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근치적 방광 절제술 후 후기 재발에 대한 성상과 예후 비교

Late recurrence of bladder cancer following radical cystectomy: characteristics and outcomes

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서울대학교 대학원

의학과 비뇨의학 전공

유 상 현

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지도교수 구 자 현

이 논문을 의학석사 학위논문으로 제출함

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유상현의 의학석사 학위논문을 인준함

2020 년 10 월

위 원 장 곽 철 (인)

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Abstract

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Purpose: There are only a few studies on characteristics and outcomes of late recurrence of urothelial carcinoma of bladder (UCB) after radical cystectomy (RC). The objective of this study was to assess characteristics and oncological outcomes of such late recurrence that developed five years after RC.

Materials and Methods: We retrospectively reviewed 570 patients who underwent RC and bilateral regional lymphadenectomy for UCB at our institution. Comparisons of post-recurrence disease-specific survival (DSS) according to the timing of recurrence and the site of recurrence were performed using Kaplan-Meier survival curves and log-rank test. Cox regression model was fitted to assess factors for post-recurrence DSS.

Results: Disease recurrence occurred in 214 (37.5%) patients, including 20 (9.3%) who had late recurrences. Median time from RC to recurrence was 13.0 (IQR, 6.0-32.0) months. There were no significant differences in clinicopathological factors between early- and late- recurrence groups. Post-recurrence 5-year DSS was not significantly different (21.6% vs. 14.1%, p = 0.344) between early- and late- recurrence groups. However, it was worse in the non-urothelial recurrence group compared to that in the urothelial recurrence group (14.0% vs. 19.4%, p = 0.056). Older age (HR 1.03, 95% CI

1.01-1.05, p = 0.001), non-organ confined disease at RC (HR 1.73, 95% CI 1.15-2.61, p = 0.008), and lymph node invasion (HR 1.58, 95% CI 1.01-2.45, p = 0.043) were significant predictors for post-recurrence 5-year DSS. **Conclusions:** Late recurrence after radical cystectomy with lymphadenectomy is not common. However, it cannot be overlooked. Late recurrence had similar characteristics to early recurrence. Interestingly, the time to recurrence did not affect post-recurrence survival.

Keywords: urinary bladder, carcinoma, late recurrence, survival

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Introduction

After radical cystectomy (RC) with pelvic lymph node dissection for muscle-invasive and high-risk non-muscle invasive urothelial carcinoma of bladder (UCB), disease recurrence occurs in up to 50% of patients[1]. Prognosis of disease after recurrence varies[1-4] . Most disease recurrences occur within the first 2 or 3 years after RC[5-6] . Late recurrences (LRs) of disease after RC are rare. Thus, investigations on it are also rare[4]. Solsona et al.[7] have investigated LR (defined as recurrence at least 3 years after RC) and found that LR has a better survival than early recurrences (ERs). Soria et al.[8] have confirmed that LR (defined as recurrence at least 5 years after RC) has better overall survival than ER in a multicenter cohort.

However, the consensus on prognosis of LR after disease recurrence has not been established. Rink et al.[9] have found that the risk of disease-specific mortality is the highest when the time to recurrence is shorter than 1 year after RC. When the time to recurrence was longer than 1 year from RC, the risk of disease-specific mortality continued to fall but only slightly as time from RC to recurrence increased. As such, the natural history of disease recurrence after

RC and predictors for disease-specific mortality were assessed[9]. However, there are only a few studies on factors and outcomes on LR of UCB after RC[7-10] . The objective of the present study was to assess characteristics and oncological outcomes of LR that developed five years after RC and investigate factors associated with post-recurrence survival.

Materials and Methods

From 1995 to 2013, 652 patients underwent RC and bilateral regional lymphadenectomy for UCB at our institution. Eighty-two patients who underwent neoadjuvant treatment were excluded from the database. Thus, medical records of 570 patients were reviewed retrospectively. The present retrospective study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Hospital Clinical Research Institute (approval code: H-1901-083-1004).

