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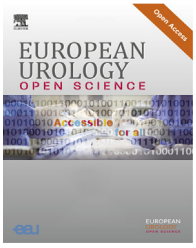

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Statistics in Urology

Metastatic Sites in Rare Genitourinary Malignancies and Primary Cancer Sites in Genitourinary Organ Metastases: A Secondary Analysis Using the Japanese Pathological Autopsy Registry Database

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Abstract

Background: The epidemiology of metastases from rare genitourinary cancer and metastases to genitourinary organs from other primary neoplasms remains poorly understood.
Objective: To investigate the epidemiology of rare genitourinary metastases from rare genitourinary organ–type cancer and to genitourinary organs using data from a large national autopsy registry in Japan.
Design, setting, and participants: A secondary analysis of the data reported in the Annual of the Pathological Autopsy Cases in Japan and the Japanese Mortality Database from 1993 to 2020 was performed.
Outcome measurements and statistical analysis: Via a retrospective epidemiologic analysis, we evaluated the frequency (probability of occurrence [number per person]) and proportion (percentage) of metastases from upper urinary tract, adrenal, testicular, urethral, and penile cancers. Moreover, the sites of primary tumors metastasizing to genitourinary organs were examined.
Results and limitations: In Japan, the mortality rate of upper urinary tract cancer is increasing rapidly. In the integrated database with 365 099 autopsies and 835 959 metastatic organs, the major metastatic sites (range of frequency ratios) of rare genitourinary organ–type cancers were the lungs (0.38–0.47), liver (0.21–0.56), bone (0.16–0.33), adrenal gland (0.10–0.20), peritoneum (0.0–0.16), and kidneys (0.07–0.22). The major primary sites (range of proportions) of genitourinary organ metastases were the respiratory tract (5.6–34.0%), stomach (4.7–27.0%), hematologic site (0.9–24.9%), lymphoid (2.4–22.2%), bladder (0.8–20.0%), prostate (0.7–14.1%), rectal (2.0–11.7%), and pancreas (2.6–11.0%). The cancers with a high likelihood of genitourinary metastasis were respiratory and stomach cancers. However, the study lacked individual-level information, and there might be a concomitant selection bias in this autopsy study.

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Conclusions: This large-scale autopsy database analysis identified the epidemiology of metastasis from rare genitourinary organ–type cancer and the origins of metastasis to genitourinary organs.
Patient summary: This study provides valuable metastatic epidemiologic data and clinical information that are fundamental to the mechanisms of genitourinary metastasis.

1. Introduction

Understanding the natural history of primary and metastatic cancers is essential. The genitourinary system for urology includes the organs of the male reproductive system (such as the prostate, penis, and testis), the urinary system (such as the kidney, renal pelvis, ureter, bladder, and urethra), and the adrenal gland. Although the metastatic patterns were reviewed in the World Health Organization Classification of Pathology, the number of reviews on rare genitourinary organ–type cancers such as upper urinary tract cancer (UUTCA), adrenal, testicular, urethral, and penile cancers is limited [1–4]. In addition, metastases to the genitourinary organs are rare [1,5].

The metastatic epidemiology can provide important information for assessing the metastatic site of each primary cancer and the primary site of cancer of unknown origin, and for considering biological metastatic mechanisms. There are several studies on rare genitourinary cancer metastases [6–10] and metastases to genitourinary organs [11–23]. Nevertheless, these are limited due to the small number of cases evaluated. Further, several of these reports were conducted before the early 2000s. The adaption of previous epidemiologic data, such as screening, treatment systems, life expectancy, and exposure to carcinogenic risks, as a reference in contemporary cancer epidemiology is unclear due to differences in the medical and social environments.

Although limited to cases involving fatal diseases, a pathologic examination at autopsy remains the gold standard for confirming metastatic sites in malignant tumors. The Japanese Society of Pathology publishes the Annual of the Pathological Autopsy Cases, which was first published in 1960, from medical institutions throughout Japan [24]. This registry database is a valuable public dataset that has been examining the association between primary cancer and metastatic sites based on the International Classification of Diseases, tenth revision (ICD-10) since 1993. Moreover, it collects data from approximately 1.2 million autopsies until 2020. However, these reports are published annually and biased due to the autopsies [25]. Therefore, an integrated analysis and the actual distribution of deaths based on cancer type should be considered when interpreting the frequency of metastases in the primary sites.

This study aimed to evaluate the number, frequency, and proportion of metastatic sites according to rare genitourinary organ–type cancer and the primary site of genitourinary metastases, using the data published in the Annual of the Pathological Autopsy Cases in Japan and the Japanese Mortality Database, to adjust data for temporal variations in autopsies.

2. Patients and methods

2.1. Data collection and processing

This research project was approved by the Research Ethics Review Board of Toranomon Hospital (approval no. 2451), and it was conducted in accordance with the provisions of the Declaration of Helsinki. All data cited in this paper were derived from published information. Thus, the need for informed consent was waived. Three authors (S.O., T.H., and M.H.) triple checked the input errors and consistency in the database.

We extracted a cross-tabulation table between the primary site of malignancy and organ metastasis from the Annual of the Pathological Autopsy Cases in Japan from 1993 to 2020, which was compiled according to the codes in ICD-10. The primary malignancy site was defined to include suspected malignancy and nonfatal primary cancer in patients with multiple cancers. A metastatic organ was defined as invasion and distant metastases in the Annual of the Pathological Autopsy Cases. The number of metastases was counted as one organ metastasis, even if there were multiple metastases in a single organ. The number of autopsy cases according to the primary site in each year was extracted from other tables because of multiple metastatic organs per case and overlapping primary sites in the metastatic organ analysis. For latent cancers, we extracted the cases of prostate, thyroid, lung, kidney, liver, and stomach cancers, as described previously. To obtain the number of actual cases analyzed, the number of latent cancer cases was subtracted from the number of each autopsy case. The average number of latent cancers was substituted for the years in which these were not reported for kidney, liver, and stomach cancers.

Aggregate information on the number of mortalities based on cancer type since 1993 was extracted from the Japanese Mortality Database [26]. The number of autopsies according to primary malignancy in each year was adjusted for the number of deaths, and the estimated adjusted metastatic number was calculated. Since the Japanese Mortality Database [26] was based on ICD-9 before 1994, mortality information before 1994 was used for data integration by linking ICD-9 and ICD-10 [27].

The classification of the primary sites collected was defined in conjunction with ICD-10 (Table 1). In particular, the sites of primary genitourinary cancers (ICD-10) were as follows: penis (C60), testis (C62), kidney (C64), renal pelvis (C65), ureter (C66), bladder (C67), urethra (C68.0, 68.1), adrenal glands (C74), and upper urinary tract (C65, 66). Male patients with primary lesions in the genitalia (C63) and those with lesions in other urinary organs (C68.8, 68.9) for which the site was difficult to identify were excluded from the analysis. Owing to the high incidence and favorable prognosis of prostate cancer (C61), this study observed multiple nonfatal cases. Therefore, a prostate cancer analysis was excluded from the analysis. Organs such as the adrenal gland, bladder, kidney, penis, prostate, renal pelvis, and testis were selected for each genitourinary metastatic organ.

