Impact of pretreatment asymptomatic renal dysfunction on the clinical course after esophagectomy

Yuki Kirihataya[1] · Kohei Wakatsuki[1] · Sohei Matsumoto[1] · Hiroshi Nakade[1] · Tomohiro Kunishige[1] · Shintaro Miyao[1] · Masayuki Sho[1]

A brief title: Asymptomatic renal dysfunction as risk of complications after esophagectomy

[1] Department of Surgery, Nara Medical University School of Medicine, Nara, Japan

Correspondence to: Masayuki Sho

Department of Surgery, Nara Medical University

840 Shijo-cho, Kashihara, Nara 634-8522, Japan

E-mail: m-sho@naramed-u.ac.jp

Tel.: +81-744-29-8863, Fax: +81-744-24-6866

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Abstract

Purpose Although recent large-scale clinical studies have shown that preoperative renal insufficiency is associated with an increased risk of postoperative complications after esophagectomy, whether or not asymptomatic renal dysfunction has an impact on the postoperative course after esophagectomy is unclear.

Methods A total of 177 patients who underwent esophagectomy between May 2009 and December 2018 were enrolled. The renal function was evaluated based on the pretreatment estimated glomerular filtration rate (eGFR). Patients were divided into two groups according to the eGFR cut-off value of 55 ml/min per 1.73 m^2.

Results Seventeen patients were classified as the low eGFR group, while 160 were classified as the normal eGFR group. The rate of severe complications in the low eGFR group was significantly higher than that in the normal eGFR group. Only a low eGFR was a significant complication risk factor. However, there were no marked differences in the mortality or survival between the low and normal eGFR groups.

Conclusion We demonstrated for the first time that pretreatment asymptomatic renal dysfunction may be a significant risk factor for severe morbidity after esophagectomy.

Introduction

Esophagectomy for esophageal cancer is associated with higher morbidity and mortality rates (2.7%–11.4%) than other gastrointestinal surgeries, although advances in surgical techniques and perioperative management have made it possible to perform esophagectomy relatively safely [1,2]. Preoperative complications are reportedly associated with postoperative complications in cases of esophageal cancer [3,4]. An older age, poor performance status, corticosteroid use, squamous cell cancer, chronic lung disease, and malnutrition are known predictors of complications after standard esophagectomy [5–7]. Postoperative sepsis reflects a deep impairment of the immune response, which is potentially associated with cancer recurrence and mortality [8]. Information on the risks of postoperative complications is important for performing proper perioperative management and obtaining informed consent from patients.

Renal dysfunction remains a major risk factor because it is related to not only the metabolic and coagulopathic disorders secondary to uremia and anuria but also other co-morbidities [9,10]. Preoperative renal insufficiency is a well-known risk factor for postoperative complications after cardiac and vascular surgery [11,12]. There is a subpopulation of patients with asymptomatic renal dysfunction with no need for hemodialysis. Preoperative renal failure and postoperative complications have also been reported for cancer. In pancreatic cancer, Nagai et al. [13] reported that mild asymptomatic renal dysfunction was

an independent risk factor for severe postoperative complications and grade B/C pancreatic fistula after pancreatoduodenectomy when patients were divided into two groups according to an estimated glomerular filtration rate (eGFR) cut-off value of 55 ml/min per 1.73 m^2. In gastric cancer, Matsumoto et al. [14] reported that the incidences of anastomotic leakage and intraabdominal abscess in the mild CKD group was higher than that in the control group when patients with gastric cancer were divided according to their eGFR. Such asymptomatic renal dysfunction has thus been reported to be a risk for surgery for gastric and pancreatic cancer. However, to our knowledge, no studies have addressed the impact of such asymptomatic renal dysfunction on the postoperative outcome after esophagectomy.

Given the above, the present study tried to clarify the short- and long-term outcomes after esophagectomy in patients with such asymptomatic renal dysfunction.

Patients and methods

Patients

A total of 192 patients underwent esophagectomy between May 2009 and December 2018 in Nara Medical University Hospital. Twelve patients with R2 resection and three treatment-related deaths were excluded from this study. The remaining 177 patients were retrospectively analyzed.

Patients provided their written informed consent before treatment according to the rules and regulations of our institution. This study was approved by the ethics committees of Nara Medical University Hospital (approval no. 2540).

