法の有用性が示されており，二次化学療法の実施が推奨される(グレードB)．二次化学療法のレジメンは一次治療に応じて，一次治療がゲムシタビン塩酸塩ベースの治療であればフッ化ピリミジン薬を中心とした治療を，一次治療がフッ化ピリミジンベースの治療であればゲムシタビン塩酸塩を中心とした治療を選択する(グレードC1)."と改訂されている．

7. ステント療法部門(表6)

ガイドライン2013で新たに追加された部門でJA尾道総合病院の花田敬士先生がチーフを務めている．CQ6-1 "閉塞性黄疸を伴う切除不能例に胆道ドレナージは推奨されるか？"は推奨"切除不能膵癌に対する胆道ドレナージは，推奨される(グレードB)．切除不能膵癌に対する胆道ドレナージは，開腹による外科的減黄術より内視鏡的減黄術が推奨される(グレードB)."となっている．

CQ6-2は"切除不能膵癌に対する胆道ドレナージのアプローチルートは，経皮的と内視鏡的のどちらがよいか？"で推奨は"切除不能膵癌に対する胆道ドレナージは内視鏡的に行うことが勧められる(グレードB)."となっている．

CQ6-3 "膵癌による閉塞性黄疸に対するステントの種類は何が推奨されるか？"で，推奨は"膵癌切除不能例による閉塞性黄疸に対しては，プラスチックステント(plastic stent：PS)よりも開存期間の長い自己拡張型メタリックステント(self-expandable metallic stent：SEMS)が推奨される(グレードC1)．SEMSのなかでは被覆型(covered type)の開存期間がuncovered typeより長いことが報告されている(グレードC1)．施設ごとの技術，診療体制，患者の状態によってuncovered typeやPSの選択を考慮してもよい."となっている．coveredとuncoveredのどちらを推奨するかで公聴会，パブコメを通じてもかなり議論されたCQである．推奨としてはcoveredとuncoveredともに利用可能な推奨としている．

表6　局所進行切除不能膵癌

6ステント療法（チーフ：花田先生）

CQ6-1　閉塞性黄疸を伴う非切除例に胆道ドレナージは推奨されるか？（菅野先生）

CQ6-2　胆道ドレナージのアプローチルートは、経皮的と内視鏡的のどちらが良いか？（糸井先生）

CQ6-3　膵癌による閉塞性黄疸に対するステントの種類は何が推奨されるか？（伊佐山先生）

CQ6-4　胃十二指腸閉塞をきたした非切除例に対する治療法は何が推奨されるか？(花田先生)

CQ6-4は"胃十二指腸閉塞をきたした切除不能例に対する治療法は 何が推奨されるか？"で推奨は"全身状態が良好で比較的長期の予後が期待される症例には外科的胃空腸吻合術，それ以外の症例には内視鏡的十二指腸ステント挿入術が推奨される(グレードB)."となっている．

4　おわりに

膵癌診療ガイドラインは2006年[1]，2009年[2]そして2回目の改訂後に2013年10月[3]に金原出版より出版された．膵癌診療ガイドラインも版を重ねるごとに内容も充実してきているが，2016年改訂を目指し，日本膵臓学会膵癌診療ガイドライン改訂委員会で改訂活動を開始している．

文　献

1) 日本膵臓学会膵癌診療ガイドライン作成小委員会：科学的根拠に基づく膵癌診療ガイドライン2006年版．金原出版，東京，2006
2) 日本膵臓学会膵癌診療ガイドライン改訂委員会：科学的根拠に基づく膵癌診療ガイドライン2009

年版．金原出版，東京，2009
3) 日本膵臓学会膵癌診療ガイドライン改訂委員会：科学的根拠に基づく膵癌診療ガイドライン2013年版．金原出版，東京，2013
4) Maeda A, Boku N, Fukutomi A et al : Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01). Jpn J Clin Oncol 38 : 227–229, 2008
5) Minds診療ガイドライン選定部会：Minds診療ガイドライン作成の手引き2007．医学書院，東京，2007

*　　*　　*

INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2014) 21, 527–534 doi: 10.1111/iju.12367

JUA Cancer Registration Statistics

Oncological outcomes of renal pelvic and ureteral cancer patients registered in 2005: The first large population report from the Cancer Registration Committee of the Japanese Urological Association

Hiroyuki Fujimoto,[1,2] Hiroyuki Nakanishi,[1,2] Tsuneharu Miki,[1,3] Hiro-omi Kanayama,[1,4] Chikara Ohyama,[1,5] Kazuhiro Suzuki,[1,6] Hiroyuki Nishiyama,[1,7] Masatoshi Eto,[1,8] Seiji Naito,[1,9] Tomoharu Fukumori,[1,4] Yoshinobu Kubota,[1,10] Satoru Takahashi,[1,11] Yukio Homma[1,12] and Kazumi Kamoi[1,3]

[1]Cancer Registration Committee, Japanese Urological Association, [2]Urology Division, National Cancer Center Hospital, Tokyo, [3]Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine, Kyoto, [4]Department of Urology, School of Medicine, University of Tokushima, Tokushima, [5]Department of Urology, Hirosaki University Graduate School of Medicine, Aomori, [6]Department of Urology, Gunma University School of Medicine, Gunma, [7]Department of Urology, Faculty of Medicine, University of Tsukuba, Ibaraki, [8]Department of Urology, Faculty of Life Sciences, Kumamoto University, Kumamoto, [9]Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, [10]Department of Urology, Yokohama City University Graduate School of Medicine, Kanagawa, [11]Department of Urology, Nihon University, Tokyo, [12]Department of Urology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Abbreviations & Acronyms
JUA = Japanese Urological Association

Correspondence: Hiroyuki Fujimoto M.D., Urology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Email: juacr@nifty.com

Received 30 October 2013; accepted 30 October 2013. Online publication 23 December 2013

Objectives: To describe the clinical and pathological characteristics and the outcomes of renal pelvic and ureteral cancer patients diagnosed in 2005 in Japan.

Methods: In 2011, data were collected from renal pelvic and ureteral cancer patients diagnosed in 2005. A total of 1509 registered patients from 348 institutions were analyzed. Epidemiology and survival were analyzed based on each cancer location and on cancer multiplicity.

Results: The 5-year overall survival of the 1509 patients was estimated at 0.64. Open surgery was carried out in 409 renal pelvic cancer cases (66.9%) and 315 ureteral cancer cases (63.0%). The retroperitoneal approach was common, and lymph node dissection was carried out in approximately one-third of open surgery cases and one-fifth of laparoscopic cases. Approximately 60% of the operated unilateral renal pelvic or ureteral cancer was diagnosed as invasive, and just 14.6% was diagnosed as stage pTa. Distribution of the estimated worst tumor grade was significantly different for renal pelvic cancer and ureteral cancer.

Conclusions: This article presents the first large population report of survival data in Japanese renal pelvic and ureteral cancer patients. In comparison with the Japanese bladder cancer database report in 1999–2001 from the Cancer Registration Committee of the Japanese Urological Association, the pathological characteristics of renal pelvic and ureteral cancer were diagnosed as aggressive.

Key words: epidemiology, Japanese, renal pelvic cancer, survival, ureteral cancer.

Introduction

Urothelial cancer was reported to be the 10th most common cancer among Japanese males in 2007.[1] Among the types of urothelial cancer, bladder cancer is most frequently seen, but renal pelvic and ureteral cancer are uncommon with reported incidence of 5–10% of all urothelial cancers.[2,3] The JUA has collected data on clinical and pathological characteristics, and outcomes of bladder cancer since 1982. However, because of the lower incidence of renal pelvic and ureteral cancer, data collection by the JUA did not include these patients until the establishment of the computer-based registration of urological cancer. Similarly, large series on descriptive epidemiology, and treatment of renal pelvic and ureteral cancer have also been limited.

In 2011, to analyze the clinicopathological characteristics and outcomes of renal pelvic and ureteral cancer patients in Japan, the JUA initiated collection of data from renal pelvic and ureteral cancer patients who were clinically diagnosed in 2005, including patient background, diagnosis modality, main treatment and outcomes. By comparing these data with those on bladder cancer in the JUA database, we tried to identify whether the characteristics of renal pelvic and ureteral cancer, and those of bladder cancer are the same.

Methods

In 2011, data from renal pelvic and ureteral cancer patients diagnosed in 2005 were collected as the computer-based registry database of the JUA. Secondary renal pelvic and ureteral cancer patients after bladder cancer were excluded from this registry. From 348 Japanese institutions, 1538 patients were registered including 29 patients with secondary renal pelvic and ureteral cancer patients after bladder cancer. Excluding these 29 patients, 1509 records were analyzed in the present study. Information on sex, age, race, family history, medical history, cigarette smoking status, symptoms, diagnosis method, cancer location, clinical stage, initial main treatment method, recurrence and survival was collected.

In the analysis of clinical characteristics, the cancer was categorized as unilateral renal pelvic cancer without ureteral cancer, unilateral ureteral cancer without renal pelvic cancer, unilateral renal pelvic with concomitant ureteral cancer, and bilateral renal pelvic and/or ureteral cancer. Existence of concomitant bladder cancer did not affect these four categories. The cancer located at the ureteropelvic junction was categorized as renal pelvic cancer. Unilateral renal pelvic cancer without ureteral cancer and unilateral ureteral cancer without renal pelvic cancer were analyzed separately. Furthermore, in the analysis of operative trends and pathological characteristics, unilateral pelvic cancer without concomitant ureteral and bladder cancer (i.e. renal pelvic cancer alone) and unilateral ureteral cancer without concomitant renal pelvic and bladder cancer (i.e. ureteral cancer alone) were selected to simplify the outcome. The second edition of the *General Rule for Clinical and Pathological Studies on Renal Pelvic and Ureteral Tumor* edited by the JUA and The Japanese Society of Pathology was referenced for clinical and pathological information.[4]

For statistical analysis, the Fisher exact test was used to evaluate the association among categorical variables, and the Mann–Whitney *U*-test assessed differences among variables with a continuous distribution across dichotomous categories. The univariate survival probabilities were determined using the Kaplan–Meier method with differences estimated using the log–rank test. Overall survival and cancer-specific survival were calculated for several variable factors. All statistical analyses were carried out using JMP 5.1 (SAS Institute, Cary, NC, USA) and the open-source *R* statistical software v2.13.0.

