Master's Thesis of Medicine

Association between angiolymphatic invasion and oncological outcomes among bladder urothelial carcinoma patients underwent radical cystectomy

방광 요로상피암종에 대해 근치방광절제를 행한 환자들에서의 혈관 림프관 침윤의 예후적 영향 분석

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Association between angiolymphatic invasion and oncological outcomes among bladder urothelial carcinoma patients underwent radical cystectomy

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Abstract

Purpose

To determine the association between angiolymphatic invasion (ALI) and urothelial bladder cancer in patients undergoing radical cystectomy (RCx).

Materials and Methods

This multicenter retrospective study enrolled 495 patients with urothelial bladder cancer who underwent RCx from 2007 to 2019. The patients were stratified into two groups based on the presence of ALI. The effects of ALI on cancer-specific survival (CSS), overall survival (OS), and recurrence-free survival (RFS) were analyzed using the Kaplan-Meier method and Cox regression hazard models.

Results

The median age of the 495 patients in the study was 65 years, with median and mean follow-up duration of 23.3 and 37.1 months, respectively. ALI was observed in 182 (36.8%) patients and was significantly associated with worse RFS, CSS, and OS ($p<0.001$, $p=0.012$, and $p=0.01$, respectively). Multivariate analysis after adjusting for significant variants showed that tumor stage (>T2) and ALI were independent predictors of CSS; conversely, lymph node (LN) metastasis was not. However, after adjusting for variants, multivariate analysis showed that tumor stage >T2, ALI, LN metastasis, and positive surgical margin were independent predictors for RFS. Tumor grade (High grade) was not a significant predictor.

Conclusions

ALI was an independent predictor of CSS and RFS.

Keyword : Urothelial carcinoma; bladder; Radical cystectomy; Angiolymphatic invasion; survival rate; Recurrence free survival

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Chapter 1. Introduction

According to a report from the early 2000s (1998–2002), 10,246 cases of primary bladder cancer occurred during this period. In addition, the 2021 Korea National Cancer Incidence database reported that bladder cancer is the 10th leading cause of cancer incidence and mortality in men. [1].

Among patients newly diagnosed with bladder cancer, 25% have muscle-invasive bladder cancer (MIBC). Radical cystectomy (RCx) with extended bilateral lymphadenectomy is generally the leading treatment for MIBC or refractory high-grade non-MIBC. With pathological staging, this procedure can provide an exact evaluation of both bladder cancer and regional lymph nodes (LNs). Several variables significantly related to disease-specific survival in bladder cancer have been investigated. In particular, LN metastases have been considered predictors of bladder cancer-related survival. [2, 3] To date, several studies have established predictor score variables for adverse prognoses, such as age, tumor stage, and LN density (COBRA score) [4]. Along with this prognostic value related to the LN, lymphovascular invasion or angiolymphatic invasion (ALI) are also controversial variables.

ALI is a poor prognostic factor for other solid tumors, such as those of the upper urinary tract, prostate, liver, and colorectal. [5, 6] Several articles assessing if the angiolymphatic channel allows the dissemination of invaded tumor have reported poor prognosis for patients with bladder cancer who underwent RCx or transurethral resection [7]. However, other

studies have found that ALI is insignificant compared to other variables [8] or less significant in urothelial bladder cancer than in squamous cell carcinoma of the bladder. [9]

This study aimed to evaluate the prognostic value of ALI for RCx in urothelial carcinoma bladder cancer.

Chapter 2. Body

2.1. Materials and Methods

Study population

The retrospective, multicenter, full-scale survey assessed 495 patients who underwent robotic-assisted radical bladder cystectomy between April 2007 and October 2019 and was approved by the Institutional Review Board (IRB no. 2019AN0102). Of the 495 patients, ALI was present in 182 patients. The exclusion criteria were non-transitional cell carcinoma histology, a history of neoadjuvant therapy, and incomplete data. The surgical technique and extent of lymphadenectomy (standard, extended, limited) were decided based on the surgeon's discretion. Regional lymphadenectomy was performed based on preoperative imaging or intraoperative examinations.

