Table 4 Clinicopathological characteristics in patients treated with intravesical chemotherapy (IVI), Bacillus Calmette-Guérin (BCG) instillation, and no adjuvant therapy

Patients	IVI chemotherapy No. patients (%)	BCG instillation No. patients (%)	No IVI treatment No. patients (%)	*P*-value
	1314	396	1527	
Age				0.853
≤70	671 (51.1)	199 (50.3)	790 (51.7)	
>70 years	643 (48.9)	197 (49.8)	737 (48.3)	
Gender				0.287
Male	1038 (79.0)	323 (81.6)	1239 (81.1)	
Female	276 (21.0)	73 (18.4)	288 (18.9)	
Papillary type				<0.001
Yes	1224 (93.2)	325 (82.1)	1389 (91.0)	
No	69 (5.3)	57 (14.4)	86 (5.6)	
Unknown	21 (1.6)	14 (3.5)	52 (3.4)	
Tumor stalk				<0.001
Yes	925 (70.4)	225 (56.8)	1101 (72.1)	
No	316 (24.1)	143 (36.1)	326 (21.4)	
Unknown	73 (5.6)	28 (7.1)	100 (6.55)	
Multiplicity				<0.001
Yes	588 (44.8)	242 (61.1)	482 (31.6)	
No	690 (52.5)	132 (33.3)	988 (64.7)	
Undetected	14 (1.1)	10 (2.5)	9 (0.6)	
Unknown	22 (1.7)	12 (3.0)	48 (3.1)	
Tumor size				<0.001
<1 cm	369 (28.1)	101 (25.5)	543 (35.6)	
1–3 cm	716 (54.5)	197 (50.0)	768 (50.3)	
>3 cm	180 (13.7)	68 (17.2)	126 (8.25)	
Uncountable	15 (1.1)	13 (3.3)	17 (1.1)	
unknown	34 (2.6)	17 (4.3)	73 (4.8)	
Pathological T category				<0.001
pTa	672 (51.1)	120 (30.3)	859 (56.3)	
pT1	642 (48.9)	276 (69.7)	668 (43.8)	
Grade				<0.001
G1	287 (21.8)	37 (9.3)	458 (30.0)	
G2	817 (62.2)	178 (45.0)	855 (56.0)	
G3	210 (16.0)	181 (45.7)	214 (14.0)	

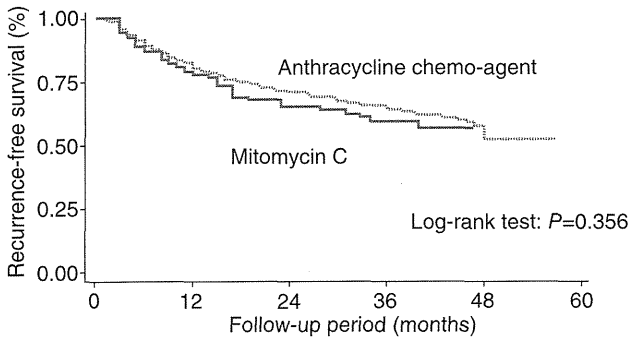


Fig. 3 Kaplan–Meier curve for tumor recurrence in patients treated with adjuvant intravesical chemotherapy comparing an anthracycline chemo-agent and mitomycin C treatment.

Discussion

In the present study, we characterized the clinical outcome of newly diagnosed non-muscle invasive bladder cancer in a large contemporary series of patients from a Japanese bladder cancer registry and determined the predictors for tumor recurrence. Overall, bladder tumor multiplicity, a tumor size greater than 3 cm, pathological stage T1, tumor grade G3, and the absence of adjuvant intravesical instillation were found to independently increase the risk of tumor recurrence. Numerous publications have reported the same prognostic indicators as ours for tumor recurrence in non-muscle invasive bladder cancer.[1–3] Recently, a combined analysis was carried out using data from 2596 non-muscle invasive bladder cancer patients collected from seven European Organization for Research and Treatment of Cancer (EORTC) trials.[4] In the analysis, six clinicopathological risk factors, namely multiplicity, tumor size, prior recurrence rate, pathological stage, concomitant CIS, and tumor grade were determined. Four of the six predictors for tumor recurrence in the present study were shared with their indicators; however, the big difference between their study

Table 5 The 1-year and 3-year recurrence-free survival rates according to clinicopathological characteristics in patients treated with intravesical chemotherapy