Results

Clinical characteristics of renal pelvic and ureteral cancer

Among the 1509 registered patients, 764 (50.7%) had unilateral renal pelvic cancer and 692 (45.9%) had unilateral ureteral cancer. A total of 46 (3.1%) had unilateral renal pelvic and ureteral cancer, and five (0.3%) had bilateral upper tract cancer. Two patients had cancer of unknown cancer location. The characteristics of unilateral renal pelvic patients and unilateral ureteral cancer patients are summarized in Table 1. In total, 68.4% were male, and 77.4% presented with symptomatic cancer. For clinical stage, 90% patients were estimated as M0 and 83.7% were cN0. Regarding initial main treatment, 86.7% patients were operated on, 6.4% received palliative care and 5.1% received systemic chemotherapy. At presentation, 13.3% patients had concomitant bladder cancer. After treatment, one-third of patients (29.4%) developed subsequent bladder cancer, but contralateral occurrence was rare (0.93%). The median follow up for the total 1509 registered patients was 1272 days (range 0–2378 days).

Comparison of renal pelvic cancer and ureteral cancer showed that differences for sex (Fisher's exact test $P = 0.015$) and age (Mann–Whitney *U*-test $P = 0.0023$) were statistically significant. The rate of clinical T2 and T3, node-positive, stage IV and subsequent bladder cancer occurrence seemed to differ between renal pelvic and ureteral cancers, but was not significant. The 5-year overall survival for the 1509 patients was estimated to be 0.64 (95% confidence interval 0.61–0.67, renal pelvic cancer 0.66, ureteral cancer 0.64). Overall and cause-specific survival data for patients with unilateral renal pelvic or ureteral cancer are summarized in Figure 1.

Other characteristics are summarized as supporting information in Table S1.

Operative trends in renal pelvic cancer alone and ureteral cancer alone

In total, 1308 patients were initially operated on. Of those, 611 unilateral renal pelvic cancer patients without concomitant ureteral and bladder cancer (i.e. renal pelvic cancer alone), and 500 unilateral ureteral cancer patients without concomitant renal pelvic and bladder cancer (i.e. ureteral cancer alone) were selected to simplify the analysis of the operative mode. The incidence of several factors was collected individually among those who received open surgery, pure laparoscopic surgery and hand-assisted laparoscopic operation (Table 2).

Open surgery was carried out in 409 renal pelvic cancer cases (66.9%) and 315 ureteral cancer cases (63.0%). The retroperitoneal approach was common, and lymph node dissection was carried out in approximately one-third of open surgery cases and one-fifth of laparoscopic cases. The T-stage distribution of the patients treated by the open surgery, pure laparoscopic surgery and hand-assisted laparoscopic surgery did not differ.

Pathological characteristics of renal pelvic cancer alone and ureteral cancer alone

The pathological characteristics of the 611 operated patients with unilateral renal pelvic cancer alone, and the 500 operated patients with unilateral ureteral cancer alone are summarized in Table 3. Variables included predominant histopathology, pathological cancer stage, extent of lymph node dissection, worst tumor grade, infiltration pattern, surgical margin, ureteral margin, pelvic margin, lymphatic involvement and venous involvement. For renal pelvic and ureteral cancers, pTa cancer was rare (14.6%) and pT3 cancer was more common. The distribution of the worst tumor grade was significantly different (Fisher's exact test $P < 0.005$) for renal pelvic cancer and ureteral cancer patients. The prevalence of pT2/pT3 was significantly different (Fisher's exact test $P < 0.0001$) for renal pelvic cancer patients (54/272) and ureteral cancer patients (126/178). Survival of the operated patients with renal pelvic cancer alone or ureteral cancer alone is summarized in Figure 2. In both cancers, pT and pN stages were shown to be significant

Table 1 Patients' characteristics according to tumor locations

	Total cases (n = 1509)		Unilateral renal pelvic cancer (n = 764)		Unilateral ureteral cancer (n = 692)	
	n	%	n	%	n	%
Sex						
Male	1032	68.39	543	71.07	450	65.03
Female	477	31.61	221	28.93	242	34.97
Median/mean age, years (range)	71/69.8 (27–97)		70/68.9 (34–77)		72/70.8 (32–77)	
≤49	45	2.98	31	4.06	13	1.88
50–54	63	4.17	40	5.24	21	3.03
55–59	127	8.42	77	10.08	44	6.36
60–64	187	12.39	97	12.70	84	12.14
65–69	338	22.40	113	14.79	105	15.17
70–74	327	21.67	150	19.63	170	24.57
75–79	298	19.75	150	19.63	136	19.65
≥80	234	15.51	106	13.87	119	17.20
Symptom						
Negative	312	20.68	137	17.93	168	24.28
Positive	1168	77.40	610	79.84	514	74.28
Clinical T stage						
cTis	46	3.05	14	1.83	29	4.19
cTa	143	9.48	72	9.42	64	9.25
cT1	379	25.12	186	24.35	185	26.73
cT2	341	22.60	144	18.85	183	26.45
cT3	340	22.53	222	29.06	108	15.61
cT4	95	6.30	51	6.68	35	5.06
cTx	165	10.93	75	9.82	88	12.72
Clinical N stage						
cN0	1258	83.37	608	79.58	612	88.44
cN1-3	193	12.79	125	16.36	57	8.24
cNx	58	3.84	31	4.06	23	3.32
Clinical M stage						
cM0	1356	89.86	668	87.43	644	93.06
cM1	102	6.76	69	9.03	28	4.05
cMx	51	3.38	27	3.53	20	2.89
Stage classification						
Stage 0, I	564	37.38	269	35.21	278	40.17
Stage II	313	20.74	130	17.02	170	24.57
Stage III	238	15.77	145	18.98	86	12.43
Stage IV	253	16.77	158	20.68	81	11.71
Uncertain	141	9.34	62	8.12	77	11.13
Initial main treatment						
Operation	1308	86.68	663	86.78	601	86.85
Systemic chemotherapy	77	5.10	48	6.28	27	3.90
Therapeutic irrigation	15	0.99	6	0.79	7	1.01
Radiation therapy	10	0.66	2	0.26	8	1.16
Palliative care	96	6.36	43	5.63	48	6.94
Uncertain	3	0.20	2	0.26	1	0.14
Cancer multiplicity						
Concomitant bladder cancer	201	13.32	65	8.51	118	17.05
Subsequent bladder cancer	444	29.42	190	24.87	239	34.54
Subsequent contralateral cancer	14	0.93	4	0.52	8	1.16

prognostic factors. The 5-year survival rate for pT3 renal pelvic cancer (64.5%) was better than that for pT3 ureteral cancer (46.8%).

The bladder cancer recurrence-free rate of the operated renal pelvic patients without another concomitant urothelial cancer was 0.73 at 2 years and 0.67 at 5 years, and that of operated ureteral cancer patients without another concomitant urothelial cancer was 0.66 at 2 years and 0.57 at 5 years. The bladder cancer recurrence-free rate in renal pelvic cancer patients was better than that of ureteral cancer (log–rank $P = 0.009$). The operation mode whether open, laparoscopic or hand-assisted laparoscopic did not affect bladder cancer recurrence. These data are summarized as supporting information in Figure S1.

Therapeutic trend in metastatic renal pelvic cancer and ureteral cancer

Overall, 102 patients (6.8%) showed distant metastasis. Initial therapy was carried out for 39 patients (38.2%) by operation,

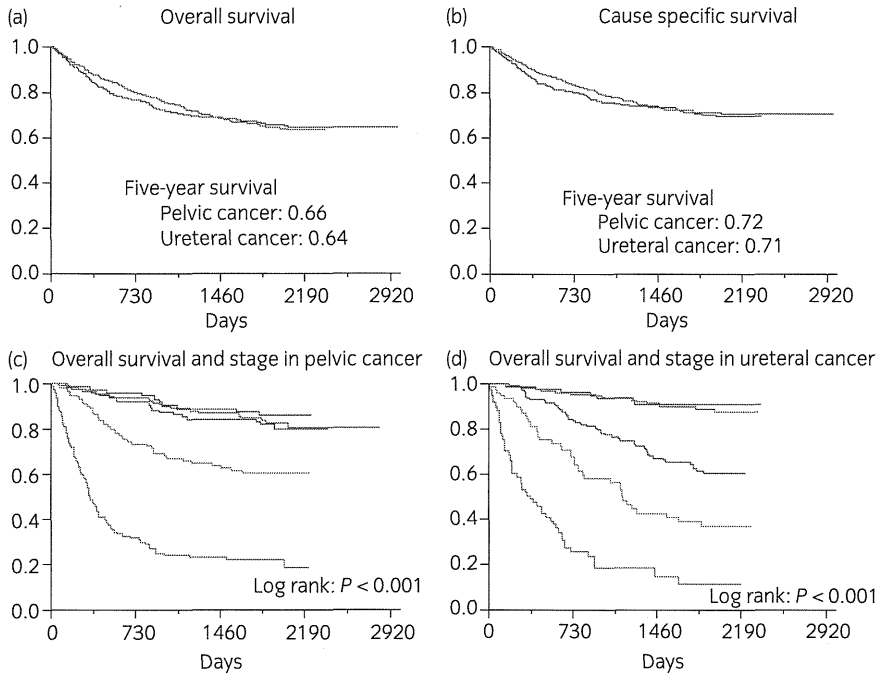

Fig. 1 Kaplan–Meier survival curves for unilateral renal pelvic and ureteral cancer. (a) Overall survival, (b) cause-specific survival, (c) overall survival and stage in pelvic cancer and (d) overall survival and stage in ureteral cancer. (a) ——, Pelvic cancer (n = 764); ——, ureteral cancer (n = 692); (b) ——, pelvic cancer (n = 764); ——, ureteral cancer (n = 692); (c) ——, 0 (n = 85); ——, I (n = 177); ——, II (n = 125); ——, III (n = 137); ——, IV (n = 158); (d) ——, 0 (n = 89); ——, I (n = 181); ——, II (n = 167); ——, III (n = 81); ——, IV (n = 81).

