Detecting asymptomatic recurrence after radical cystectomy contributes to better prognosis in patients with muscle-invasive bladder cancer

（筋層浸潤性膀胱癌における膀胱全摘術後の再発とその予後についての検討：無症候性再発の検索は良好な予後につながる）

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Abstract

Introduction: The prognostic benefit of oncological follow-up to detect asymptomatic recurrence after radical cystectomy (RC) remains unclear. We aimed to assess whether routine follow-up to detect asymptomatic recurrence after RC improves patient survival.

Methods: We retrospectively analyzed 581 RC cases for muscle invasive bladder cancer at four hospitals between May 1996 and February 2017. All patients had regular follow-up examinations with urine cytology, blood biochemical tests, and computed tomography after RC. We investigated the first site and date of tumor recurrence. Overall survival in patients with recurrence stratified by the mode of recurrence (asymptomatic group vs. symptomatic group) was estimated using the Kaplan–Meier method with the log–rank test. Cox proportional hazards regression analysis via inverse probability of treatment weighting (IPTW) was used to evaluate the impact of the mode of diagnosing recurrence on survival.

Results: Of the 581 patients, 175 experienced relapse. Among those, 12 without adequate data were excluded. Of the remaining 163 patients, 76 (47%) were asymptomatic and 87 (53%) were symptomatic at the time of diagnosis. The most common recurrence site and symptom were lymph nodes (47%) and pain

(53%), respectively. Time of overall survival after RC and from recurrence to death were significantly longer in the asymptomatic group than symptomatic group. A multivariate Cox regression analysis using IPTW showed that in the patients with symptomatic recurrence was an independent risk factor for overall survival after RC and survival from recurrence to death.

Conclusion: Routine oncological follow-up for detection of asymptomatic recurrence contributes to a better prognosis after RC.

Keywords: radical cystectomy; recurrence; asymptomatic; symptomatic; Survival

Introduction

A radical cystectomy (RC) with an extended pelvic lymph node dissection is the standard treatment for non-metastatic muscle-invasive bladder cancer (MIBC) [1, 2]. Long-term outcomes and predictors of disease relapse after RC are well documented [1–4]. Despite advances in patient selection, surgical techniques, and adjuvant/neoadjuvant therapies, disease recurrence remains substantial, which is affecting approximately 38%–49% of patients within 10 years even in high-volume institutes [1, 2, 4]. Once recurrence has occurred, the prognosis is dismal. Various surveillance regimens after RC have been proposed to date [4–7]; however, the intensity of recommended follow-up methods, frequency, and choice of imaging differ among experts. Moreover, limited evidence is available describing the benefit of routine oncological follow-up to detect asymptomatic recurrence after RC and the results are controversial [6–8]. Giannarini et al. and Boorjian et al. noted the prognostic benefit of asymptomatic tumor recurrence [7, 8]. On the other hand, Volkmer et al. [6] found no overall survival advantage for those with asymptomatic vs. symptomatic tumor recurrence. Because a prospective randomized study is not feasible, statistical methods must be used to remove the effects of

confounding factors due to non-random treatment assignment in retrospective studies. In this study, we compared the impact of mode of diagnosis (asymptomatic vs. symptomatic) at recurrence on patient survival after RC and survival after recurrence using an inverse probability of treatment weighting (IPTW) strategy.

Materials and Methods

Ethics statement

This retrospective study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the Ethics Committee of the Hirosaki University School of Medicine (authorization number: 2015–184 and 2015–258).

Patient selection

Between May 1996 and February 2017, 581 adult patients underwent RC and urinary diversion in the Hirosaki University Hospital, the Aomori Rosai Hospital, the Mutsu General Hospital, and the Aomori Prefectural Central Hospital. We stratified the patients into two groups based on diagnosed mode of recurrence between the patients with asymptomatic recurrence

(asymptomatic group) or with symptomatic recurrence (symptomatic group).

Evaluation of variables

The analyzed variables were age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), history of cardiovascular disease (CVD), hypertension (HTN), diabetes mellitus (DM), clinical and pathological stage, blood loss, operative duration, postoperative complications, renal function, neoadjuvant therapy, urinary diversion, and diagnosed mode of recurrence (asymptomatic vs. symptomatic). Postoperative complications within 30 days were evaluated by the Clavien–Dindo classification [9]. Renal function was evaluated using the estimated glomerular filtration rate (eGFR). The following equation was used to estimate eGFR for Japanese patients; it is a modification of the abbreviated Modification of Diet in Renal Disease Study formula: eGFR mL/min/1.73 m2 = 194 × sCr−1.094 × age−0.287 (× 0.739, if female) [10]. Tumor stage and grade were assigned according to the 2009 TNM classification of the Union of International Cancer Control [11].

Neoadjuvant chemotherapy (NAC)

Since September 2004, we have treated MIBC patients with two or three

courses of NAC. NAC comprises a platinum-based combination regimen using either gemcitabine plus cisplatin (GCis), gemcitabine plus carboplatin (GCb), or methotrexate, vinblastine, adriamycin, and cisplatin (MVAC). Regimens were selected based on guidelines regarding eligibility for the proper use of cisplatin [12] and the patient's overall status.

Surgical procedure

All patients underwent RC, urinary diversion, and a standard pelvic lymph node dissection (PLND) procedure, which included the removal of the obturator, external iliac, hypogastric, and common iliac lymph node chains (there were no paraaortic or paracaval dissections). All RCs were performed by high-volume surgeons using the same basic technique [13]. An orthotopic ileal neobladder construction, ileal conduit diversion, or cutaneous ureterostomy were performed according to previously reported methods [14–17].