Data and definition

A comprehensive review of the medical records was performed to evaluate various clinicopathological factors including patient demographics, medical comorbidities, preoperative laboratory values, tumor pathological characteristics, and perioperative data. The pathological diagnosis was classified as benign disease, malignant disease other than squamous cell carcinoma (SCC), and SCC. As a result, 1 benign primary disease, 32 malignant tumors other than SCC, and 144 SCCs were included. According to medical comorbidities, cardiovascular disease included coronary artery disease, atrial fibrillation, and cerebral infarction. Renal disease included diabetic nephropathy, and chronic kidney disease. Respiratory disorder included chronic obstructive pulmonary disease, bronchial asthma, interstitial pneumonia, and bronchial ectasia. A total of 108 patients received neoadjuvant chemotherapy. The renal function was evaluated by calculating the eGFR based on the results of laboratory examination at the first visit to our hospital. The eGFR was calculated using the following formula: eGFR (ml/min per 1.73 m^2) = 194 × sCr - 1.094 × Age - 0.287 (× 0.739 if the patient is female) [15].

Outcome assessments

The incidence of postoperative complications was evaluated, and the severity of complications was defined according to the Clavien-Dindo classification [16]. If more than one complication occurred in a single patient, the most severe grade was considered for the present analysis. Severe complications were defined as those of grade IIIb and higher. We further evaluated various outcome parameters, including the length of the postoperative hospital stay and the prognosis. The date of the last follow-up was November 2019.

Statistical analyses

The parameters were compared using Mann-Whitney U Test, the χ^2 test, or Fisher's exact test as appropriate. Continuous variables were expressed as the mean and standard deviation. The odds ratios (OR) for severe postoperative complications were calculated using logistic regression model. The overall survival (OS) was calculated from the date of initial treatment with surgery until death or the last follow□up. The survival curve was estimated according to the Kaplan–Meier method, and differences were analyzed using the log□rank test. All reported P□values were two□sided. P□value of <0.05 was considered statistically significant, and confidence intervals (CIs) were calculated at the 95% level. The statistical analyses were performed using the SPSS software program, version 19.0 (SPSS, Chicago, IL, USA).

Results

Cut-off value of the eGFR

To determine the optimal cut-off value of the eGFR to predict postoperative complications, we set and evaluated various eGFR values in relation to complications of grade IIIb and higher. As a result, we defined 55 ml/min per 1.73 m^2 as the cut-off value and classified all patients into either low or normal eGFR groups based on this value. A total of 160 patients (90.4%) with an eGFR of ≥55 ml/min per 1.73 m^2 were classified as the normal eGFR group, while the 17 patients (9.6%) with an eGFR of <55 ml/min per 1.73 m^2 were classified as the low eGFR group (Fig. 1).

Patient clinicopathological characteristics according to the eGFR status

The patient characteristics of each group are summarized in Table 1. The patients in the low eGFR group were significantly older than those in the normal eGFR group ($p < 0.01$). There were more men in the low eGFR group than in the normal eGFR group ($p = 0.04$). While the serum creatinine level in the low eGFR group was significantly higher than that in the normal eGFR group ($p < 0.01$), there were no marked differences in the hemoglobin or albumin values between the two groups. There were also no marked differences in preoperative comorbidities,

tumor location, tumor size, clinical and pathological T-factor, clinical or pathological N-factor, stage, reconstructed substitute, extent of lymphadenectomy, number of dissected nodes, or rate of residual tumor between the two groups. Preoperative therapy was performed more frequently in the normal eGFR group than in the low group, although the difference did not reach statistical significance ($p = 0.07$).

Perioperative data

We then compared the perioperative data between the two groups (Table 2). There were no significant differences between the two groups in the operating time or intraoperative blood loss. In total, 108 patients (61%) developed postoperative complications. While there were no marked differences between the two groups in total postoperative complications, the rate of respiratory events was significantly higher in the low eGFR group than in the normal eGFR group ($p = 0.02$). Respiratory events were aspiration pneumonia in five of six cases in the low eGFR group, and two of those five cases required intensive-care unit (ICU) management. Furthermore, the low eGFR group had a higher rate of severe complications (IIIb and higher in Clavien-Dindo classification) than the normal eGFR group (24% vs. 7%, $p = 0.04$).

