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JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2020, 50(9)1068–1075
doi: 10.1093/jjco/hyaa072
Advance Access Publication Date: 29 May 2020
Original Article

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Prognostic significance of non-urothelial carcinoma of bladder: analysis of nationwide hospital-based cancer registry data in Japan

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Received 19 January 2020; Editorial Decision 1 May 2020; Accepted 5 May 2020

Abstract

Objectives: To identify the prognosis of pure non-urothelial carcinoma (non-UC) of bladder and to compare them with those of pure urothelial carcinoma (UC).

Methods: We used Japan's nationwide hospital-based cancer registry data to extract histologically confirmed pure non-UC and UC cases of bladder diagnosed in 2008–2009. We estimated the 5-year overall survival (OS) by a Kaplan–Meier analysis.

Results: A total of 8094 patients with confirmed histological subtypes of bladder cancer were identified. The most common pure non-UC was squamous cell carcinoma (SQ, $n = 192$, 2.4%) followed by adenocarcinoma (AC, $n = 138$, 1.7%) and small cell neuroendocrine carcinoma (SmC, $n = 54$, 0.7%). The proportion of female patients (48%) was significantly higher in the SQ group compared with the pure UC group ($P < 0.001$). The 5-year OS rate of the non-UC patients was significantly worse than that of the UC patients (40 vs. 61%, $P < 0.001$). According to stages, the 5-year OS rates of the stage I and III non-UC patients were significantly worse than those of the UC patients ($P = 0.001$). Considering histologic subtypes and stages, the 5-year OS rates of the stage I SQ patients were worse than those of the AC and SmC patients (46, 68 and 64%, respectively).

Conclusion: The prognosis of pure non-UC was worse than that of pure UC, especially in the stage I and III non-UC patients. To improve these patients' oncologic outcomes, a more aggressive surgical approach may be necessary in stage I patients with non-UC, especially in pure SQ.

Key words: non-urothelial carcinoma, bladder cancer, hospital-based cancer registry

Introduction

The most common histology of bladder cancer is urothelial carcinoma (UC), and non-urothelial carcinoma (non-UC) of bladder had been recognized as a rare entity. However, recent studies demonstrated that bladder cancer with a non-UC component accounts for approximately 25–30% of bladder cancers (1,2). Another study reported that more patients are diagnosed as having bladder cancer with a non-UC more recently, based on the two periods 1990–2000 and 1991–2013 (21 and 35%, respectively) (3). Along with the widespread recognition of the aggressive behaviour of non-UC, the 2016 World Health Organization (WHO) classification has recommended that the percentage of non-UC elements be provided in

pathology reports (4). Although bladder cancer patients with a non-UC are diagnosed more frequently at advanced stages compared with patients with UC (1,2,5), the precise prognostic impact of the non-UC has not been established compared with UC.

Moschini et al. reported that approximately two-thirds of non-UC cases had mixed variants consisting of UC and non-UC elements (2). They also showed that the prognosis of pure non-UC was significantly worse than that of pure UC, whereas the prognoses of mixed non-UC were similar to that of pure UC. Although some studies reported that the prognosis of patients with pure adenocarcinoma (AC) was similar to that of patients with pure UC (6,7), another investigator described poorer prognoses in patients with pure AC compared with patients with pure UC (8). In contrast, other studies showed similar prognoses in patients with pure small cell neuroendocrine carcinoma (SmC) and those with squamous cell carcinoma (SQ) (3,9), and significantly poorer prognoses were reported in patients with pure SmC and pure SQ compared with patients with pure UC (5,6,10).

The reported proportions of pure AC, SQ and SmC in all bladder cancers were approx. 1.0%, 1.3–1.4% and 0.35–1%, respectively (11–14). These contradictory results may be due to the low incidence of pure non-UC of bladder. Most of the evidence for pure non-UC is derived from high-volume centres with a long observation period or from a large-scale population-based study; however, the former is not free from changes in treatment strategies during the study period, while the latter is limited by bias from differences in hospital care volume or treatment skills.

Herein, to identify the prognosis of pure non-UC compared with those of pure UC, we retrospectively analysed the cases of patients newly diagnosed with pure AC, SQ or SmC between January 2008 and December 2009 by using the hospital-based cancer registry (HBCR) data from Japan's nationwide designated cancer care hospitals (DCCHs).

