) studies included overlapping

101 patients or duplicated data. Instead, the study with the largest sample size would be selected if

102 more than one study included overlapping patients. This systematic review was performed

103 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement

104 (PRISMA)(Moher et al. 2010). Ethical approval and patient consent were waived because all

105 available data were extracted from previous publications.

106 **Data extraction and assessment of methodological quality**

107   The basic information including first author, year of publication, region, recruitment period,

108   number of patients who underwent LNU or ONU, age of patients, follow-up, oncological

109   outcomes, and adjusted factors were extracted by two researchers (S Zhang and Y Luo)

110   independently. Any disagreement or uncertainty was determined by group discussion, and a

111   consensus was obtained. The data were extracted from the original articles. For incomplete data,

112   we attempted to contact the corresponding author to acquire primary data. During data extraction,

113   multivariate outcomes rather than univariate outcomes were preferred when both results were

114   provided. If multivariate results were not available, univariate outcomes were an alternative to

115   conduct this analysis. Publication bias and sensitivity analyses were applied. The quality

116   assessments of cohort studies were conducted according to the Newcastle-Ottawa Scale (NOS),

117   which was developed to assess bias risk including three domains with eight items. Five or more

118   stars out of a total of nine stars was regarded as good quality.(Wells GA 2008)

119   **Statistical analysis**

120   All data and analysis were conducted using STATA 13 software (Stata Corp LP, College

121   Station, TX, USA). The survival outcomes were evaluated by hazard ratios (HR) and 95%

122   confident intervals. I^2 statistics and the chi-square test were calculated for heterogeneity

123   detection. When P≥ 0.1 and I^2≤ 50%, a fixed-effects model was performed; otherwise, a random

124   effects model was applied. An inverse variance method was used to calculate the pooled hazard

125   ratio. Sensitivity analyses were conducted to test the stability of the pooled results. Egger's test

126   for publication bias was performed only in outcomes that enrolled more than ten studies.(Egger

127   et al. 1997) Additionally, we conducted subgroup and multivariable meta-regression in IRFS

128 according to the different approach of LNU (retroperitoneal vs transperitoneal), sample size of

129 LNU (< 100 vs ≥ 100) and publication year. A P value of less than 0.05 was deemed

130 statistically significant.

131

132 **Results**

133 **Description of included studies**

134 In total, 1506 citations were retrieved by the initial search strategy. After three rounds of

135 screening, there were 21 cohort studies for quantitative synthesis. The PRISMA flow diagram is

136 presented in Figure. 1. Table 1 shows the detailed characteristics of the included studies. The

137 Newcastle Ottawa Scale (NOS) assessment showed that all included cohort studies had relatively

138 well controlled quality.

139

140 **Survival outcomes**

141 1. Oncological Recurrence

142 The IRFS was reported in thirteen articles, which included LNU (n=1959) and ONU

143 (n=4281).(Favaretto et al. 2010; Fradet et al. 2014; Ishikawa et al. 2010; Ito et al. 2013; Kim et al.

144 2015; Kitamura et al. 2014; Kobayashi et al. 2012; Koda et al. 2007; Kume et al. 2006; Ploussard

145 et al. 2015; Terakawa et al. 2008; Xylinas et al. 2013; Zou et al. 2014) The meta-analysis results

146 showed no significant difference in the IRFS between LNU and ONU management (HR 1.05, 95%

147 CI: 0.92-1.18; $P = 0.134$, $I^2 = 31.1\%$; Fig. 2). The ExRFS was described in four studies including

148 patients who underwent LNU (n=836) and ONU (n=4315).(Capitanio et al. 2009; Rieken et al.

149   2014; Walton et al. 2011; Yafi et al. 2012) The pooled results showed that LNU management

150   decreased the risk of extravesical recurrence (HR 0.80, 95% CI: 0.64-0.96; P = 0.859, I^2 = 0.0%;

151   Fig. 3). Five studies including LNU (n=1126) and ONU (n=1403)(Ariane et al. 2012; Fairey et al.

152   2013; Favaretto et al. 2010; Metcalfe et al. 2012; Terakawa et al. 2008) reported the UnRFS. The

153   pooled analysis of the available HRs showed that the different surgical procedures were not

154   significantly correlated with disease recurrence (HR 1.10, 95% CI: 0.93-1.28; P = 0.337, I^2 =

155   12.0%; Fig. 4).

156   2. Mortality

157   Among the four studies that provided the HRs of OS, there were 1442 LNU patients and 3119

158   ONU patients.(Fairey et al. 2013; Kim et al. 2015; Metcalfe et al. 2012; Rieken et al. 2014)

159   There was significant heterogeneity (P = 0.091, I^2 = 53.7%; Fig. 5), and a random model was

160   applied. The model showed that neither LNU nor ONU significantly increased the risk in the

161   overall survival (HR 0.91, 95% CI: 0.66-1.17; Fig. 5). The CSS was described in ten articles, in

162   which 2518 patients were treated by LNU and 8342 patients were treated by ONU.(Ariane et al.

163   2012; Capitanio et al. 2009; Fairey et al. 2013; Ishikawa et al. 2010; Kim et al. 2015; Ploussard

164   et al. 2015; Rieken et al. 2014; Walton et al. 2011; Yafi et al. 2012; Zou et al. 2014) The pooled

165   results indicated that LNU could improve the cancer specific survival (HR 0.79, 95% CI: 0.68-

166   0.91; P = 0.186, I^2 = 28.1%; Fig. 6).