Follow-up protocol for surveillance

Oncological follow-up after RC was performed following the National Comprehensive Cancer Network guideline, the European Association of

Urology guidelines, and previously reported pathology protocols [4, 18]. Our follow-up protocol consisted of complete blood counts, serum chemistry screenings, ultrasound imaging of abdomen, computed tomography (CT) and chest radiography every 3–6 months for at least five years. Based on the pathological outcomes after RC, patients were divided into two groups: high-risk (pT3 or higher, positive in lymphovascular invasion [LVI] and with pathological lymph node involvement [pN+], or non-urothelial carcinoma components) or normal-risk. Our standard protocol for high-risk patients generally recommends CT follow-up every three months for the first two years after surgery, semi-annually for the next three years, and annually thereafter in patients without any evidence of disease recurrence. A CT protocol for normal-risk patients generally recommends follow-up every six months for the first five years and annually thereafter in patients without any evidence of disease recurrence (Fig. 1). Additional examinations such as a bone scan or brain imaging were performed when clinically indicated. Disease recurrence was classified as in the lymph nodes, visceral organs, local pelvis, bone, urothelium (urethra plus upper urinary tract), or brain. Non-invasive, superficial urothelial recurrences were excluded from the present study. Lymph node recurrence included metastasis to local pelvic, paraaortic,

thoracic, mediastinal, and paratracheal lymph nodes. Visceral organ recurrence included metastasis to the liver, lungs, adrenal glands, and other intra-abdominal organs. The first recurrence after RC was recorded. We also analyzed whether the first tumor recurrence was detected when the patient was in an asymptomatic state based on scheduled routine follow-up imaging or whether it was diagnosed by symptom-driven examinations. The vital status was identified from death certificates or physician's correspondence. For patients followed elsewhere, the cystectomy registry at our institution monitored outcomes annually by correspondence with the patient and treating physician.

Adjuvant and salvage therapy

Adjuvant chemotherapy and/or radiotherapy were not administered routinely. Salvage therapy was indicated when a visible tumor was identified. Systemic chemotherapy after recurrence consisted of a platinum-based combination regimen, including GCis, GCb, gemcitabine, carboplatin and docetaxel (GCD), docetaxel, ifosfamide and nedaplatin (DIN) or MVAC. Regimens were selected based on residual renal function and a patient's overall status.

Statistical analysis

Statistical analyses of data were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA), GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA), and R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using Fisher's exact test or a chi-squared test. Differences between the groups were statistically compared using a Student's t-test for normally distributed data or the Mann–Whitney U test for data that were not normally distributed. All tests were two-sided and a P value <0.05 was considered statistically significant. Overall survivals between the asymptomatic and symptomatic groups were estimated as time from RC to date of death, or time from first recurrence to date of death from any cause using the Kaplan–Meier method and compared with the log rank test. Cox proportional hazards regression models were used to evaluate the impact of the mode of diagnosing recurrence on survival, and hazard ratios (HRs) with 95% confidence intervals were calculated. Due to limited sample numbers, we performed a multivariate Cox proportional hazards regression analysis using IPTW, which reweights both affected and unaffected groups to emulate a propensity score-matched population [19], to evaluate the impact of symptom on survival (overall survival since the radical cystectomy

and since the recurrence diagnosis). Variables included in the IPTW analysis were age, sex, ECOG PS, HTN, CVD, DM, NAC, urinary diversion, pT3 or 4, LVI, pN, number of metastatic sites, and visceral metastasis.

Results

Baseline characteristics

Of the 581 patients, 175 patients (30%) were diagnosed with disease recurrence with a median follow-up duration of 17.7 months (interquartile range: 8.4–40.0). Among those, 12 patients without adequate data were excluded from the present study. Of 163 patients, 76 (47%) were detected during regular follow-up examinations in an asymptomatic state (asymptomatic group), while in 87 (53%) recurrence was detected by symptom-driven examinations (symptomatic group) (Fig. 2A). Patients' clinicopathological characteristics and distributions are presented in Table 1. A total of 68 patients (42%) underwent RC and orthotopic ileal neobladder construction. Eighty-six patients (53%) received neoadjuvant chemotherapy, which was basically composed of a platinum-based combination regimen including GCis or GCb. Except for chemotherapy frequency after recurrence, no significant differences in patient background or tumor variables were noted

between the groups.

Characteristics of recurrence site

Recurrence sites were significantly different between the groups. The lymph node (66%) was significantly frequent in the asymptomatic group, whereas the local pelvis (45%) and bone (25%) were significantly frequent in the symptomatic group (Fig.2B). The most common symptom reported among the 87 patients who experienced symptomatic recurrence was pain in 46 (53%) followed by gastrointestinal symptoms in 18 (21%; Fig. 2C).

Oncological outcomes

The number of deaths due to cancer and deaths of any cause were 133 and 143, respectively. The recurrence-free survival after RC was not significantly different between the asymptomatic and the symptomatic group (P = 0.1437; Fig. 3A). Cancer-specific survival after RC was significantly longer in patients in the asymptomatic group compared with the symptomatic group (median 31.7 vs. 13.0 months, respectively, P = 0.0001; Fig. 3B). Similarly, overall survival after RC was significantly longer in patients in the asymptomatic group than in the symptomatic group (median 31.7 vs. 11.9 months,

respectively, P < 0.0001; Fig. 3C). In addition, overall survival after recurrence was significantly longer in patients in the asymptomatic group than in the symptomatic group (median 12.7 vs. 4.5 months, respectively, P < 0.0001; Fig. 3D). To assess the trend of recurrence, we compared the number of patients with recurrence between the asymptomatic and symptomatic groups. Overall, trends of tumor recurrence showed a similar pattern between these groups. However, the number of tumor recurrences within the first 12 months was significantly higher in the symptomatic group (n = 64, 74%) than in the asymptomatic group (n = 40, 53%) (P = 0.006; Fig 4A). The number of tumor recurrences was significantly higher in high-risk patients (n = 84, 69%) than in normal-risk patients (n = 20, 49%) within 12 months (P = 0.021; Fig. 4B). Normal-risk patients experienced a significantly higher incidence of symptomatic recurrence (n = 15, 63%) within 12 months after RCs than of asymptomatic recurrence (n = 5, 29%) (P = 0.037; Fig. 4C). High-risk patients experienced a significantly higher incidence of symptomatic recurrence (n = 49, 78%) within 12 months after RCs than of asymptomatic recurrence (n = 35, 59%) (P = 0.028; Fig. 4D).