Methods

Data sources

To provide high-quality cancer care, the Japanese Ministry of Health, Labour and Welfare has designated cancer care hospitals in Japan. As previously described (15), the data, including patients' characteristics, route to discovery, stage information or first-course of treatments, from these cancer care hospitals are submitted annually to the Center for Cancer Control and Information Services at the National Cancer Center, analysed and distributed as the National Cancer Statistics Report. We obtained the HBCR data of patients diagnosed in 2008–2009 from the Center in order to investigate the clinicopathological features, the treatment patterns or the prognoses of patients with rare cancers in urology as a clinical research. Since the data on survival after diagnosis were only available for patients diagnosed in 2008–2009 at the time of planning this study, we selected this patient cohort for the present analysis.

We used the HBCR data from the nationwide DCCHs to identify bladder cancer patients diagnosed in 2008–2009. Well-trained cancer registrars at each hospital register the details of diagnosed cancer cases based on standardized criteria. The data include the patients' demographics, tumour characteristics and the first course of treatment. All tumours are initial cases that are newly diagnosed cases or newly evaluated cases at the hospital where the tumour was diagnosed or treated at another hospital (15). The first course of treatment is defined as a treatment that is planned for improving the cancer prognosis at an initial diagnosis. As treatment modalities, the present data include surgery, radiation therapy, chemotherapy or immunotherapy. 'Surgery' includes open, laparoscopic and endoscopic surgery. In the cases of bladder cancer, open or laparoscopic surgery generally includes a partial or radical cystectomy, and endoscopic surgery includes the transurethral resection of bladder tumour (TURBT). It is not possible to identify patients who have received a second TURBT since only information about whether the patient has undergone endoscopic surgery is available in this registry. 'Chemotherapy' is systemic intravenous therapy, targeted therapy or intravesical therapy. Immunotherapy includes intravesical administration of Bacillus Calmette-Guerin (BCG). The HBCR data from 251 DCCHs in 2008–2009 had the patients' survival information at 5 years after their diagnoses. All of the data were obtained from the hospitals that had a >90% follow-up rate for all cancer patients.

The identification of bladder cancer cases

We identified eligible cases from the database based on the following inclusion criteria: patient (i) newly diagnosed with a malignant bladder tumour (C67) except for a malignant urachal tumour (C67.7) in 2008–2009; (ii) who had a histologically confirmed tumour with International Classification of Disease for Oncology 3rd edition (ICD-O-3) histology codes such as 8120–8131 for pure UC, 8051–8070 for pure SQ, 8140–8490 for AC or 8041 for SmC and (iii) a diagnosis of clinical stage I–IV. We excluded 24 cases with the histology code 8000 (malignant neoplasm) since we could not specify the histological subtype. In the 2008–2009 cohort, the staging information was based on the sixth UICC TNM Classification. In addition, this cohort did not include cases with carcinoma *in situ*. We thus excluded stage 0 cases (i.e. Ta and TisN0M0) from the present analysis, although 390 cases classified as TaN0M0 were identified from the database.

Statistical analyses

We compared variables between groups using Fisher's exact probability test for categorical variables and the Mann–Whitney U-test for continuous variables. The 5-year overall survival (OS) rate was analysed by the Kaplan–Meier method and compared between groups by the log-rank test. All statistical comparisons were two-sided, and *P*-values <0.05 were considered significant. SPSS® 25.0 for Windows® (SPSS, Chicago, IL) was used.

Ethical considerations

The study protocol and data processing were approved by the Tsukuba University Hospital Ethical Board (H29–267). In rare-disease research, there are sometimes less than 10 cases, and the patients' privacy should be considered before publication since the publication of patient details can lead to the unwanted identification of patients. We therefore report the proportion of those cases in the text or tables in accord with the recommendations from Japan's Ministry of Health, Labour and Welfare.

Results

A total of 8094 patients with bladder cancer with confirmed histological subtypes were identified (Fig. 1). Table 1 summarizes the clinical characteristics of the eligible patients. A total of 384 (4.7%) patients had a pure non-UC of bladder. The most common pure non-UC was