		% 1-Year (mean ± SE)	% 3-Year (mean ± SE)	*P*-value
Age				0.695
	≤70 years	79.2 ± 0.02	64.7 ± 0.02	
	>70 years	81.6 ± 0.02	63.4 ± 0.02	
Gender				0.025
	Male	79.2 ± 0.01	62.7 ± 0.02	
	Female	84.6 ± 0.02	69.7 ± 0.03	
Papillary type				0.209
	Yes	80.7 ± 0.01	64.7 ± 0.02	
	No	74.5 ± 0.05	57.6 ± 0.06	
Tumor stalk				0.016
	Yes	82.0 ± 0.01	66.4 ± 0.02	
	No	76.2 ± 0.02	58.9 ± 0.03	
Multiplicity				<0.001
	No	85.6 ± 0.01	69.6 ± 0.02	
	Yes	73.8 ± 0.02	57.5 ± 0.02	
Size				0.004
	≤3 cm	81.8 ± 0.01	65.6 ± 0.02	
	>3 cm	70.7 ± 0.04	55.8 ± 0.04	
Pathological T category				0.002
	pTa	84.0 ± 0.02	68.1 ± 0.02	
	pT1	76.4 ± 0.02	60.1 ± 0.02	
Grade				0.001
	G1/2	82.1 ± 0.01	66.1 ± 0.02	
	G3	71.1 ± 0.03	54.5 ± 0.04	

and ours is that their population has included both primary and recurrent cases. A more homogenous population of patients who initially diagnosed non-muscle invasive bladder tumor was evaluated in our current study.

Overall, 12.2% received BCG instillation in our study. In the subgroup of patients treated with BCG instillation, no clinicopathological factors were associated with tumor recurrence. Kaplan–Meier analysis demonstrated that the recurrence-free survival in the BCG instillation group was significantly higher than that in the intravesical chemotherapy group especially in pT1G3 patients ($P = 0.039$), which was confirmed by others.[11] Furthermore, BCG instillation was significantly selected in patients with multiple, larger, and higher pathological stage tumors, compared with intravesical chemotherapy. These results suggested that BCG instillation was carried out for the prevention of recurrence in a relatively smaller percentage of high risk patients than would have been expected from the current clinical situation.[12,13] One reason for the difference in the percentage of BCG instillations carried out between 1999–2001 and the present is that the current clinical management for non-muscle invasive bladder cancer is highly affected by the guidelines.[14,15]

In our subgroup consisting of the 1314 patients treated with adjuvant intravesical chemotherapy, multivariate analyses demonstrated that male gender, bladder tumor multiplicity, a tumor size greater than 3 cm, and pathological stage T1 were independent risk factors for tumor recurrence. Only about 10% of the patients were treated with MMC intravesical chemotherapy. Au *et al.* reported that intravesical chemotherapy using a modified 40 mg dose of MMC accompanied by a decrease in urine volume during the procedure and urine alkalinization significantly improved the therapeutic benefit of traditional MMC treatment for the prevention of tumor recurrence.[16] Meanwhile, Huncharek *et al.* have showed that maintenance intravesical chemotherapy reduced tumor recurrence, when compared with a single course of induction chemotherapy.[17] Further study is warranted to prove the therapeutic benefit with these modalities, especially in Japanese patients who have these risk factors for recurrence. In our multivariate analyses, gender is an independent predictor for tumor recurrence in patients treated with adjuvant intravesical chemotherapy but not in overall patients. There has been no study to evaluate the influence of gender for tumor recurrence in a large series of bladder cancer patients treated with intravesical chemotherapy. The exact reason why female patients have better outcome for tumor recurrence than male patients has to be elucidated in a future study.

Frydenberg *et al.* conducted a survey of a population cancer registry that included about 700 newly diagnosed non-muscle invasive bladder cancers between 1990 and 1995 in Victoria of Australia. Logistic regression analysis revealed that tumor grade and pathological T stage were independent factors affecting the risk of recurrence. Less than 10% of the patients received adjuvant intravesical chemotherapy or immunotherapy.[18] Gårdmark *et al.* analyzed the clinical characteristics of about 10 000 newly diagnosed cases of bladder cancer obtained from the Swedish National Bladder Cancer Register between 1997 and 2001.[19] A large number of the patients, even in the high risk group, were still undertreated and they concluded that the survival rate of bladder cancer in Sweden during this period seemed to remain at the levels previously reported for the 1980s. The accumulation of data provided by a large cancer registry is of great importance to understanding the

Table 6 *Univariate and multivariate Cox regression analysis for tumor recurrence in patients treated with intravesical chemotherapy*

		Univariate	Multivariate		
		P-value	Hazard ratio	95% CI	*P*-value
Age		0.660			
	≤70 years				
	>70 years				
Gender		0.030			0.008
	Male		1		
	Female		0.71	0.55–0.91	
Papillary type		0.706			
	Yes				
	No				
Tumor stalk		0.023			
	Yes				
	No				
Multiplicity		<0.001			<0.001
	No		1		
	Yes		1.67	1.37–2.03	
Size		0.005			0.028
	≤3 cm		1		
	>3 cm		1.34	1.03–1.73	
Pathological T category		0.003			0.004
	Ta		1		
	T1		1.33	1.09–1.62	
Grade		0.002			
	G1/2				
	G3				

CI, confidence interval.