Data collection and pathologic evaluation

Clinical and pathological information was retrospectively obtained from patients' information charts from the affiliated hospital for bladder cancer research (seven medical institutions). Staff pathologists from each institution examined all specimens according to the institutional protocol. The American Joint Committee on Cancer/tumor, node, and distant metastasis (TNM) classification system was used for clinical staging, and the World Health Organization classification was used for pathological staging. Clinicopathological data included age, sex, comorbidities, tumor

stage, tumor grade, surgical margin, ALI, perineural invasion, squamous or glandular metaplasia, and carcinoma in situ (CIS). ALI was defined as the presence of tumor cells within the arterial, venous, or lymphatic lumen and was assessed using routine light microscopic examination with hematoxylin and eosin staining.

Statistical analyses

Descriptive statistics were obtained to verify patient demographic data and health status differences.

We divided the patients into ALI and non-ALI groups according to the primary tumor. The two groups were evaluated using the chi-square test for categorical variables and the independent t-test for continuous variables. The Kaplan-Meier method was used to calculate time-dependent outcomes such as recurrence-free, cancer-specific, and overall survival, and differences were assessed using log-rank statistics. Univariate and multivariate survival analyses were performed using the Cox proportional hazards regression model to evaluate the prognostic significance of the pathological variables. Statistical significance was set at $p<0.05$. All analyses were performed using SPSS version 22.0 (IBM Co., Armonk, NY, USA).

2.2. Results

Baseline characteristics of patients

The baseline characteristics of all the patients in the study are shown in Table 1. The median age of the 495 patients was 65 years. The median and mean follow-up durations were 23.3 and 37.1 months, respectively (range 0–134 months). Most of the patients were male (418 patients, 84%). ALI was present in 182 (36.8%) of the patients. The baseline characteristics of the non-ALI group were similar to those of the ALI group (n=313, 63.2%).

Patients with ALI were significantly older (67.3 vs. 64.6, p=0.006), had lower American Society of Anesthesiologist (ASA) grade (ASA 1 = 22.5% vs. 36.1%, p=0.006), and higher rate of hydronephrosis (34.6% vs. 19.5%, p=0.001). However, there were no significant differences in other patient characteristics, such as body mass index, sex, smoking history, preoperative glomerular filtration rate, or pre-existing comorbidities (diabetes, hypertension) (Table 1).

Perioperative and pathological outcomes

Among the 495 patients who underwent robotic-assisted radical cystectomy (RCx), there was no significant difference in the mean operation time (424 vs. 440 min, p=0.236). Similarly, no significant difference was found in estimated blood loss (527 vs. 522 cc, p=0.913). However, the ALI group had a relatively higher rate of transfusion (18.1%

vs. 16.0%, p = 0.444) and fewer complications (57.7% vs. 61.7%, p = 0.657), but there was no significance (Table 1).

The final pathologic outcomes included significantly higher T stages, such as T3 and T4, and significantly lower T stages, such as Ta to T2, in the ALI group (p<0.001). Similarly, higher tumor grades (74.6% vs. 50.6%, p<0.001) and higher rates of LN invasion (48.1% vs. 10.4%, p<0.001), were observed in the ALI group. Perineural invasion (37.6% vs. 8.9%, p<0.001), squamous metaplasia (11.6% vs. 6.6%, p=0.010), and glandular metaplasia (7.7% vs. 2.3%, p=0.001) were frequently observed in patients with ALI. However, the CIS was significantly higher in the non-ALI group (0.6% vs. 17.0%, p<0.001). No significant difference was found in the percentage of positive surgical margins between the two groups (4.4% vs. 2.7%, p=0.185).