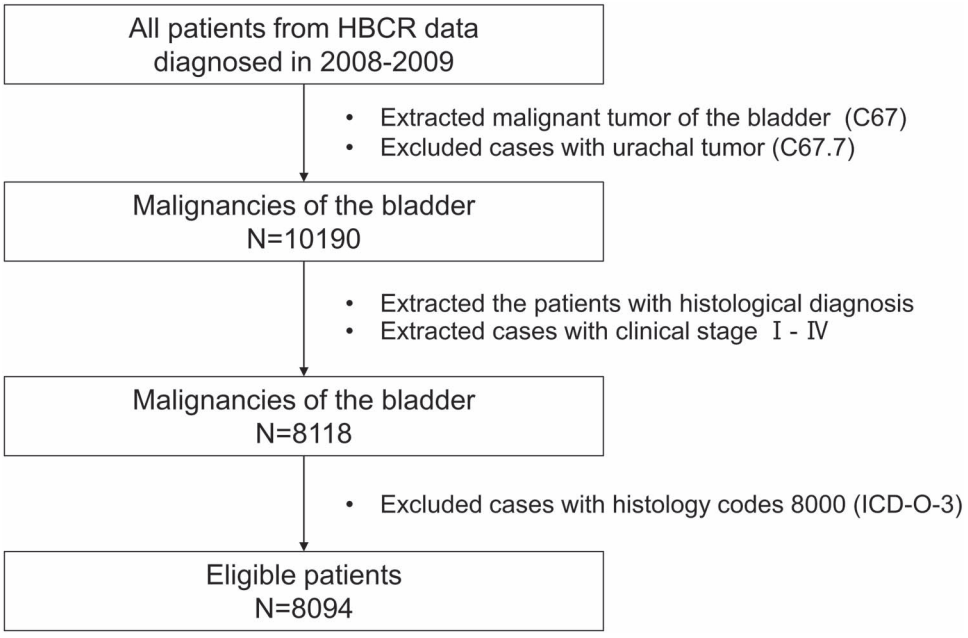

Figure 1. Eligibility of the bladder cancer patients.

SQ ($n = 192$, 2.4% of all of the bladder cancers) followed by AC ($n = 138$, 1.7%) and SmC ($n = 54$, 0.7%). The other forms included histological subtypes such as carcinoma (not otherwise specified, $n = 53$) or sarcoma ($n = 10$). We excluded these cases from further analysis since the numbers of some of the most common subtypes were small (<10 cases). Thus, the uses of the term 'non-UC' in the following text, tables and figures include pure AC, SQ and SmC.

The median age of all patients was 73 (range 1–99 years), and there was no significant difference in patient age among the histologic subtypes. Among the patients with SQ, the proportion of females (48%) was significantly higher than that in the UC group (22%) ($P < 0.001$). In contrast, male patients with SmC accounted for approximately five times that of female patients with SmC, but there was no significant difference in the gender distribution compared with UC. The ratio of stage III/IV in the patients with all non-UC subtypes was significantly higher than that of the UC group. The ratio of SQ patients was the highest; in particular, stage III and IV patients accounted for 60%.

Table 2 describes the additional treatments after TURBT according to the tumour stages and histologic subtypes. The proportion of patients who underwent radical surgery including partial or radical cystectomy at stage I was significantly higher in the non-UC group compared with the UC group (20 vs. 10%, $P = 0.002$). Among the patients at stage II–III, the proportions of patients who underwent radical surgery were 25–27% in the UC group and 31–33% in the non-UC group, respectively. In terms of the proportion of patients who underwent a combination of surgery and chemotherapy, there was no significant difference among the UC and non-UC groups. Considering the histologic subtypes, the proportions of the AC, SQ and SmC patients who underwent a combination of surgery and chemotherapy were 15.2, 15.1 and 18.5%, respectively. The proportion of patients with SmC tended to be higher than the proportions of patients with other subtypes.

The 3- and 5-year OS rates of all of the patients with UC were 71 and 61%, whereas the 3- and 5-year OS rates of all of the patients with non-UC were 48 and 40%, respectively. Both the 3- and 5-year OS rates of the patients with non-UC were significantly worse than those of the patients with UC ($P < 0.001$). As shown in Fig. 2, the OS rates of the stage I and III patients with non-UC were significantly worse than that of the UC patients ($P = 0.001$). In terms of histologic subtypes, the 3- and 5-year OS rates of the groups of patients were as follows: AC, 51 and 40%; SQ, 45 and 40% and SmC, 51 and 43%. There was no significant difference in the OS at 3 or 5 years among these histologic subtypes.

Figure 3 illustrates the OS values according to histologic subtype and stage. Among the stage I patients, the 5-year OS rates of the patients with AC, SQ and SmC were 68, 46 and 64%, respectively. The 5-year OS rate of the SCC patients was significantly worse than that of the AC patients ($P = 0.018$), whereas there was no significant difference in the OS between the SQ and SmC groups ($P = 0.22$). Among the stage IV patients, the 5-year OS rates of the patients with AC, SQ and SmC were 3, 23 and 12%, respectively. The 5-year OS rate of the AC patients was significantly worse than that of the SQ patients ($P = 0.033$), whereas there was no significant difference in the OS between the AC and SmC groups ($P = 0.74$).