Table 1 – Summary of cancer types analyzed and case number of reports

Cancer group	ICD-10	Analysis case (*N*)	Reported case (*N*)	Latent case (*N*)	Death case (*N*)
Primary genitourinary cancers					
Penile cancer	C60	155	155	–	3420
Prostate cancer	C61	10 369	22 083	11 714	258 058
Testicular tumor	C62	604	604	–	2479
Kidney cancer	C64	5970	7513	1543[a]	107 749
Bladder cancer	C67	6717	6717	–	173 796
Adrenal cancer	C74	761	761	–	5467
Upper urinary tract cancer	C65, C66	2795	2795	–	71 911
Renal pelvic cancer	C65	1591	1591	–	36 172
Ureteral cancer	C66	1204	1204	–	35 739
Genital cancer	C51, C52, C68.0.1	523	523	–	10 932
Urethral cancer	C68.0.1	86	86	–	1677
Other major primary cancers					
Anal cancer	C21	209	209	–	8984
Bile duct cancer	C24	5450	5450	–	284 456
Bone cancer	C40, C41	925	925	–	11 776
Cervix cancer	C53	2921	2921	–	70 188
Colon cancer	C18	22 416	22 416	–	782 119
Esophagus cancer	C15	11 489	11 489	–	302 087
Gall bladder cancer	C23	5290	5290	–	178 640
Stomach cancer	C16	40 559	41 491	932[b]	1 360 383
Hematologic tumor	C90–96	28 939	28 939	–	312 269
Liver cancer	C22	41 423	42 879	1456[c]	872 618
Lymphoid tumor	C26.1, C81–88	16 408	16 408	–	268 226
Mammary cancer	C50	7589	7589	–	313 654
Ovarian cancer	C56	4033	4033	–	123 515
Pancreas cancer	C25	18 329	18 329	–	699 525
Rectal cancer	C19, C20	9274	9274	–	378 022
Respiratory cancer	C33, C34	55 378	57 682	2304	1 743 424
Retroperitoneal sarcoma	C45, C48.0	3486	3486	–	50 207
Skin cancer	C43, C44, C46	2591	2591	–	34 854
Thyroid cancer	C73	5123	11 206	6083	41 887
Uterus cancer	C54	2270	2270	–	46 429
Other cancers	–	29 071	29 071	–	529 760

ICD-10 = International Classification of Diseases, tenth revision; *N* = number of cases.
[a] This value includes data from 110 cases with missing value supplements.
[b] This value includes data from 429 cases with missing value supplements.
[c] This value includes data from 676 cases with missing value supplements.

2.2. Statistical analysis

The R software (version 4.2.3) and a spreadsheet program for data processing, general statistical analysis, and graph generation were used. The crude and death-adjusted numbers of organ metastases were analyzed according to primary cancer. Death-adjusted metastatic number per year was calculated for the number of metastases per year divided by the number of autopsies per year in the Annual of the Pathological Autopsy Cases in Japan. Then, it was multiplied by the number of deaths in the Japanese Mortality Database. The metastatic frequency (probability of occurrence; ratio of number per person) of each primary cancer site was calculated as the ratio of the number of metastases per number of autopsies. The proportion (percentage) of organ metastases based on each primary cancer was calculated as the proportion of the number of each organ metastasis to the total number of all metastatic organs. The frequency and death-adjusted metastatic event number according to each primary tumor to genitourinary organ metastasis and the genitourinary organ metastasis proportion by primary cancer were analyzed. The frequency of metastasis in each organ and the proportion of organ metastases based on primary genitourinary cancer are presented as Cleveland dot plots [28]. The proportion, frequency, and death-adjusted numbers of tumors metastasizing to the genitourinary organ are shown in the Nightingale's Rose Chart, and heatmap figures using the R package ggplot2 and ComplexHeatmap [29]. The default clustering method used was "hierarchical clustering" with a "Euclidean distance." The outlier tests of the metastatic proportion using the Smirnov-Grubbs test in the R package outliers and Tukey Fences (K = 1.5) were performed to explore tumor-specific metastatic sites [30]. The outliers in both tests were considered as characteristic associations between the primary cancer site and genitourinary organ metastasis. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the pathologic autopsy cases in Japan

In total, 365 099 autopsies and 835 959 metastatic organs were analyzed in the integrated database from 1993 to 2020. The autopsy patients were Japanese, mostly Asians, with a male-to-female ratio of 2.28 and a mean age of 69.3 yr. The total metastatic frequency (95% confidence interval [CI]) for the number of organ sites with metastatic spread per person in all analyzed cases was 2.289 (2.285–2.295).

Table 1 shows the summary of cancer types analyzed and the number of autopsy reports and deaths via the analysis of primary genitourinary cancers. The total metastatic frequencies (95% CI) of each cancer per person were as follows: penis, 2.019 (1.802–2.256); testis, 2.551 (2.426–2.682); upper urinary tract, 2.875 (2.812–2.938); adrenal, 3.350 (3.221–3.482); and urethra, 3.570 (3.182–3.992).

For the metastases to the genitourinary organs, the analysis included 53 125 adrenal metastases, 36 645 kidney