37 (36.3%) received systemic chemotherapy, two (2.0%) received radiation therapy and 24 (23.5%) received palliative care only. In total, 66 of 102 initially metastatic patients (64.7%) received systemic chemotherapy. The systemic chemotherapy regimen was methotrexate, vinblastine, adriamycin and cisplatin for 46 patients (69.7%); methotrexate, epirubicin and cisplatin for nine patients (13.6%); and gemcitabine and cisplatin for three patients (4.5%).

Discussion

The present report is the first large-scale study of characteristics and survival of upper urinary tract cancer patients in Japan based on multi-institutional registry data. Renal pelvic and ureteral cancer was uncommon, and cancer multiplicity in the upper urinary tract cancer was complicated. This large-scale study helps simplify the analysis of operative mode, pathological information, and prognosis of the unilateral renal pelvic cancer alone and unilateral ureteral cancer alone.

Comparison with the Japanese bladder cancer database emphasized the different diagnosed characteristics of renal pelvic, ureteral and bladder cancers. Regarding tumor invasion, approximately 60% of the operated unilateral renal pelvic or ureteral cancer was diagnosed as invasive, and just 14.6% was stage pTa in the present study. In addition, nearly 50% of the operated cases were diagnosed with histological grade 3 as the worst histological grade. The Japanese bladder cancer database report in 1999–2001 showed that the worst histological grade was 8.8% with G1, 53.5% with G2, and 37.3% with G3.[5] The worst histological grade and stage distribution of upper urinary tract cancer had higher malignant potential than bladder cancer.

In comparison with operated unilateral renal pelvic cancer and ureteral cancer, overall and cause-specific survival were similar. However, the distribution of worst tumor grade, the prevalence of pT2/pT3 disease, and 5-year survival in pT3 cancer were differed between renal pelvic and ureteral cancer. In the present study, T classification was based on the second edition of the *General Rule for Clinical and Pathological Studies on Renal Pelvic and Ureteral Tumor* edited by the JUA and The Japanese Society of Pathology.[4] In renal pelvic cancer, pT3 disease is defined as "invasion beyond muscularis into peripelvic fat or the renal parenchyma in renal pelvic cancer". The pT3 category of renal pelvic cancer has reportedly included a heterogeneous group of patients.[6,7] In the present study, pT3 cancer included tumors with collecting ductal involvement cancer without direct invasion, or microscopic direct invasion cancer. These factors probably caused differences between renal pelvic and ureteral cancer in prevalence proportion of pT2/pT3 disease and 5-year survival in pT3 cancer.

The standard method of operation for upper urinary tract cancer is nephroureterectomy with bladder cuff resection. In the present study, 95.3% of unilateral renal pelvic cancer and 93.6% of unilateral ureteral cancer was treated by nephroureterectomy. This study included patients with upper urinary tract cancer in 2005. At that time, open surgery and the retroperitoneal approach were most common. Lymph node dissection was not carried out in 65% of unilateral renal pelvic cancer cases and 69.0% of unilateral ureteral cancer cases. The laparoscopic operation and the operation for pelvic cancer tended to omit lymph node dissection. Pelvic lymph node dissection was known to be an important procedure in radical cystectomy for bladder cancer patients. However, the role of lymph node dissection with nephroureterectomy was still controversial. Recent reports showed survival benefit with lymph node dissection.[8,9] So the approach to the lymph nodes might be changing in upper urinary tract cancer.

The incidence of subsequent bladder cancer after operation was reported to be approximately 15–50%.[10,11] In the present study, 29.4% of the total cases had bladder cancer recurrence, and 81.1% of those developed in less than 2 years. Most previous studies agreed that 80–90% of bladder cancer recurrences

Table 2 Operative trend in unilateral renal pelvic or ureteral cancer without concomitant another urothelial cancer

	Unilateral renal pelvic cancer alone (n = 611)		Unilateral ureteral cancer alone (n = 500)	
	n	%	n	%
Operation method 1				
Nephroureterectomy	582	95.3	468	93.6
+Cystectomy	0	0.0	3	0.6
Nephrectomy	22	3.6	0	0.0
Partial ureterectomy	0	0.0	5	1.0
Endoscopic surgery	4	0.7	3	0.6
Probe laparotomy	3	0.5	3	0.6
Uncertain	0	0.0	18	3.6
Operation method 2				
Open surgery	409	66.9	315	63.0
Pure laparoscopic	128	20.9	125	25.0
Hand assisted laparoscopic	65	10.6	48	9.6
Approach of the surgery				
Retroperitoneal	479	78.4	424	84.8
Peritoneal	128	20.9	67	13.4
Transurethral	4	0.7	8	1.6
Others	4	0.7	4	0.8
Lymph node dissection				
Biopsy only	28	4.6	9	1.8
Limited	146	23.9	115	23.0
Extended	18	2.9	15	3.0
Not performed	397	65.0	345	69.0
Uncertain	11	1.8	10	2.0
Radicality of the operation				
Curative	598	97.9	494	98.8
Non-curative	65	10.6	35	7.0
Palliative	10	1.6	1	0.2
Operation methods and approach				
Open surgery	409		315	
Retroperitoneal	307	75.1	266	84.4
Peritoneal	102	24.9	47	14.9
Pure laparoscopic	128		125	
Retroperitoneal	110	85.9	113	90.4
Peritoneal	18	14.1	12	9.6
Hand assisted laparoscopic	65		48	
Retroperitoneal	59	90.8	42	8.8
Peritoneal	6	9.2	6	1.3
Operation methods and T stage lymph node dissection				
Open surgery	409		315	
Tis	1	0.2	11	3.5
Ta	37	9.0	19	6.0
T1	97	23.7	83	26.3
T2	89	21.8	98	31.1
T3	132	32.3	53	16.8
T4	22	5.4	7	2.2
Pure laparoscopic	128		125	
Tis	2	1.6	2	1.6
Ta	22	17.2	18	14.4
T1	36	28.1	41	32.8
T2	21	16.4	39	31.2
T3	32	25.0	15	12.0
T4	3	2.3	0	0.0
Hand-assisted laparoscopic	65		48	
Tis	0	0.0	2	4.2
Ta	6	9.2	9	18.8
T1	26	40.0	12	25.0
T2	8	12.3	14	29.2
T3	20	30.8	8	16.7
T4	2	3.1	1	2.1
Operation methods and lymph node dissection				
Open surgery	409		315	
Biopsy only	21	5.1	2	0.6
Performed	130	31.8	86	27.3
Not performed	246	60.1	216	68.6
Uncertain	12	2.9	11	3.5
Pure laparoscopic	128		125	
Biopsy only	5	3.9	5	4.0
Performed	23	18.0	32	25.6
Not performed	96	75.0	87	69.6
Uncertain	4	3.1	1	0.8
Hand-assisted laparoscopic	65		48	
Biopsy only	2	3.1	2	4.2
Performed	9	13.8	10	20.8
Not performed	53	81.5	34	70.8
Uncertain	1	1.5	2	4.2

Table 3 Pathological characteristics of operated unilateral renal pelvic or ureteral cancer without another concomitant urothelial cancer

	Unilateral renal pelvic cancer alone (n = 611)		Unilateral ureteral cancer alone (n = 500)	
	n	%	*n*	%
Predominant histopathology				
Urothelial carcinoma	579	94.8	466	93.2
Squamous cell carcinoma	16	2.6	10	2.0
Carcinoma *in situ*	4	0.7	12	2.4
Adenocarcinoma	2	0.3	4	0.8
Small cell carcinoma	1	0.2	2	0.4
Uncertain	10	1.6	6	1.2
Pathological T stage				
pTa	89	14.6	73	14.6
pTis	10	1.6	23	4.6
pT1	123	20.1	78	15.6
pT2	54	8.8	126	25.2
pT3	272	44.5	178	35.6
pT4	50	8.2	9	1.8
pTX	13	2.1	11	2.2
Pathological N stage				
pN0	124	20.3	107	21.4
pN1	21	3.4	14	2.8
pN2	33	5.4	7	1.4
pN3	2	0.3	0	0.0
pNX	431	70.5	372	74.4
Worst tumor grade				
G0	0	0.0	1	0.2
G1	29	4.7	36	7.2
G2	291	47.6	186	37.2
G3	279	45.7	260	52.0
GX	12	2.0	17	3.4
Infiltration pattern				
Not infiltrated	61	10.0	62	12.4
INF-α	165	27.0	97	19.4
INF-β	203	33.2	179	35.8
INF-γ	64	10.5	63	12.6
Uncertain	118	19.3	99	19.8
Surgical margin				
ew0	509	83.3	411	82.2
ew1	31	5.1	36	7.2
ewx	71		53	10.6
Ureteral margin				
u0	547	89.5	429	85.8
u1	7	1.1	25	5.0
ux	57	9.3	46	9.2
Pelvic margin				
p0	426	69.7	398	79.6
p1	26	4.3	4	0.8
px	159	26.0	98	19.6
Lymphatic involvement				
ly0	368	60.2	293	58.6
ly1	185	30.3	151	30.2
lyx	58	9.5	56	11.2
Venous involvement				
v0	392	64.2	331	66.2
v1	160	26.2	115	23.0
vx	59	9.7	54	10.8

appear in the first 2 years of follow up,[12] similar to these results. Although the incidence of bilateral upper urinary tract cancer, either synchronous or metachronous, was reported to be 1–4%,[13] the incidence of subsequent bilateral disease (median follow up 1272 days) was less than 1% (0.3% in synchronous disease and 0.9% in metachronous disease) in the present study. A Japanese study group recently reported that the incidence of subsequent bladder cancer differs significantly between open surgery and laparoscopic operation.[14] In the present study, however, the recurrence rate for open surgery, and for both