trends in the clinical characteristics of the disease and its treatment management, and to providing an opportunity for analysis of the indicators predicting prognosis.[20]

The present study has several limitations. First, the results were obtained from a dataset created by data only from centers participating in the bladder cancer registry. Since all of the centers in Japan do not participate in the cancer registry, the dataset does not include data for all bladder cancers in Japan. However, approximately 180 institutions participate in the cancer registry in Japan and the dataset contained data for approximately 6000 patients so we believe that the results represent an accurate reflection of the characteristics of patients with newly diagnosed bladder cancer and its clinical outcome in the period from 1999 and 2001.[21] Another limitation is that the follow-up period was short. Median follow-up was 24 months and this bias might affect the understanding of true risk factors and the natural course of non-muscle invasive bladder cancer and make us unable to analyze the prediction of tumor progression and survival. In fact recurrence-free survival in our study was somewhat better than that reported in another large series.[3] Several papers pointed out the importance of the use of data from long-term follow-up of non-muscle invasive bladder cancer.[22,23] Further study would be warranted to accumulate long-term follow-up data in the bladder cancer registry.

In conclusion, patients with multiple tumors, a tumor size greater than 3 cm, tumor grade G3, or pathological T1 tumors were at greater risk, whereas those treated with intravesical BCG instillations had a decreased risk of tumor recurrence in the overall patient population. In patients treated with intravesical chemotherapy, male gender, bladder tumor multiplicity, a tumor size greater than 3 cm, and pathological stage T1 were independent risk factors for tumor recurrence. Further study of datasets created from longer follow-up data is warranted in order to analyze tumor progression and disease survival.

References

1 Allard P, Bernard P, Fradet Y, Tetu B. The early clinical course of primary Ta and t1 bladder cancer: a proposed prognostic index. *Br. J. Urol.* 1998; **81**: 692–8.

2 Kurth KH, Denis L, Bouffioux C *et al.* Factors affecting recurrence and progression in superficial bladder tumours. *Eur. J. Cancer* 1995; **31A**: 1840–6.

3 Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodriguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. *J. Urol.* 2000; **163**: 73–8.

4 Sylvester RJ, van der Meijden AP, Oosterlinck W *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur. Urol.* 2006; **49**: 466–5.

5 Akagashi K, Tanda H, Kato S *et al.* Recurrence pattern for superficial bladder cancer. *Int. J. Urol.* 2006; **13**: 686–91.

6 Nomi M, Gohji K, Okamoto M, Takenaka A, Ono Y, Fujii A. Results of transurethral resection plus adjuvant intravesical chemotherapy for superficial bladder cancer. *Int. J. Urol.* 1998; **5**: 534–9.

7 Sakai I, Miyake H, Harada K, Hara I, Inoue TA, Fujisawa M. Analysis of factors predicting intravesical recurrence of superficial transitional

cell carcinoma of the bladder without concomitant carcinoma *in situ*. *Int. J. Urol.* 2006; **13**: 1389–92.
8 Takashi M, Wakai K, Hattori T *et al.* Multivariate evaluation of factors affecting recurrence, progression, and survival in patients with superficial bladder cancer treated with intravesical bacillus Calmette-Guerin (Tokyo 172 strain) therapy: significance of concomitant carcinoma *in situ*. *Int. Urol. Nephrol.* 2002; **33**: 41–7.
9 Japanese Urological Association, The Japanese Society of Pathology. *General Rule for Clinical and Pathological Studies on Bladder Cancer*, 2nd edn. Kanehara & Co. Ltd, Tokyo, 1993.
10 Japanese Urological Association, The Japanese Society of Pathology. *General Rule for Clinical and Pathological Studies on Bladder Cancer*, 3rd edn. Kanehara & Co. Ltd, Tokyo, 2001.
11 Hara I, Miyake H, Takechi Y *et al.* Clinical outcome of conservative therapy for stage T1, grade 3 transitional cell carcinoma of the bladder. *Int. J. Urol.* 2003; **10**: 19–24.
12 Lamm DL, van der Meijden AP, Akaza H *et al.* Intravesical chemotherapy and immunotherapy: how do we assess their effectiveness and what are their limitations and uses? *Int. J. Urol.* 1995; **2**: 23–35.
13 Lee C, Park MS. Prophylactic treatment of superficial bladder tumor. *Int. J. Urol.* 1998; **5**: 511–20.
14 Hall MC, Chang SS, Dalbagni G *et al.* Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J. Urol.* 2007; **178**: 2314–30.
15 Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C. Guidelines on bladder cancer. *Eur. Urol.* 2002; **41**: 105–12.
16 Au JL, Badalament RA, Wientjes MG *et al.* Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. *J. Natl. Cancer Inst.* 2001; **93**: 597–604.
17 Huncharek M, Geschwind JF, Witherspoon B, McGarry R, Adcock D. Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trials. *J. Clin. Epidemiol.* 2000; **53**: 676–80.
18 Frydenberg M, Millar JL, Toner G *et al.* Management of superficial bladder cancer in Victoria: 1990 and 1995. *ANZ J. Surg.* 2005; **75**: 270–4.
19 Gardmark T, Bladstrom A, Hellsten S, Malmstrom PU, Members of the Swedish National Bladder Cancer Registry. Analysis of clinical characteristics, management and survival of patients with Ta T1 bladder tumours in Sweden between 1997 and 2001. *Scand. J. Urol. Nephrol.* 2006; **40**: 276–82.
20 Cancer Registration Committee of the Japanese Urological Association. Clinicopathological statistics on registered prostate cancer patients in Japan: 2000 report from the Japanese Urological Association. *Int. J. Urol.* 2005; **12**: 46–61.
21 Okuyama A, Kohri K, Akaza H *et al.* The report of clinical statistical studies on registered bladder cancer patients in Japan 1999–2001. *Nippon Hinyoukika Gakkai Zasshi* 2006; **97**: NP2–31. (In Japanese.)
22 Cookson MS, Herr HW, Zhang ZF, Soloway S, Sogani PC, Fair WR. The treated natural history of high risk superficial bladder cancer: 15-year outcome. *J. Urol.* 1997; **158**: 62–7.
23 Holmang S, Hedelin H, Anderstrom C, Johansson SL. The relationship among multiple recurrences, progression and prognosis of patients with stages Ta and T1 transitional cell cancer of the bladder followed for at least 20 years. *J. Urol.* 1995; **153**: 1823–6.