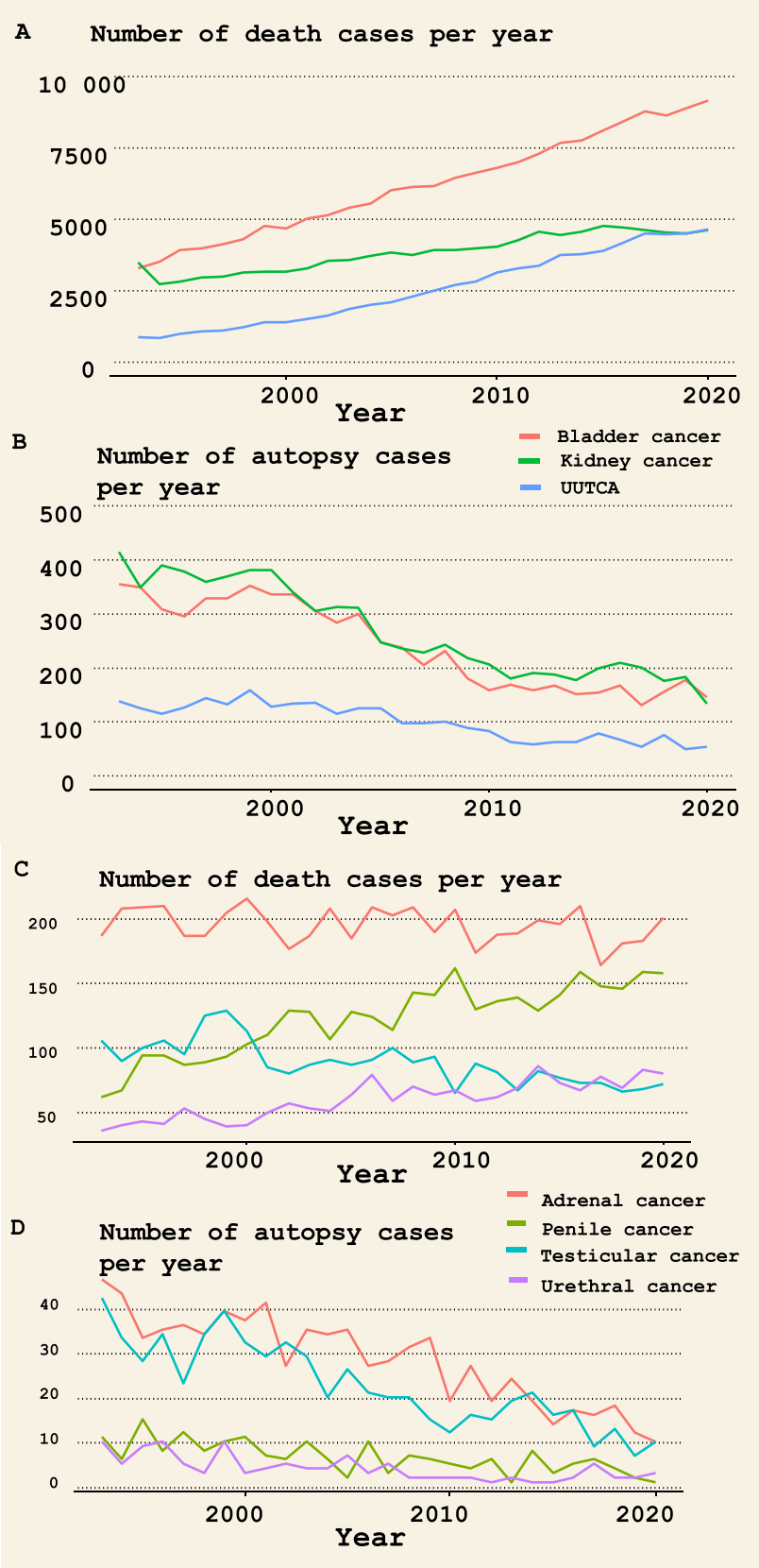

Fig. 1 – Changes in the number of deaths in Japan and the number of autopsies in genitourinary organ–type cancers: changes in (A) the number of deaths in Japan and (B) the number of autopsies in the database over time for bladder, kidney, and upper urinary tract cancers and changes in (C) the number of deaths in Japan and (D) the number of autopsies in the database over time for adrenal, penile, testicular, and urethral cancers. UUTCA = upper urinary tract cancer.

metastases, 12 329 bladder metastases, 3930 prostate metastases, 2715 testicular metastases, 1104 renal pelvis metastases, and 115 penile metastases.

3.2. Trends in deaths and pathologic autopsy cases in Japan

Figure 1A (bladder cancer, kidney cancer, and UUTCA) and Figure 1C (adrenal, testicular, penile, and urethral cancers) show the trends in genitourinary cancer–related deaths in Japan and the number of autopsies according to primary genitourinary cancer in the Japanese Pathological Autopsy Report. The mortality rate of UUTCA was increasing, similar to that of bladder cancer. However, it was increasing more rapidly than other genitourinary cancers. In contrast, the number of deaths from other rare genitourinary organ–type cancers, such as urethral, testicular, penile, and adrenal cancers, did not change. Despite the increased number of deaths, the number of autopsies exhibited a decreasing trend, as depicted in Figure 1B (bladder cancer, kidney cancer, and UUTCA) and Figure 1D (adrenal, testicular, penile, and urethral cancers).

3.3. Metastatic sites in rare genitourinary organ–type cancers

The major metastatic sites (range of frequency ratios [number per person] and proportions) of rare genitourinary cancers were the lungs (0.38–0.47 and 13.0–18.8%, respectively), liver (0.21–0.56 and 10.5–16.6%, respectively), bone (0.16–0.33 and 6.5–9.8%, respectively), adrenal gland (0.10–0.20 and 4.8–6.8%, respectively), peritoneum (0.09–0.16 and 4.5–5.5%, respectively), and kidney (0.07–0.22 and 3.5–6.7%, respectively). Figure 2 and Supplementary Table 1 show the frequency of metastasis in each organ. Figure 3 depicts the proportion of organ metastases in UUTCA with bladder and kidney cancers. The proportion