Uni- and multivariate Cox proportional hazards regression analyses

Univariate Cox regression analyses showed that age, LVI, chemotherapy cycles after recurrence diagnosis, and symptomatic recurrence were significant risk factors for overall survival after RC (Table 2, upper part). Similarly, age, chemotherapy cycles after recurrence diagnosis, and symptomatic recurrence were significant risk factors for overall survival after recurrence diagnosis (Table 2, upper part). A multivariate Cox regression analysis using IPTW revealed that symptomatic recurrence was an independent risk factor for overall survival after RC ($P < 0.001$, HR: 1.94, 95% CI: 1.38–2.72) and after recurrence diagnosis ($P < 0.001$, HR: 2.18, 95% CI: 1.55–3.08) (Table 2, lower column).

Discussion

In the present study, our results showed that 53% of patients presented with symptoms at recurrence after RC. We found that with symptomatic recurrence, patients had a significantly worse prognosis than with asymptomatic recurrence. Patients with an asymptomatic recurrence frequently experienced lymph node recurrence, whereas local pelvic recurrence was more frequent in symptomatic patients. The multivariate

analysis using IPTW revealed that the presence of symptoms at recurrence was a significant predictor of poor overall survival after RC (HR: 1.94) and after recurrence diagnosis (HR: 2.18). However, it was difficult to eliminate the influence of lead-time biases. The definition of asymptomatic is something that is difficult to translate into "early" diagnosis. We could not exclude the possibility of the presence of symptoms that depend on a late diagnosis. To address this difficulty, we compared recurrence-free survival between the groups and found that they were not significantly different (P = 0.1437). In addition, the number of chemotherapy cycles after diagnosis of recurrence was significantly higher in the asymptomatic group (Table 1). It was also an independent predictor in the univariate analysis (Table 2). These results suggested that the detection of asymptomatic recurrence has potential to secure sufficient time for a multimodal therapy after relapse. The rationale for these follow-up examinations is to detect tumor recurrence at an early stage that can be cured or at least treated with a better prognosis. However, it continues to be debated whether a routine oncological follow-up to detect asymptomatic recurrence after RC improves patient survival [6–8]. The impact of regular surveillance on the long-term prognosis have been investigated in several malignancies and most studies found no survival benefit for regular

follow-up in colorectal cancer [20, 21], breast cancer [22], endometrial cancer [23], or lung cancer [24]. In bladder cancer, only three studies have investigated the benefit of routine oncological follow-up; their conclusions were controversial. In a series of 1,270 patients who underwent RC, Volkmer et al. found no overall survival advantage in those with asymptomatic vs. symptomatic tumor recurrence [6]. On the other hand, Giannarini et al. noted that of 479 patients who underwent RC with orthotopic ileal neobladder reconstruction, those diagnosed with asymptomatic recurrence during routine follow-up had significantly improved cancer-specific and overall survival compared to patients diagnosed after symptomatic relapse [7]. Boorjian et al. reported the prognostic benefit in detecting asymptomatic recurrence in a series of 1,599 patients who underwent RC [8]. However, the definition of survival benefit was different among the studies; RC to death [8] or recurrence to death [6]. Addressing both, our finding supports the benefit of routine oncological follow-up after RC in both “survival after RC” and “survival after recurrence”, in agreement with previous reports of Giannarini et al. and Boorjian et al. [7, 8]. Yafi et al. proposed a stage-based protocol for surveillance of patients after RC [4]. Their extensive examination of recurrence patterns in a large multi-institutional project emphasizes the need

for earlier strict surveillance in patients with extravesical and node-positive disease. It is reasonable that strict surveillance of the high-risk patients is done. However, we observed a significantly higher number of symptomatic recurrences in the patients at normal risk (Fig. 4C). It suggested that further subgrouping is needed to clarify the efficacy and to limit over-investigation in the normal-risk group. Although the detection of asymptomatic recurrence contributed to better oncological outcomes after RC, there have been grave concerns that not only we detect the recurrence earlier, but just identifying the difference between rapid and slow growing diseases. Although LVI was selected as a prognostic factor, it was not different between the asymptomatic (63%) and symptomatic groups (59%). Indeed, not all patients with LVI relapsed after RC. Obvious tumor progression that is missed during routine follow-up suggests the existence of biological heterogeneity between rapid- and slow-growing tumors that could not have been detected by a conventional pathological examination. Our results show that there are clear differences in recurrence sites between symptomatic and asymptomatic recurrence. Asymptomatic recurrences were more frequently lymph-node metastases, whereas symptomatic recurrences were more frequently in the local pelvis and/or bone. For a better understanding of tumor biology, not only the mode