RC was performed for muscle-invasive UCB or high-risk non-muscle invasive UCB refractory to transurethral resection of bladder tumor with medical therapy according to guideline recommendations[10-11]. Open or laparoscopic approach was used. The extent of lymphadenectomy varied at surgeon's discretion. Adjuvant chemotherapy is defined as Cisplatin-based combination chemotherapy combined with either methotrexate, vinblastine, and adriamycin, or gemcitabine which was given within 3 months after RC to patients with pT3–4 with or without pN+. Patients were followed up every 3 months for the first year, every 6 months for the next 4 years, and then annually thereafter. Evaluation included physical examination, blood analysis, urine

cytology, and imaging of the abdomen/pelvis/chest. Bone scan was also performed for patient suspected of metastasis. Disease recurrence was confirmed by imaging or pathologic findings.

Clinicopathological data included age, gender, operative approach, urinary diversion type, pathological tumor stage, tumor grade, lymph node involvement, surgical margin status, histologic variants, lymphovascular invasion, receipt of adjuvant therapy, and recurrence time/location. All surgical specimens were analyzed by uropathologists. Pathologic tumor staging was assessed according to the 2010 American Joint Committee on Cancer/UICC TNM classification, 7th edition[12]. Tumor grading was assessed according to the World Health Organization 2004 classification[13]. LR was defined as disease recurrence occurring 5 or more years after RC, whereas ER was defined as disease recurrence occurring. Recurrence location was categorized as remnant urothelium versus nonurothelial site. The time to recurrence was defined as the duration from the date of RC to the date of disease recurrence. The cause of death was identified from medical record or death certificate.

To compare patient groups, Chi-square tests were used for categorical variables while Mann-Whitney U were used for continuous variables. The Kaplan-Meier method was used to assess post-recurrence disease-specific survival (DSS) as the duration from disease recurrence to any-cause death.

Comparison based on timing and location of disease recurrence was performed using log-rank test. Predictors associated with LR were evaluated with a logistic regression model. Variables in the multivariate model included age, gender, organ-confinement, histologic variants, surgical margin status, lymphovascular invasion, nodal stage, and receipt of adjuvant therapy. Cox regression model was built to assess predictors associated with DSS. All statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). All tests were two-sided and p values of less than 0.05 were considered as statistically significant.

Results

Of 570 patients, 214 (37.5%) developed disease recurrence, 295 (51.8%) died, and 184 (32.3%) died of UCB. Clinical characteristics and pathological features are showed in Table 1. Among 214 recurred patients, 20 (9.3%) were in the LR group. Median time from RC to recurrence was 13.0 (interquartile range (IQR), 6.0-32.0) months. In the ER group, median time from RC to recurrence was 11.0 [IQR, 6.0-24.3] months. In the LR group, median time from RC to recurrence was 85.0 (IQR, 72.5-124.5) months. The histogram distribution of ER and LR is described in Figure 1. Twenty-three patients underwent laparoscopic surgery while other patients underwent open surgery. Locally advanced tumor stage (pT3/4) and positive lymph node were observed in 198 (34.7%) and 85 (14.9%) patients, respectively. Positive soft tissue surgical margin was observed in 12 (5.6%) patients. Adjuvant chemotherapy was performed in 135 (23.7%) patients. None of these factors showed significant differences between ER and LR groups.

Among 214 patients who had disease recurrence, 86 (40.2%) had multiple recurrences (Table 2). Distribution of the site of recurrence was not significantly different ($p = 0.106$) between ER and LR groups. The most

common non-urothelial sites were abdominopelvis and lymph nodes in both groups.