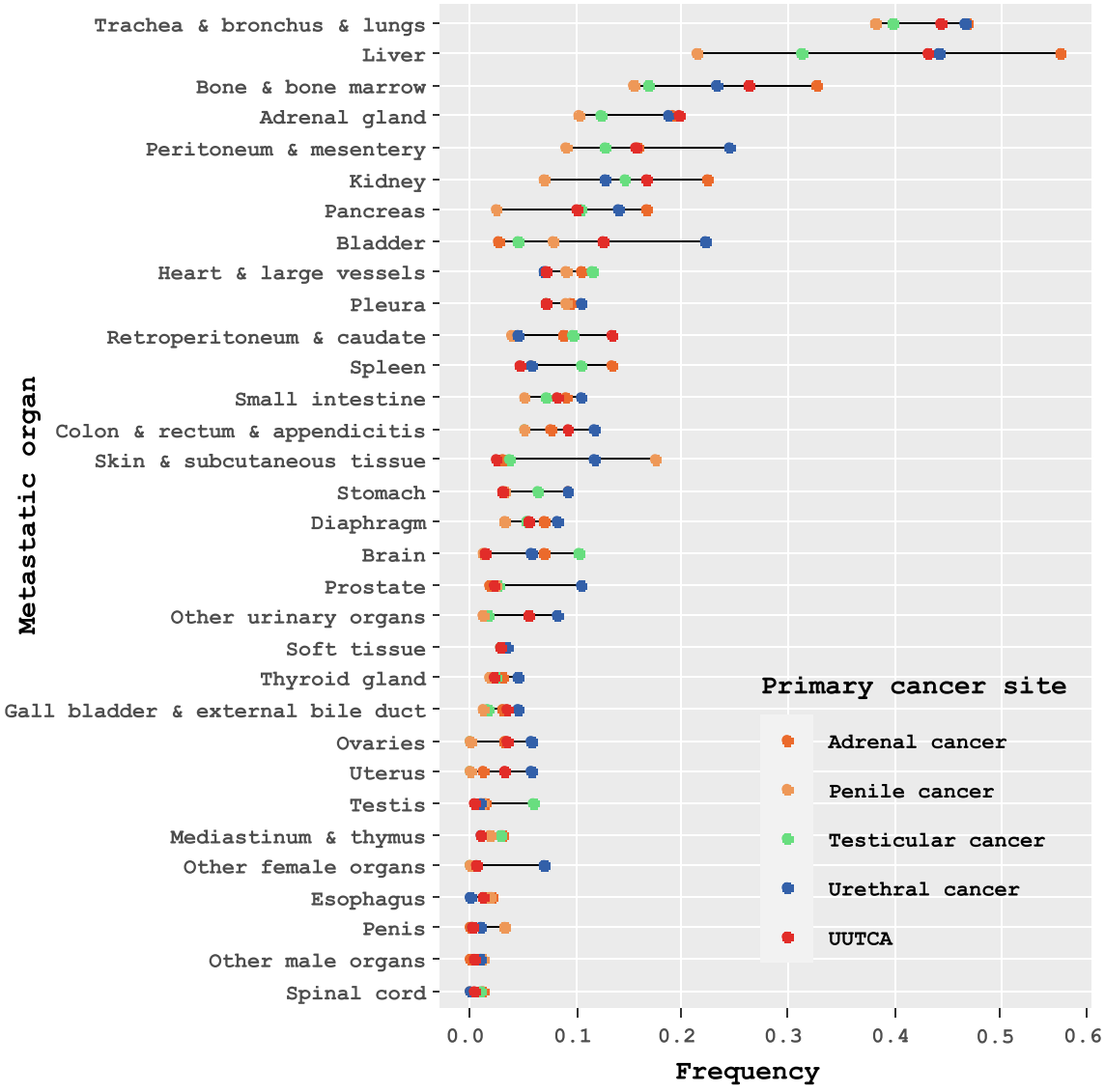

Fig. 2 – Cleveland dot plots for the frequency of metastasis in each organ in rare genitourinary organ–type cancers based on the integrated autopsy data. Each metastatic organ is represented by a color-coded dot plot (red: adrenal cancer, moss green: penile cancer, light green: testicular cancer, blue: urethral cancer, and UUTCA: purple). The frequency of metastases (the ratio of metastases per person) is the number of metastatic organs divided by the number of autopsy reported cases. UUTCA = upper urinary tract cancer.

of organ metastases in UUTCA was compared with that in kidney cancer, which is anatomically closer, and bladder cancer, which has a similar pathology. Compared with kidney cancer and UUTCA (green numbers in Fig. 3), the metastatic organs with a difference of over 2% in proportion were the lungs (15.4%, 16.3%, and 19.3% in UUTCA, renal pelvic cancer, and kidney cancer, respectively), adrenal gland (6.8%, 8.1%, and 9.0%, respectively), cardiovascular system (2.5%, 2.8%, and 5.5%, respectively), and pleura (2.5%, 2.8% and 4.9%, respectively), and compared with bladder cancer (red numbers in Fig. 3), these organs were the liver (15.0% and 12.4% in UUTCA and bladder cancer, respectively), colon (3.2% and 5.7%, respectively), and prostate (0.8% and 3.8%, respectively). Figure 4 shows the proportion of organ metastases from other rare genitourinary organ–type cancers. Supplementary Tables 2 and 3 present detailed data on each cancer, including the number and proportion of crude and death-adjusted metastases. The metastatic sites of each cancer were unique in each cancer type.

3.4. *Proportion of metastases to genitourinary organs from the primary tumor*

Figure 5 shows the Nightingale's Rose Chart for the proportion of the ten major tumors metastasizing to the genitourinary organs (Fig. 5A) and a schematic diagram of the death-adjusted predicted proportion of the top five primary sites in genitourinary organ metastases (Fig. 5B). Table 2 shows the estimated number and proportion of primary sites with the number of deaths adjusted, which indicates the predicted probability of the primary site when genitourinary organ metastases are found. The major primary malignancies metastasizing to the genitourinary organs (the range of proportions) were the respiratory (5.6–34.0%), stomach (4.7–27.0%), hematologic (0.9–24.9%), lymphoid (2.4–22.2%), bladder (0.8–20.0%), prostate (0.7–14.1%), rectal (2.0–11.7%), and pancreatic (2.6–11.0%) cancers. Supplementary Table 4 shows the crude data. Figure 6 depicts the association between the metastatic genitourinary