Risk factors for severe complications

Next, we analyzed the risk factors for severe postoperative complications after esophagectomy. The statistical analysis indicated that only a low eGFR was a significant risk factor for the incidence of severe complications (Table 3).

The postoperative survival and recurrence

Finally, we examined the impact of the eGFR on the patient prognosis. As shown in Figure 2, there was a tendency toward differences in the OS rate between the groups ($p = 0.08$). There were no significant differences in the rate of death from other diseases between the normal eGFR group (17 of 160; 11%) and the low eGFR group (2 of 17; 12%) ($p = 0.58$). In the normal eGFR group, 44 out of 160 cases relapsed, and in the low eGFR group, 6 out of 17 cases relapsed, but there was no significant difference between the groups ($p = 0.49$). There were also no significant differences between the groups in any of the recurrence patterns, including lymphogenous, hematogenous, disseminated, and local (normal eGFR group vs. low eGFR group; lymphogenous: 44 [28%] vs. 6 [35%], $p = 0.28$; hematogenous: 22 [14%] vs. 4 [24%], $p = 0.17$; disseminated: 4 [3%] vs. 1 [6%], $p = 0.42$; local: 10 [6%] vs. 2 [12%], $p = 0.39$). Regarding the cause of death, there were no significant differences between the normal and low eGFR groups (death from cancer: 39 [23%] vs. 6 [35%], p = 0.33; death from other diseases: 17 [11%] vs. 2 [2%], p = 1.00). Within 1 year, 3 out of 160 (2%) in the normal eGFR group and 2 out of 17 (12%) in the low group died from other diseases.

Discussion

Some studies have reported that preoperative renal insufficiency was associated with increased postoperative complications after various types of surgery, including cardiac and general surgery [11,12,17]. The present findings suggest that patients with pretreatment asymptomatic renal dysfunction might be at an increased risk for morbidity and mortality after esophageal resection. Accordingly, we obtained a number of important findings, as described below.

First, there were significant correlations between a low eGFR and advanced age, while there were no significant correlations between a low eGFR and perioperative variables. Data suggest that asymptomatic renal dysfunction may represent patient frailty. Second, there were significant correlations between the eGFR status and grade IIIb/IV complications ($p = 0.04$). In particular, there was a correlation between a low eGFR and the incidence of respiratory complications ($p = 0.02$). The statistical analysis indicated that only a low eGFR was an independent risk factor for grade IIIb/IV complications. Therefore, our data suggest that asymptomatic renal dysfunction had a significant negative impact on clinically relevant postoperative complications after esophagectomy.

There are several mechanisms potentially underlying the association of asymptomatic renal dysfunction with increased morbidity after esophagectomy. First, the tissue vulnerability

in patients with renal dysfunction may be related to increased complications [18]. Second, perioperative fluid management may be involved. To prevent renal insufficiency, excessive fluids may have been administered to patients with mildly elevated serum creatinine levels. Third, a number of studies have shown that renal insufficiency is associated with an impaired immune system in humans [19,20]. For instance, uremia causes inflammation and reduces the immune response, thereby resulting in increased susceptibility to infection. Although relatively few studies have addressed the impact of mild renal dysfunction on immunity, a potentially inadequate immune response may have exacerbated the severity of complications after esophagectomy [21]. An important question how long does it take for asymptomatic renal dysfunction to induce various adverse influences on tissue vulnerability and immune system may be raised. Although it is likely to take considerably long time, there is no study to address this critical issue.

Next, considering renal insufficiency and increased respiratory complications, previous reports have reported that the age, Brookman index, chronic obstructive pulmonary disease, delirium, and clinical stage are risk factors for postoperative pulmonary complications [22,23]. The incidence of pulmonary morbidities after esophagectomy is high, reportedly occurring in 13.4%–38.2% of cases, and can be a major cause of surgery-related mortality [24,25]. In the present study, we showed that postoperative pulmonary complications were more frequent in the low eGFR group than in the normal eGFR group. Although the precise mechanisms of