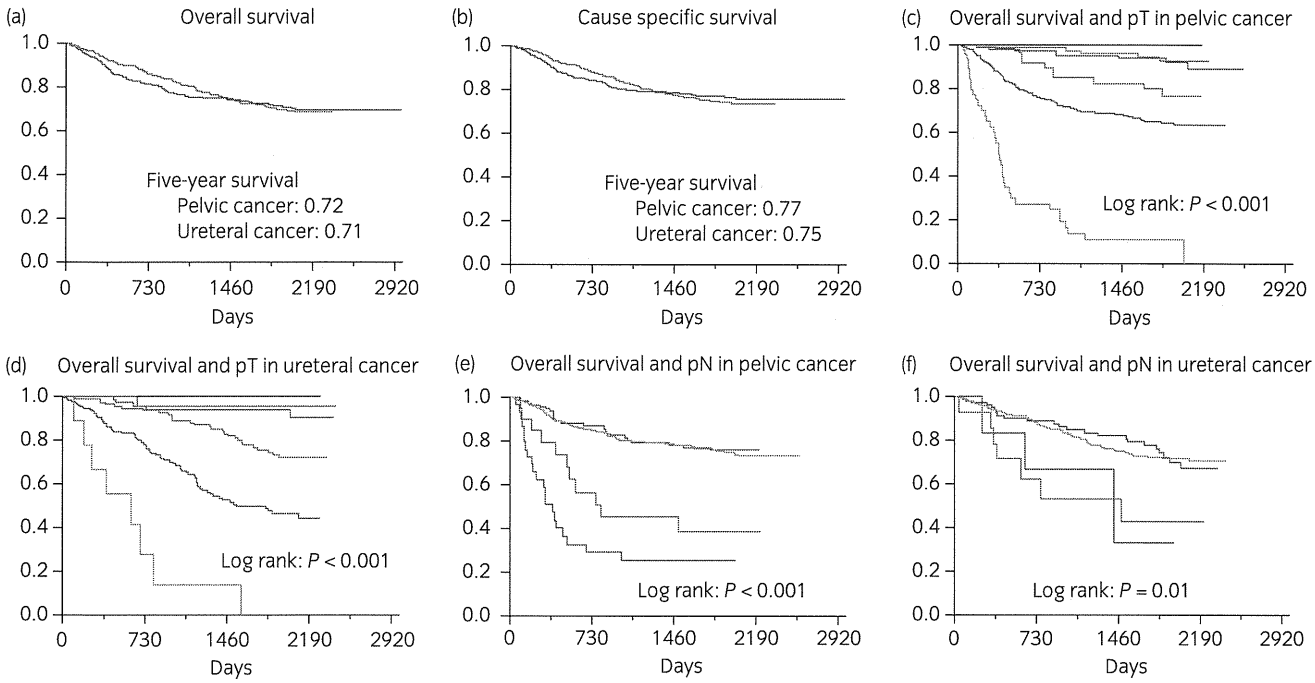

Fig. 2 Kaplan–Meier survival curves for operated unilateral pelvic cancer without concomitant ureteral and bladder cancer, and for operated unilateral ureteral cancer without concomitant renal pelvic and bladder cancer. overall survival (a), cause cancer-specific survival (b), overall survival and pT in pelvic cancer (c), overall survival and pT in ureteral cancer (d), overall survival and pN in pelvic cancer (e), overall survival and pN in ureteral cancer (f). Both pT and pN were revealed as significant factors. (a) ——, pelvic cancer (n = 611); ——, ureteral cancer (n = 500); (b) ——, pelvic cancer (n = 611); ——, ureteral cancer (n = 500); (c) ——, pT1 (n = 123); ——, pT2 (n = 54); ——, pT3 (n = 272); ——, pT4 (n = 50); ——, pTa (n = 89); ——, pTis (n = 10); (d) ——, pT1 (n = 78); ——, pT2 (n = 126); ——, pT3 (n = 178); ——, pT4 (n = 9); ——, pTa (n = 73); ——, pTis (n = 23); (e) ——, pN0 (n = 124); ——, pN1 (n = 21); ——, pN2 (n = 23); ——, pNx (n = 428); (f) ——, pN0 (n = 106); ——, pN1 (n = 14); ——, pN2 (n = 7); ——, pNx (n = 370).

hand-assisted and pure laparoscopic surgery seemed similar, although the reason why is unclear.

Conclusion

The present article is the first nationwide large-population report of epidemiological and survival data from renal pelvic and ureteral cancer patients in Japan. Open nephroureterectomy without lymph node dissection was the most common operative method for non-metastatic upper urinary tract cancer in 2005. Pathological tumor grade and invasive characteristics seem to be higher than those of bladder cancer. More detailed analysis will be carried out by the working group of the Cancer Registration Committee of the JUA.

Acknowledgments

These clinicopathological statistics are based on the results from a number of institutions in Japan (Table S2). We are grateful for the cooperation of many Japanese urologists, and for special efforts to analyze and summarize the data by T Hara (Urology Division, National Cancer Center Hospital, Tokyo), Y Ishida and M Hayakawa, a secretary of the cancer registration office. This document was created by the Cancer Registration Committee of the Japanese Urological Association.

Conflict of interest

None declared.

References

1 The Editorial Board of the cancer Statistics in Japan Foundation for Promotion of Cancer Research. Cancer Statistic in Japan 2012, 2012.
2 Margulis V, Shariat SF, Matin SF *et al.* Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer* 2009; **115**: 1224–33.
3 Roupret M, Zigeuner R, Palou J *et al.* European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. *Eur. Urol.* 2011; **59**: 584–94.
4 Japanese Urological Association. *General Rule for Clinical and Pathological Studies on Renal Pelvic and Ureteral Tumor. The Second Ed.* Kanehara & Co. Ltd, Tokyo, 2002.
5 Okajima E, Fujimoto H, Mizutani Y *et al.* Cancer death from non-muscle invasive bladder cancer: report of the Japanese Urological Association of data from the 1999–2001 registry in Japan. *Int. J. Urol.* 2010; **17**: 905–12.
6 Fujimoto H, Tobisu K, Sakamoto M, Kamiya M, Kakizoe T. Intraductal tumor involvement and renal parenchymal invasion of transitional cell carcinoma in the renal pelvis. *J. Urol.* 1995; **153**: 57–60.
7 Yoshimura K, Arai Y, Fujimoto H *et al.* Prognostic impact of extensive parenchymal invasion pattern in pT3 renal pelvic transitional cell carcinoma. *Cancer* 2002; **94**: 3150–6.
8 Roscigno M, Shariat SF, Margulis V *et al.* The extenet of lymphadenectomy seems to be associated with better survival in patients with nonmetastatic upper-tract urothelial carcinoma: how many lymph mode should be removed? *Eur. Urol.* 2009; **56**: 512–19.
9 Kondo T, Hashimoto Y, Kobayashi H *et al.* Template-base lympadenectomy in urothelial carcinoma of the upper urinary tract: impact on patients survival. *Int. J. Urol.* 2010; **17**: 848–54.
10 Milojevic B, Djokic M, Sipetic-Grujicic S *et al.* Bladder cancer after managing upper urinary tract transitional cell carcinoma: risk factors and survival. *Int. Urol. Nephrol.* 2011; **43**: 729–35.

11 Xylinas E, Rink M, Margulis V, Karakiewicz P, Novara G, Shariat SF, Upper Urothelial Carconoma Collaboration (UTUCC). Multifocal carcinoma in situ of the upper tract is associated with high risk of bladder cancer recurrence. *Eur. Urol.* 2012; **61**: 1069–70.
12 Azemar M-D, Comperat E, Richard F, Cussenot O, Roupret M. Bladder recurrence after surgery for upper urinary tract urothelial cell carcinoma: frequency, risk factors, and surveillance. *Urol. Oncol.* 2011; **29**: 130–6.
13 Murphy DM, Zincke H, Furlow WL. Management of high grade transitional cell cancer of the upper urinary tract. *J. Urol.* 1981; **125**: 25–9.
14 Ito A, Shintaku I, Satoh M *et al.* Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP monotherapy study group trial. *J. Clin. Oncol.* 2013; **31**: 1422–7.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 Bladder cancer recurrence in operated renal pelvic or ureteral cancer without concomitant another urothelial cancer. Recurrence rate in renal pelvic and ureteral cancer (A) and recurrence rate by surgical method (B).
Table S1 The other patient characteristics in total 1509 cases.
Table S2 Institutions that were registered.

INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2014) 21, S1–S6 doi: 10.1111/iju.12441

JUA Cancer Registration Statistics

Clinical characteristics and oncological outcomes of testicular cancer patients registered in 2005 and 2008: The first large-scale study from the Cancer Registration Committee of the Japanese Urological Association

Tsuneharu Miki,[1,2] Kazumi Kamoi,[1,2] Hiroyuki Fujimoto,[1,3] Hiro-omi Kanayama,[1,4] Chikara Ohyama,[1,5] Kazuhiro Suzuki,[1,6] Hiroyuki Nishiyama,[1,7] Masatoshi Eto,[1,8] Seiji Naito,[1,9] Tomoharu Fukumori,[1,4] Yoshinobu Kubota,[1,10] Satoru Takahashi,[1,11] Kazuya Mikami[1,12] and Yukio Homma[1,13]

[1]The Cancer Registration Committee of the Japanese Urological Association, [2]Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine, Kyoto, [3]Urology Division, National Cancer Center Hospital, Tokyo, [4]Department of Urology, School of Medicine, The University of Tokushima, Tokushima, [5]Department of Urology, Hirosaki University Graduate School of Medicine, Aomori, [6]Department of Urology, Gunma University School of Medicine, Gunma, [7]Department of Urology, Faculty of Medicine, University of Tsukuba, Ibaragi, [8]Department of Urology, Faculty of Life Sciences, Kumamoto University, Kumamoto, [9]Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, [10]Department of Urology, Yokohama City University Graduate School of Medicine, Kanagawa, [11]Department of Urology, Nihon University, Tokyo, [12]Department of Urology, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, [13]Department of Urology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Abbreviations & Acronyms
AFP = α-fetoprotein
BEP = cisplatin, bleomycin and etoposide
CBDCA = carboplatin
EAU = European Association of Urology
EP = etoposide and cisplatin
GCT = germ cell tumor
HCG = human chorionic gonadotropin
IGCCC = International Germ Cell Consensus Classification
JUA = Japanese Urological Association
LDH = lactate dehydrogenase
NSGCT = non-seminoma germ cell tumor
PNET = primitive neuroectodermal tumor
RPLND = retroperitoneal lymph node dissection
RT = radiation therapy
ULN = upper limit of normal
VIP = cisplatin, ifosfamide and etoposide

Correspondence: Tsuneharu Miki M.D., Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kyoto 602-9566, Japan. Email: tmiki@koto.kpu-m.ac.jp

Received 6 February 2014; accepted 11 February 2014.
Online publication 13 April 2014

Objectives: To describe the clinical and pathological characteristics and oncological outcomes of testicular cancer diagnosed in Japan, we report the results of the testicular cancer registration carried out by the Japanese Urological Association.