167   3. Subgroup analysis and multivariable meta-regression for IRFS

168   In subgroup analysis for the effect of different approaches of LNU on IRFS, no difference were

169   seen among people with retroperitoneal laparoscopy (HR 1.04, 95% CI: 0.77-1.32; P = 0.598, I^2

170 = 0.0%; Fig. 7) and transperitoneal laparoscopy (HR 0.81, 95% CI: 0.48-1.13; P = 0.548, I^2 =

171 0.0%; Fig. 7). The subgroup of five studies with sample sizes of LNU more than 100 had a

172 combined HR of 1.31 (95% CI, 0.92-1.70) with significant heterogeneity (P = 0.011, I^2 = 69.5%;

173 Fig. 8), while the subgroup of eight studies with sample sizes of less than 100 had a combined

174 HR of 0.97 (95% CI: 0.67-1.16) without significant heterogeneity (P = 0.919, I^2 = 0.0%; Fig. 8).

175 Multivariable meta-regression showed no particular influence of different approaches of LNU (P

176 = 0.431), sample size (P = 0.899) and publication year (P = 0.729) on the results.

177

178 **Publication bias and sensitivity analysis**

179 The publication bias detection was conducted by Egger's asymmetric test and only for IRFS

180 outcomes. The P value of the linear regression was 0.515, and no significant publication bias was

181 observed (Fig. S1). We also performed sensitivity analyses of IRFS and CSS, and no significance

182 change was observed (Fig. S2 and Fig. S3).

183

184 **Discussion**

185 Recently, some retrospective studies have paid attention to the predictors of disease recurrence in

186 patients with UTUC after RNU; these studies found that CIS, previous bladder cancer,

187 laparoscopic surgery and distal ureteral management were risk factors for disease

188 recurrence.(Xylinas et al. 2014) A systemic review concluded that a laparoscopic approach

189 significantly increased the risk of intravesical recurrence.(Seisen et al. 2015) However, there are

190 many studies that suggested that laparoscopic surgery could provide equivalent oncologic control

191   compared with open surgery.(Favaretto et al. 2010; Ishikawa et al. 2010) Therefore, we

192   conducted this meta-analysis enrolling twenty-one retrospective studies that contained various

193   oncologic outcomes to assess whether LNU would show a tendency toward a poor prognosis for

194   UTUC patients.

195   Open nephroureterectomy, the traditional surgical approach that could support a durable tumor

196   control, has long been accepted as the standard surgical treatment for UTUC, especially for high-

197   risk UTUC(Roupret et al. 2015). As a viable minimally invasive therapy, LNU was developed in

198   an effort to reduce the morbidity of the surgical management and had advantages of lesser blood

199   loss, shorter hospital stay and oncologic outcomes compared with ONU. With a median follow-

200   up of 45 months of 1261 UTUC patients who underwent ONU (n = 926) or LNU (n = 335),

201   Xylinas *et al* showed that the laparoscopic approach was associated with a higher risk of

202   intravesical recurrence compared with open surgery (HR=1.5, 95% CI, 1.17-1.93).(Xylinas et al.

203   2014) It was suggested that the high pressure pneumoperitoneum during LNU might trigger

204   tumor dissemination and could result in a higher rate of recurrence, which contributed to the

205   debate on oncologic outcomes of UTUC patients after laparoscopic procedures. Few cases of

206   laparoscopic port-side seeding were reported in some literature in the early years, and Rouprêt *et*

207   *al* proposed that ensuring a closed system during laparoscopic surgery and avoiding direct

208   contact between instruments and tumors might favor tumor control.(Roupret et al. 2015) In 150

209   laparoscopic surgeries, Ariane *et al* reported three cases of laparoscopic port-side seeding

210   occurred in early experiences. After the widespread use of laparoscopic bags for specimen

211   extraction, no cases happened.(Ariane et al. 2012) Our pooled results demonstrated that LNU

212 could provide equivalent tumor control of intravesical recurrence and unspecified RFS compared

213 to ONU. However, the majority of the enrolled studies reported negative control for ONU in

214 extravesical recurrence. Our results showed that ONU was an independent risk for ExRFS.

215 However, considering that there were only four articles enrolled, whether open surgery increased

216 the risk of extravesical recurrence still needs further exploration. Our analysis based on the

217 current evidence did not support the view that laparoscopic surgery increased the risk of disease

218 recurrence of patients with UTUC after nephroureterectomy.

219 Regarding survival outcomes, our data demonstrated that LNU was comparable to ONU in

220 overall survival, and superior in cancer specific survival. In the first randomized prospective

221 study, the cancer specific survival rate and the metastasis free survival rate were significantly

222 different between the LNU and ONU groups, which favored ONU after matching for pT3 and

223 high-grade tumors.(Simone et al. 2009) In the 2015 EAU guidelines, invasive or large (T3/T4

224 and/or N+/M+) tumors were deemed as contraindications for a laparoscopic approach.(Roupret

225 et al. 2015) Recently, Kim *et al* retrospectively analyzed the data of 371 UTUC patients who

226 underwent ONU (n = 271) or LNU (n = 100); the results indicated that LNU had worse five-year

227 OS and CSS rates than the ONU group only in locally advanced disease (pT3/T4) after

228 stratifying by pathological stages.(Kim et al. 2015) However, this conclusion was not identified

229 in Arian's research in tumors of the pathological stages of pT3/T4.(Ariane et al. 2012) A recent

230 study including 749 muscle-invasive UTUC patients who underwent ONU (n = 527) or LNU (n

231 = 222) also indicated that the oncological outcomes of LNU were not inferior to the outcomes of

232 ONU.(Miyazaki et al. 2015) Although our analysis did not include a subgroup analysis of

233   survival outcomes (OS and CSS) in locally advanced UTUC patients because of a lack more

234   relevant survival data, our results might be reliable because the majority of our data were

235   extracted from multivariate analyses, the majority of which adjusted for the effect of tumor

236   stages and grades. Furthermore, a previous systematic review also showed that no significant