of diagnosis (asymptomatic vs. symptomatic) at recurrence but also biomarkers that predict the malignant potential are essential. Genome-based molecular classification is one potential biomarker [25, 26]. One of the basal MIBC types is associated with shorter disease-specific and overall survival because of its highly invasive and metastatic potential at presentation [25]. Such phenotypes are associated with an epithelial–mesenchymal transition and bladder cancer stem-cell biomarkers [27]. There is an urgent need for the development of a biology-based molecular biomarker for the classification of bladder cancer to inform clinical management. The present study had several limitations. To begin, it was a retrospective study with a small number of patients with recurrence. We could not control all variables including selection bias, the influence of lead-time biases, and other unmeasurable confounding factors. Secondly, a prospective randomized study comparing a symptom-based follow-up would be ideal to clarify the survival benefit of a routine screening protocol. However, without robust evidence that routine follow-up is ineffective, this study would be difficult to conduct due to ethical concerns. Therefore, the accumulation of evidence from well-planned retrospective studies is essential. Thirdly, our results cannot be applied to other nations because the entire Japanese population is covered by universal health

insurance (maximum copayment from 10% to 30%). Despite these limitations, our results support the idea that an effective follow-up protocol following curative surgery should detect recurrence in the early stages of the disease and that detection with asymptomatic recurrence should secure sufficient time to implement a multimodal therapy after relapse.

Conclusions

Routine oncological follow-up for the detection of asymptomatic recurrence has the potential to contribute a better prognosis after RC. Further investigation with a well-designed study is necessary to assess the survival benefit of a surveillance protocol in patients with MIBC.

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References

1. Studer UE, Burkhard FC, Schumacher M, Kessler TM, Thoeny H, Fleischmann A, et al. Twenty years experience with an ileal orthotopic low pressure bladder substitute--lessons to be learned. J Urol. 2006;176:161–6. doi:10.1016/s0022-5347(06)00573-8.

2. Hautmann RE, Abol-Enein H, Hafez K, Haro I, Mansson W, Mills RD, et al. Urinary diversion. Urology. 2007;69:17–49. doi:10.1016/j.urology.2006.05.058.

3. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19:666–75.

4. Yafi FA, Aprikian AG, Fradet Y, Chin JL, Izawa J, Rendon R, et al. Surveillance guidelines based on recurrence patterns after radical cystectomy for bladder cancer: the Canadian Bladder Cancer Network experience. BJU Int. 2012;110:1317–23. doi:10.1111/j.1464-410X.2012.11133.x.

5. Stenzl A, Cowan NC, De Santis M, Kuczyk MA, Merseburger AS, Ribal MJ, et al. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. Eur Urol. 2011;59:1009–18. doi:10.1016/j.eururo.2011.03.023.

6. Volkmer BG, Schnoeller T, Kuefer R, Gust K, Finter F, Hautmann RE. Upper urinary tract recurrence after radical cystectomy for bladder cancer--who is at risk? J Urol. 2009;182:2632–7. doi:10.1016/j.juro.2009.08.046.

7. Giannarini G, Kessler TM, Thoeny HC, Nguyen DP, Meissner C, Studer UE. Do patients benefit from routine follow-up to detect recurrences after radical cystectomy and ileal orthotopic bladder substitution? Eur Urol. 2010;58:486–94. doi:10.1016/j.eururo.2010.05.041.

8. Boorjian SA, Tollefson MK, Cheville JC, Costello BA, Thapa P, Frank I. Detection of asymptomatic recurrence during routine oncological followup after radical cystectomy is associated with improved patient survival. J Urol. 2011;186:1796–802. doi: 10.1016/j.juro.2011.07.005.

9. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg.2009;250:187–96.doi:10.1097/SLA.0b013e3181b13ca2.

10. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92. doi:10.1053/j.ajkd.2008.12.034.

11. Sobin LH, Gospodarowicz MK, Wittekind C, International Union against

Cancer., ebrary Inc. TNM classification of malignant tumours. 7th ed. Chichester, West Sussex, UK ; Hoboken, NJ: Wiley-Blackwell; 2009.

12. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol. 2011;12:211–4. doi:S1470-2045(10)70275-8 [pii] 10.1016/S1470-2045(10)70275-8.

13. Koie T, Ohyama C, Yamamoto H, Hatakeyama S, Kudoh S, Yoneyama T, et al. Minimum incision endoscopic radical cystectomy in patients with malignant tumors of the urinary bladder: clinical and oncological outcomes at a single institution. Eur J Surg Oncol. 2012;38:1101–5. doi:10.1016/j.ejso.2012.07.115.

14. Koie T, Hatakeyama S, Yoneyama T, Ishimura H, Yamato T, Ohyama C. Experience and functional outcome of modified ileal neobladder in 95 patients. Int J Urol. 2006;13:1175–9. doi:10.1111/j.1442-2042.2006.01525.x.

15. Koie T, Hatakeyama S, Yoneyama T, Hashimoto Y, Kamimura N, Ohyama C. Uterus-, fallopian tube-, ovary-, and vagina-sparing cystectomy followed by U-shaped ileal neobladder construction for female bladder cancer patients: oncological and functional outcomes. Urology. 2010;75:1499–503. doi:10.1016/j.urology.2009.08.083.

16. Bricker EM. Bladder substitution after pelvic evisceration. Surg Clin North Am. 1950;30:1511–21.

17. Toyoda Y. A new technique for catheterless cutaneous ureterostomy. J Urol. 1977;117:276–8.

18. Stewart-Merrill SB, Boorjian SA, Thompson RH, Psutka SP, Cheville JC, Thapa P, et al. Evaluation of current surveillance guidelines following radical cystectomy and proposal of a novel risk-based approach. Urol Oncol. 2015;33:339 e1-8. doi:10.1016/j.urolonc.2015.04.017.

19. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34:3661–79. doi:10.1002/sim.6607.

20. Virgo KS, Vernava AM, Longo WE, McKirgan LW, Johnson FE. Cost of patient follow-up after potentially curative colorectal cancer treatment. JAMA. 1995;273:1837–41.