increased risk of respiratory complications in patients with mild renal dysfunction remain unclear, there are potential reasons. First, as mentioned above, perioperative fluid infusion may be involved. However, we found that there was no significant difference in daily fluid balance during surgery and the intensive care unit stay between the normal and low eGFR groups (data not shown). Although it is still controversial about optimal fluid management, it is unlikely that perioperative water balance simply cause pulmonary complications after esophagectomy [18]. Second, the impaired swallowing function in older patients might be related to the increased risk of aspiration pneumonia, since the patients in the low eGFR group were significantly older compared to the normal eGFR group. However, there was no significant direct relationship between patients' age and respiratory complications ($p = 0.25$). Third, the renal dysfunction may cause chronic inflammation and endothelial dysfunction, thereby resulting in pulmonary edema and worsen respiratory status after highly invasive surgery. Furthermore, renal dysfunction may also cause the impaired immune function leading to susceptibility to infection. Taken together, the respiratory complications may be based on multiple reasons and mechanisms in patients with mild renal dysfunction. Further studies are required to clarify the underlying mechanisms and establish the optimal perioperative management approach after esophagectomy.

Finally, we evaluated the impact of asymptomatic renal dysfunction on the patient survival. Our data also indicated that asymptomatic renal dysfunction had no significant impact

on mortality after esophagectomy. Furthermore, the results also demonstrated that asymptomatic renal dysfunction had no impact on the patient prognosis, although severe complications increased, regardless of the original disease pathology. However, the survival rate tended to be lower in the low eGFR group than in the normal eGFR group, while there were no marked differences in the type or rate of recurrence between the two groups. Although the true impact of pretreatment asymptomatic renal dysfunction on the patient prognosis remains unclear, the relatively low rate of preoperative therapies might have been associated with the poor prognosis in the patients in the low eGFR group. Taken together, these findings suggest that esophagectomy may be justified for patients with renal dysfunction, even if there are increased risks of postoperative complications—specifically respiratory events—after esophagectomy.

Several limitations should be considered before drawing a definitive conclusion. First, this was retrospective study performed at a single center with a relatively small sample size. Furthermore, whether or not the eGFR cut-off value of 55 ml/min per 1.73 m^2 used in this study is indeed optimum remains unclear. These findings should be prospectively validated in larger cohort in the future.

In conclusion, to our knowledge, this is the first report to address the clinical impact of pretreatment asymptomatic renal dysfunction on the postoperative clinical course after esophagectomy. We should be aware that asymptomatic renal dysfunction may be a significant

risk factor for severe morbidity after esophagectomy. Although it had no impact on the mortality or long-term survival, performing careful postoperative management and obtaining proper informed consent from patients with renal dysfunction are needed.

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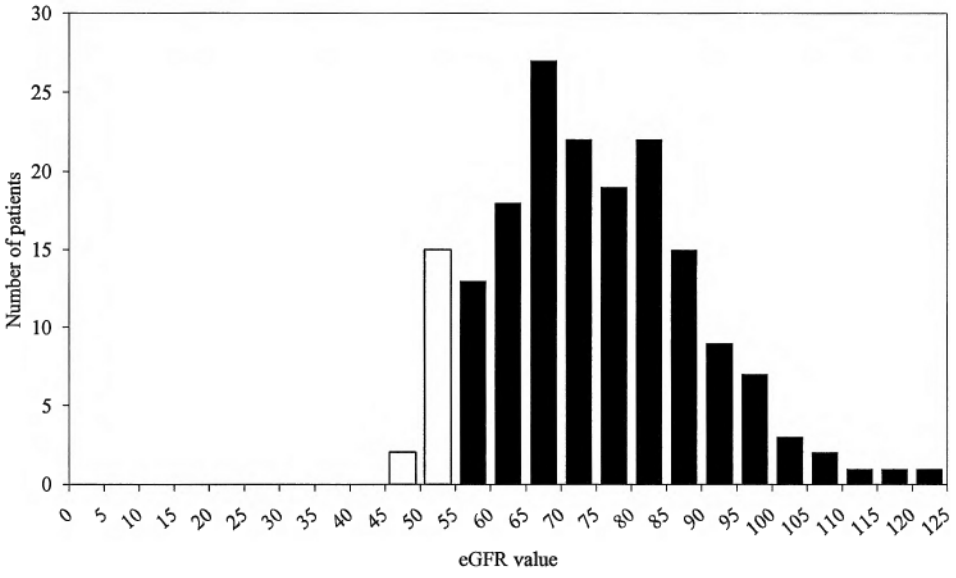
Figure legends

Fig. 1 Distribution of the estimated glomerular filtration rate (eGFR) value. Patients with an eGFR <55 ml/min per 1.73 m^2 were classified as the low eGFR group (white bar), while those with an eGFR of ≥55 ml/min per 1.73 m^2 were classified as the normal eGFR group (black bar).