INTERNATIONAL JOURNAL OF UROLOGY

The Japanese Urological Association affiliated with Urological Association of Asia

International Journal of Urology (2010) 17, 905–913 doi: 10.1111/j.1442-2042.2010.02633.x, 10.1111/j.1442-2042.2010.02640.x

Original Article: Clinical Investigation

Cancer death from non-muscle invasive bladder cancer: Report of the Japanese Urological Association of data from the 1999–2001 registry in Japan

Eijiro Okajima,[1,2] Hiroyuki Fujimoto,[1,3] Yoichi Mizutani,[1,4] Eiji Kikuchi,[1,5] Hirofumi Koga,[1,6] Shiro Hinotsu,[1,7] Nobuo Shinohara,[1,8] Tsuneharu Miki[1,4] and the Cancer Registration Committee of the Japanese Urological Association*

[1]Working Group of the Bladder Cancer Registration Committee of the Japanese Urological Association, [2]Department of Urology, Nara City Hospital, Nara, [3]Department of Urology, National Cancer Center Hospital, Tokyo, [4]Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine, Kyoto, [5]Department of Urology, Keio University School of Medicine, Tokyo, [6]Department of Urology, Harasanshin Hospital, Fukuoka, [7]Graduate School of Medicine and Public Health, Kyoto University, Kyoto, and [8]Department of Urology, Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

Objectives: Our aim was to clarify the risk factors of cancer death in order to reduce mortality from T1 bladder cancer.
Methods: The Japan registration database (1999–2001) was used for the analysis. Data were collected at least 3 years after the initial diagnosis. Cause-specific survival using a Kaplan–Meier survival estimation with the log–rank method was evaluated. Univariate and multivariate analysis using the Cox proportional hazard model was also carried out. The 1997 TNM classification was used for pathological staging, and the 1973 WHO classification was used for pathological grading.
Results: There were 76 cancer deaths among a total of 1919 clinical T1 cases. Regardless of the subsequent treatment strategies, non-papillary tumor appearance, non-peduncular tumor stalk, multiple tumors, a tumor size greater than 3 cm, positive urinary cytology and pathological grade 3 were found to be statistically significant in cancer death by univariate analysis. By multivariate analysis, non-papillary tumor appearance, positive urinary cytology and a tumor size greater than 3 cm were confirmed as significant risk factors. Cancer death cases were found in 47.4% of worst-grade 2 tumors, and in 67.1% of predominantly grade 1 or 2 tumors.
Conclusion: Non-papillary tumor appearance, positive urinary cytology and a tumor size greater than 3 cm should be included to enable the assessment of risk criteria in cancer death from T1 bladder cancer.

Key words: etiology, Japan, neoplasms, urinary bladder.

Correspondence: Eijiro Okajima MD PhD, Department of Urology, Nara City Hospital, 1-50-1, Higashikideracho, Nara 630-8305, Japan. Email: e-okajima@nara-jadecom.jp
*Members of the Cancer Registration Committee of the Japanese Urological Association: Tsuneharu Miki (Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine), Tomoaki Fujioka (Department of Urology, Iwate Medical University), Tomohiko Ichikawa (Department of Urology, Graduate School of Medicine, Chiba University), Seiji Naito (Department of Urology, Faculty of Medical Sciences, Kyushu University), Kenjiro Kohri (Department of Urology, Graduate School of Medical Sciences, Nagoya City University), Hideyuki Akaza (Urology and Andrology, Graduate School of Comprehensive Human Sciences, University of Tsukuba), Hiroyuki Fujimoto (Urology Division, National Cancer Center Hospital), Yoichi Mizutani (Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine), Tadao Kakizoe (National Cancer Center), Akihiko Okuyama (Department of Urology, Graduate School of Medicine, Osaka University).