Predictive factors of LR were also investigated. However, multivariable logistic regression model showed that no factors were statistically significant. Post-recurrence 5-year DSS was better in the LR group than that in the ER group (21.6% vs. 14.1%, Figure 2). However, the difference between the two was not statistically significant (p=0.344). Five (25%) patients in the LR group experienced recurrence after 10 years from RC and the latest recurrence occurred 25.5 years after RC. Post-recurrence 5-year DSS was associated with the location of recurrence. It was worse in the non-urothelial recurrence group compared with that in the urothelial recurrence group (14.0% vs. 19.4%). This difference had borderline significance (p=0.056). When analyzed for only muscle-invasive UCB, ER (vs LR; 9.9% vs 33.3%; p=0.166) and non-urothelial recurrence site (vs urothelial site; 9.8% vs 20.2%; p=0.761) were not significantly associated with adverse post-recurrence 5-year DSS. In the setting of non-muscle-invasive UCB, non-urothelial recurrence site (vs urothelial site; 17.3% vs 31.2%; p=0.037) was significantly associated with adverse post-recurrence 5-year DSS.

Predictive factors of post-recurrence DSS were also assessed (Table 3). Multivariable Cox regression analysis showed that older age (HR: 1.03, 95%

CI: 1.01-1.05, p= 0.001), non-organ confined disease at RC (HR: 1.73, 95% CI: 1.15-2.61, p = 0.008), and pathologically nodal invasion (HR: 1.58, 95% CI: 1.01-2.45, p = 0.043) were significantly associated with an increased risk of disease-specific death. However, ER or non-urothelial recurrence did not show statistical significance. When analyzed for only the LR group, older age (HR: 1.16, 95% CI: 1.03-1.31, p= 0.014) was still significant, however, non-organ confined disease at RC (HR: 1.72, 95% CI: 0.06-51.38, p = 0.755) and pathologically nodal invasion (HR: 3.41, 95% CI: 0.03-401.20, p = 0.614) were not significant.

Discussion

We found that disease recurrence at least 5 years after RC was not common (3.5%) in our institution with postoperative long-term follow-up. In patients with disease recurrence, there was no significant difference in post-recurrence DSS between ER and LR groups. Post-recurrence DSS was affected by the location of recurrence. It was worse in the non-urothelial recurrence group than that in the urothelial recurrence group. Older age, non-organ confined disease, and pathologically nodal invasion were associated with the risk of disease-specific mortality after adjusting for clinicopathological factors having possible association with outcomes.

The overall recurrence rate in our study (37.5%) was almost consistent with that in previous studies[2,7,14]. Additionally, patients with LR accounted for 9.3% and 3.5% of total recurrence and total patients with RC, respectively. Linder et al.[10] have reported similar LR rate of 10% in 832 patients with disease recurrence. Soria et al.[8] have also shown similar LR rate of 12.2% in a multicenter study of 548 patients with disease recurrence. Solsona et al.[7] found 10.4% of patients with recurrence experienced LR. However, the definition of LR was disease recurrence after three years from RC. Only 1% experienced

relapse after 5 years from RC[7]. Such difference in LR rate among studies could be due to different characteristics of patients group. Solsona et al.[7] did not exclude patients with neoadjuvant therapy. Soria et al.[8] reported more lymph node metastasis (47.8% vs 14.9%) but less positive surgical margin (9.7% vs 5.6%) than our study. In our study, the LR rate was quite small. However, the proportion of recurrences was not negligible.

There have been several reports that patients with ER have worse prognosis compared with patients with LR[7,8,10]. Niegisch et al.[15] reported early clinical recurrence rate of both patients open RC with robotic-assisted RC. They found that early clinical recurrence was observed in 10 out of 89 patients with robotic-assisted RC (11%) and in 7 out of 59 patients with open RC (12%, $p = 0.9$). However, the association of the time to recurrence with post-recurrence survival is not based on a sufficient amount of literatures. Moreover, the time to recurrence lost its significant association with post-recurrence survival after adjusting for impacts of clinicopathologic factors in prior investigations[7,8,10]. In our study, post-recurrence 5-year DSS did not show significant differences between ER and LR groups, in contradiction with previously reported results. Considering different characteristics of patient population, a variety of studies based on large cohorts in diverse races are needed in the future.

The impact of the location of recurrence on post-recurrence survival in the present study was similar to results of previous studies[8,10] . We also found that the non-urothelial recurrence group had worse post-recurrence 5-year DSS compared to the urothelial recurrence group. However, it is hard to discern if newly detected tumor involving urothelium is a disease recurrence or a metachronous lesion. Regardless of the origin, disease recurrence has an important effect on cancer prognosis and further management.