21. Jeffery M, Hickey BE, Hider PN, See AM. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2016;11:CD002200. doi:10.1002/14651858.CD002200.pub3.

22. Rojas MP, Telaro E, Russo A, Moschetti I, Coe L, Fossati R, et al. Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev. 2005:CD001768. doi:10.1002/14651858.CD001768.pub2.

23. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101:520–9. doi:10.1016/j.ygyno.2006.02.011.

24. Younes RN, Gross JL, Deheinzelin D. Follow-up in lung cancer: how often and for what purpose? Chest. 1999;115:1494–9.

25. Choi W, Porten S, Kim S, Willis D, Plimack ER, Hoffman-Censits J, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell. 2014;25:152–65. doi:10.1016/j.ccr.2014.01.009.

26. McConkey DJ, Choi W, Dinney CP. Genetic subtypes of invasive bladder cancer. Curr Opin Urol. 2015;25:449–58. doi:10.1097/mou.0000000000000200.

27. Chan KS, Espinosa I, Chao M, Wong D, Ailles L, Diehn M, et al. Identification, molecular characterization, clinical prognosis, and therapeutic targeting of human bladder tumor-initiating cells. Proc Natl Acad Sci U S A. 2009;106:14016–21. doi:10.1073/pnas.0906549106.

Figure Legends

Fig. 1. Standard protocol for surveillance after radical cystectomy. Based on the pathological outcomes after radical cystectomy, patients were divided into two groups (high-risk or normal-risk) for the risk stratification. Further investigations such as bone scans were ordered when clinically indicated. High-risk: ≥pT3, positive in lymphovascular invasion (LVI+), or pathological lymph node involvement (pN+).

Fig. 2. Patient selection and characteristics of recurrence.
(A) Of 163 patients with disease recurrence, 76 (47%) were detected during regular follow-up examinations in an asymptomatic state while in 87 (53%) recurrence was detected by symptom-driven examinations. (B) Recurrence in a lymph node (66%) was significantly frequent in the asymptomatic group, whereas that in the local pelvis (45%) and bone (25%) were significantly frequent in the symptomatic group. (C) The most common symptom reported among the 87 patients who experienced symptomatic recurrence was pain in 46 (53%) followed by gastrointestinal symptoms in 18 (21%).

Fig. 3. Prognostic evaluations between asymptomatic and symptomatic recurrence.

(A) The recurrence-free survival after radical cystectomy (RC) was not significantly different between the asymptomatic and the symptomatic group ($P = 0.1437$). (B) Cancer-specific survival after RC was significantly longer in patients in the asymptomatic group compared with the symptomatic group ($P = 0.0001$). (C) Overall survival after RC was significantly longer in patients in the asymptomatic group than in the symptomatic group ($P < 0.0001$). (D) Overall survival after recurrence was significantly longer in patients in the asymptomatic group than in the symptomatic group ($P < 0.0001$).

Fig. 4. Time course from radical cystectomy to recurrence.

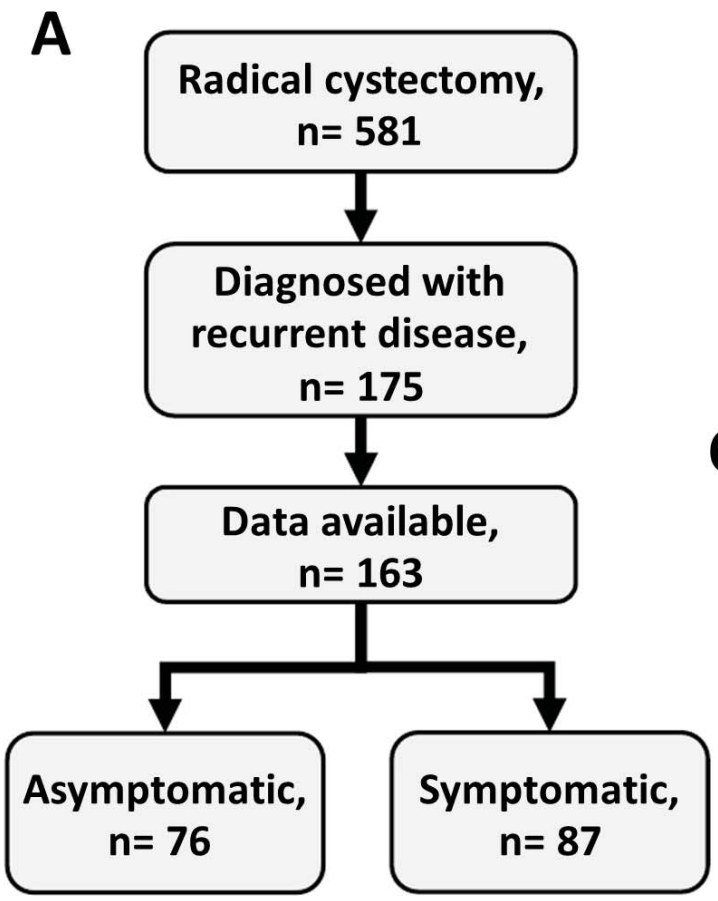
(A) The number of tumor recurrences within the first 12 months was significantly higher in the symptomatic group (n = 64, 74%) than in the asymptomatic group (n = 40, 53%) ($P = 0.006$). (B) The number of tumor recurrences within the first 12 months was significantly higher in high-risk patients (n = 84, 69%) than in normal-risk patients (n = 20, 49%) ($P = 0.021$). (C) After 12 months, patients in the normal-risk group experienced significantly more frequently symptomatic (n = 15, 63%) than asymptomatic