Received 9 December 2009; accepted 18 August 2010.
Online publication 5 October 2010

Introduction

Bladder cancer can be classified roughly into the following three major categories: (i) non-muscle-invasive low malignant potential; (ii) invasive high malignant potential; and (iii) carcinoma *in situ*. The first category is characterized by its non-muscle-invasive nature; it can be cured by transurethral intervention and is not life-threatening, but the recurrence rate is greater than 50%. This category includes Ta (no invasion) and T1 (invasion limited to the submucosa). The second category is considered muscle-invasive (staged as T2 or more), and has a high risk of development into a systemic disease; that is, it is life-threatening. The third category (staged as Tis) is completely different from the carcinoma *in situ* of other organs. In the urinary bladder, it has a highly malignant cell morphology and is recognized as a malignant cancer cell, but often remains undetected by cystoscopy or radiographic examination. Accordingly, it can be diagnosed only pathologically by urinary cytology or biopsy of the urothelial cells.

Although most cases of bladder cancer are classified into the aforementioned three categories, some superficial non-muscle-invasive T1 tumors present with the pathological, clinical and biological characteristics of invasive tumors.[1–3] Cancer death after bladder-sparing treatment within 5 years is reported in 16–23% of cases involving T1 high-grade tumors.[4–6] Because the gold standard in the treatment of organ-confined bladder cancer at high risk of proceeding into a systemic disease is radical cystectomy, superior disease control can be achieved by using cystectomy or other invasive procedures for all T1 diseases.[7,8] However, cystectomy itself constitutes invasive treatment and requires urinary diversion, which reduces the quality of life thereafter.[9]

An urgent and important issue to be addressed in the treatment of urinary bladder cancer is the inability to properly identify life-threatening disease in T1 cases.

To improve the progress of bladder cancer treatment, the Japanese Urological Association (JUA) carried out the registration of bladder tumor cases, including 5959 patients initially diagnosed between 1999 and 2001, from institutions all over Japan.[10] The aim of this registration was to pinpoint trends in treatment strategies and evaluate the outcomes of these trends.

In the present study, we analyzed 1919 T1 bladder cancer cases in the registry database, with a special focus on cancer death (CD) within the short period surveyed, with the aim of finding risk factors to enable the identification of life-threatening T1 bladder cancer cases.

Methods

Registration of bladder cancer

Through annual meetings and publications sent to all members of JUA, we informed of and requested the registration of all new patients with bladder tumors in 1999, 2000 and 2001, and distributed CD-ROMs with the General Rules for Clinical and Pathological Studies on Bladder Cancer.[11,12]

These CD-ROMs contained a program developed by National Cancer Center staff. The patient's age, sex, occupation, race, concomitant malignancy, family history, past history, symptoms and the imaging studies carried out were registered as background factors in each case. Also recorded were the findings of cystoscopy and urinary cytology, the purpose and pathological results of the initial transurethral resection (TUR), the TNM classification based on both pathological and clinical evaluation after TUR, and the initial planned treatment after TUR. The 1997 TNM classification was used for pathological staging, and the 1973 WHO classification was used for pathological grading. We then collected data at a point 3 years after the initial pathological diagnosis (e.g. in 2002 for cases initially diagnosed in 1999). In other words, registration included the 3-year outcome of the cases after initial diagnosis.

Patients

In the present study, we analyzed T1 cases without lymph node metastasis or distant metastasis. The inclusion criteria allowed pathologically proven T1 bladder cancer cases, whereas the exclusion criteria barred cases with a diagnosis higher than T1 or those with metastatic evidence from other examination types, such as cystoscopic, surgical, computed tomography, magnetic resonance imaging examination and so on. Among the total of 5959 registered bladder cancer cases, there were 1919 cases of T1 bladder cancer without lymph node metastasis or distant metastasis.

Plans after the initial TUR are summarized in Table 4. Intravesical instillation included the following chemotherapeutic agents: adriamycin, pirarubicin (THP), THP-ADM, mitomycin C, pharmorubicin and peplomycin. The "Others" category included palliative therapy methods, such as oral anti-cancer agents and laparotomy, simple or partial cystectomy, and any type of combination therapy. Because the number of events (i.e. cancer deaths) was less than 80, there was too much variation among plans to allow plan-based assessment of risk factors using the Cox proportional hazard model in multivariate analysis.