237   differences in the stages of pT3/T4 or pathologic grades were observed in the LNU group

238   compared with the ONU group.(Ni et al. 2012)

239   Previous systematic reviews on the oncologic outcomes comparing LNU with ONU were

240   published in 2012.(Ni et al. 2012; Rai et al. 2012) These cumulative analyses conducted by using

241   non-time to event data suggested that LNU could offer reliable perioperative safety and

242   comparable oncologic efficacy compared to ONU. The meta-analysis conducted by Ni *et al*

243   indicated that LNU could improve the 5-yr CSS   and decrease the rates of the overall recurrence

244   and bladder recurrence. Recently, Seisen *et al* observed that LNU was a significant predictor of

245   the IRFS in their meta-analysis enrolling in six studies (HR 1.62; 95% CI: 1.18-2.22).(Seisen et

246   al. 2015) After enrolling more available HRs extracted from multivariate or univariable Cox

247   regression, our results showed there was no significant difference in IRFS between LNU and

248   ONU management, different from the studies of Ni *et al* and Seisen *et al*. We thought the

249   conclusion that LNU could improve the CSS should be interpreted cautiously, although this

250   conclusion was consistent with the previous opinion of Ni *et al*.

251   Several limitations must be acknowledged in our meta-analysis. First, this meta-analysis was

252   based on retrospective studies. Although all of these studies were of high quality (＞5 stars)

253   according to the modified Newcastle-Ottawa Scale, the intrinsic bias of cohort studies existed.

254 Next, the covariates controlled in the Cox regression analysis were different, which might

255 introduce bias into our analysis. Finally, the time interval of the studies enrolled was more than

256 20 years. During this period, improvements in surgical techniques and medical materials should

257 be considered. Additionally, these analyses did not include hand assisted laparoscopic

258 nephroureterectomy because its relevant HR by Cox regression analysis for oncologic outcomes

259 was reported in few literatures, and it is frequently deemed as an inferior approach compared

260 with LNU or ONU in terms of the recurrence free survival and intravesical recurrence free

261 survival rates.(Kitamura et al. 2014) Given the low incidence of UTUC, high quality level data

262 were so scarce that our results should be interpreted cautiously. The oncological outcomes of

263 LNU and ONU should be verified by prospective randomized controlled trials, especially for

264 locally advanced disease.

265

266 **Conclusion**

267 Based on our meta-analysis of the current evidence, LNU could provide equivalent prognostic

268 effects for upper tract urothelial carcinoma as ONU, and LNU had better results in the ExRFS

269 and CSS. However, considering all eligible studies with the intrinsic bias of retrospective study

270 design, the results should be interpreted with cautions, and prospective randomized controlled

271 trials are still needed.

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Table-1

Characteristics of the studies included in the systematic review

Table 1. Characteristics of the studies included in the systematic review

Study	Country	Duration	N of pts (ONU/LNU)	Age (yrs) (ORNU/LRNU)	Follow up (month) (ONU/LNU)	Outcomes	Approach of LNU	NOS	Adjusted factors
Favaretto 2010	USA	2002-2008	109/53	Md73 (IQR67-78) Md71 (IQR64-76)	Md23	UnRFS, IRFS	Mixed	6	Age, ASA, pT, Grade, pN, CIS, PBC
Fradet 2014	Canada	1990.1-2010.6	267/345	Md67 (IQR59-75)	Md24.8 (IQR7.69-56.76)	IRFS	NA	7	Age, Smoking, PH, Previous abdominal radiotherapy, DUM, CIS, TL, AC
Ito 2013	Japan	2005.12-2008.11	39/33	NA	R2.6-39.3	IRFS	RE	6	Sex, Age, TS, pT, UC, Grade, CIS, Histology type, AC
Kim 2015	Korea	1992-2012	271/100	Md64.7 (IQR57.7-70.8)	Md50.8 (IQR26.6-103.6)	OS,CSS, IRFS	TR	8	Age, ASA, PBC, UC, pT,Grade, LVI, Variant histology of urothelial carcinoma, TL, SM, AC Grade
Kitamura 2014	Japan	1995.4-2010.8	34/65	Md69 (R32-88) Md65 (R53-71)	Md70 (R6-192)	IRFS	Mixed	6	

Study	Country	Period	N	Age		Outcomes		Score	Variables
Zou 2014	CHN	1999.1-2013.2	101/21	Mn63.7 (R35-80)	Md53 (R3-159)	IRFS,CSS	TR	7	Gender, PH, TS, TL, Size, Appearance, Necrosis, pT, Grade, Multifocality, CIS, SM, LVI
Yafi 2012	Canada	1990-/	591/46	Md68 (IQR61-75)	Md37 (IQR18-68)	ExRFS, CSS	NA	6	Age, Race, Gender, TL, pT, Grade, CIS, LVI, pN
Walton 2011	Multi central	1987-2008	703/70	Md68 (IQR61-75)	Md34 (IQR15-65)	ExRFS, CSS	NA	7	Age, Gender, Race, PBC, DUM,TL, Grade, pT, pN, LVI, CIS
Taweemonkongsap 2008	Thailand	2001.4-2007.1	29/31	Mn66.8 (R39-88) Mn63.8 (R26-79)	Mn27.9 (R3-63) Mn26.4 (R3-72)	UnRFS	RE	5	pT, Grade
Metcalfe 2012	Canada	1990-2010	403/446	Mn69.7 (SD10.7)	Mn26.4 (R7.2-60)	UnRFS, OS	NA	8	Region, Age, Symptoms, TL, pT, Grade, CIS, PBC, NeoAC, AC, Salvage chemotherapy, Salvage radiation therapy, SM, Smoking, Previous abdominal RT, pN
Kume 2006	Japan	1996-2003	28/13	Mn65.07 (SD9.46) Mn65.31 (SD10.69)	Mn55.7 (SD29.4) Mn34.2 (SD10.9)	IRFS	RE	6	Multiple tumors, pT, Grade, OT
Koda 2007	Japan	1995.1-2005.8	27/29	Mn67.4 (SD11.3)	Mn46.2 (R 1-97)	IRFS	RE	6	Sex, Side, Age, pT, Grade, OT, AC,