Methods: Testicular cancer survey was conducted by the Japanese Urological Association in 2011 to register newly diagnosed testicular cancers in 2005 and 2008. The survey included details such as age, presenting symptoms, physical examination findings, tumor markers, histopathology, clinical stage, initial treatment and clinical outcomes.

Results: We analyzed 1121 cases of testicular primary germ cell tumor among 1157 registered patients. The median age was 37.0 years. Seminomas and non-seminomatous germ cell tumors accounted for 61.9% and 38.1%, respectively. Measurements of tumor markers were documented in 98.6% of the patients; however, there was an unsatisfactory uniform measurement of human chorionic gonadotropin, which made it difficult to evaluate the International Germ Cell Consensus Classification in all patients. The 1- and 3-year overall survival rates from the entire cohort were 98.3% and 96.8%, respectively. According to the International Germ Cell Consensus Classification, 3-year overall survival rates in the good, intermediate, and poor prognosis group were 99.1%, 100% and 79.9%, respectively.

Conclusions: The present report is the first large-scale study of the characteristics and survival of testicular cancer patients in Japan based on multi-institutional registry data, and showed a good prognosis even in an advanced stage. The improved survival attributed substantially to accurate diagnosis and effective multimodal treatment.

Key words: epidemiology, germ cell tumor, Japanese, survival, testicular cancer.

Introduction

Testicular cancer is a relatively rare disease, which delivers little experience for each facility and therefore, the case accumulation in Japan has been difficult. The incidence of testicular cancer in Japan has been thought to be 1.1–2.7 per 1 000 000 population per year,[1] which is lower than Western countries.[2] Although there is a relatively large cross-sectional study of prognosis and cancer incidence based on the national cancer registry, the annual report from the Japan National Cancer Institute unfortunately excludes the report of testicular cancer. The JUA initiated urological cancer registries from 2000, and provided the general rule for clinical and pathological studies on testicular tumor in 2005[3] and the JUA guideline for testicular cancer in 2009.[4] The JUA also carried out a testicular cancer survey in 2011 to register newly diagnosed testicular cancers in 2005 and 2008. The objective of the present study was to report demographics, treatment trends and clinical outcomes on registered testicular cancers in Japan.

Table 1 Clinical characteristics of registered germ cell tumors

Mean age ± SD (years)	37.0 ± 10.6
Past history of scrotal/inguinal surgery	170 (14.0%)
Presenting symptoms	*n* = 1121
Scrotal/inguinal mass or pain	1053 (93.9%)
Abdominal mass or pain	29 (2.6%)
Fever	20 (1.8%)
Respiratory symptom	9 (0.8%)
Gynecomastia	6 (0.5%)
Abdominal mass on physical examination	75 (6.7%)
Laterality of scrotal mass	*n* = 1121
Right	575 (51.3%)
Left	520 (46.4%)
Bilateral	6 (0.5%)
Uncertain	20 (1.8%)

Table 2 Tumor markers

AFP (ng/mL)	*n* = 1090
<20	810 (73.3%)
20–1000	197 (17.8%)
1001–10 000	59 (5.3%)
>10 000	24 (2.2%)
HCG measurement	*n* = 1041
Total or intact HCG (mIU/mL)	360 (34.6%)
HCG-β subunit (ng/mL)	681 (65.3%)
Total or intact HCG (mIU/mL)	*n* = 360
<0.7	154 (42.8%)
0.7–5000	181 (50.2%)
5001–50 000	9 (2.5%)
>50 000	16 (4.4%)
HCG-β subunit (ng/mL)	*n* = 681
<0.1	306 (44.9%)
0.1–1000	370 (54.3%)
1001–10 000	4 (0.6%)
>10 000	1 (0.1%)
LDH (IU/L)	*n* = 1035
<ULN	490 (47.3%)
ULN – 1.5 × ULN	213 (20.6%)
1.5 × ULN – 10 × ULN	307 (29.7%)
>10 × ULN	25 (2.4%)

Methods

The Cancer Registration Committee of the JUA carried out a testicular cancer registry program in 2011 to collect the data of patients with testicular cancer diagnosed in 2005 and 2008 from the accredited training institutes for board certification in urology. The survey included details such as age, presenting symptoms, physical examination findings, tumor markers, histopathology, clinical stage, initial treatment and clinical outcomes.

Excluding lymphoma, a total of 1157 patients of testicular primary or extra-gonadal germ cell tumors were registered from 274 institutions nationwide (432 patients in 2005 and 725 patients in 2008). Among these, 1139 patients were diagnosed as so-called germ cell tumor, and the other 18 cases were PNET, malignant mesothelioma, adenomatoid tumor, rhabdomyosarcoma, leiomyoma/leiomyosarcoma, carcinoid, spermatic cord/gonadal stromal tumor, rete testis adenocarcinoma and epidermoid cyst. Another 18 patients were diagnosed with extragonadal germ cell tumor. In the present study, we explored a review of 1121 patients with testicular-primary germ cell tumor. The patients with abnormal AFP values more than 20 ng/mL were regarded as NSGCT. Recording HCG values was encouraged, but many of the institutions reported HCG-β subunit by ng/mL, which was not suitable for the IGCCC.[5] In the present study, HCG measurement was evaluated when it was reported by mIU/mL. LDH was evaluated depending on its normal range for each facility. Pathological details were followed according to the reports from each facility.

We evaluated symptoms, tumor markers, clinical stage, initial treatment and survival data. The survival interval was calculated from the date of high orchidectomy, if the date of diagnosis was not mentioned. Survival rates were calculated using Kaplan–Meier method and compared by log–rank test. $P < 0.05$ was designated as statistical significance. All statistical analyses were carried out using JMP version 10 (SAS, Cary, NC, USA).

Results

Demographics

Age ranged from 0 to 76 with the peak from 30 to 35 years, and generally followed the normal distribution (Table 1). The median and mean ages were 36 and 37.0 years, respectively. Out of 1121 patients, 170 patients (14.0%) had a previous history of inguinal or scrotal surgery, 1053 patients (93.9%) were admitted for a scrotal/inguinal mass or pain. Other symptoms, such as abdominal pain ($n = 29$), fever ($n = 20$), respiratory symptoms ($n = 9$) or gynecomastia ($n = 6$), were reported as presenting symptoms. On the physical examination, the abdominal mass was palpable in 75 (6.7%) patients. Laterality of scrotal mass was on the right side in 575 patients (51.3%), the left side in 520 patients (46.4%) and both sides in six patients (0.5%).

Tumor markers

Any tumor markers were measured in 1105 patients (98.6%) (Table 2). AFP was examined in 1090 patients (97.2%), and was abnormally elevated (>20 ng/mL) in 280 (25.7%) of them. A total of 24 patients showed an extremely elevated AFP value of 10 000 ng/mL or more in which the maximum value was 81 470 ng/mL. HCG was measured in 1041 patients, but just 360 of them (34.6%) were expressed by mIU/mL unit. The rates of HCG measurement by mIU/mL unit in 2005 and 2008 were 120 (32.1%) and 240 (36.0%), respectively, without statistical difference. A total of 16 patients showed an extremely elevated total/intact HCG value more than 50 000, in which the maximum value was 1 905 422 mIU/mL. There was a patient with an extremely elevated HCG-β subunit of 69 190 ng/mL. LDH was elevated at more than 10-fold the normal levels in 25 patients (2.4%). Persistent elevation of tumor markers after primary orchidectomy was observed in 242 patients (21.6%).

Pathological features

Pathological diagnosis of primary lesions was obtained in all patients (Table 3). The surgical interventions for primary lesion were carried out as follows: partial resection of testis or

Table 3 Primary treatment and pathological features

Primary treatment for testis	*n* = 1121
High orchidectomy	1112 (99.2%)
Simple orchidectomy	4 (0.4%)
Non-curative resection	1 (0.1%)
Biopsy	4 (0.4%)
Histology	*n* = 1107
Pure seminoma	702 (63.4%)
Pure embryonal carcinoma	47 (4.2%)
Pure teratoma	23 (2.1%)
Pure yolk sac tumor	15 (1.4%)
Pure choriocarcinoma	9 (0.8%)
Pure other forms	2 (0.2%)
Mixed forms	309 (27.9%)
Elements	*n* = 1107
Seminoma	891 (80.8%)
Embryonal carcinoma	268 (24.2%)
Yolk sac tumor	202 (18.0%)
Teratoma	197 (18.2%)
Choriocarcinoma	88 (7.9%)
Seminoma/NSGCT† classification	*n* = 1088
Seminoma	673 (61.9%)
NSGCT	415 (38.1%)

†NSGCT classification includes pure seminoma with AFP >20 ng/mL.

testicular biopsy in four patients (0.4%), incomplete resection in 1 (0.1%), high orchidectomy in 1112 patients (99.2%) and simple orchidectomy in four patients (0.4%). Pathological records included seminomatous element in 891 patients, teratoma in 197, choriocarcinoma in 88, yolk sac tumor in 202 and embryonal carcinoma in 268 patients. A total of 673 patients (60.0%) were designated for seminoma criteria and 415 patients (37.0%) were designated for NSGCT criteria.