The distribution of cases according to factors (papillary or otherwise, stalk status, multiplicity, size, urinary cytology, worst and predominant grade by pathological examination, and infiltration type) is shown in Table 2. Negative urine cytology corresponds to class I and II, suspicious urine cytology corresponds to class III, and positive urine cytology corresponds to class IV and V. There were some cases with incomplete registration. It should be noted that "unknown/blank" was found for "infiltration type" in 71.7% of all 1919 cases.

Analysis

To clarify risk factors related to survival, we carried out univariate analysis on the factors involved in CD and/or cause-specific survival (CSS; such as age, gender, smoking habits, cystoscopic findings and pathological factors of TUR specimens) regardless of treatment after the initial TUR. We excluded non-informative ("unknown/blank") cases from the analysis. CSS was examined using the Kaplan–Meier survival estimation with the log–rank method and univariate analysis with the Cox proportional hazard model. We also carried out testing to ascertain whether factors with statistical significance in univariate analysis fitted in multivariate analysis using the Cox proportional hazard model. Because CD was not found with worst-grade 1 tumors, we calculated the hazard ratio of grade 1 and 2 tumors compared with grade 3 tumors.

Table 1 Distribution of cases according to age and sex

	All cT1 ($n = 1919$)	CD ($n = 76$)	Survivors ($n = 1843$)
Age (years)			
–49	107 (5.6%)	2 (2.6%)	105 (5.7%)
50–59	277 (14.4%)	12 (15.8%)	265 (14.4%)
60–69	534 (27.8%)	13 (17.1%)	521 (28.3%)
70–79	651 (33.9%)	29 (38.2%)	622 (33.7%)
80–	350 (18.2%)	20 (26.3%)	330 (17.9%)
Sex			
Male	1524 (79.4%)	55 (72.4%)	1469 (79.7%)
Female	395 (20.6%)	21 (27.6%)	374 (20.3%)

No statistical significant difference was found between the categories of each factor by log–rank testing. CD, cancer death.

Results

Univariate analysis of factors in CSS regardless of treatment strategies

A total of 1919 T1 cases were analyzed, all involving TUR. CD occurred in 76 (3.96%) of these within the relatively short survey period, and CSS 3 years after the initial diagnosis was 95.5% according to Kaplan–Meier's survival estimation curve.

Association of age and smoking habits with CD

Distribution of age and sex in relation to CSS is shown in Table 1. The Kaplan–Meier survival estimation shows no statistical difference ($P > 0.05$) between age or smoking habits and CSS under the log–rank method. Note that 37.8% of cases were non-informative in terms of smoking habits.

Correlation of each cystoscopic finding with CD and CSS

Of the 1919 cases, 35 patients did not undergo cystoscopy.

Based on this informative data, non-papillary tumors (Fig. 1a), non-peduncular tumors (showing a 3-year survival rate of 96.7 for cases with peduncular tumors and 93.1% for non-peduncular; the log–rank probability was 0.002), multiplicity (showing a 3-year survival rate of 93.6 for cases with multiple tumors and 97.5% for solitary; the log–rank probability was 0.001) and larger-sized tumors (Fig. 1b) were assessed as risk factors in CD by log–rank testing.

Correlation of pathological findings with CSS

Results of urinary cytology: Urinary cytology was carried out in 80.8% of the 1919 cases before TUR. A positive result in urinary cytology was assessed as a risk factor with CSS by log–rank testing (Fig. 1c).

Predominant histological type: Pathological examination of TUR samples showed that the predominant histological type in 98.7% of cases was urothelial carcinoma. Adenocarcinoma and squamous cell carcinoma were found predominantly in 0.6% and 0.3% of cases, respectively. The difference in histological type could not be assessed, because very few cases showed pathology other than urothelial carcinoma.

Concomitant CIS was found in 74 of the 1919 T1 bladder cancer cases. Cancer death was found in three cases (4.1%). No statistically significant association of concomitant CIS with CD was found using the log–rank method ($P = 0.421$) or by univariate analysis with the Cox proportional hazard model ($P = 0.798$).

Histological grade: Worst-grade 3 tumors were assessed as risk factors in CD by log–rank testing. The 3-year survival rate was 100.0% for cases with histological worst-grade 1, 95.9% for grade 2, and 93.2% for grade 3. The log–rank probability was 0.017 for grade 1 versus grade 2, 0.022 for grade 2 versus grade 3, and 0.001 for grade 1 vs grade 3. There were 10 Gx excluded cases.

Predominant grade 3 tumors were assessed as risk factors in CD by log–rank testing. The 3-year survival rate was 99.0% for cases with histological predominant grade 1, 95.2% for grade 2, and 92.0% for grade 3. The log–rank probability was 0.002 for grade 1 versus grade 2, 0.044 for grade 2 versus grade 3, and <0.001 for grade 1 versus grade 3.

It should also be noted that 47.4% of CD cases involved worst-grade 2 tumors and 67.1% were predominant grade 1 or 2 (Table 2).

Infiltration type: Of the 1919 cases, 71.7% were non-informative.