Study	Location	Period	N	Age	Follow-up	Outcomes	Type	Score	Covariates
				Mn71.4 (SD8.2)	Mn16.4 (R1-57.5)				PBC
Ploussard 2015	multicentres	1989-2012	2826/922	Md70 (IQR60-74)	Md32.7 (IQR13.6-67.4)	IRFS, CSS	NA	7	Age, Sex, Ureter location, Multifocality, LN, DUM, pT, High grade, CIS, AC
Rieken 2014	muticentres	1987-2007	2042/450	Md69.2 (IQR62-77)	Md36	ExRFS, OS,CSS	NA	5	Univariable Cox regression
Fairey 2013	Canada	1994-2009	403/446	Md70.5 Md72.4	Md26.4 (IQR7.2-60)	UnRFS, OS,CSS	Mixed	7	Age, Sex, AC, pT, pN, Grade, SM
Capitanio 2009	muticentres	1987-2007	979/270	Mn68.3 (R27-97) Mn70.2 (R36-94)	Md49	ExRFS, CSS	NA	7	Age, pT, pN, Grade, LVI, ECOG PS, pN, PBC, Previous endoscopy, CIS
Ariane 2012	France	1995-2010	459/150	Md69.8 (R60.9-76) Md69.5 (R63-77)	Md27 (R10-48)	UnRFS, CSS,	TR	6	Gender, Age, ASA physical status, TL, pT, Grade, pN, LVI
Kobayashi 2012	Japan	2005.1-2009.4	151/137	Md71.4 (R32-89)	Md20.2 (R3.0-61.6)	IRFS	RE	6	TL, Time of ligation of the ureter, UC.
Terakawa 2008	Japan	2000.1-2005.12	111/66	Mn71.3 (SD9.6) Mn 68.7 (SD9.5)	Mn31 (R12.0-80.5)	IRFS	RE	7	Age, TS, TL, Multifocality, OT, DUM, pT, Grade, pN, LVI, SM
Ishikawa 2010	Japan	1990-2005	165/43	Md70 (R39-90)	Md8 (R2-105)	IRFS, CSS	RE	5	Univariable Cox regression
Xylinas 2013	France	1995-2009	350/132	Mn69.2 (IQR60-76)	Mn39.5 (IQR25-60)	IRFS	NA	6	Age, Gender, TL, Multifocality, PBC, Endoscopic management, pT, Grade, CIS, LVI, pN

3   Abbreviations:

4   yrs - years; N of pts - number of patients; Mn - mean; Md - median; R - range; IQR - interquartile range; NA - not
5   applicable; IRFS -intravesical recurrence free survival; ExRFS -extravesical recurrence free survival; UnRFS - unspecified
6   recurrence free survival; OS - overall survival; CSS - cancer specific survival; RE - retroperitoneal; TR - transperitoneal ;
7   NOS - Newcastle-Ottawa Scale; pT - pTstage; pN - pNstage; TL - tumor location; PH -previous hydronephrosis; DUM -
8   distal ureter management; TS - tumor side; UC - urinary cytology; SM - surgical margin; PBC - previous bladder cancer;
9   ASA - American Society of Anesthesiology physical status; AC - adjuvant chemotherapy; OT - operation time;CIS -
10 carcinoma in situ; LVI - lymphovascular invasion; ECOG PS - Eastern Cooperative Oncology Group performance score.
11