Clinical stage

A total of 344 patients (30.7%) with any metastatic lesion (N + or M+) were reported (Table 4). Among 281 patients (25.1%) with lymph node metastasis, the retroperitoneal lymph node was the most frequent site noted in 279 patients. M1 lesion was found in 175 patients (15.6%). The most frequent metastatic lesion site was the lung (124 patients), and other sites were the liver, brain and bones in that order. Overall, the JUA staging system categorized stage I in 729 patients (67.9%), stage II in 153 patients (14.2%) and stage III in 191 patients (17.8%). According to the IGCCC, a total of 258 patients were classified into the good, intermediate and poor prognosis group by 119 (46.1%), 82 (31.8%), and 57 (22.1%), respectively.

Treatments

As an adjuvant treatment for stage I seminoma ($n = 502$), RT was carried out in 79 patients (15.7%), chemotherapy was carried out in 13 patients (2.6%), including BEP in four patients and CBDCA in nine patients, and RPLND was carried out in two patients (0.4%; Table 5). As adjuvant therapy for stage I NSGCT ($n = 165$), chemotherapy was carried out in 15 patients (9.1%), including BEP/EP in 14 patients and CDBCA in one patient; RPLND was carried out in three patients (1.8%) and RT was carried out in five patients (3.0%). For 143 patients with metastatic seminoma, chemotherapy was carried out in 87

Table 4 Clinical stage

T classification	
T0	4 (0.4%)
T1/Tis	698 (62.3%)
T2	290 (25.9%)
T3	76 (6.8%)
T4	9 (0.8%)
TX	44 (3.9%)
N classification	
N0	840 (74.9%)
N1	87 (7.8%)
N2	80 (7.1%)
N3	51 (4.5%)
N+ (unclassified N stage)	63 (5.6%)
M classification	
M0	942 (84.0%)
M1	175 (15.6%)
M1a	135 (12.0%)
M1b	40 (3.6%)
MX	4 (0.4%)
Metastatic site	*n* = 344 (30.7%)
Retroperitoneal lymph nodes	279 (81.1%)
Cervical lymph nodes	32 (9.3%)
Lung	124 (36.0%)
Liver	21 (6.1%)
Bone	6 (1.7%)
Brain	10 (2.9%)
JUA classification†	*n* = 1073
I	729 (67.9%)
II	153 (14.2%)
IIA	114 (10.6%)
IIB	39 (3.6%)
III	191 (17.8%)
III0	44 (4.1%)
IIIA	15 (1.4%)
IIIB	92 (8.6%)
IIIC	40 (3.7%)
IGCCC	*n* = 258
Good	119 (46.1%)
Intermediate	82 (31.8%)
Poor	57 (22.1%)

†JUA classification: See Appendix I.

patients (60.8%), including BEP/EP/alterations in 84 patients, CBDCA in one patient and VIP in one patient, RT was carried out in 43 patients (30.0%) and RPLND was carried out in 21 patients (3.0%). For 237 patients with metastatic NSGCT, chemotherapy was carried out in 220 patients (92.8%), including BEP/EP/alterations in 204 patients and VIP in 14 patients.

Survival data

The survival rate was calculated using 1034 patients who fulfilled the criteria of JUA staging (see Appendix I), as well as seminoma/non-seminoma histology. During the observation period of 4–1844 days with a median of 933 days, 1- and 3-year overall survival rates were 98.3% and 96.8%, respectively (Fig. 1). According to the seminoma/NSGCT criteria, 1- and 3-year overall survival rates were 99.8% and 99.5% in seminoma and 95.6% and 92.2% in NSGCT, respectively (Fig. 2). According to the JUA classification and seminoma/NSGCT criteria, 1- and 3-year overall survival rates were 100%

Table 5 Treatment for seminoma and NSGCT

	Stage I seminoma	Stage I NSGCT	Metastatic seminoma	Metastatic NSGCT
No. patients	502	165	143	237
Chemotherapy	13 (2.6%)	15 (9.1%)	87 (60.8%)	220 (92.8%)
CDBCA monotherapy	9	1	1	
BEP/EP/Alterations	4	14	84	204
VIP			1	14
Unknown/others			1	2
Radiation therapy	79 (5.7%)	5 (3.0%)	43 (30.0%)	5 (2.1%)
Extirpation surgery	2 (0.4%)	3 (1.8%)	21 (14.7%)	23 (9.7%)
Surveillance alone	408 (81.3%)	142 (86.1%)		

Multimodal treatment for metastatic seminoma in eight patients. Multimodal treatment for metastatic NSGCT in 11 patients.

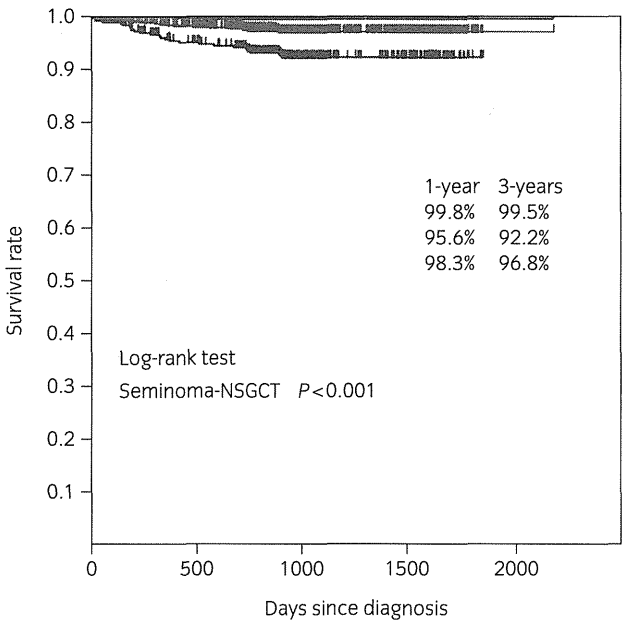

Fig. 1 Overall survival in seminoma and NSGCT. ——, Seminoma (n = 657); ——, NSGCT (n = 377); ——, overall (n = 1034).

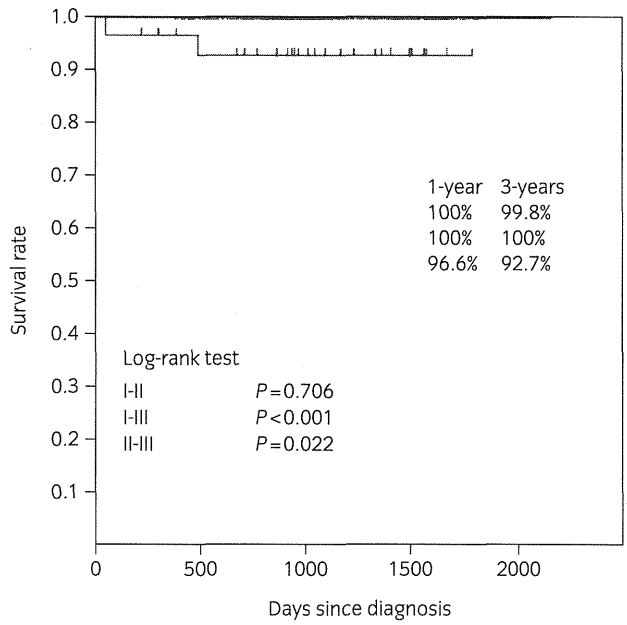

Fig. 2 Overall survival in seminoma stratified by JUA classification. ——, Stage I (n = 552); ——, stage II (n = 76); ——, stage III (n = 31).

and 99.8% in stage I seminoma, 100% and 100% in stage II seminoma, 96.6% and 92.7% in stage III seminoma, 99.3% and 98.5% in stage I NSGCT, 96.9% and 95.1% in stage II NSGCT, and 91.0% and 83.7% in stage III NSGCT, respectively (Figs 3,4). According to the IGCCC, 1- and 3-year overall survival rates were 99.4% and 99.1% in the good prognosis group, 100% and 100% in the intermediate prognosis group, and 83.7% and 79.9% in the poor prognosis group (Fig. 4).

Discussion

The current study was carried out by the JUA to comprehensively aggregate the national registration for testicular cancer, and was the first attempt to evaluate the distribution of histology and clinical stages as well as treatment variation for testicular cancer using a large cohort of patients. For the treatment of patients with testicular cancers in clinical practice, guidelines from the JUA, EAU or National Comprehensive Cancer Network are currently updated,[4,6,7] but the diagnosis and treatment policy for testicular cancer might be varied between facilities. In fact, various kinds of test kits are available to measure HCG levels. The measurement of HCG activity shown by mIU/mL is possible using two types of commercially available measurement kits, which include intact HCG (measuring the bound units of α and β chains) and total HCG (measuring free β-HCG, HCG cutting type, cutting-free β-HCG in addition to intact HCG). These measurements were recommended as the general rule for clinical and pathological studies on testicular tumor published in 2005. In the present study, these measurements were reported in approximately 40% of patients. In contrast, the use of free β-HCG assay kits (units: ng/mL) was more prevalent in even 60% of patients. In fact, the present study fails to evaluate the IGCCC in all patients because of the difficulty in adjustments of these assays.

High orchidectomy was carried out in 98.2% of patients as the treatment for primary lesion. This could be because the importance of this procedure not only for surgical resection, but also for correct histological diagnosis is understood. Histopathological findings showed a high prevalence of pure seminoma, accounting for approximately 60%, which was

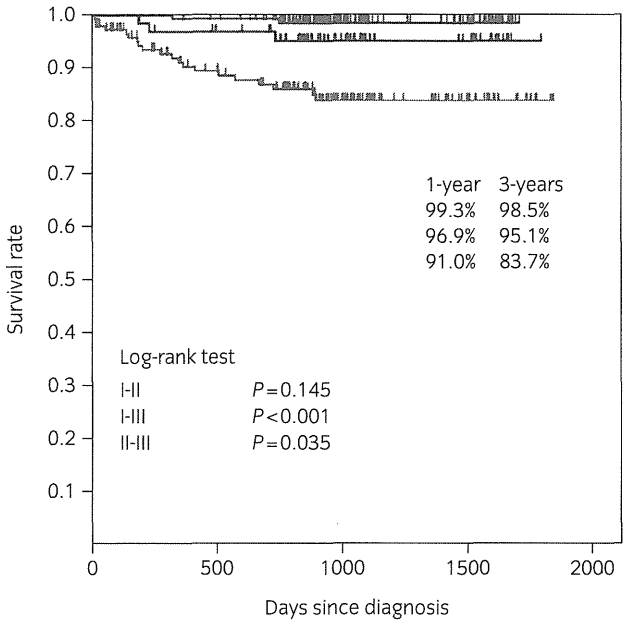

Fig. 3 Overall survival in NSGCT stratified by JUA classification. ——, Stage I (n = 162); ——, stage II (n = 68); ——, stage III (n = 145).