The subgroup analysis for only muscle invasive UCB group and only nonmuscle invasive UCB group was performed, respectively. In muscle invasive UCB group, ER and Nonurothelial recurrence were not significantly associated with adverse post-recurrence 5-year DSS. However, it is an interesting finding that nonurothelial recurrence site was significantly associated with adverse postrecurrence 5-year DSS in the relatively small nonmuscle invasive group. There is a sufficient possibility for muscle invasive UCB group to show significant relationship between nonurothelial recurrence and adverse post-recurrence 5-year DSS if the number of patients is more adequately attained to achieve a clinical significance.

Mitra et al.[4] have identified higher pathologic tumor stage, lymph node metastasis, positive surgical margin, higher age, female gender, and shorter time from RC to disease recurrence as predictive factors of disease-specific

mortality among 1,545 patients with UCB recurrence after RC with bilateral lymphadenectomy from 16 international institutions. Moschini et al.[18] also have identified older age, higher pathological stage, prostatic stromal invasion with urothelial carcinoma, higher number of positive nodes as predictive factors of disease-specific mortality among 893 male patients treated with radical cystoprostatectomy for nonmetastatic bladder cancer, and prostatic stromal invasion with urothelial carcinoma confers a poor survival expectation. We also found that non-organ confined disease, lymph node invasion, and higher age were predictive factors and female gender was a borderline significant predictive factor of DSS. The rate of positive surgical margin was lower in this study compared to that in the previous study (5.6% vs. 10.9%). This could be attributed to different results of significance of the positive surgical margin. Pathological tumor stage and lymph node invasion are two most well-known predictive factors for oncological prognosis[2,16,17], similar to results of our study. However, when it comes to the LR group, only older age was associated with an increased risk of disease-specific death.

This study was limited by its retrospective and non-randomized design. Surveillance regimen after RC was not standardized. It might have impacted the detection of disease recurrence. Management for disease recurrence also varied. It might have affected survival. Moreover, surgical procedure such as

lymphadenectomy was based on surgeon's decision. Patient data such as smoking history and performance status were missing in our study. Nevertheless, this study is meaningful in that it draws conclusions that are contrary to previously reported literatures. The longer the disease survival with the development of treatment, the more important the information and evidence of LR will be. Further studies, especially with prospective multi-institutional data, are warranted to establish evidence of disease prognosis and surveillance regimen.

Conclusion

LR after RC with lymphadenectomy is not common. However, it cannot be overlooked. LR does not have different characteristics from ER. Post-recurrence DSS of LR is also similar to that of ER. Age, non-organ confined disease, and lymph node invasion still play an important role in predicting disease-specific mortality following recurrence. This study suggests the need for long-term surveillance and patient counseling.

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Table 1. Clinical characteristics and pathological features

	ER, n (%)	LR, n (%)	p value	No recurrence, n (%)
Total number	194 (34.0%)	20 (3.5%)		356 (62.5%)
Gender, male	165 (85.1%)	17 (85.0%)		305 (85.7%)
Age at RC, years, median	65.0	60.0	0.112	65.0
(IGR)	(58.0-71.0)	(50.5-72.0)		(59.0-71.8)
Operation type				
Open	193 (99.5%)	20 (100.0%)		334 (93.8%)
Laparoscopy	1 (0.5%)	0 (0.0%)		22 (6.2%)
Diversion			0.268	
Conduit	158 (81.4%)	15 (75.0%)		231 (64.9%)
Neobladder	36 (18.6%)	5 (25.0%)		125 (35.1%)
Concomittant urethrectomy	6 (3.1%)	0 (0.0%)		7 (2.0%)
No. pT			0.354	
T1 or less	48 (24.8%)	9 (45.0%)		189 (53.1%)
T2	46 (23.7%)	4 (20.0%)		76 (21.3%)
T3/4	100 (51.5%)	7 (35.0%)		91 (25.6%)
No. pN+	50 (25.8%)	2 (10.0%)	0.472	33 (9.3%)
Median no. of removed LN	8.0 (3.0-16.0)	9.0 (3.0-18.5)	0.768	12.0 (3.0-20.0)
(IQR)				
Positive surgical margin	10 (5.2%)	0 (0.0%)	0.604	2 (0.6%)
LVI	100 (51.5%)	7 (35.0%)	0.240	85 (23.9%)
Adjuvant chemotherapy	70 (36.1%)	8 (40.0%)	0.729	57 (16.0%)