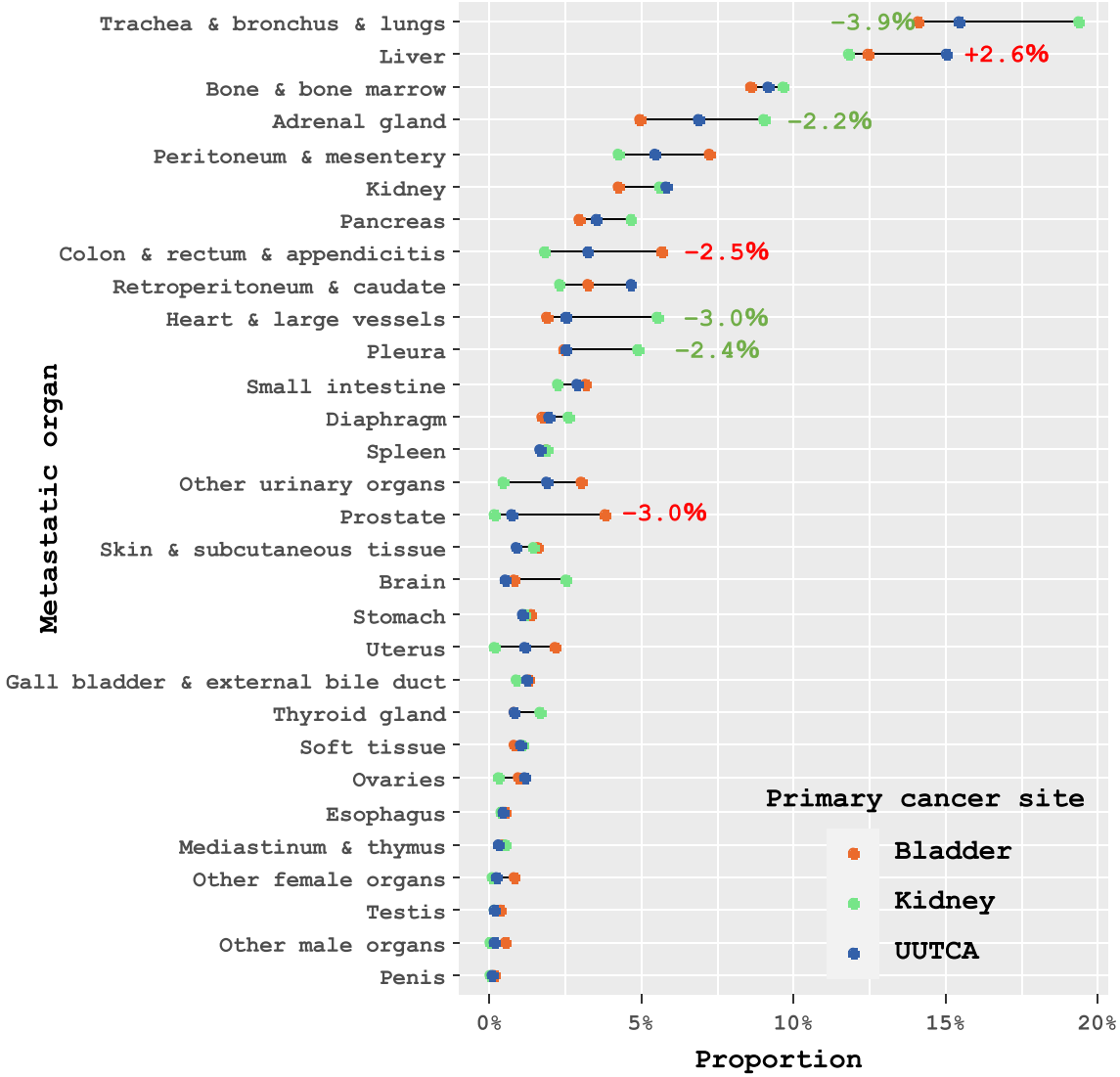

Fig. 3 – Cleveland dot plots for the proportions of metastatic organ in bladder cancer, kidney cancer, and upper urinary tract cancer (UUTCA) based on the integrated autopsy data. Each metastatic site is represented by a color-coded dot plot (red: bladder cancer, green: kidney cancer, and blue: UUTCA). The metastatic organs had a difference of >2% in UUTCA compared with those in kidney (green numbers) and bladder (red numbers) cancers. The proportion of metastatic organ is the percentage of the number of each organ metastasis to the total number of all metastatic organs.

organs and the primary tumor origin. Further, it shows the frequency according to each primary tumor origin (red-blue heatmap, left), frequency of genitourinary organ metastasis (green heatmap, middle), death-adjusted number of each genitourinary organ metastasis (bar graph, top), primary cancer origin (bar chart. middle), and death-adjusted event number of metastases to each genitourinary organ (purple heatmap, right). In terms of the genitourinary organs, metastases were common in the adrenal glands, kidneys, and bladder. Lung, kidney, and pancreatic cancers were more likely to metastasize to the adrenal glands, adrenal cancer and hematolymphoid tumors to the kidneys, and intrapelvic cancers to the bladder. In terms of the frequency of genitourinary organ metastases according to the primary site, several metastatic combinations were characterized significantly by the outlier tests. Kidney metastasis was commonly observed in lymphoid tumors (0.029); penile metastasis in penile (0.032), genital (0.008), anal (0.005), bladder (0.003), and testicular (0.003) cancers; prostate metastases in anal (0.077) and bladder (0.070) cancers; renal pelvic metastases in upper urinary tract (0.023) and bladder (0.012) cancers; and testicular metastases in testicular (0.060), hematologic (0.039), and lymphoid (0.037) tumors.

4. Discussion

Various factors are associated with distant metastasis [31]. Embryologically and anatomically, genitourinary organs have a high affinity to each other. However, the frequency of metastasis from adrenal cancer during autopsy is approximately 1.5 times higher than that from penile cancer. Adrenal cancer exhibited a high blood flow–rich organ metastatic tendency to the liver, bone, kidney, pancreas, and spleen. Meanwhile, penile cancer had a low blood

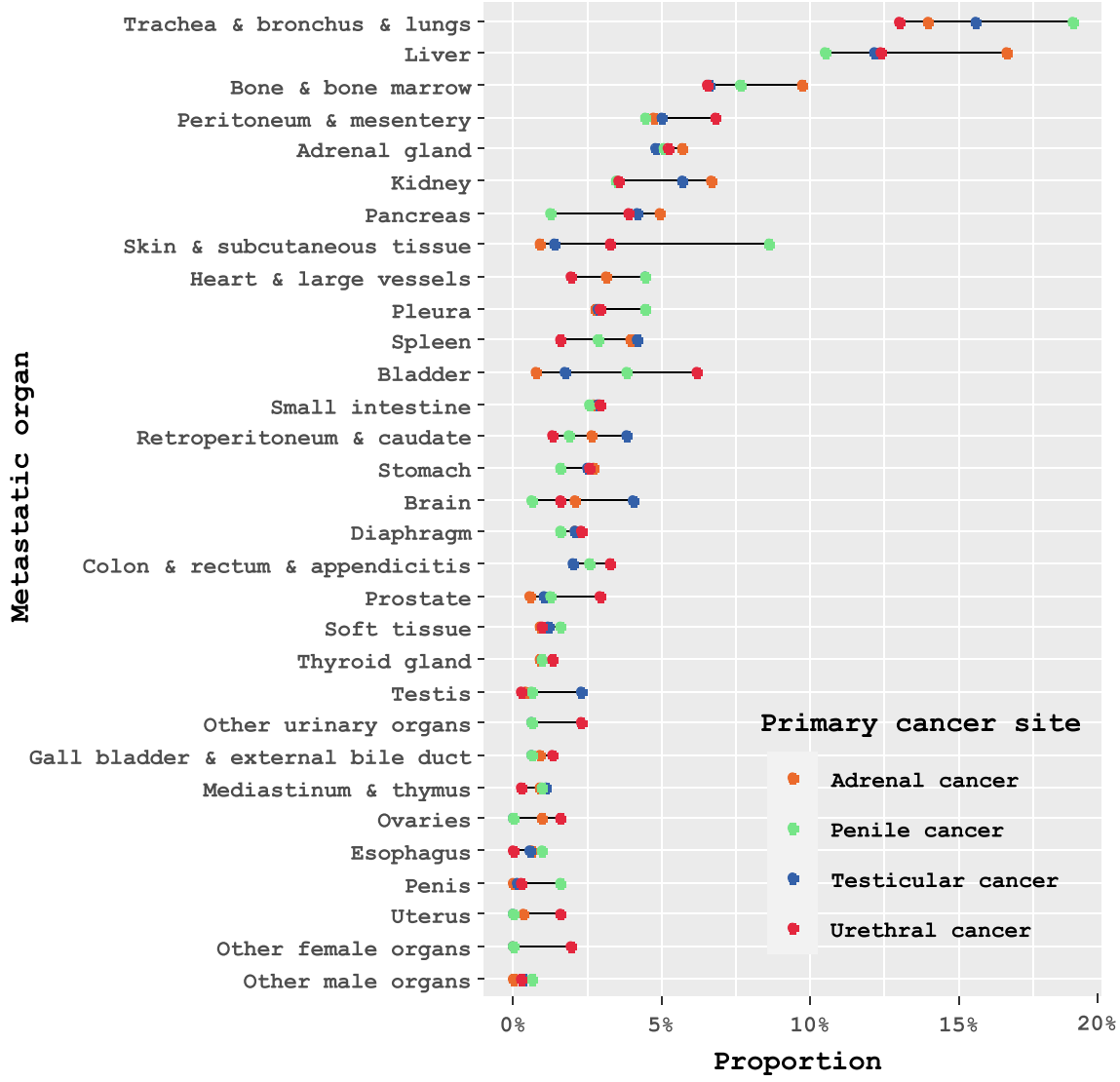

Fig. 4 – Cleveland dot plots for the proportions of metastatic organ in adrenal, penile, testicular, and urethral cancers based on the integrated autopsy data. Each metastatic site is represented by a color-coded dot plot (red: adrenal cancer, green: penile cancer, blue: testicular cancer, and purple: urethral cancer). The proportion of metastatic organ is the percentage of the number of each organ metastasis to the total number of all metastatic organs.