Based on the informative cases, infiltration types β and γ were assessed as risk factors in CD as compared with type α by log–rank testing. The 3-year survival rate was 99.0% for cases with α-type infiltration, 92.9% for β-type, and 89.9% for γ-type. The log–rank probability was 0.003 for α-type

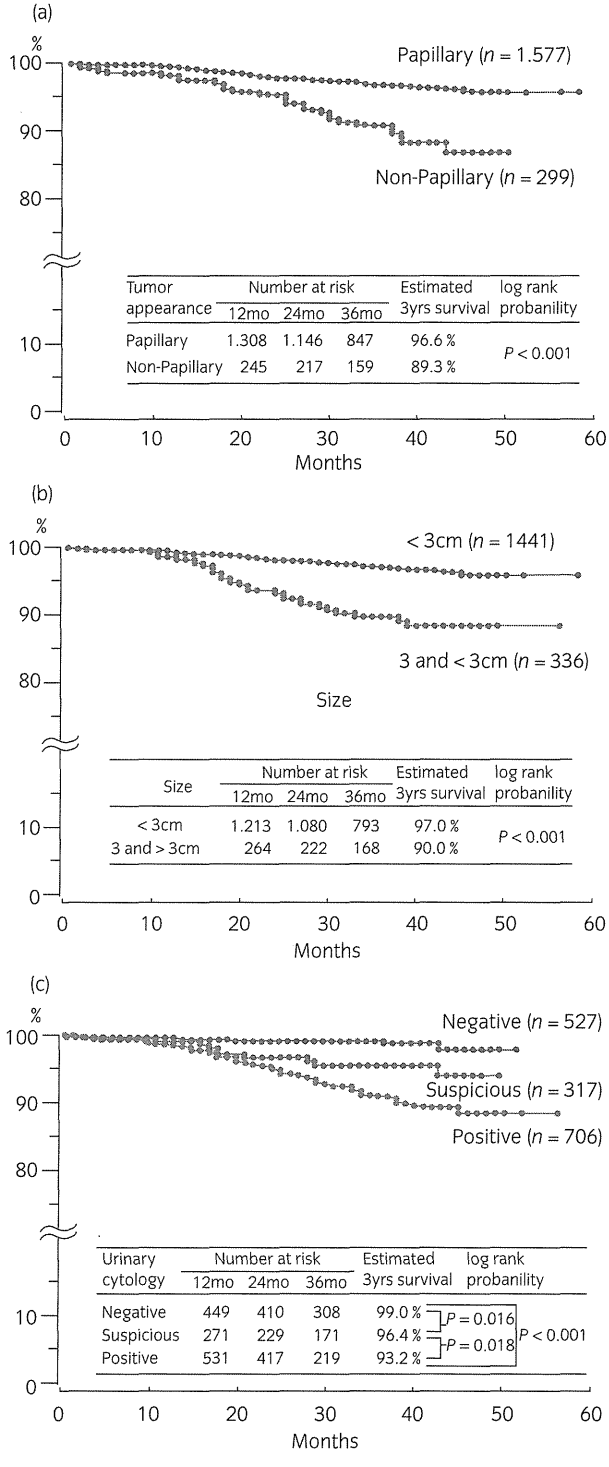


Fig. 1 Cause-specific survival (CSS) according to cystoscopic findings before transurethral resection. (a) CSS according to tumor appearance. Kaplan–Meier's survival estimation curve is shown here. Of the 1919 cases, 52 (2.7%) non-informative cases were excluded. (b) CSS according to tumor size. Kaplan–Meier's survival estimation curve is shown here. Of the 1919 cases, 142 (7.4%) non-informative cases were excluded. (c) CSS according to urinary cytology. Kaplan–Meier's survival estimation curve is shown here. Of the 1919 cases, 369 (19.2%) non-informative cases were excluded.

versus β-type, 0.596 for β-type versus γ-type, and 0.001 for α-type versus γ-type.

Multivariate analysis of factors in CSS regardless of treatment strategies (Table 3)

All factors analyzed by log–rank testing also showed statistical significance by univariate analysis using the Cox proportional hazard model.

Although infiltration types β and γ were found to be statistically significant risk factors by univariate analysis, they were excluded in multivariate analysis because the number of cases with data on infiltration type was too small to allow model analysis.

As shown in Table 2, each factor lacks data to some extent. Overall, even without data on infiltration type, multivariate analysis includes 1354 (70.6%) of all 1919 cases and 51 (67.1%) of all 76 cancer death cases.

As a result, non-papillary tumor appearance, a tumor size greater than 3 cm and suspicious/positive urinary cytology were found to be independent risk factors, with the strongest risk factor being tumor size greater than 3 cm.

Discussion

Here, we have presented data on registered T1 bladder cancer cases in Japan with a particular focus on CD. Although this is not a cohort study, it is the first investigation regarding the 3-year outcome of nearly 2000 T1 bladder cancer cases in Japan.