ER, early recurrence; LR, late recurrence; IQR, interquartile range; LN, lymph node; LVI, lymphovascular invasion.

Table 2. Recurrence sites in patients with ER and LR

Variables	ER, n (%)	LR, n (%)	p value
No. pts	194 (90.7%)	20 (9.3%)	
Multiple recurrences	77 (39.7%)	9 (45.0%)	0.408
Site			0.106
Urothelial	31 (16.0%)	6 (30.0%)	0.106
- urethra	5 (16.1%)	1 (16.7%)	
- upper urinary tract	26 (83.9%)	5 (83.3%)	
Non-urothelial	163 (84.0%)	14 (70.0%)	
- abdominopelvic	81 (41.8%)	6 (30.0%)	
- chest	38 (19.6%)	3 (15.0%)	
- lymph node	78 (40.2%)	7 (35.0%)	
- bone	45 (23.2%)	4 (20.0%)	
- brain	3 (1.5%)	0 (0.0%)	

ER, early recurrence; LR, late recurrence

Table 3. Multivariable Cox regression analysis for predictive factors of disease-specific survival following recurrence after radical cystectomy

	HR (95% CI)	p value
Age at RC	1.03 (1.01-1.05)	0.001
Gender	1.55 (0.99-2.42)	0.058
Non-organ confined	1.73 (1.14-2.61)	0.008
Histologic variants	0.98 (0.86-1.11)	0.735
Surgical margin status	1.31 (0.60-2.84)	0.496
Lymphovascular invasion	1.19 (0.81-1.73)	0.383
pN+	1.58 (1.01-2.45)	0.043
Adjuvant chemotherapy	1.09 (0.73-1.61)	0.679
Non-urothelial recurrence	1.30 (0.81-2.08)	0.281
Late recurrence	1.21 (0.67-2.19)	0.526

RC, radical cystectomy; LR, late recurrence

Figure 1. Histogram distribution of early and late recurrences according to postoperative period.

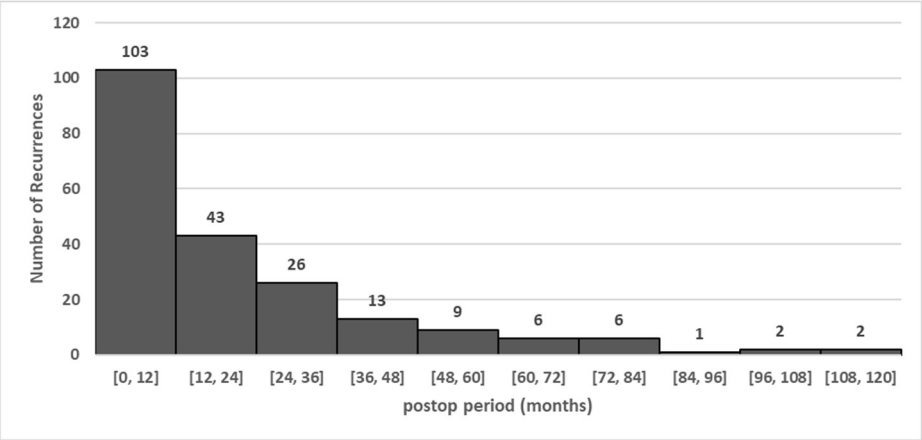
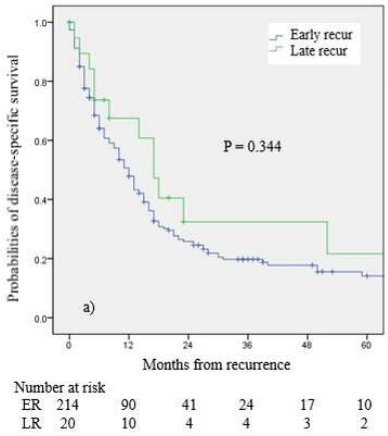
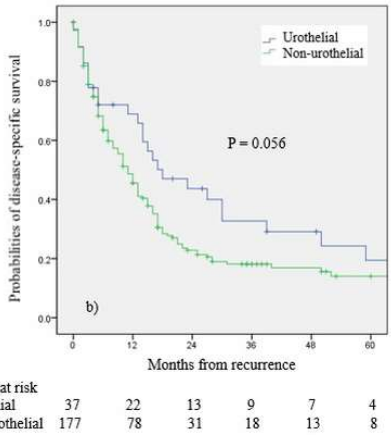