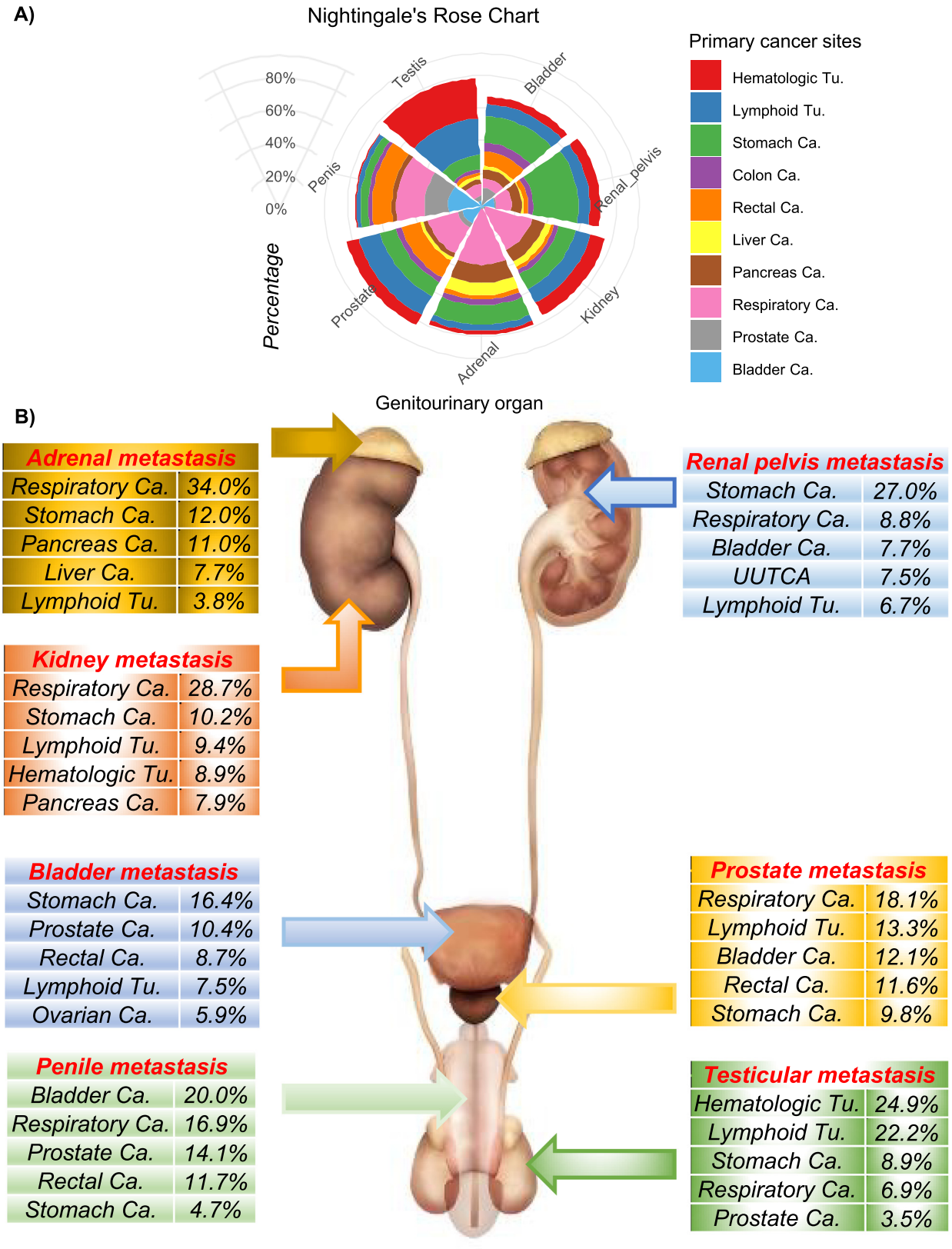

Fig. 5 – (A) Nightingale's Rose Chart of the ten major primary cancers and (B) the schema of the top five primary cancers that metastasize to genitourinary organs. The proportions of the ten primary cancer sites in genitourinary organ metastases were compared according to each organ in the Nightingale's Rose Chart. Proportions are the estimated number of cases of each primary cancer as a percentage of the estimated total number of all primary cancers in each genitourinary metastatic organ. Ca. = cancer; Tu. = tumor; UUTCA = upper urinary tract cancer.

Table 2 – Estimated case number (death-adjusted numbers) and proportion of primary cancer metastasis to the genitourinary organ in death-adjusted data