Figure-1

Screening Flow Diagram
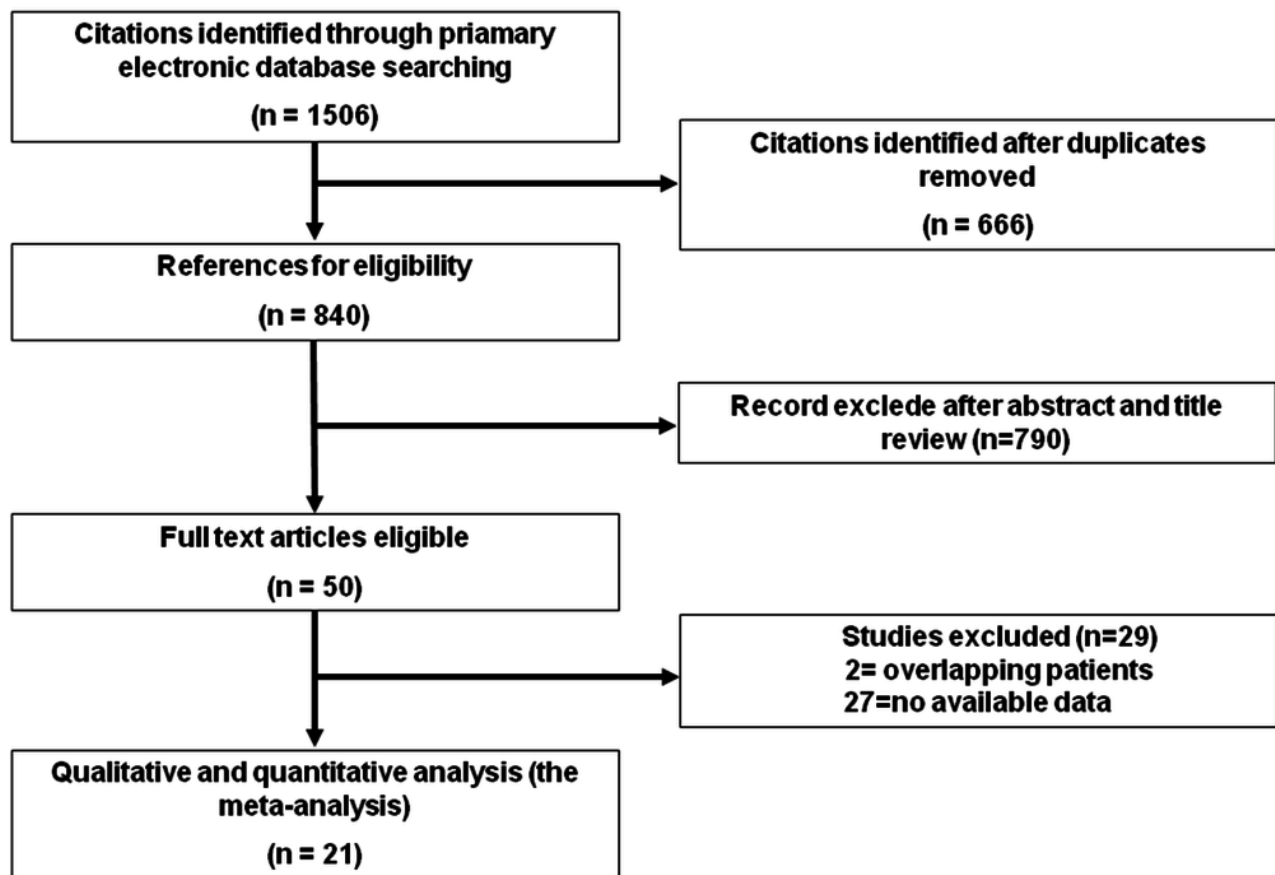
Figure-2

Forest Plot of Intravesical Recurrence Free Survival (IRFS) Hazard Ratio
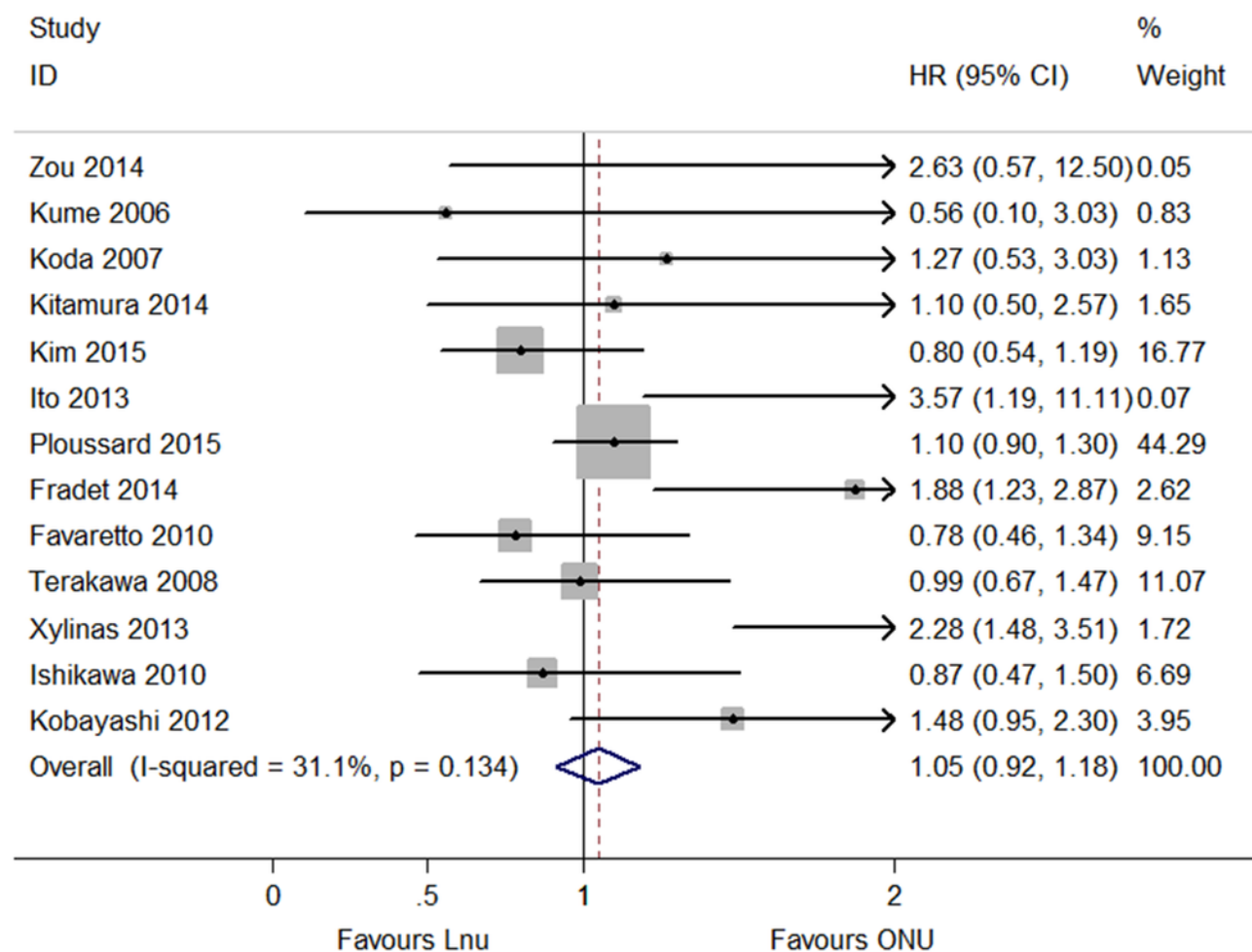
Figure-3