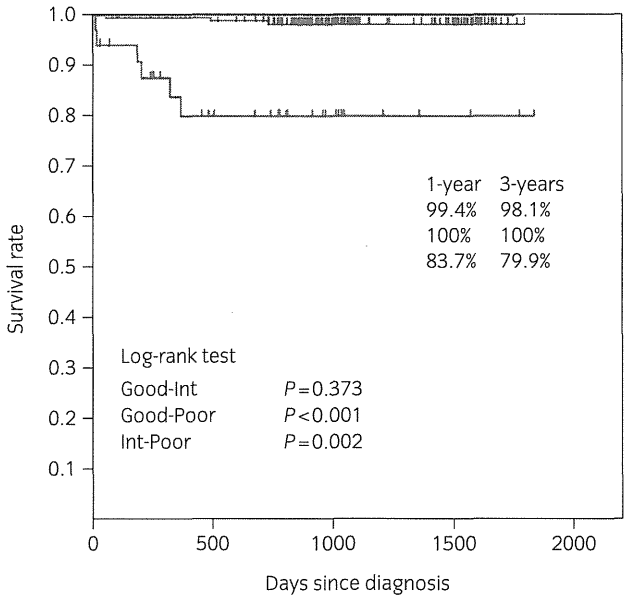

Fig. 4 Overall survival stratified by IGCCC. ——, Good (n = 119); ——, intermediate (n = 82); ——, poor (n = 57).

consistent with a historical report.[8] The most frequent metastatic sites were the retroperitoneal lymph node and lung in the present study.

The 25-Gy irradiation to the pelvis and para-aortic lymph node regions reportedly lowers the relapse rate for stage I seminoma by approximately 5%.[9] In the present study registered in 2005 and 2008, radiation therapy for stage I seminoma was still a common procedure reported in 15.7% of patients, which might have since been reduced because of the recent guideline clearly highlighting the risk of infertility and increased incidence of secondary malignancies.[6,7]

The introduction of chemotherapy has made testicular cancer a treatable disease. Even in patients with metastases, modern chemotherapy offers a cure rate of at least 80%.[10] The combination of BEP chemotherapy was reported in 1987, and became a standard treatment for metastatic testicular cancers.[11] Three or four courses of BEP are recommended depending on the risk groups.[12] Four courses of EP and three courses of BEP chemotherapy are equally recommended for patients with good prognosis.[13] BEP and EP therapy were widely used for both seminoma and NSGCT in more than 90% of patients in this survey. Other combinations, such as VIP, were used as initial chemotherapy for testicular cancer, which remained at approximately 6% of cases of NSGCT.

As for the survival rate, the Japan National Cancer Center reported a 5-year overall survival rate of 92% based on 369 patients with testicular cancer registered in six centers from 1993 to 1999. The 5-year survival rates according to progression of disease was shown to be 97.8% in patients without metastasis, 100% in patients with regional lymph node metastasis and 70.7% in patients with distant metastasis.[8] The current survey showed 3-year overall survival of more than 95% in all patients and 92.7% 3-year survival rate even in stage III patients. Although it is difficult to compare two cohorts with different observation periods, the survival rates in the present survey might be consistent with or better than the data from the previous report. The original paper from the IGCCC reported 5-year survival rates in the good, intermediate and poor prognosis groups of 91%, 79%, and 48%, respectively.[5] Even in the selected patients who had the proper HCG measurement, the IGCCC in the present study documented 3-year overall survival rates in the good, intermediate and poor prognosis groups of 99.1%, 100%, and 79.9%. This dramatic improvement in the treatment of testicular cancer can be attributed to accurate diagnosis by using available tumor markers and sophisticated imaging modalities, as well as improved surgical techniques and effective chemotherapy.

The present report is the first large-scale study of the characteristics and survival of testicular cancer patients in Japan based on multi-institutional registry data, and showed a good prognosis even at an advanced stage. The improved survival was attributed to substantially by accurate diagnosis and effective multimodal treatment.

Acknowledgments

These clinicopathological statistics are based on the results from a number of institutions in Japan (Table S1). We are grateful for the cooperation of many Japanese urologists.

Conflict of interest

None declared.

References

1 *Cancer Incidence in Five Continents*, Vol. IX. IARC Scientific Publications. IARC, Lyon, 2009, 578–81.
2 La Vecchia C, Bosetti C, Lucchini F *et al.* Cancer mortality in Europe, 2000–2004, and an overview of trends since 1975. *Ann. Oncol.* 2010; **21**: 1323–60.

3 Japanese Urological Association and Japanese Pathological Society. *General Rules for Clinical and Pathological Studies on Testicular Tumors*, 3rd edn. Kanehara, Tokyo, 2005.
4 Japanese Urological Association. *The 2009 Edition of the Testicular Cancer Clinical Practice Guidelines*. Kanehara, Tokyo, 2009.
5 International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J. Clin. Oncol.* 1997; **15**: 594–603.
6 Albers P, Albrecht W, Algaba F *et al.* EAU guidelines on testicular cancer: 2011 update. *Eur. Urol.* 2011; **60**: 304–19.
7 National Comprehensive Cancer Network. 2014. *Testicular Cancer Guideline* (Version 1). [Cited 6 Feb 2014.] Available from URL: http://www.nccn.org/
8 Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T; Research Group of Population-Based Cancer Registries of Japan. Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. *Jpn. J. Clin. Oncol.* 2011; **41**: 40–51.
9 Warde P. Prognostic factors for relapse in stage seminoma managed by surveillance: a pooled analysis. *J. Clin. Oncol.* 2002; **20**: 4448–52.
10 Feldman DR, Bosl GJ, Sheinfeld J, Motzer RJ. Medical Treatment of Advanced Testicular Cancer. *JAMA* 2008; **299**: 672–84.
11 Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N. Engl. J. Med.* 1987; **316**: 1435–40.
12 de Wit R, Roberts JT, Wilkinson PM *et al.* Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3-or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. *J. Clin. Oncol.* 2001; **19**: 1629–40.
13 Culine S, Kerbrat P, Kramar A *et al.* Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). *Ann. Oncol.* 2007; **18**: 917–24.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Institutions that were registered.

Appendix I

JUA staging system for testicular cancer (2005; established based on Boden–Gibb's staging system)
Stage I: Confined to testis
Stage II: RPLN involved below diaphragm
  IIA: RPLN <5 cm
  IIB: RPLN 5 cm or more
Stage III: Distant metastasis
  III0: No evident radiographic metastasis with elevated tumor marker
  IIIA: LN above diaphragm without visceral organs involved
  IIIB: Lung metastasis
    IIIB1: 4 or less lung metastasis, all <2 cm
    IIIB2: 5 or more lung metastasis or >2 m in size
  IIIC: Visceral metastasis other than lung

日外会誌　115　臨時増刊号（3）：51-53，2014

第114回日本外科学会定期学術集会記録
第12回臨床研究セミナー　第3部　外科臨床研究の実践

膵・消化管NETの臨床研究

（2014年4月5日受付）

京都大学名誉教授，関西電力病院神経内分泌腫瘍センター長
今村　正之

1. はじめに

NETは希少疾患であり，臨床研究のためには多施設の協力の下に症例数を確保しなければならない．一昨年9月に日本神経内分泌腫瘍研究（JNETS）が設立されて，317施設会員が参加して，患者登録事業とガイドライン作成，研究の促進を目的として活動している．NETに関する最新情報と研究会について述べる．

2. NETとは？

NETは全身に発生するが，消化器発生が約60%と多く，膵NETが多い．次いで肺・気管支・胸腺が27%である．アジア地域と欧米では消化管NETの分布が異なり，本邦を含めてアジアでは直腸，次に胃が多いが，欧米では小腸が多い．腫瘍細胞が分泌顆粒を有することがNETの証明であるが，クロモグラニンAとシナプトフィジンの染色陽性が証明となる．本質的に悪性との認識が広がり，WHO（国際保健機構）の消化器系腫瘍病理分類で2000年にカルチノイドの呼称が消え，2010年には患者の予後と相関するKi67指数のGrade分類を利用するG1，G2，G3分類が採用されている（表1）[1]．

3. 本邦での実態調査

伊藤らによると，2005年の調査で人口10万人当たり新規発症数は膵NETが1.01人，消化管NETは2.10人であったが，2010年の調査では膵NET 1.27人，消化管NET　3.51人と増加していた[2][3]．特に非機能性NETが増加している．これは米国でこの30年間にNET発生数が5倍に増加したという成績と呼応している．MEN1の合併が約10%あり，診療においては見逃しやすいので注意が必要である．

4. 機能性NETの診療上の課題

機能性NETは特徴的ホルモン症状が出現した時点で医師を訪れるが，低血糖や胃酸分泌過剰，移動性壊死性紅斑，激しい下痢などの症状からインスリノーマやガストリノーマ，グルカゴノーマ，VIPオーマなどを想起できないことも多い．初診から3～7年を経て診断確定に至るという報告がある．これらの内インスリノーマとグルカゴノーマは膵に発生し，VIPオーマやソマトスタチノーマは膵と十二指腸などに発生し，ガストリノーマは他の腹腔内臓器や時に心膜に発生する．このような場合ソマトスタチン受容体シンチグラフィー（SRS）が局在診断に有用であるが，本邦では未承認である．