Figure 4 provides the OS rates of the UC patients between the patients who underwent surgery alone and those who were treated with a combination of surgery and chemotherapy. Among these UC patients at stage III–IV, the 5-year OS rates in the combination group were significantly higher (53% in stage III and 33% in stage IV) compared with those in the surgery-alone group (45 and 22%, respectively). In contrast, as shown in Fig. 5, there was no significant difference in the OS among the patients with a non-UC at any stage. Considering histologic subtypes, the 5-year OS rates of the AC patients ($n = 41$), SQ patients ($n = 72$) and SmC patients ($n = 15$) between the surgery-alone group and the combination group were 40 and 30%, 60 and 60%, 17 and 56%, respectively. Although the 5-year OS rate of the SmC patients in the combination group was higher than that in the surgery-alone group, there was no significant difference in the OS between the corresponding groups.

Table 1. Clinical characteristics of the patients with bladder cancer

		All (%)	UC (%)	AC (%)	SQ (%)	SmC (%)	Other (%)
No. of patients		8094 (100)	7573 (93.6)	138 (1.7)	192 (2.4)	54 (0.7)	137 (1.7)
Age	Median (range)	73 (1–99)	73 (16–99)	73 (49–94)	73 (39–94)	73 (45–90)	73 (1–96)
Sex	Male	6304 (77.9)	5979 (79.0)	102 (73.9)	99 (51.6)	99 (51.6)	79 (57.7)
	Female	1790 (22.1)	1594 (21.0)	36 (26.1)	93 (48.4)	9 (16.7)	58 (42.3)
	Male/female ratio	3.52	3.75	2.83	1.06*	5.00	1.36*
Stage	I	4514 (55.8)	4379 (57.8)	47 (34.1)	35 (18.2)	17 (31.5)	36 (26.3)
	II	1766 (21.8)	1647 (21.7)	36 (26.1)	43 (22.4)	15 (27.8)	25 (1 8.2)
	III	1060 (13.1)	928 (12.3)	21 (15.2)	65 (33.9)	12 (22.2)	34 (24.8)
	IV	754 (9.3)	619 (8.2)	34 (24.6)	49 (25.5)	10 (18.5)	42 (30.7)
	III + IV/I + II ratio	0.29	0.26	0.66*	1.46*	0.69*	1.25*

*$P < 0.01$ compared with UC.

AC: adenocarcinoma, SCC: squamous cell carcinoma, SmC: small-cell neuroendocrine carcinoma, UC: urothelial carcinoma.

Table 2. Additional treatment after TURBT according to stage and histologic subtype

	Surgery[a] only (%)	Surgery[a] + chemotherapy (%)	Chemotherapy only (%)	Immunotherapy only (%)	Radiation therapy only (%)	Radiation + chemotherapy (%)	No treatment (%)	Others (%)
Stage I								
UC ($n = 4379$)	9.9	3.2	17.3	12.1	0.1	1.0	48.9	7.7
Non-UC ($n = 99$)	20.2*	40	12.1	6.1	1.0	1.0	45.5	10.1
Stage II								
UC ($n = 1647$)	24.9	12.8	13.2	4.4	5.2	7.8	26.6	5.1
Non-UC ($n = 94$)	33.0	19.1	6.4	0.0*	1.1	3.2	30.9	6.4
Stage III								
UC ($n = 928$)	27.0	26.3	7.8	1.1	7.9	8.4	14.9	6.7
Non-UC ($n = 98$)	30.6	20.4	6.1	0.0	10.2	11.2	14.3	7.1
Stage IV								
UC ($n = 619$)	10.2	21.3	25.4	1.0	8.4	9.7	15.8	8.2
Non-UC ($n = 93$)	11.8	19.4	18.3	1.1	10.8	5.4	20.4	12.9

[a]Radical cystectomy or partial cystectomy.

*$P < 0.05$ compared with UC.

Discussion

The results of our analyses of 384 patients with a pure non-UC (AC, SQ, and SmC) of bladder drawn from large-scale HBCR data showed that the prognosis of those patients was significantly worse than that of the patients with pure UC. The prognostic difference was due mainly to the poor prognoses of the patients with a non-UC of bladder at stage I or III. We also obtained several relevant findings regarding the trends of the clinicopathological features and the management of patients with a non-UC of bladder in Japan.