Cancer-specific survival (CSS), overall survival (OS), and recurrence-free survival (RFS) outcomes

Total disease recurrence occurred in 153 (30.9%) patients, and 70 (14.1%) had died at the time of final follow-up (except for the following loss). Recurrence was significantly higher in the ALI group (38.5% vs. 26.5%, p<0.001)

The most frequent recurrence site was the LN with 47 (29.9%) patients, followed by lungs (23.6%), bone (17.2%), and the liver and neobladder/conduit (12.7%). Other sites of recurrence included the ureter (4.5%) and urethra (3.2%) in all patients. There was a single incidence of

kidney, ureter, and urethral recurrence in the ALI group. LNs were the most frequent recurrence site in the non-ALI group with 29 (34.1%) patients, but in the ALI group, the lungs was the most frequent recurrence site (20 patients, 27.8%). However, there was no significant difference in recurrence sites between the two groups, except for liver recurrence (p=0.017) (Table 2).

Of all the 70 (14.1%) mortality cases, cancer-specific death was reported in 39 (7.9%) patients. ALI was significantly associated with low RFS, CSS, and OS (p<0.001, p=0.012, and p=0.01, respectively).

The 5-year and 10-year OS were higher in ALI patients; the 5-year and 10-year CSS and RFS showed similar results. The percentages are shown in Fig. 1. The mean OS time was 95.7 min in ALI vs. 109.3 min in non-ALI; CSS time was 108.7 min in ALI vs. 120.3 min in non-ALI; RFS time was 65.9 min in ALI vs. 89.1 min in non-ALI. (Fig. 1)

Multivariate and Univariate Cox proportional hazards models to predict bladder cancer recurrence and survival among all 495 patients in the study are shown in Table 3, with all variables calculated in the analysis. In univariate analysis, the tumor stage (>T2), ALI, and LN metastasis were all associated with bladder cancer-specific death. Multivariate analysis after adjusting for the significant variants showed that tumor stage (>T2) and ALI were independent predictors of CSS (hazard ratio [HR]=1.632, 95% confidence interval [CI]: 1.035–2.571, p=0.035; HR=2.396, 95% CI: 1.256–4.571, p=0.008); conversely, LN metastasis was not. (p=0.209). (Table 3-1)

In RFS, Tumor stage (>T2), tumor grade (High grade), ALI, LN metastasis, and positive surgical margins were associated with univariate analysis. However, after adjusting for variants on multivariate analysis, tumor stage >T2, ALI, LN metastasis, and positive surgical margin were independent predictors of RFS. Tumor grade (High grade) was not a significant predictor. (Table 3-2)

2.3. Discussion

Identifying the prognostic factors associated with the survival and recurrence of bladder cancer is crucial for selecting the treatment choice. Several guidelines include pathological stage, LN metastases, and tumor size as prognostic factors for survival and recurrence. However, the prognostic value of ALI for RCx in patients with bladder cancer remains controversial. Some studies have shown that this pathological property is associated with worse survival outcomes [10-14], while others have not [8, 15-18]. Some subgroup analyses showed that ALI and lower RFS were not significantly correlated, especially in Asian populations [19]. Canter et al. demonstrated that ALI was significant only in pT3 patients using univariate analysis of OS, CSS, and RFS [20]. In multivariate analysis, ALI was also a significant predictor of worse overall and disease-specific survival ($p<0.01$ and $p=0.007$, respectively), but RFS was not. ($p=0.1$). According to a multi-institutional retrospective study by Lotan et al., ALI was significant for predicting survival and recurrence, specifically in LN-negative patients [21]. They also reported the prevalence of ALI in each

pathological T stage and N stage as 9% in pT1 and 78% in pT4. Our study also showed a similar percentage (7.8% in pT1, 72.7% in pT4) of ALI prevalence. In the N stage, 72% of LN+ had ALI, while only 26% of LN− had ALI. This result was similar to our study, which showed that 76% of LN + patients were ALI positive.

To the authors' knowledge, this is the largest study in the nation to date retrospectively analyzed a multi−institutional database of patients who underwent RCx to evaluate the effect of ALI on tumor survival and recurrence. ALI was significantly associated with poor OS, CSS, and RFS. The 5−year OS was 82.7% and 75.7% in non−ALI and ALI patients, respectively. Similarly, the 10−year OS was 65.0% and 58.9% in non−ALI and ALI patients, respectively. This is similar to other studies that reported lower 5−year or 10−year OS or CSS in patients with ALI. [8, 14]. Also, in line with previous reports [19, 21], ALI was pathologically present in 36% of specimens.