Primary cancer group (ICD-10)	Genitourinary metastatic organ						
	Adrenal gland Adjusted *n*[a] (%[b])	Bladder Adjusted *n* (%)	Kidney Adjusted *n* (%)	Penis Adjusted *n* (%)	Prostate Adjusted *n* (%)	Renal pelvis Adjusted *n* (%)	Testis Adjusted *n* (%)
Accessory sinus cancer (C31)	918 (0.1)	69 (0.0)	703 (0.1)	0 (0.0)	26 (0.0)	12 (0.0)	164 (0.4)
Adrenal cancer (C74)	988 (0.1)	162 (0.1)	1186 (0.1)	7 (0.3)	107 (0.1)	18 (0.1)	76 (0.2)
Anal cancer (C21)	2338 (0.2)	2320 (0.8)	820 (0.1)	18 (0.7)	718 (0.7)	50 (0.2)	18 (0.0)
Bile duct cancer (C24)	33 583 (2.4)	3652 (1.2)	13 585 (1.7)	0 (0.0)	263 (0.3)	838 (3.1)	86 (0.2)
Bone cancer (C40, 41)	1389 (0.1)	459 (0.1)	2262 (0.3)	0 (0.0)	115 (0.1)	11 (0.0)	233 (0.5)
Brain cancer (C70, 71)	1923 (0.1)	461 (0.1)	1897 (0.2)	0 (0.0)	294 (0.3)	46 (0.2)	219 (0.5)
Cervix cancer (C53)	7215 (0.5)	14 243 (4.6)	6315 (0.8)	0 (0.0)	0 (0.0)	209 (0.8)	0 (0.0)
Colon cancer (C18)	49 047 (3.5)	16 740 (5.4)	23 121 (2.9)	59 (2.3)	3221 (3.3)	871 (3.2)	932 (2.0)
Endocrine cancer (C75)	10 (0.0)	2 (0.0)	11 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Esophagus cancer (C15)	34 622 (2.5)	2867 (0.9)	24 295 (3.1)	87 (3.5)	1924 (2.0)	571 (2.1)	732 (1.6)
Eye cancer (C69)	234 (0.0)	36 (0.0)	233 (0.0)	0 (0.0)	46 (0.0)	0 (0.0)	31 (0.1)
Gall bladder cancer (C23)	28 398 (2.0)	4947 (1.6)	12 165 (1.5)	22 (0.9)	588 (0.6)	613 (2.3)	164 (0.4)
Stomach cancer (C16)	166 476 (12.0)	50 492 (16.4)	80 884 (10.2)	117 (4.7)	9457 (9.8)	7250 (27.0)	4070 (8.9)
Genital cancer (C51, 52, 68.0-1)	2288 (0.2)	1896 (0.6)	1189 (0.1)	46 (1.8)	344 (0.4)	21 (0.1)	22 (0.0)
Germ cell tumor (C58, 62)	307 (0.0)	126 (0.0)	385 (0.0)	10 (0.4)	57 (0.1)	16 (0.1)	137 (0.3)
Testicular tumor (C62)	290 (0.0)	115 (0.0)	350 (0.0)	10 (0.4)	57 (0.1)	15 (0.1)	136 (0.3)
Hematologic tumor (C90–96)	35 182 (2.5)	14 327 (4.6)	70 431 (8.9)	23 (0.9)	6890 (7.2)	1657 (6.2)	11 377 (24.9)
Kidney cancer (C64)	17 795 (1.3)	1201 (0.4)	11 035 (1.4)	59 (2.3)	377 (0.4)	648 (2.4)	306 (0.7)
Laryngeal cancer (C32)	962 (0.1)	20 (0.0)	945 (0.1)	0 (0.0)	54 (0.1)	0 (0.0)	88 (0.2)
Liver cancer (C22)	107 369 (7.7)	6626 (2.1)	29 960 (3.8)	0 (0.0)	1938 (2.0)	279 (1.0)	938 (2.1)
Lymphoid tumor (C26.1, C81–88)	52 741 (3.8)	23 253 (7.5)	74 546 (9.4)	59 (2.4)	12 780 (13.3)	1802 (6.7)	10 161 (22.2)
Mammary cancer (C50)	46 347 (3.3)	7342 (2.4)	18 646 (2.3)	0 (0.0)	46 (0.0)	751 (2.8)	28 (0.1)
Mediastinum cancer (C37–39)	5982 (0.4)	539 (0.2)	4063 (0.5)	2 (0.1)	148 (0.2)	9 (0.0)	151 (0.3)
Nasal cavity & middle ear cancer (C30)	1028 (0.1)	170 (0.1)	912 (0.1)	0 (0.0)	69 (0.1)	0 (0.0)	127 (0.3)
Nerve cancer (C47, 72)	155 (0.0)	98 (0.0)	242 (0.0)	0 (0.0)	94 (0.1)	0 (0.0)	18 (0.0)
Oral cancer (C00–C06)	7366 (0.5)	267 (0.1)	6184 (0.8)	0 (0.0)	223 (0.2)	0 (0.0)	299 (0.7)
Ovarian cancer (C56)	13 634 (1.0)	18 154 (5.9)	8826 (1.1)	0 (0.0)	0 (0.0)	263 (1.0)	0 (0.0)
Pancreas cancer (C25)	152 355 (11.0)	17 593 (5.7)	63 013 (7.9)	65 (2.6)	2829 (2.9)	1636 (6.1)	1266 (2.8)
Penile cancer (C60)	270 (0.0)	137 (0.0)	115 (0.0)	41 (1.6)	39 (0.0)	0 (0.0)	18 (0.0)
Pharynx cancer (C10–12)	4288 (0.3)	506 (0.2)	3964 (0.5)	20 (0.8)	360 (0.4)	93 (0.3)	456 (1.0)
Prostate cancer (C61)	17 041 (1.2)	32 094 (10.4)	5819 (0.7)	356 (14.1)	2805 (2.9)	320 (1.2)	1595 (3.5)
Rectal cancer (C19, 20)	32 959 (2.4)	26 957 (8.7)	16 421 (2.1)	293 (11.7)	11 217 (11.6)	690 (2.6)	897 (2.0)
Respiratory cancer (C33, C34)	472 225 (34.0)	17 162 (5.6)	228 301 (28.7)	425 (16.9)	17 383 (18.1)	2371 (8.8)	3135 (6.9)
Retroperitoneal sarcoma (C45, 48.0)	7179 (0.5)	3177 (1.0)	7221 (0.9)	10 (0.4)	734 (0.8)	187 (0.7)	594 (1.3)
Salivary glands & tonsil cancer (C07–09)	2459 (0.2)	260 (0.1)	1466 (0.2)	0 (0.0)	207 (0.2)	75 (0.3)	89 (0.2)
Skin cancer (C43, 44, 46)	4979 (0.4)	1781 (0.6)	4800 (0.6)	16 (0.6)	641 (0.7)	179 (0.7)	626 (1.4)
Small intestine cancer (C17)	2813 (0.2)	1460 (0.5)	2390 (0.3)	0 (0.0)	311 (0.3)	60 (0.2)	214 (0.5)
Thyroid cancer (C73)	2333 (0.2)	207 (0.1)	2288 (0.3)	0 (0.0)	71 (0.1)	5 (0.0)	21 (0.0)
Upper urinary tract cancer (C65, 66)	12 689 (0.9)	8892 (2.9)	11 537 (1.5)	69 (2.7)	1791 (1.9)	2009 (7.5)	342 (0.7)
Urinary bladder cancer (C67)	14 241 (1.0)	2425 (0.8)	11 912 (1.5)	504 (20.0)	11 623 (12.1)	2068 (7.7)	1407 (3.1)
Uterus cancer (C54)	4897 (0.4)	7038 (2.3)	3704 (0.5)	0 (0.0)	0 (0.0)	91 (0.3)	0 (0.0)
Other cancers	38 029 (2.7)	18 186 (5.9)	36 308 (4.6)	208 (8.3)	6511 (6.8)	1134 (4.2)	4655 (10.2)
Total	1 387 054 (100.0)	308 345 (100.0)	794 101 (100.0)	2516 (100.0)	96 303 (100.0)	26 853 (100.0)	45 696 (100.0)

ICD-10 = International Classification of Diseases, tenth revision.
[a] Adjusted *n*: estimated case number of each genitourinary metastatic organ.
[b] %: proportion of "adjusted *n*" to the estimated total number of each genitourinary metastatic organ from all primary cancers.

flow–rich organ metastatic tendency. Therefore, even in fatal conditions, there are differences in cellular, molecular, and immunologic aspects among genitourinary cancers.

The age-adjusted incidence of UUTCA in Japan is higher than that in other countries [32], and the number of deaths is almost equal. Kidney and renal pelvic cancers, which are anatomically close, have different metastatic patterns in this registry. Our study commonly presented cases of metastasis to adjacent organs. Kidney cancer is more likely to metastasize hematogenously. However, UUTCA has a greater affinity to the peritoneum and retroperitoneum (4.9% in renal pelvic cancer and 5.5% in UUTCA) in metastatic cases. In bladder cancer and UUTCA, there are differences in metastases to adjacent organs including the colon and prostate, and distant metastasis to liver.