The most common non-UC in this cohort was SQ (2.4% of all bladder cancers) followed by AC (1.7%) and SmC (0.7%). The proportion of female patients (48%) was significantly higher in the SQ group compared with the UC group. A relatively higher proportion of female patients with SQ was also observed in earlier studies (5,16). Johansson et al. reported that the male-to-female ratio in patients with SQ of the bladder was 1.4:1 (16). Mungan et al. confirmed that the incidence of T3 and T4 non-urothelial bladder cancer was higher in female patients compared with men (T3, 21.7% in females vs. 14.5% in males; T4, 14.5 vs. 8.4%) (17). In the present study, the male-to-female ratios in the SQ patients at stages III and IV were 1:1.03 and 0.58:1, respectively. The proportion of female SQ patients at stage IV was 63%. It is not clear why the proportion of females is high among patients with SQ, but the relevance of chronic bladder inflammation to this trend has been discussed (17).

As shown in Fig. 2, the prognoses of the present non-UC patients at stage I or III were significantly worse than that of the UC patients. Notably, the prognosis of the non-UC patients at stage I was unexpectedly poor, and it was similar to those of the stage II patients: the 5-year OS rates of the non-UC patients and the UC patients were 53 and 57%, respectively (Fig. 2). Although the reason for the poor prognosis of the patients with stage I disease is not clear, it might be due to less-aggressive treatment administered to those patients. As shown in Table 2, 46% of the stage I non-UC patients received no additional treatment after transurethral resection, and the percentage of UC patients was similar to that of the non-UC patients. Cohen et al. showed that the proportion of non-UC patients presenting with clinical T1 (cT1) or less whose pathological stage was up-staged was 55.4% compared with 42.7% of the patients with UC (18). Those authors also reported that their SQ patients had the highest up-staging rate (61.8%) compared with the rates of the

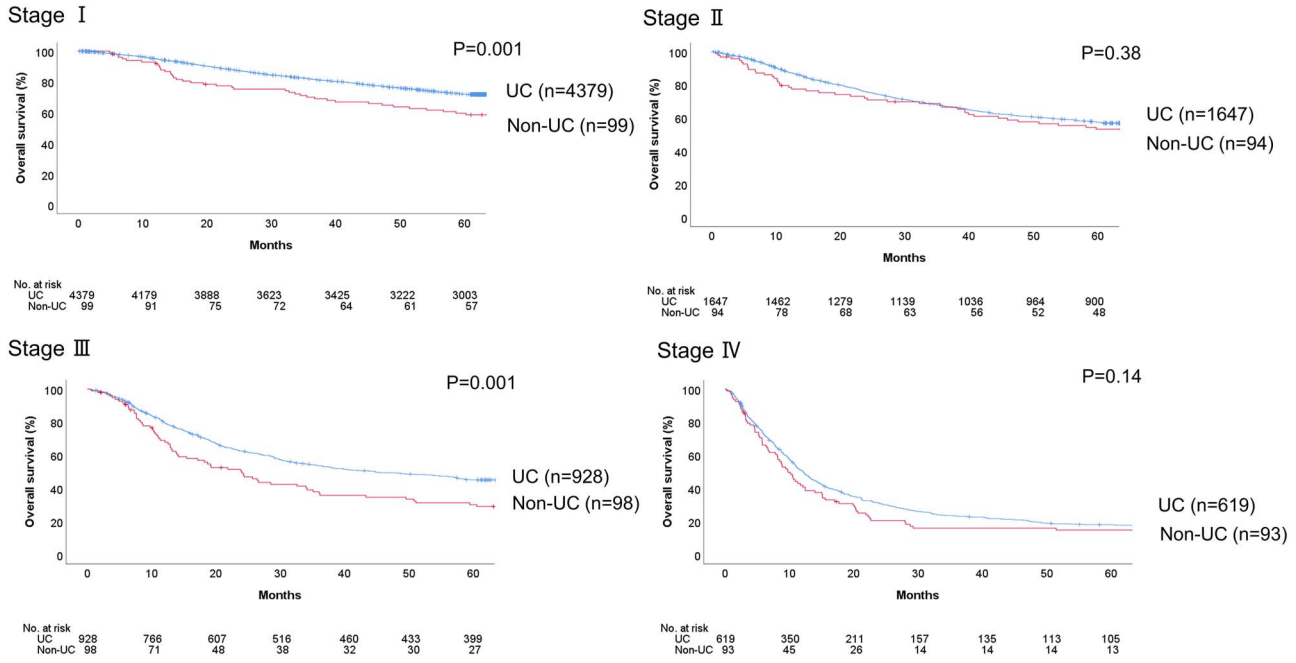

Figure 2. The overall survival (OS) of the non-urothelial carcinoma (non-UC) and urothelial carcinoma (UC) patients stratified by stages.