Fig. 2 The comparison of the overall survival between the low and normal eGFR groups.


Number of patients
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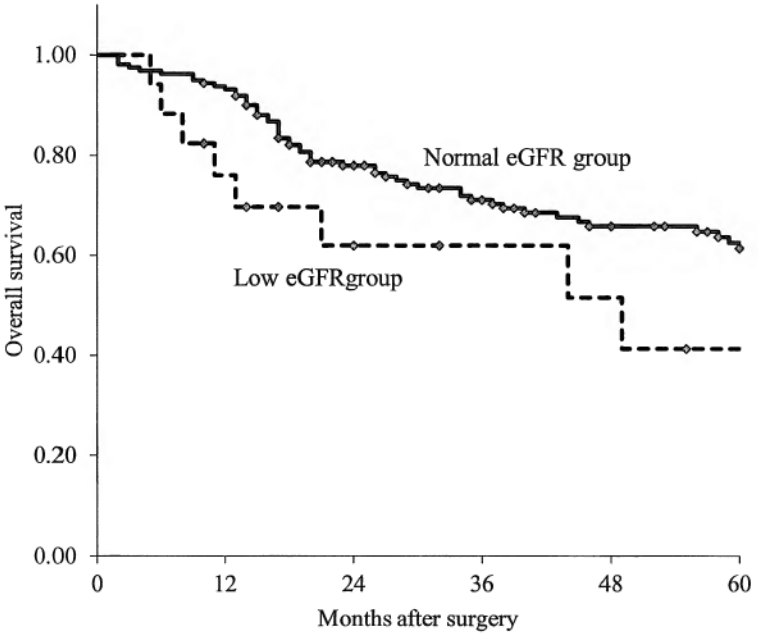
eGFR value

Fig. 1



No. at risk						
Low eGFR group	17	13	8	7	6	4
Normal eGFR group	160	149	109	86	71	56

Fig. 2

Table 1 Patient characteristics

Variables	Normal eGFR (n = 160)	Low eGFR (n = 17)	P value
Age (years)	65 ± 7.0	73 ± 7.5	<0.01
Gender (%)			0.04
Male	130 (81%)	17 (100%)	
Female	30 (19%)	0 (0%)	
Co-morbidities (%)			
All	80 (50%)	12 (71%)	0.13
Diabetes mellitus	20 (13%)	2 (12%)	0.65
Hypertension	54 (34%)	10 (59%)	0.06
Respiratory disorder	8 (5%)	2 (12%)	0.25
Cardiovascular disease	10(6%)	3(18%)	0.12
Hemoglobin (g/dl)	13.4 ± 1.7	13.5 ± 1.6	0.88
Albumin (g/dl)	4.2 ± 0.42	4.3 ± 0.32	0.34
Serum creatinine (mg/dl)	0.76 ± 0.13	1.7 ± 2.4	<0.01
Tumor location (%)			0.06
Ut	23 (14%)	3 (18%)	
Mt	79 (49%)	5 (29%)	
Lt	40 (25%)	3 (18%)	
Others	18 (11%)	4 (24%)	
Tumor size (mm)	45.1 ± 26.1	35.7 ± 17.8	0.24
Primary tumor (%) [a]			0.31
cT0/1	64 (40%)	4 (24%)	
cT2	19 (12%)	5 (29%)	
cT3	75 (47%)	8 (47%)	
cT4a/4b	1 (1%)	0 (0%)	
Regional lymph nodes (%) [a]			
cN0	63 (39%)	10 (59%)	0.12
cN1	91 (57%)	5 (29%)	
cN2	4 (3%)	2 (12%)	
cN3	1 (1%)	0 (0%)	
cStage (%) [a]			0.29
IA/IB	43 (27%)	4 (24%)	
IIA/IIB	52 (33%)	9 (53%)	
IIIA/IIIB/IIIC	61 (38%)	4 (24%)	
IV	3(2%)	0 (0%)	
Primary tumor (%) [a]			0.81
pT0/1	91 (57%)	8 (47%)	
pT2	16 (10%)	2 (12%)	