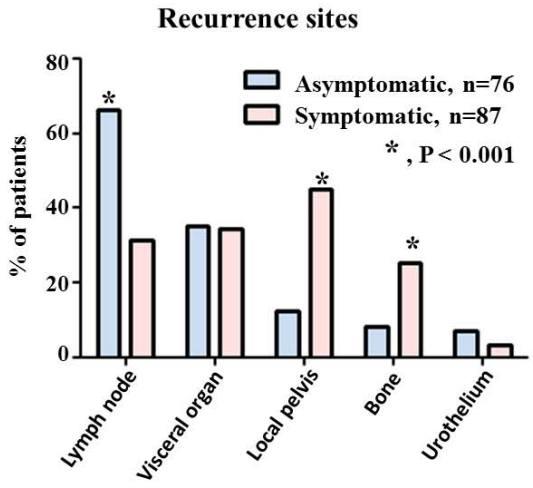
recurrence (n = 5, 29%) (P = 0.037). (D) After radical cystectomy, high-risk patients experienced a significantly higher incidence of symptomatic recurrence (n = 49, 78%) within 12 months than of asymptomatic recurrence (n = 35, 59%) (P = 0.028).

Fig. 1

Type of investigation	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Office visit	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Ultrasound	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Urine analysis and cytology	●	●		●		●		●		●		●		●
Blood and serum test Chest X-ray	●	●		●		●		●		●		●		●
CT scan of chest/abdomen/pelvis														
Normal-risk (≤ pT2, LVI-, and pN0)		●		●		●		●	●	●	●	●	●	●
High-risk (≥ pT3, LVI+, pN+, or non-UC components)	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Fig. 2


A
Radical cystectomy, n= 581
Diagnosed with recurrent disease, n= 175
Data available, n= 163
Asymptomatic, n= 76
Symptomatic, n= 87


B
Recurrence sites
Asymptomatic, n=76
Symptomatic, n=87
* , P < 0.001
% of patients
80
60
40
20
0
Lymph node
Visceral organ
Local pelvis
Bone
Urothelium

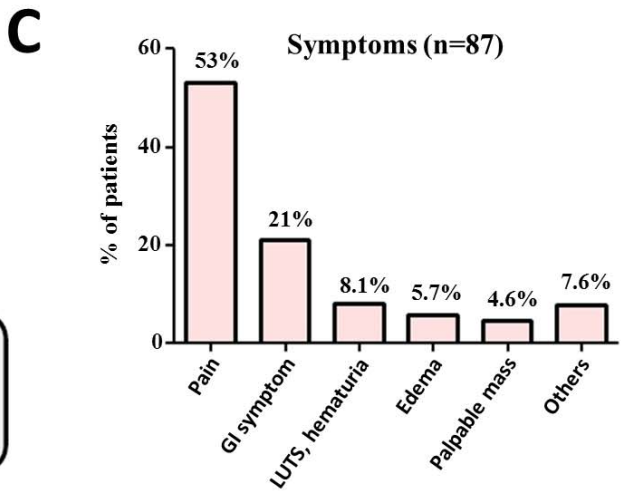

C
Symptoms (n=87)
% of patients
60
40
20
0
53%
21%
8.1%
5.7%
4.6%
7.6%
Pain
GI symptom
LUTS, hematuria
Edema
Palpable mass
Others