In addition, a multivariate analysis was performed to determine whether ALI could be an independent prognostic factor for recurrence and survival. In our analysis, ALI was an independent predictor for RFS and CSS in univariate analysis ($p=0.025$ and $p=0.008$, respectively). Other factors, such as tumor stage and LN metastasis, were also related to RFS and CSS, and tumor grade and positive surgical margin were related only to RFS in univariate analysis. In the multivariate analysis, higher T stage, LN metastasis, ALI, and positive surgical margin were significant factors for recurrence and CSS; only higher T stage and ALI were significant.

Previous studies, such as Bassi et al., reported that tumor stage and LN metastasis (not ALI) were valuable factors for survival through multivariate analysis [22]. In contrast, Canter et al. demonstrated that ALI patients showed decreased OS, CSS, and RFS in univariate analysis ($p<0.001$); however, in multivariate analysis, only OS and CSS were significant. ($p<0.01$, and $p=0.007$, respectively) [20]. Similarly, the independence of factors has been different with analysis type and survival or recurrence in several studies.

In our study, total patients tended to recur frequently in the LNs, followed by the lungs, neobladder/conduit, bones, and liver. This recurrence or progression pattern was previously shown by Elsayed et al. [23], in which metastasis occurred most frequently in LNs (5%) and lungs (6%). ALI-negative patients most frequently have recurrences in the LNs (34.1%) followed by the lung (20%). In contrast, ALI patients tended to have frequent recurrences in the lung (27.8%) rather than the LNs (25%). In addition to lymphatic infiltration, ALI is also related to hematogenous tumor dissemination. As hematogenous metastasis of the lung occurs frequently, our findings might indicate that ALI patients are more inclined to hematogenous spread than ALI-negative patients. However, owing to the limited number of studies on the relationship between progression or recurrence site and ALI, further studies are needed to analyze the relevance of ALI and local/distal recurrence patterns.

As several previous studies have been performed for other urological cancers, such as penile and prostate cancers, the relationship between ALI

in LN + patients and their worse prognostic outcome has been established [5]. ALI is theoretically related to lymphatic and vascular systems; thus, this pathological property can be strongly related to cancer cell spread [24]. Based on this characteristic of ALI as an important prognostic factor, TNM staging of some cancers includes ALI. This may help in delicate cancer staging and physicians' decision-making. There has also been some argument to include ALI with bladder cancer TNM staging, based on a study that showed ALI's prognostic value for worse RFS and OS in RCx patients (pooled HR of 1.57 and 1.59, respectively) [25,26]. However, due to the difficulty of assessing ALI at a morphological level and rarely used immunohistochemical markers that enable differentiation of lymphatic and vascular invasion at the pathological level, inclusion into TNM is not yet sufficient. [27 28].

This study has several limitations. First, it was a retrospective study; there was a risk of inherent bias. As this was a multicenter study, pathological reports at each center for ALI may be different, or the criteria for ALI may have changed during the 12-year follow-up. It is important to suggest absolute morphological criteria to define standardized ALI as vascular invasion, lymphatic invasion, or a combination of these.

Our study also did not assess the extent of pelvic LN dissection (PLND), which may generate bias; however, previous reports have shown no difference in RFS, CSS, or OS between extended and limited PLND [29]. However, these results remain controversial. This limitation of bias may have influenced our results regarding the relationship between CSS and LN

metastasis. Regarding the lowest nodal yield for determining surgical quality, as 10, 101 of 440 cases were under 10 node dissection. These results demonstrate that inappropriate PLND extent and deficiency of nodal yield may influence the results as a false-negative incurring bias. Additional information is required to define the range of PLND.

Finally, as therapeutic options have changed rapidly since the 2000s, the long-term follow-up in our study may not be accurate. Concerning these limitations, future large-scale randomized prospective trials with stringent criteria can determine the effect of ALI on patient prognosis.