Forest Plot of Extravesical Recurrence Free Survival (ExRFS) Hazard Ratio
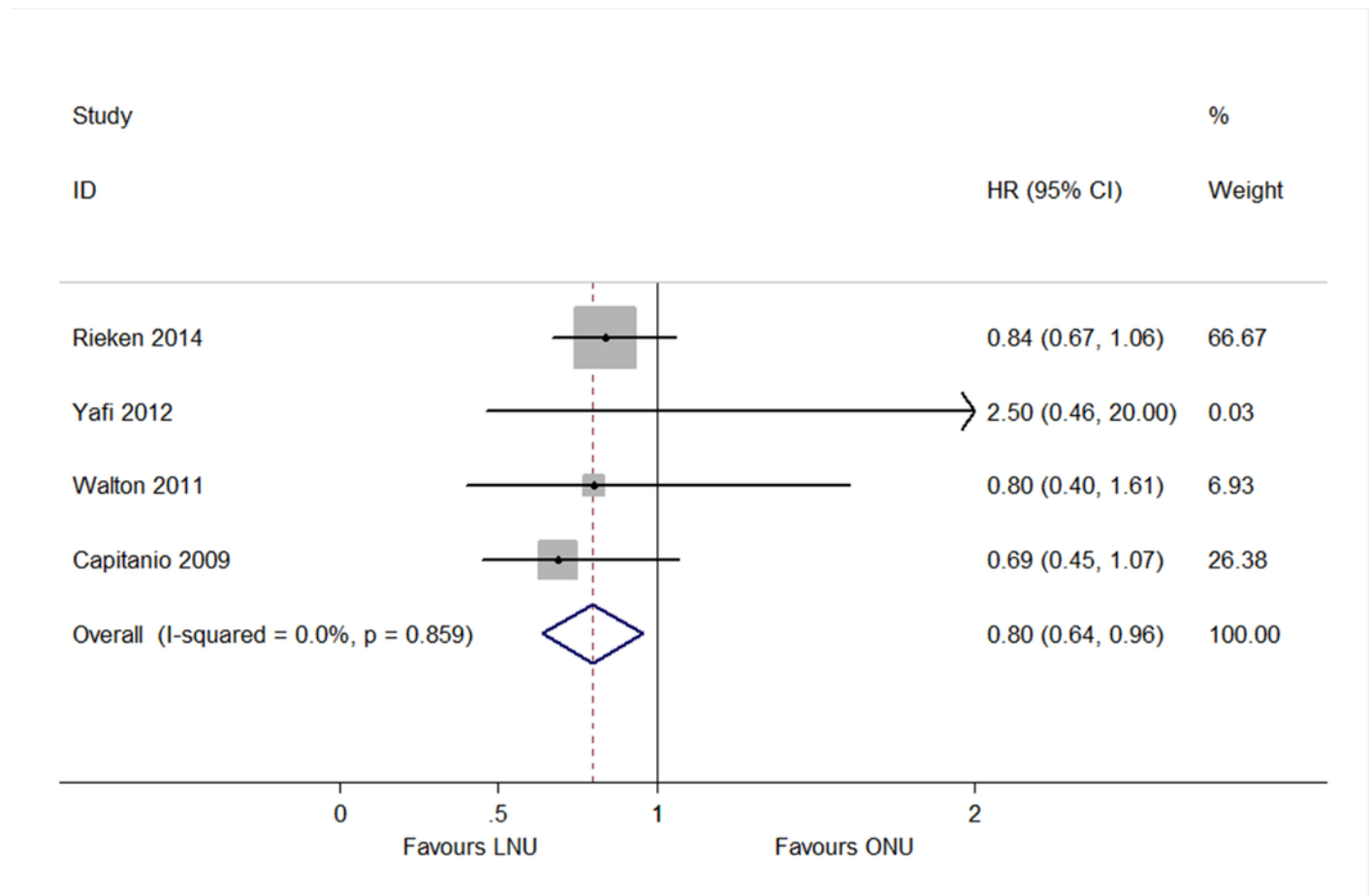
Figure-4