Fig. 3

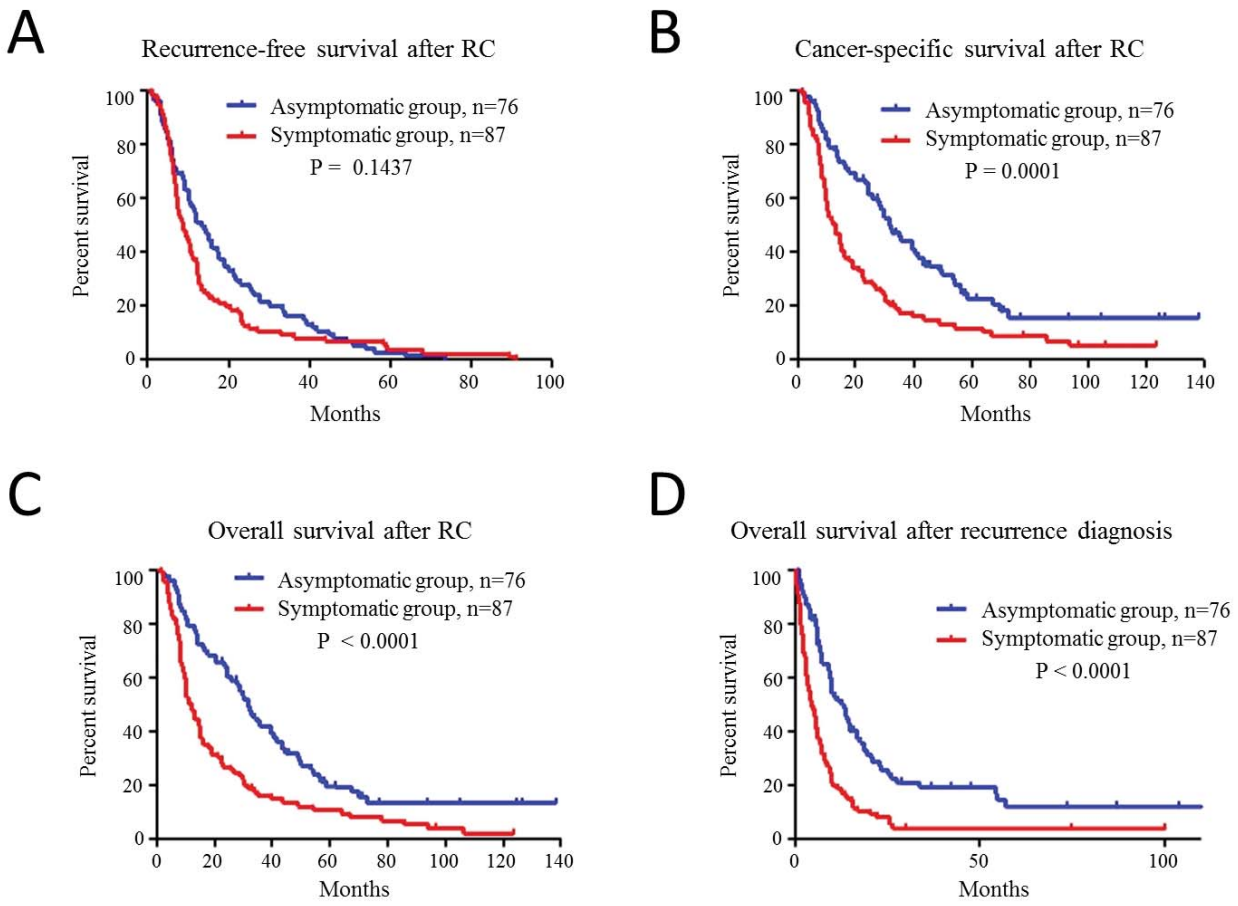

A
Recurrence-free survival after RC
Asymptomatic group, n=76
Symptomatic group, n=87
P = 0.1437
Percent survival
Months
B
Cancer-specific survival after RC
Asymptomatic group, n=76
Symptomatic group, n=87
P = 0.0001
Percent survival
Months
C
Overall survival after RC
Asymptomatic group, n=76
Symptomatic group, n=87
P < 0.0001
Percent survival
Months
D
Overall survival after recurrence diagnosis
Asymptomatic group, n=76
Symptomatic group, n=87
P < 0.0001
Percent survival
Months

Fig. 4

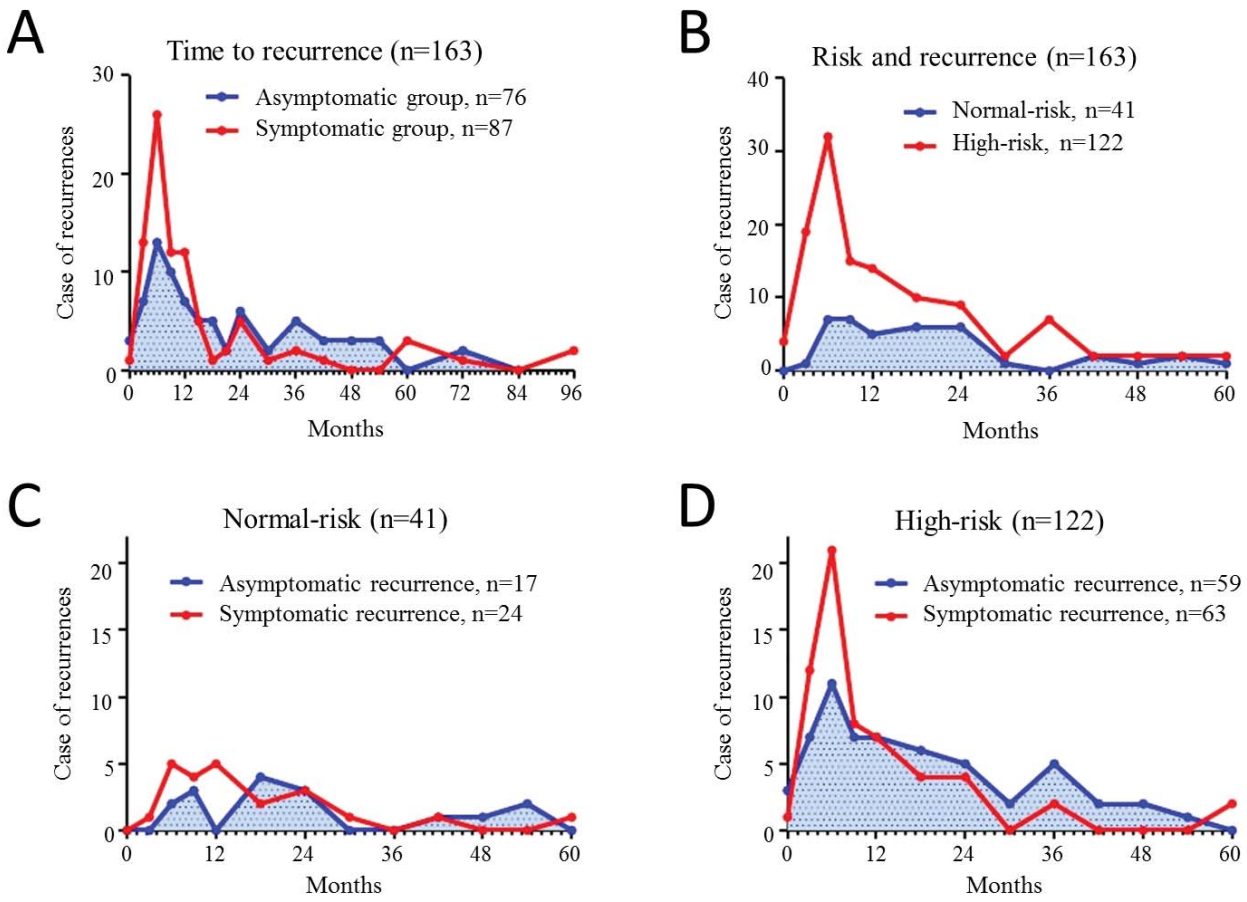

A
Time to recurrence (n=163)
Asymptomatic group, n=76
Symptomatic group, n=87
Case of recurrences
Months
B
Risk and recurrence (n=163)
Normal-risk, n=41
High-risk, n=122
Case of recurrences
Months
C
Normal-risk (n=41)
Asymptomatic recurrence, n=17
Symptomatic recurrence, n=24
Case of recurrences
Months
D
High-risk (n=122)
Asymptomatic recurrence, n=59
Symptomatic recurrence, n=63
Case of recurrences
Months