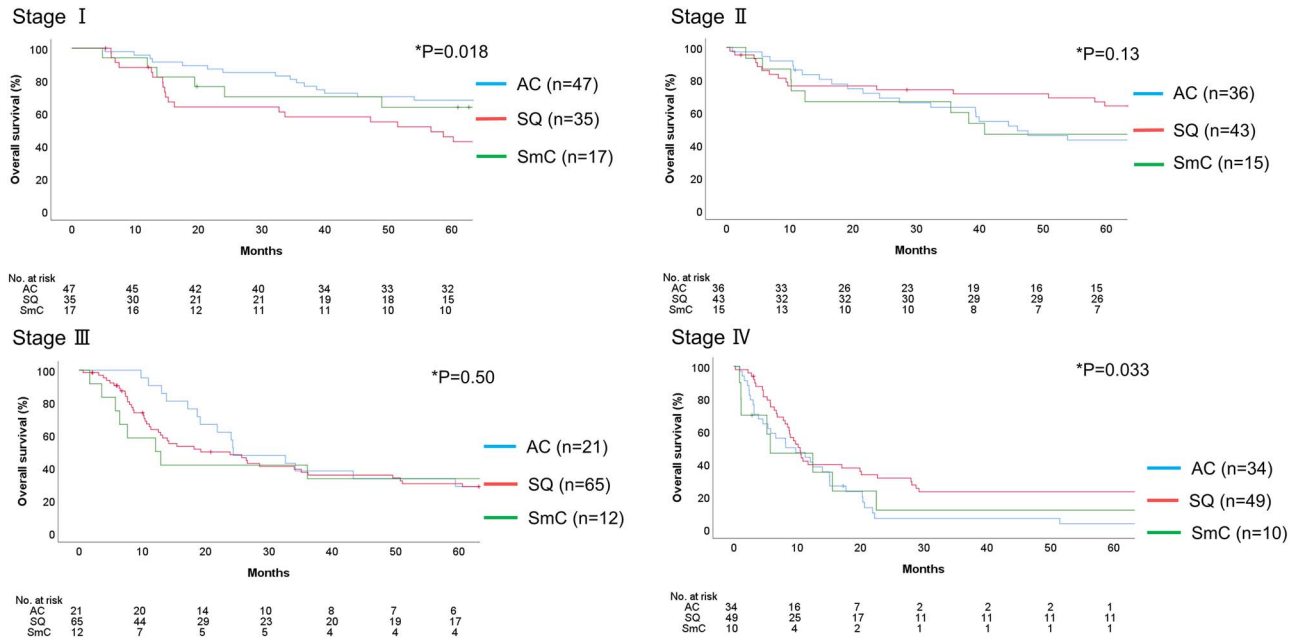

Figure 3. The OS according to histologic subtype and stage. AC: adenocarcinoma, SQ: squamous cell carcinoma, SmC: small cell neuroendocrine carcinoma. *Between AC and SQ.

patients with UC, AC and SmC (18). In the present study, the 5-year OS rates of the SQ, AC and SmC patients at stage I were 46, 68 and 64%, respectively. The prognosis of the SQ patients at stage I was significantly worse than that of the patients with AC (Fig. 3).

The appropriate treatment strategy for patients with a pure non-UC of bladder has been not established. The European Association of Urology (EAU) guidelines classify non-muscle invasive bladder cancer with non-UC as the highest-risk tumour (19). Those guidelines recommend an immediate radical cystectomy in such cases. Scosyrev et al. showed that especially in pure SQ cases, the patients with cT1 disease had higher mortality than those with pure UC when the patients were treated by conservative management (13). Scosyrev et al. also suggested that the mortality rates did not differ between SQ and UC among patients with cT1 disease who were treated by radical cystectomy. Many clinicians thus advocate the use of an early cystectomy for SQ patients with cT1 disease (19).

In the present study, 14% of the SQ patients with cT1 disease were treated by radical surgery alone, and 54% of those patients