pT3	52 (33%)	7 (41%)	
pT4a/4b	0 (0%)	0 (0%)	
Regional lymph nodes (%) [a]			0.23
pN0	79 (49%)	6 (35%)	
pN1	36 (23%)	4 (24%)	
pN2	27 (17%)	6 (35%)	
pN3	17 (11%)	1 (6%)	
pStage (%) [a]			0.46
0	9 (6%)	0 (%)	
IA/IB	53 (33%)	4 (24%)	
IIA/IIB	39 (24%)	3 (18%)	
IIIA/IIIB/IIIC	52 (33%)	10 (59%)	
IV	6 (4%)	0 (0%)	
Reconstructed substitute (%) [a]			0.50
Stomach	135 (84%)	15 (88%)	
Others	25 (16%)	2 (12%)	
Extent of lymphadenectomy (%) [a]			0.11
<2FL	31 (19%)	6 (35%)	
3FL	129 (81%)	11 (65%)	
Median number of dissected nodes	56.2 ± 23.8	49.2 ± 18.1	0.34
Residual tumor (%) [a]			0.17
R0	154 (96%)	15 (88%)	
R1	6 (4%)	2 (12%)	
Preoperative therapies (%)			0.07
Absence	59 (37%)	10 (59%)	
Presence	101 (63%)	7 (41%)	

eGFR estimated glemerular filtration rate, *UICC* Union for International Cancer Control, *FL* field lymphadenectomy, [a] UICC 7th

Table 2 Perioperative data

Variables	Normal eGFR (n = 160)	Low eGFR (n = 17)	P value
Operative data			
Operating time (min)	563.9 ± 115.2	540.8 ± 146.0	0.34
Intraoperative blood loss (ml)	441.3 ± 524.7	284.1 ± 233.6	0.13
Postoperative complication			
All (%)	95 (59%)	13 (76%)	0.20
Anastomotic leakage	32 (20%)	4 (24%)	0.47
Recurrent laryngeal nerve palsy	15 (9%)	2 (12%)	0.51
Conduit trouble	7 (4%)	1 (6%)	0.56
Infection	14 (9%)	0 (0%)	0.23
Respiratory events	18 (11%)	6 (35%)	0.02
Cardiovascular events	3 (2%)	0 (0%)	0.74
Renal failure	1 (1%)	0 (0%)	0.90
Other	24 (15%)	4 (24%)	0.27
Clavien-Dindo classification (%)			0.04
Grade 0/I/II/IIIa	149 (93%)	13 (76%)	
Grade IIIb/IVa	11 (7%)	4 (24%)	

eGFR estimated glemerular filtration rate

Table 3 Risk factors of Clacian-Dindo classification IIIb and higher

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (>65/≤65 years)	0.89	0.3-2.6	0.83	0.69	0.2-2.1	0.51
Gender (female/male)	1.25	0.3-4.7	0.74	-	-	-
Comorbidity (presence/absence)	1.95	0.6-6.0	0.24	-	-	-
Tumor location (others/Mt)	2.68	0.8-8.8	0.10	-	-	-
Tumor size (>40/≤40 mm)	0.62	0.2-1.8	0.38	-	-	-
Primary tumor (cT3-4/0-2) [a]	0.95	0.3-2.8	0.93	-	-	-
Regional lymph node (cN1-3/0) [a]	1.07	0.4-3.1	0.90	-	-	-
Extended lymphadenectomy (3/<2FL)	0.70	0.2-2.4	0.57	-	-	-
Preoperative therapies (presence/absence)	1.31	0.4-4.0	0.64	-	-	-
Hemoglobin (≤13.2/>13.2 g/dL)	2.84	1.0-8.4	0.06	-	-	-
Albumin (≤4.3/>4.3 g/dL)	1.92	0.7-5.7	0.23	-	-	-
Preoperative eGFR (<55/≥55 ml/min/1.73m^2)	4.17	1.1-14.9	0.03	4.70	1.2-17.9	0.02

eGFR estimated glemerular filtration rate, *OR* odds ratio, *CI* confidence interval, FL field lymphadenectomy

[a]UICC 7th