Chapter 3. Conclusion

The presence of ALI in patients with bladder cancer who underwent RCx resulted in significantly worse survival and recurrence outcomes. In addition, along with a high T stage, ALI was an independent predictor of CSS and RFS. Future prospective studies should be conducted to validate our results.

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Abstract in Korean

배경

방광 요로상피암종에 대해 근치적 방광절제술 시행 환자에서의 다양한 예후인자들이 제시되고 있습니다. 그 중 본 연구의 목적은 방광 요로상피암종에 대해 근치적 방광절제를 행한 환자들에서의 혈관 림프관 침윤의 예후적 영향 분석이 목적입니다.

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방법

2007년부터 2019년까지 다기관에서 근치적 방광절제를 시행한 요로상피암종 환자 495명이 후향적 데이터 분석되었습니다. 혈관림프관 침윤의 여부에 따라 환자는 두 그룹으로 분류되었습니다. 혈관림프관 침윤의 전체 생존율, 암 특이적 생존율 및 무재발 생존율에 미치는 예후적 관계는 카를란-마이어 방법 및 콕스 회귀 위험 모델를 통해 분석하였습니다.

결과

이 연구에서 495명의 환자의 평균 연령은 65세였으며, 중위값 및 평균 추적 기간은 각각 23.3개월과 37.1개월이었습니다. 혈관림프절 침윤은 182명의 환자(36.8%)에게 있었습니다. 혈관림프절 침윤은 암 특이적 생존율 및 전체 생존율 뿐만 아니라 상대적으로 나쁜 무재발 생존율과 유의하게 연관되었습니다. (각각 $p<0.001$, $p=0.012$, $p=0.01$). 다변량 분석에 대한 유의미한 변수들을 조정한 결과, 종양 단계(T2 이상)과 혈관림프절 침윤은 암 특이적 생존율에 대한 독립적인 예측변수였으며 반면 림프절 전이는 그렇지 않았습니다. 무재발 생존율에 대한 변수들을 조정한 후 다변량 분석 시행 결과 T2 이상의 종양 단계, 혈관림프절 침윤, 림프절 전이 및 양성 수술절제면 등은 무재발 생존율에 대한 독립적인 예측 변수였습니다. 반면 종양 등급(2등급 초과)는 유의한 예측 변수가 아니였습니다.

결론

근치적 방광절제술을 시행한 방광 요로상피암종 환자들에게 혈관림프절 침윤의 존재는 암 특이적 생존율 및 무재발 생존율 모두에 영향을 미치는 독립적인 예측 변수였습니다.

주요어: 요로상피암, 방광, 근치적 방광절제술, 혈관림프절 침윤, 생존율, 무재발생존율

학번: 2020-25559

Table 1. Baseline characteristics and perioperative outcomes among 496 patients who underwent radical cystectomy according to angiolymphatic invasion

		Angiolymphatic invasion		
	All (n=495)	Yes (n=182)	No (n=313)	P value
Mean age (years) ± SD	65.5 ± 10.4	67.3 ± 10.8	64.6 ± 10.1	0.006*
BMI (kg/m^2) ± SD	24.1 ± 3.1	23.8 ± 3.4	24.3 ± 2.9	0.205
Sex (%)				0.558
Male	418 (84.4)	148 (81.3)	271 (86.6)	
Female	77 (15.6)	34 (18.7)	42 (13.4)	
Smoking (%)				0.913
Never	259 (52.3)	91 (50.0)	168 (53.7)	
Former	176 (35.6)	65 (35.7)	111 (35.5)	
Current	60 (12.1)	26 (14.2)	34 (10.9)	
ASA (%)				0.006*
1	154 (31.1)	41 (22.5)	113 (36.1)	
2	306 (61.8)	120 (65.9)	186 (59.4)	