Regarding the location of genitourinary metastatic organs, metastases to the kidneys and adrenal glands were predominantly hematogenous and bilateral [1]. The kidney is a blood-rich organ [33], and a rich blood supply affects the development of metastasis in this structure. Further, adrenal metastasis is believed to be attributed to the abundance of sinusoidal blood flow [34]. The high frequency of renal pelvic metastasis from stomach cancer may be caused by peritoneal dissemination [35]. However, the urinary tract is a ductal organ with poor blood flow, and metastasis was relatively rare [20]. In prostate metastasis, the common

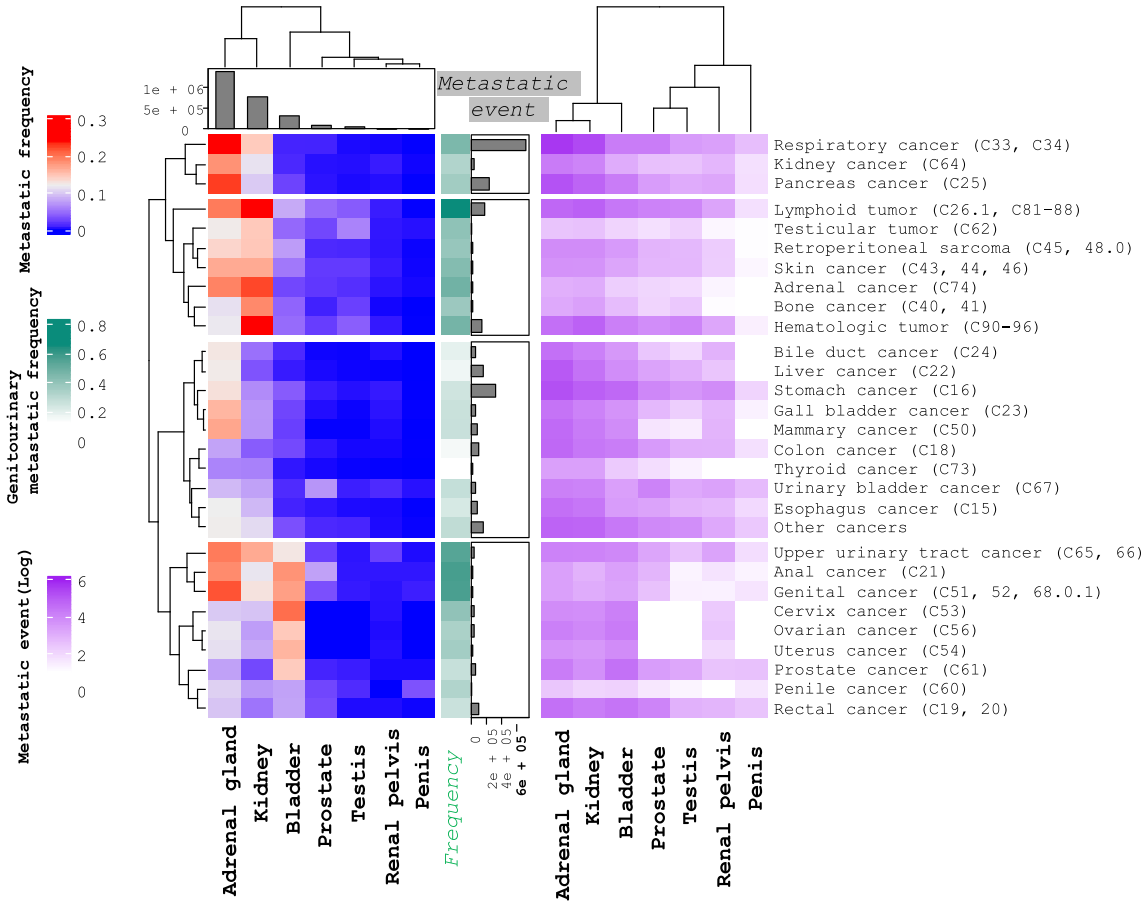

Fig. 6 – Complex heatmap of the metastatic genitourinary organs and the primary tumor origin. The red-blue heatmap (left) represents the frequency of each primary tumor origin. The green heatmap (middle) represents the frequency of genitourinary organ metastasis. The purple heatmap (right) represents the estimated number of metastases to each genitourinary organ. The bar graph at the top represents the total number of each genitourinary organ metastasis. The bar chart at the middle represents the total number of each primary cancer origin. Hierarchical clustering using Euclidean distance was used to sort the data, and those that are close to one another in the hierarchy are listed in blocks.

primary cancers were reported to be lung cancer, pancreatic cancer, and melanoma [20]. Our study revealed that the prevalence of lymphoid tumors was higher in prostate metastases. A previous study has reported testicular metastasis from hematolymphoid tumors [1]. The higher rate of hematolymphoid tumor metastasis than that of solid tumors may be related to the unique characteristics of the testicular tissue. It is referred to as "tumor sanctuary" [14], and the limited metastasis of solid tumors is caused by the lower temperature of the scrotum and the blood-testis barrier [36].

This study performed a comprehensive analysis of the database comprising a substantial number of autopsies performed at different institutions nationwide with a common ICD-10–based format. The extensive number of cases ensures that the database remains epidemiologically and statistically robust for rare organ–type cancers and metastases to genitourinary organs. By adjusting the data for the number of deaths, the real-world number, proportion, and frequency of metastases can be evaluated, allowing for a comprehensive discussion of metastases to genitourinary organs and metastases of genitourinary cancers. However, this study had several limitations that should be considered. First, it performed a secondary analysis of the database rather than an analysis based on individual cases, which prevents the presentation of detailed relationships. In addition, there was limited information regarding the histologic type of the tumors. Owing to the presence of multiple and concomitant early-stage cancers, the incidence of fatal cancers and organ metastasis with good prognosis and high-incidence cancers were challenging to assess. Second, since cases requiring autopsy were examined, the presence of a concomitant selection bias could not be ruled out, and the actual clinical and autopsy populations were divergent. Third, fatal cases were analyzed based on autopsy information.

5. Conclusions

Our study examined the epidemiology of the metastatic sites from rare genitourinary organ–type cancers and the origins of genitourinary organ metastases. Data from a comprehensive Japanese autopsy registry database were adjusted to the total number of deaths in the country. Our analysis of autopsy data is unique worldwide, and it can

provide important clinical insights into the interplay between genitourinary tissues and the biology of cancer. This study has useful real-world information on metastatic recurrence in rare genitourinary organ–type cancers and the primary cancer site of genitourinary organ metastases in primary cancers of unknown origin.

Author contributions: Tomohiko Hara had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hara.
Acquisition of data: Oka, Hara.
Analysis and interpretation of data: Oka, Hara.
Drafting of the manuscript: Oka.
Critical revision of the manuscript for important intellectual content: Hara, Ito, Hayashida, Sakaguchi, Urakami.
Statistical analysis: Hara.
Obtaining funding: Urakami.
Administrative, technical, or material support: Ito, Hayashida, Urakami.
Supervision: Ito, Sakaguchi, Urakami.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.12.004.

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