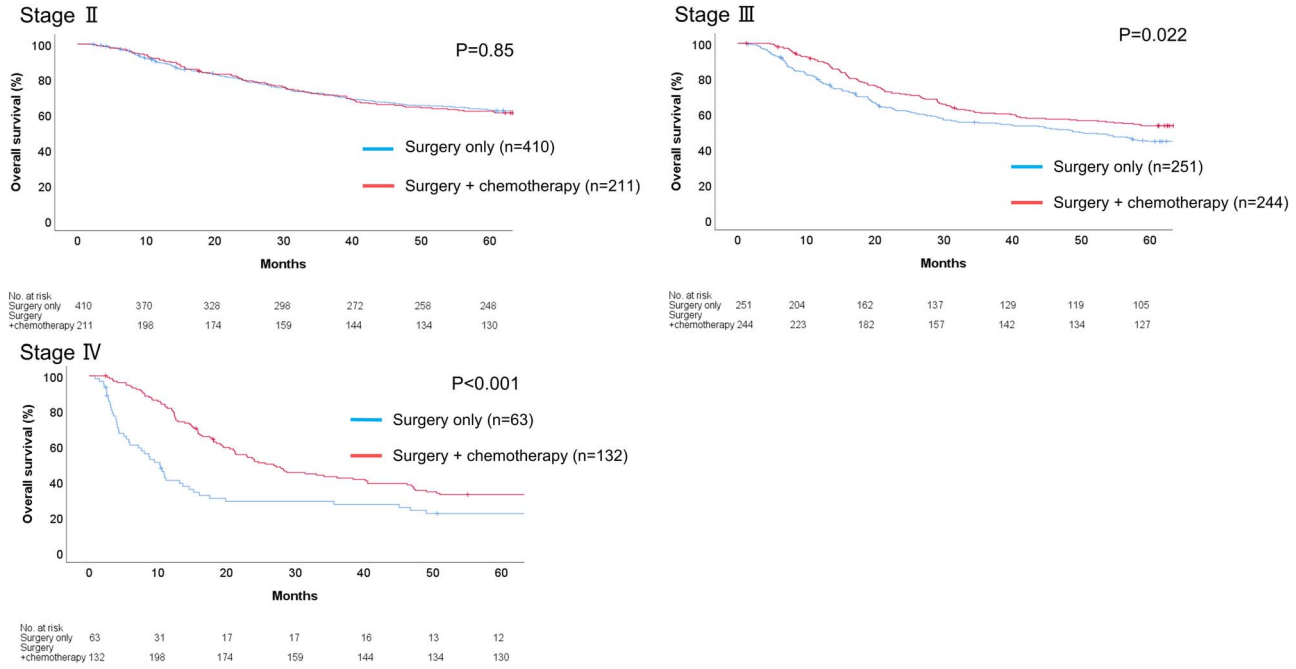

Figure 4. The OS of the UC patients according to stage and treatment.

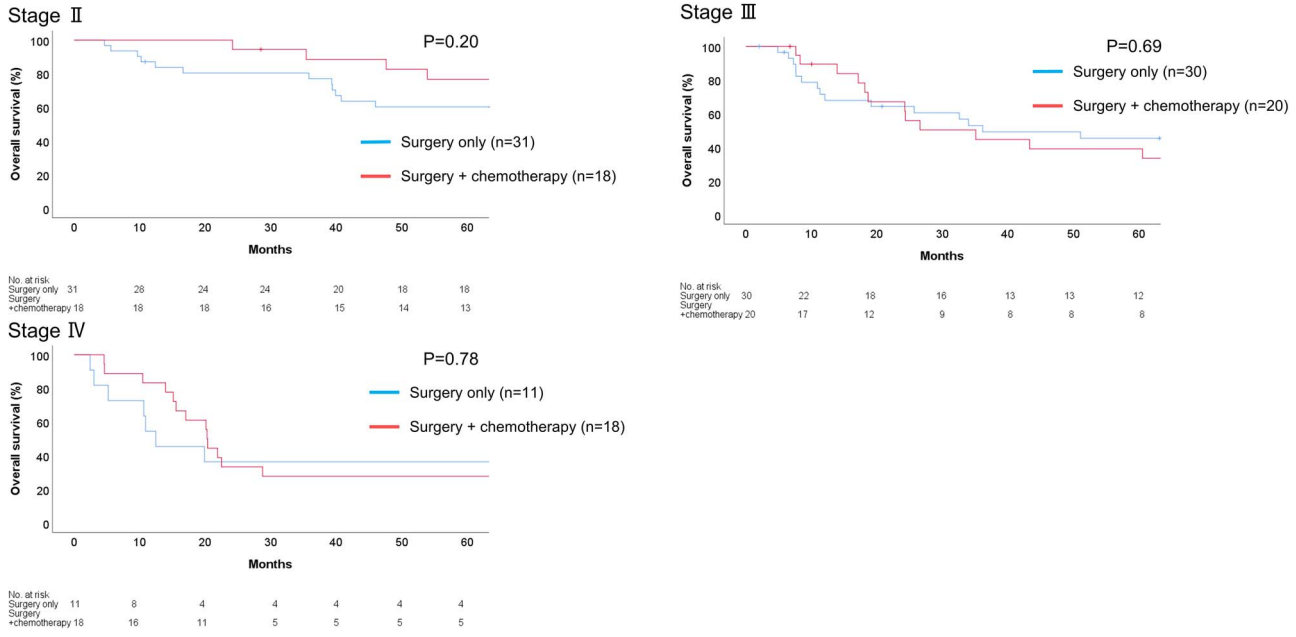

Figure 5. The OS of the non-UC patients according to stage and treatment.