Figure 2. Kaplan-Meier survival curves for post-recurrence disease-specific survival a) according to the time of recurrence or b) according to the location of recurrence in 214 patients who had disease recurrence after radical cystectomy.



Number at risk

ER	214	90	41	24	17	10
LR	20	10	4	4	3	2



Number at risk

Urothelial	37	22	13	9	7	4
Non-urothelial	177	78	31	18	13	8

국 문 초 록

유상현
학번: 2017-27706
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서론: 방광의 요로상피암 진단 후 근치적 방광 절제술을 받은 뒤 장시간 후에 재발한 경우에 대한 연구는 적게 이루어진 편이다. 이 연구는 근치적 방광절제술을 받은 후 5 년 이상 후에 뒤늦게 재발한 후기 재발에서의 종양학적 그리고 임상적 특성을 분석하고자 하였다.

대상 및 방법:
서울대병원에서 방광의 요로상피암을 진단받아 근치적 방광 절제술 (RC) 및 림프절제술을 받은 570 명의 환자를 후향적으로 분석하였다. 재발까지 걸린 시간에 따른 질병 특이 생존율 (DSS)을 카플란-마이어 생존 곡선을 통해 비교하였고, 콕스 회귀 모형을 통해 재발 후의 질병 특이 생존율에 영향을 주는 인자들을 보정하였다.

결과: 질병의 재발은 총 214 명 (37.5%)의 환자에서 발생하였으며, 이 중 5 년 이후 재발한 환자의 수는 20 명 (9.3%)이었다. RC 후 재발까지 걸린 시간은 중간값 13.0 개월 (사분범위 6.0-32.0) 이었다.

조기 재발 (5 년 이하 재발) 군과 후기 재발 (5 년 이후 재발) 군 간의 임상병리적인 유의한 차이는 보이지 않았으며, 5 년 이내 질병 특이 생존율 역시 두 군 간의 유의한 차이를 보이지 않았다 (21.6% vs. 14.1%, p = 0.344). 다만 요로 부위 이외에 재발한 경우는 요로 부위의 재발한 경우에 비해 생존율이 유의하게 낮았다. (14.0% vs. 19.4%, p = 0.056). 고령의 나이 (위험도 1.03, 95% 신뢰구간 1.01-1.05, p = 0.001), RC 당시 장기 이외에 종양이 존재했을 경우 (위험도 1.73, 95% 신뢰구간 1.15-2.61, p=0.008), 그리고 림프절 침윤 (위험도 1.58, 95% 신뢰구간 1.01-2.45, p=0.043) 등이 재발 후의 5 년 질병 특이 생존율에서 예측에 영향을 주는 유의한 인자들이었다.

결론: 근치적 방광 절제술 후 발생하는 5 년 이후의 후기 재발은 흔하지 않았지만, 간과하지 않을 정도로 일어났다. 후기 재발은 조기 재발한 경우와 비교했을 때 비슷한 성상을 보였다. 재발까지 걸린 시간은 재발 이후의 생존율에 차이를 주지 않았다.

주요어: 방광암, 종양, 후기 재발, 생존율