3	35 (7.1)	21 (11.5)	14 (4.5)	
Preoperative GFR	75.54	72.77	77.11	0.046
Hydronephrosis (%)				0.001*
No	373 (75.4)	119 (65.4)	252 (80.5)	
Yes	122 (24.6)	63 (34.6)	61 (19.5)	
DM (%)	113 (22.8)	47 (25.8)	66 (21.1)	0.160
HTN (%)	211 (42.6)	84 (46.2)	127 (40.6)	0.130
Perioperative outcomes	All (n=495)	Yes (n=182)	No (n=313)	
Operation time (min)	434	424	440	0.236
Estimated blood loss (ml)	524	527	522	0.913
Transfusion rate (%)	83 (16.8)	33 (18.1)	50 (16.0)	0.444
Complications (%)	298 (60.2)	105 (57.7)	193 (61.7)	0.657
≥ Grade 3 complications	104 (21.0)	32 (17.6)	72 (23.0)	0.210

SD, Standard Deviation; BMI, Body Mass Index; GFR, glomerular filtration rate; DM, Diabetes Mellitus; HTN, hypertension

*p values <0.05

Table 2. Pathological and oncological outcomes according to presence of angiolymphatic invasion among patients who underwent RCX

		Angiolymphatic invasion		
	All (n=440)	Yes (n=181)	No (n=259)	All
Pathological outcomes				
T stage (%)				<0.001*
Ta	10(2.3)	0(0)	10(3.9)	
T1	102 (23.2)	8 (4.4)	94 (36.3)	
T2	128 (29.1)	40 (22.1)	88 (34.0)	
T3	156 (35.5)	101 (55.8)	55 (21.2)	
T4	44 (10.0)	32 (17.7)	12 (4.6)	
CIS	45 (10.2)	1 (0.6)	44 (17.0)	<0.001*
Lymph node invasion	114 (25.9)	87 (48.1)	27 (10.4)	<0.001*
Grade (%)				<0.001*
Low	121 (27.5)	20 (11.0)	101 (38.9)	
High	266 (60.5)	135 (74.6)	131 (50.6)	

Positive surgical Margin (%)	15 (3.4)	8 (4.4)	7 (2.7)	0.185
Perineural invasion (%)	91 (20.7)	68 (37.6)	23 (8.9)	<0.001*
Squamous metaplasia (%)	38 (8.6)	21 (11.6)	17 (6.6)	0.010*
Glandular metaplasia (%)	20 (4.5)	14 (7.7)	6(2.3)	0.001*
	Angiolymphatic invasion			
Oncological outcomes	All (n=495)	Yes (n=182)	No (n=313)	
Recurrence (%)	153 (30.9)	70 (38.5)	83 (26.5)	<0.001*
Recurrence site (%)				
Neobladder/Conduit	20 (12.7)	6 (8.3)	14 (16.5)	0.158
Ureter	7 (4.5)	1 (1.4)	6 (7.1)	0.098
Urethra	5 (3.2)	1 (1.4)	4 (4.7)	0.260
Lymph node	47 (29.9)	18 (25.0)	29 (34.1)	0.293
Kidney	1 (0.6)	1 (1.4)	0 (0)	0.263
Lung	37 (23.6)	20 (27.8)	17 (20.0)	0.181
Bone	27 (17.2)	14 (19.4)	13 (15.3)	0.427

Liver	20 (12.7)	4 (5.6)	16 (18.8)	0.017*
Other	63 (40.1)	30 (41.7)	33 (38.8)	0.524
Cancer specific mortality (%)	39 (7.9)	19 (10.4)	20 (6.4)	0.012
Overall mortality (%)	70 (14.1)	31 (17.0)	39 (12.5)	0.010

SD, Standard Deviation

Table 3-1. Uni-and Multi-variate Cox proportional hazard analysis among patients who underwent RCX for cancer specific survival