Table 1, Background of patients

	Asymptomatic	Symptomatic	*P value*
n	76 (47%)	87 (53%)	
Age, years (IQR)	69 (61, 75)	70 (63, 76)	*0.252*
Sex (Male), n=	61 (80%)	64 (74%)	*0.356*
ECOG PS > 1, n=	2 (2.6%)	1 (1.1%)	*0.599*
Past history of			
Cardiovascular disease, n=	9 (12%)	7 (8%)	*0.442*
Hypertension, n=	35 (41%)	30 (34%)	*0.151*
Diabetes mellitus, n=	9 (12%)	9 (10%)	*0.806*
Preoperative eGFR (mL/min/1.73m $_2$) (IQR)	61 (46, 71)	61 (47, 76)	*0.417*
Neoadjuvant chemotherapy, n=	39 (51%)	47 (54%)	*0.755*
TNM classification			
cT3 or 4, n=	48 (63%)	55 (63%)	*0.994*
pT3 or 4, n=	43 (57%)	49 (55%)	*0.974*
pN+, n=	22 (29%)	18 (21%)	*0.274*
Tumor grade (high), n=	75 (98.7%)	86 (98.9%)	*1.000*
Lymphovascular invasion (LVI) positive, n=	48 (63%)	51 (59%)	*0.630*
Surgical outcomes			

Blood loss, kg (IQR)	1.25 (0.86, 2.05)	1.18 (0.75, 1.79)	*0.132*
Operative duration, min (IQR)	302 (245, 386)	295 (229, 360)	*0.374*
Urinary diversion			*0.525*
Ileal neobladder, n=	34 (45%)	34 (39%)	
Ileal conduit or cutaneous-ureterostomy, n=	42 (55%)	53 (61%)	
Postoperative complications (Clavien-Dindo)			
Any grades, n=	13 (17%)	21 (24%)	*0.335*
Severe (grade 3), n=	1 (1.3%)	4 (4.6%)	*0.373*
Burden of metastatic diseases			
Number of metastatic sites (IQR)	1 (1-2)	1 (1-1)	*0.965*
Visceral metastases, n=	32 (42%)	30 (52%)	*0.220*
Chemotherapy after recurrence			
Underwent, n=	44 (58%)	34 (39%)	*0.019*
Number of cycles (IQR)	2 (0-3)	1 (0-2)	*0.011*
Deceased, n=	61	82	*0.009*

IQR: interquartile range, ECOG PS: Eastern Cooperative Oncology Group Performance Status, SD: standard deviation, LVI: lymph-vascular invasion

Table 2, Uni- and multivariate Cox regression analyses for prognosis

		OS after radical cystectomy			OS after recurrence diagnosis		
Univariate analysis	Risk factor	P value	HR	95%CI	P value	HR	95%CI
Age	Continuous	*0.002*	1.03	1.01-1.05	*<0.001*	1.03	1.02-1.05
Sex	Male	*0.231*	0.77	0.50-1.18	*0.826*	0.95	0.62-1.47
ECOG PS	>1	*0.260*	1.78	0.65-4.83	*0.110*	2.27	0.83-6.19
eGFR	Continuous	*0.078*	0.99	0.98-1.00	*0.213*	1.00	0.99-1.00
Hypertension (HTN)	Positive	*0.780*	1.05	0.75-1.47	*0.566*	1.10	0.79-1.54
Cardiovascular disease (CVD)	Positive	*0.228*	1.29	0.85-1.95	*0.099*	1.42	0.94-2.15
Diabetes Mellitus (DM)	Positive	*0.783*	0.93	0.54-1.59	*0.655*	0.89	0.52-1.51
Neoadjuvant chemotherapy (NAC)	Underwent	*0.670*	1.07	0.77-1.49	*0.542*	0.90	0.65-1.26
Urinary diversion	Neobladder	*0.190*	0.8	0.57-1.12	*0.209*	0.81	0.58-1.13
Tumor grade	High	*0.524*	1.38	0.51-3.75	*0.261*	1.77	0.65-4.79
pT	≥ pT3	*0.069*	1.36	0.98-1.90	*0.305*	1.19	0.85-1.66
pN	Positive	*0.237*	1.22	0.88-1.70	*0.978*	1.00	0.70-1.42
Lymphovascular invasion (LVI)	Positive	*0.009*	1.58	1.12-2.22	*0.159*	1.28	0.91-1.79

Number of metastatic sites	Continuous	*0.172*	1.14	0.94-1.38	*0.300*	1.10	0.92-1.32
Visceral metastasis	Positive	*0.065*	1.36	0.98-1.84	*0.053*	1.38	1.00-1.92
Chemotherapy cycles after recurrence diagnosis	3 or more	*0.031*	0.67	0.46-0.96	*0.008*	0.60	0.42-0.87
Mode of recurrence	Symptomatic	*<0.001*	1.97	1.41-2.76	*<0.001*	2.25	1.60-3.15
Multivariate analysis (IPTW*)							
Mode of recurrence	Symptomatic	*<0.001*	1.94	1.38-2.72	*<0.001*	2.18	1.55-3.08

*, including age, sex, ECOG PS, HTN, CVD, DM, NAC, type of urinary diversion, pT, pN, LVI, number of metastatic sites, and visceral metastasis. IPTW: inverse probability of treatment weighting