膵・十二指腸領域の機能性NETの局在診断には，選択的刺激薬注入法（SASI　test）が有用である．インスリノーマと類似の低血糖症状を呈してCT，EUSなどで腫瘍が不明の場合，成人型focal nesidioblastosisが疑われる．私たちは全例を膵切除術で治癒させてきた．切除膵を検討すると膵管周辺のB細胞新生やB細胞発芽像やびまん性のラ島新生が見つかる[4]．

MEN1に随伴するガストリノーマは十二指腸に発生する．私たちはMEN1に随伴するガストリノーマはSASI testによる局在診断の下で治癒切除できることを報告してきた[9]．13%で膵にもガストリノーマがあった[5]．MEN1では膵に非機能性NETや微小グルカゴノーマなどが多発する．いづれも2cm以上になれば切除が推奨される．

表1　膵・消化管 NET WHO 分類 2010

WHO1980	WHO2000	WHO2010
I カルチノイド	1. 高分化内分泌腫瘍（WDET）[a] 2. 高分化内分泌癌（WDEC）[a] 3. 低分化内分泌癌/小細胞癌（PDEC）	1. NET G1 2. NET G2[b] 3. NEC（大細胞または，小細胞がん）[b, c]
II Mucocarcinoid III Mixed forms carcinoid-adenocarcinoma	4. 混合腺・内分泌癌（MEEC）	4. 混合腺・内分泌癌（MANEC）
IV Pseudotumor lesions	5. Tumor-like lesions（TLL）	5. 過形成・前癌病変

G, grade；NEC, neuroendocrine carcinoma；NET, neuroendocrine tumor.
[a]. G2 NET は，WHO 分類 2000 で定義された WDEC と必ずしも一致しない．
[b]. カッコ内は ICD-O（International Classification of Diseases for Oncology）コード．
[c].「NET G3」の表現がこのカテゴリーで使用されてきたが，NET が高分化型と定義された為推奨されない．

Bosman FT, et al. *WHO Classification of Tumours of the Digestive System* 4th Edition. Lyon, France：IARC Press；2010.

5. 非機能性 NET の診療上の課題

非機能性 NET は CT などで偶然，見つかることが多い．その 25% で初診時に肝転移を伴う．膵非機能性 NET を経過観察する場合も多かったと思われるが，現在，NCCN ガイドラインと本邦のガイドラインでは，切除が推奨されている．患者の年齢，一般状態などを考慮して直ぐ切除しない場合には，3〜6 月毎の画像診断が必要とされている．膵 NET の肝転移の可能性は深刻に受け止めて，50 歳までの患者であれば，膵切除に慣れている施設で切除を検討すべきであり，膵頭部の 1cm 以下の NET で被膜を有する場合には，核出術が適応と考えている．これらは JNETS での臨床研究で検証される予定である．

6. 肝転移治療薬に関する臨床研究

NET の治療薬としては唯一，ストレプトゾシン（STZ）が欧米で使用されて来た．本邦では未承認のために個人輸入という手段を用いて，主として東京大学と京都大学で単独あるいは 5FU との併用で使用されてきた．数年前に欧米でソマトスタチン類似薬（オクトレオチド LAR）の消化管 NET への有用性が，多施設無作為化臨床試験で証明された[6]．次いで膵 NET に対して分子標的薬であるエベロリムスとスニチニブの有用性が国際的多施設無作為化臨床試験で明らかにされ[7][8]，これらは本邦でも比較的早く承認された．STZ も近く承認の見通しと思われる．肝転移治療の選択肢をどのように組み合わせて使うかが，臨床研究の対象となる重要な課題である．

7. ソマトスタチン受容体を利用する診療法（本邦未承認）の有用性

本邦では ^{111}In を用いる SRS が承認されないが，欧米では ^{68}GaDOTATOCPET/CT が標準的となっている[9]．本邦では京都大学放射線診断科の中本裕士講師らが合成して研究として実施している．従来の SRS に比し数段優れていて，感度 93%，特異度 91% と報告された．EU 諸国では ^{68}GaDOTATOCPET/CT で陽性となった病変に対しては Peptide receptor radionuclide therapy（PRRT）が有用であることが示されている．PRRT とは，^{90}Y や ^{177}Lu を標識したソマトスタチン類似薬を静脈投与する内照射治療である．500 人を超える NET 肝転移患者に対して CR+PR が約 30% と良好な成績である[10]．導入が進まない中，患者が海外へ渡航している現状である．

8. 日本神経内分泌腫瘍研究会（JNETS）の臨床研究の促進事業について

2012 年 9 月に日本神経内分泌腫瘍研究会（JNETS jnets.umin.jp/）が設立された．事業として，1）NET 患者登録事業，2）診療ガイドラインの作成とその改定，3）年 1 回の学術集会の開催，4）各種委員会とプロジェクト研究事業を挙げている．全国から内科，外科，腫瘍内科，病理，放射線科，呼吸器外・内科，遺伝医学などの 317 施設が会員となって下さり活動を開始している．患者登録に際しては，research questions

を設定して登録項目を決定した.

文　献

1) Bosman FT, Carneiro F, Courelard A, et al.: WHO Classification of Tumours of the Digestive System 4th Edition. IARC Press, Lyon, France, 2010.
2) Ito T, Sasano H, Tanaka M, et al.: Epidemiological study of neuroendocrine tumors in Japan. J Gastroenterol, 45 : 234-243, 2010.
3) Ito t, et al.: in press.
4) 今村正之：神経内分泌腫瘍の概念と最新情報の概要. 消化器外科, 36 (13) : 1825-1832, 2013.
5) Imamura M, Komoto I, Ota S, et al.: Biochemical curative surgery for gastrinoma in multiple endocrine neoplasia type-1 patients. World J Gastroenterol, 17 (10) : 1343-1353, 2011.
6) Rinke A, Müller HH, Schade-Brittinger C, et al.: Placebo-controlled, double blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group. J Clin Oncol, 27 : 4656-4663, 2009.
7) Yao J, Shah MH, Ito T, et al.: RAD001 in advanced neuroendocrine tumors. Third trial (RADIANT-3) study group: Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med, 364 : 514-523, 2011.
8) Raymond E, Dahan L, Raoul JL, et al.: Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med, 364 : 501-513, 2011.
9) Treglia G, Castaldi P, Rindi G, et al.: Diagnostic performance of Gallium-68 somatostatin receptor PET and PET/CT in patients with thoracic and gastroenteropancreatic neuroendocrine tumours: a meta-analysis. Endocrine, 42 (1) : 80-87, 2012.
10) Kwekkeboom DJ, De Herder WW, Kam BL, et al.: Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0, Tyr3] Octreotate: Toxicity, Efficacy, and Survival. Clin Oncol, 26 : 2124-2130, 2008.

利益相反：なし

2014年4月号(Vol. 37 No. 4)

膵NET

Pancreatic neuroendocrine tumor

増井 俊彦* 上本 伸二**
Toshihiko Masui *Shinji Uemoto*

●要旨●膵NETはWHO2010によるグレード分類のほかに機能性・非機能性による分類によっても病態が違い，比較的希少な疾患であることも相まって，いまだ標準治療が確立されていない分野である。近年，高分化型膵NETに対する薬物療法として分子標的薬であるエベロリムス，スニチニブがランダム化第3相試験で無増悪生存期間を延長することが示され，本邦でも2011年以降，保険承認となった。また，従来の化学療法にても近々ストレプトゾシンが保険承認される見込みであり，アルキル化剤であるテモゾロミドが有効である可能性が示されるなど，この分野での薬物療法の発展は著しい。しかしながら，術前，術後療法に限ると現在前向き研究が行われ始めている段階であり，現段階では有効とされる報告がないのが実情である。

● key words：分子標的薬，エベロリムス，スニチニブ，ストレプトゾシン，テモゾロミド

はじめに

neuroendocrine tumor（NET）とは神経内分泌細胞に由来する腫瘍の総称であり，ペプチドホルモンおよびアミン産生能を有し，神経内分泌マーカーとして高分化型ではクロモグラニンAあるいはシナプトファイジンを発現していることが特徴である。膵，消化管，胸腺，気管支，副腎，下垂体など全身の諸臓器に発生しその発生母地によって遺伝子異常が異なり，病態，悪性度も異なることが知られている[1]。NETはWHO2010分類にて予後の点から分裂能に応じて3種類に分類されることとなった（表1）。さらに治療するうえでは機能性，非機能性の分類による病態の違いも重要である。このようにNETは他の癌に比して多様性をもっていること，また，それぞれの多様性に応じて病態が異なることを理解する必要がある。

Itoらによると，膵に発生するNETは本邦では新規発症が10万人に1.01人という希少疾患である[2]。米国のSEERデータベースによると周囲への浸潤のない膵NETでも生存率中央値が136カ月であり[3]，発見時に30～87%遠隔転移をもつとされることから[3)~6)]，潜在的には悪性疾患と考えるべきである。したがって膵NETに対する治療は基本的には外科的手段による腫瘍全切除をめざすべきであるが，可能であればさらなるmodalityの追加にて予後向上をはかることが望まれる。

化学療法，薬物療法は2000年代になるまでは海外ではストレプトゾトシンあるいはドキソルビシン，5-FUが使用されていたが[7)8)]，本邦では薬物治療は保険未承認であり使用困難であった。近年，膵NETの遺伝子解析が進んできたことと，それに対応する分子標的薬が開発されてきており，2011年にmTOR阻害薬であるエベロリムス，2012年にチロシンキナーゼ阻害薬であるスニチニブが本邦にて承認され，高分化，中分化の膵NETに対して使用可能となった。一方，化学療法薬としては，テモゾロミドがカペシタビンとの併用での有効性などが示されてきているが[9)~11)]，いまだ本邦では使用可能となっていない。なお，以前より海外で使用されていたストレプトゾトシンは抗腫瘍効果の再評価を行った後，本邦でも使用できるよう申請中である。

このように膵NETに対する薬物療法は世界的にもデータの蓄積を行いどのようなタイプの腫瘍に効果が高いのかの検討が徐々に始まっている段階である。し

* 京都大学大学院医学研究科肝胆膵・移植外科
** 同教授