received no additional treatment after TURBT. The 5-year OS rates of the patients who underwent radical surgery and the patients who received no additional treatment were 50 and 50%, respectively. Since we could not evaluate the statistical significance of the differences in OS between groups because the sample size was too small, further investigations are necessary to confirm the usefulness of an immediate cystectomy for SQ patients with cT1 disease.

A number of randomized studies including Japanese studies have shown the effectiveness of neoadjuvant chemotherapy for muscle-invasive urothelial bladder cancer (20–23). Our present analyses also revealed that UC patients who were treated with a combination of surgery and chemotherapy had a significantly better prognosis than the patients who were treated with surgery only (Fig. 4). The difference was more remarkable in stage IV UC patients. As shown in Table 2, approx. 30% of stage IV UC patients underwent surgery (radical cystectomy or partial cystectomy), and two-thirds of the patients also received chemotherapy. Herr et al. reported that 80 of 207 (39%) patients with unresectable or

regionally metastatic bladder cancer underwent post-chemotherapy surgery (24). The authors showed the favorable prognosis for patients who responded well to chemotherapy. In contrast, as shown in Fig. 5, the effectiveness of a combination of surgery and chemotherapy was not shown in the present patients with non-UC. As with UC patients, approx. 30% of stage IV non-UC patients underwent surgery. But, there was no difference in OS between patients treated with surgery alone and patients treated with surgery and chemotherapy (Fig. 5). However, when limited to patients with pure SmC, the patients in the combination group tended to show better oncological outcomes compared with the patients in the surgery-alone group: the 5-year OS rates of the patients in the corresponding groups were 56 and 17%, respectively. However, there was no significant difference between the two groups due to the limited number of patients. Koay et al. reported the 5-year OS rates of SmC patients who treated with the bladder sparing approach and the combination of cystectomy and chemotherapy were 19 and 26%, respectively (25). The OS of SmC patients in the present study seemed to be relatively better than that in previous studies (25,26). Although this prognostic difference may be due to a small amount of SmC components in some of the registered cases in this study, there is no available information on the amount of non-UC components in the HBCR data.

In cases of a non-UC of bladder, the benefit of neoadjuvant chemotherapy has been established only in cases with SmC (27) and in UC with squamous or glandular differentiation (28,29). The effectiveness of neoadjuvant chemotherapy has been shown in a population-based study of patients with SmC (26). Our present findings clearly demonstrated the need to develop more effective systemic treatments for patients with SQ or AC of bladder.

Our study has several limitations due to the availability of retrospective data in the HBCR. First, there was no detailed information about the clinical status of the individual patients in this registry. Second, the data included details of only the registered information that was provided at the registering facilities. Since all registered tumours are newly diagnosed or evaluated cases, the impact of relapsed or recurrent disease on prognosis cannot be discussed. In terms of chemotherapy, there is no way to know whether the chemotherapy is systemic intravenous therapy, targeted therapy or intravesical therapy. Therefore, we cannot discuss the outcomes of stage I patients who received intravesical therapy in the present study. In addition, there is no available information about the regimens or the setting of neoadjuvant or adjuvant therapy. Third, since there were no ICD-O-3 codes specified for the mixed variants consisting of UC and non-UC elements, it was not possible to identify a mixed variant case. Finally, the reports included data only from the DCCHs that play a central role of cancer care in regional communities, and although these hospitals are expected to provide patients with high-quality anti-cancer care, other hospitals may treat the patients with management that differs from that used at the patients' former hospitals. The latter hospitals may be more likely to treat with conservative management for non-UC patients, especially elderly patients.

In conclusion, despite these limitations, the results of the present study demonstrated that the prognoses of patients with pure AC, SQ or SmC of bladder were worse than the prognoses of the patients with pure UC. This prognostic difference was due mainly to poor prognoses, especially among the patients with non-UC at stage I and III. To improve the oncologic outcomes, a more aggressive surgical approach may be necessary in patients with non-UC at stage I, especially in those with pure SQ.

Funding

This work was supported in part by a Grant-in-Aid for Cancer Research (H29-013) from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest statement

None declared.

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