	Univariate analysis			Multi-variate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.026	0.993-1.060	0.121			
Sex (female vs male)	0.899	0.376-2.149	0.811			
BMI	0.907	0.817-1.007	0.067			
Tumor stage (≥T2 or not)	2.398	1.099-5.232	0.028*	1.632	1.035-2.571	0.035*
Tumor grade (High / Low)	1.652	0.638-4.276	0.301			
CIS +	0.962	0.340-2.720	0.942			
Angiolymphatic invasion	2.253	1.191-4.260	0.012*	2.396	1.256-4.571	0.008*
LN +	2.414	1.238-4.703	0.010*	1.647	0.757-3.583	0.209
Positive surgical margin	1.530	0.208-11.241	0.676			
Preoperative GFR	0.997	0.983-1.011	0.639			
History of Smoking	1.702	0.899-3.223	0.103			

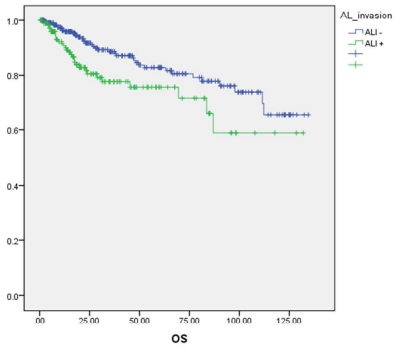
BMI, Body Mass Index; GFR, glomerular filtration rate; DM, Diabetes Mellitus; HTN, hypertension; CI, confidence interval

Table 3-2. Uni-and Multi-variate Cox proportional hazard analysis among patients who underwent RCX for recurrence free survival

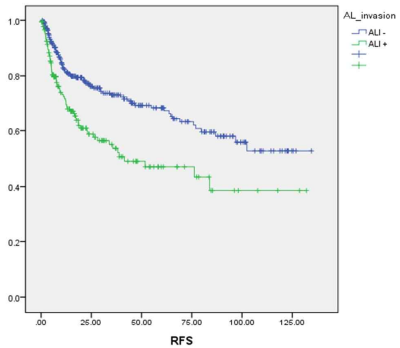
		Univariate analysis			Multi-variate analysis	
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.006	0.991-1.021	0.450			
Sex (female vs male)	0.749	0.497-1.128	0.167			
BMI	0.982	0.932-1.034	0.485			
Tumor stage (≥T2 or not)	2.713	1.817-4.049	<0.001*	1.938	1.209-3.107	0.006*
Tumor grade (High / Low)	1.700	1.030-2.805	0.038*	1.087	0.580-2.037	0.794
CIS +	0.780	0.442-1.378	0.393			
Angiolymphatic invasion	1.875	1.361-2.582	<0.001*	1.717	1.071-2.753	0.025*
LN +	2.702	1.939-3.765	<0.001*	1.837	1.254-2.692	0.002*
Positive surgical margin	2.910	1.425-5.943	0.003*	4.090	1.831-9.137	0.001*
Preoperative GFR	0.998	0.991-1.005	0.565			
History of Smoking	1.074	0.782-1.474	0.660			

BMI, Body Mass Index; GFR, glomerular filtration rate; DM, Diabetes Mellitus; HTN, hypertension; CI, confidence interval

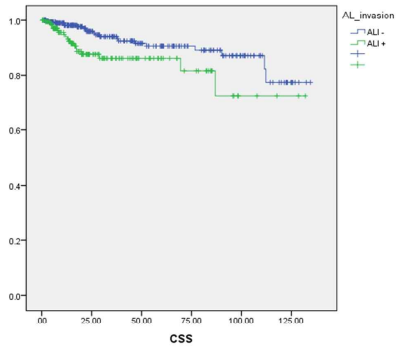
Figure 1. Oncological outcomes (Overall survival, Cancer specific survival and Recurrence free survival) according to presence of angiolymphatic invasion among patients who underwent RCx.



5yr OS : ALI (+) 75.7% vs ALI (-) 82.7%
10yr OS : ALI (+) 58.9% vs ALI (-) 65.0%



5yr RFS : ALI (+) 47.1% vs ALI (-) 68.5%
10yr RFS : ALI (+) 38.6% vs ALI (-) 52.7%



5yr CSS : ALI (+) 86.2% vs ALI (-) 90.5%
10yr CSS : ALI (+) 72.6% vs ALI (-) 76.7%