Forest Plot of Unspecified Recurrence Free Survival (UnRFS) Hazard Ratio

Study

ID   HR (95% CI)   Weight

Ariane 2012   1.27 (0.88, 1.83) 13.90

Fairey 2013   1.24 (0.98, 1.57) 36.04

Favaretto 2010   0.88 (0.57, 1.38) 19.12

Metcalfe 2012   1.14 (1.09, 1.84) 22.07

Taweemonkongsap 2008   0.67 (0.30, 1.49) 8.86

Overall (I-squared = 12.0%, p = 0.337)   1.10 (0.93, 1.28) 100.00

0   .5   1   2
Favours LNU   Favours ONU
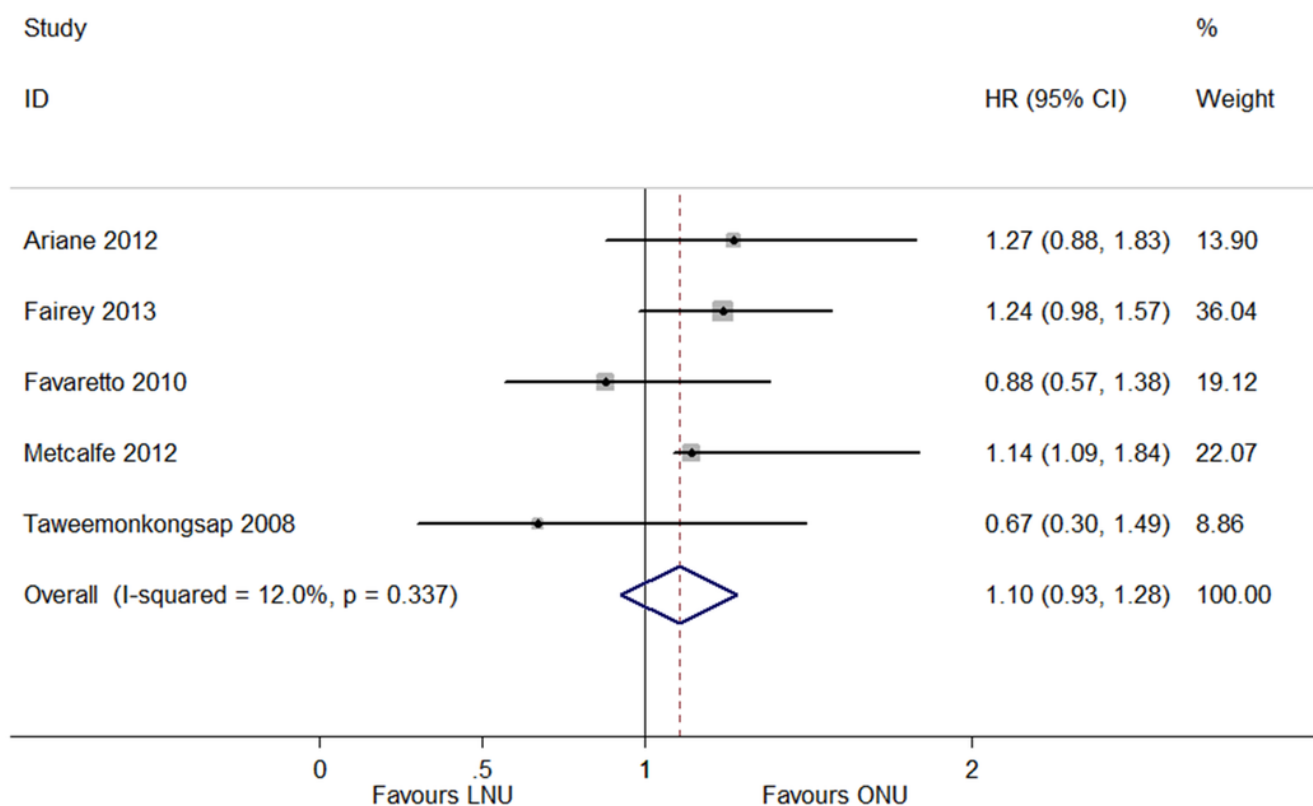
Figure-5

Forest Plot of Overall Survival (OS) Hazard Ratio

Figure showing forest plot:

Study ID	HR (95% CI)	% Weight
Metcalfe 2012	0.87 (0.62, 1.27)	27.52
Rieken 2014	0.80 (0.63, 1.01)	39.51
Kim 2015	2.21 (1.38, 3.53)	4.97
Fairey 2013	0.89 (0.63, 1.27)	27.99
Overall (I-squared = 53.7%, p = 0.091)	0.91 (0.66, 1.17)	100.00

NOTE: Weights are from random effects analysis

Favours LNU   Favours ONU
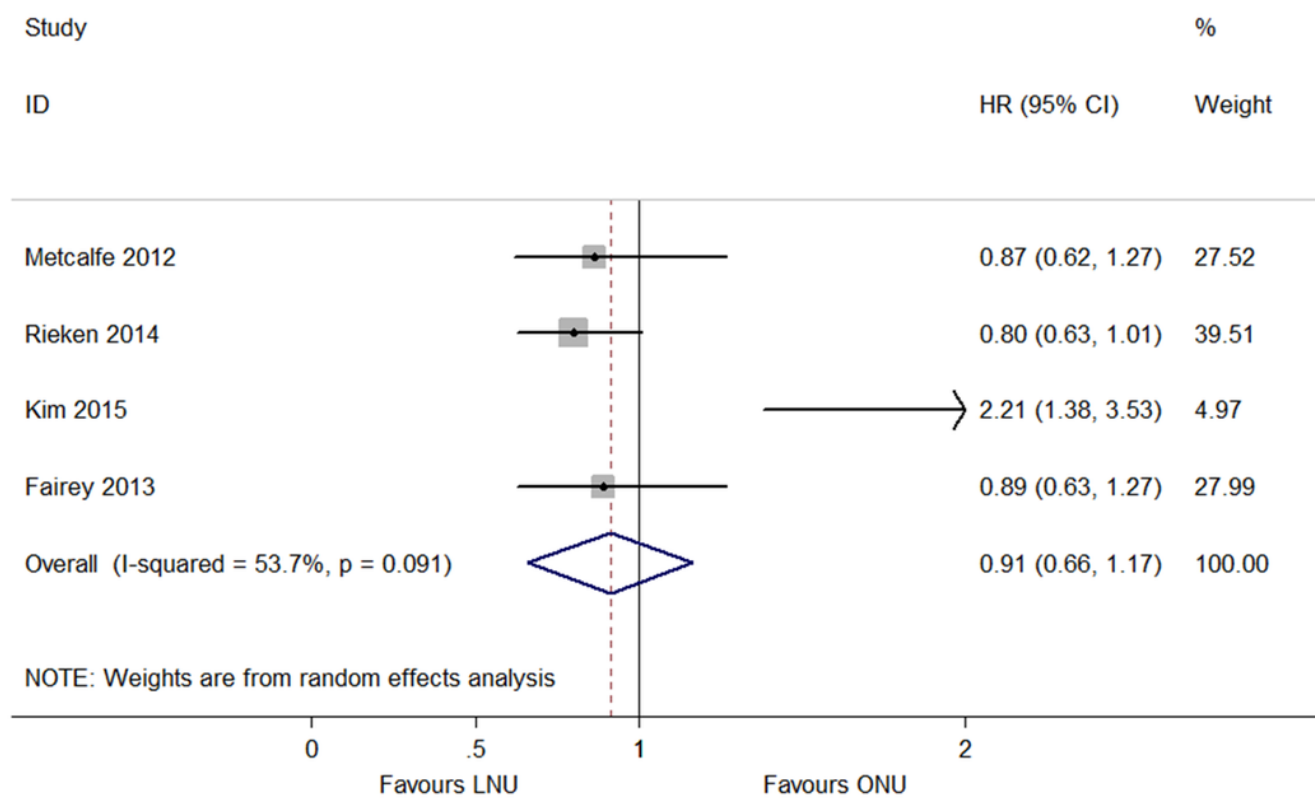
Figure-6

Forest Plot of Cancer Specific Survival (CSS) Hazard Ratio

Forest plot:

Study ID	HR (95% CI)	% Weight
Ariane 2012	0.51 (0.25, 1.01)	8.98
Capitanio 2009	0.65 (0.39, 1.09)	10.67
Fairey 2013	0.90 (0.60, 1.37)	8.82
Ploussard 2015	0.95 (0.80, 1.20)	32.68
Kim 2015	2.08 (1.23, 3.52)	1.00
Walton 2011	0.96 (0.44, 2.06)	1.99
Rieken 2014	0.71 (0.53, 0.94)	31.10
Yafi 2012	3.33 (0.50, 33.33)	0.00
Ishikawa 2010	0.90 (0.30, 2.13)	1.56
Zou 2014	0.42 (0.13, 1.41)	3.19
Overall (I-squared = 28.1%, p = 0.186)	0.79 (0.68, 0.91)	100.00

Favours LNU   Favours ONU

Figure-7.png

Forest Plot of subgroup analysis for IRFS - stratified by LNU approach
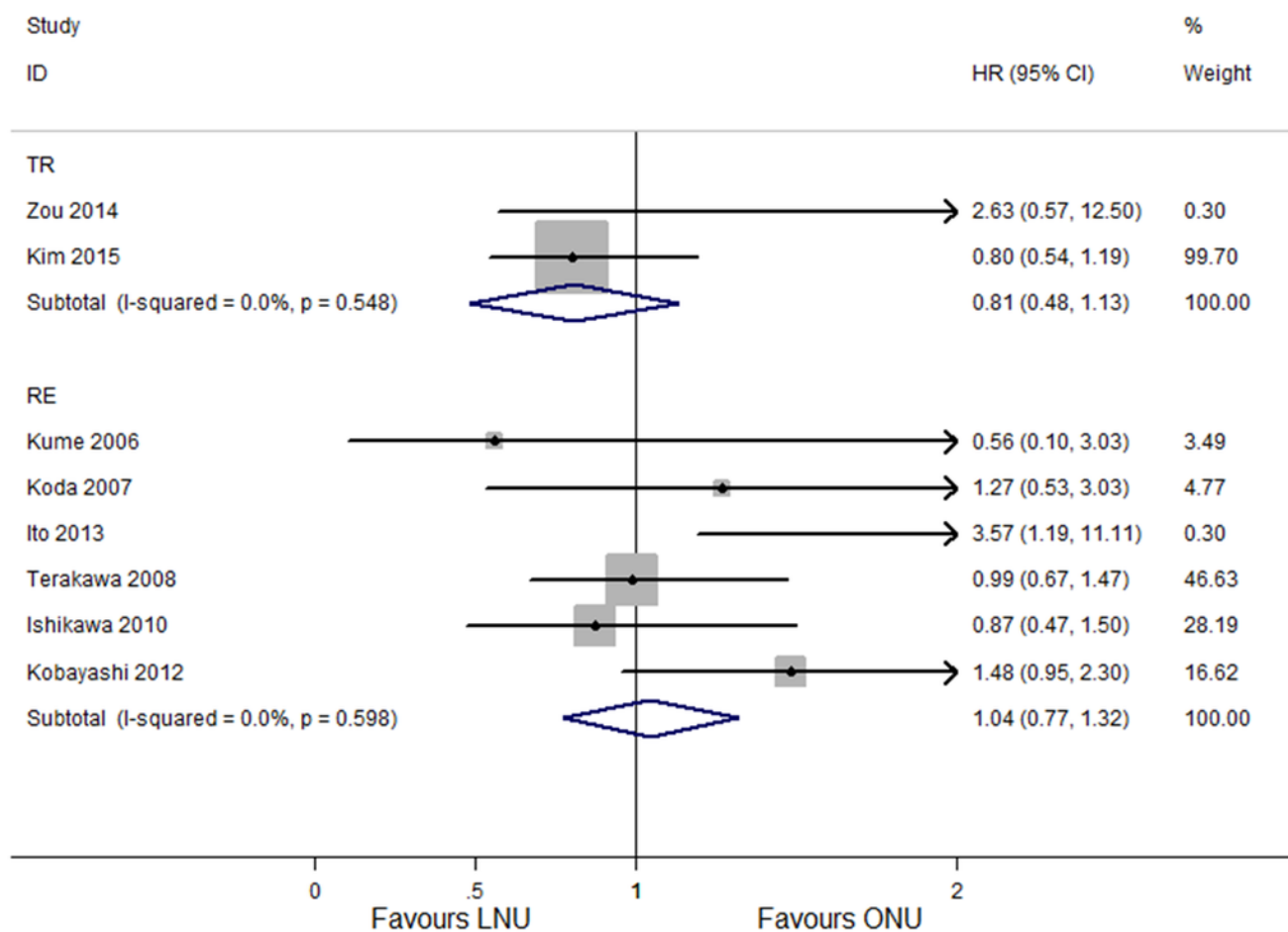
Figure-8.png

Forest Plot of subgroup analysis for IRFS - stratified by sample size