Stage T1 bladder cancer is a non-muscle-invasive condition that reportedly shows a favorable clinical outcome without invasive treatment, such as systemic chemotherapy or radical cystectomy requiring urinary diversion. An overall view of 5959 registered bladder cancer cases shows[10] that clinical T1 cases represent 38% of all bladder cancer patients, and that their 3-year survival rate was more than 90%. As opposed to non-invasive Ta, T1 is a non-muscle but invasive type of bladder cancer, and this population is known to be heterogeneous in terms of the clinical outcome.[3] To avoid treatment failure in clinical T1, we tried to distinguish CD cases in the database of registered patients in terms of clinical factors.

We screened the risk factors of age, sex, smoking habits, cystoscopic findings and pathological findings in TUR specimens, regardless of treatment after the initial TUR. The first three factors showed no association with CSS. In contrast, known risk factors for an unfavorable clinical outcome[13–16] were statistically associated with CD, but the survival difference was found to be less than 10% for each factor by the Kaplan–Meier survival estimation.

The largest hazard ratio was positive cytology to negative cytology, followed by infiltration γ to α from univariate

Tables 2 Distribution of cases according to possible risk factors – cystoscopic findings and pathological findings

	All cT1 (n = 1919)	CD (n = 76)	Survivors (n = 1843)
Tumor appearance			
Papillary	1577 (82.2%)	45 (59.2%)	1532 (83.1%)
Non-papillary	299 (15.6%)	27 (35.5%)	263 (14.3%)
Unknown/blank	52 (2.7%)	4 (5.2%)	48 (2.6%)
Tumor stalk			
Peduncular	1072 (53.5%)	30 (39.5%)	1042 (56.5%)
Non-peduncular	717 (37.4%)	41 (53.9%)	676 (36.7%)
Unknown/blank	130 (6.8%)	5 (6.6%)	125 (6.8%)
Multiplicity			
Solitary	904 (47.1%)	21 (27.6%)	883 (46.3%)
Multiple	913 (47.7%)	47 (61.8%)	866 (47.0%)
Unknown/blank	102 (5.3%)	8 (10.5%)	94 (5.1%)
Tumor size			
<3 cm	1441 (75.1%)	37 (48.7%)	1404 (76.2%)
3 and >3 cm	336 (17.5%)	27 (35.5%)	309 (16.8%)
Unknown/blank	142 (7.4%)	12 (15.8%)	130 (7.1%)
Urinary cytology			
Positive	706 (36.8%)	49 (64.5%)	657 (35.6%)
Suspicious	317 (16.5%)	10 (13.2%)	307 (16.7%)
Negative	527 (27.5%)	5 (6.6%)	522 (28.3%)
Unknown/blank	369 (19.2%)	12 (15.8%)	357 (19.4%)
Histological grade			
Worst G1	168 (8.8%)	0 (0.0%)	168 (9.1%)
G2	1026 (53.5%)	36 (47.4%)	990 (53.7%)
G3	715 (37.3%)	40 (52.6%)	675 (36.6%)
GX	10 (0.5%)	0 (0.0%)	10 (0.5%)
Predominant G1	363 (18.9%)	3 (3.9%)	360 (19.5%)
G2	1176 (61.3%)	48 (63.2%)	1128 (61.2%)
G3	372 (19.4%)	24 (31.6%)	338 (18.3%)
GX	18 (0.9%)	1 (1.3%)	17 (0.9%)
Infiltration type			
α	286 (14.9%)	3 (3.9%)	283 (15.4%)
β	205 (10.7%)	12 (15.8%)	193 (26.7%)
γ	52 (2.7%)	4 (5.3%)	48 (2.6%)
Unknown/blank	1376 (71.7%)	57 (75.0%)	1319 (71.6%)

CD, cancer death; TUR, transurethral resection.

analysis using the Cox proportional hazard model. Unfortunately, the infiltration type could not be used for multivariate analysis with this model as a result of a significant lack of registered data. By applying the other factors with statistical significance by univariate analysis to multivariate analysis, it was found that a tumor size greater than 3 cm was the strongest independent risk factor, followed by positive urinary cytology and non-papillary tumor appearance at diagnosis. In contrast, the predominant histological grades were not found to be risk factors by multivariate analysis.

Based on these results, it might be appropriate to design possible risk criteria for T1 bladder cancer death using a combination of factors with statistical significance by multivariate analysis without the inclusion of any histological grade.

Many investigators have tried to distinguish cases with poor prognosis,[9,17,18] and most of these studies have started from T1G3, which is considered to result in a poor clinical outcome. It was also confirmed in the present study that worst- and predominant-grade 3 tumors were associated with CSS by univariate analysis. Nonetheless, we found that nearly half of CD cases involved worst-grade 2 tumors, and that more than two-thirds involved predominant grade 1 or 2 tumors, as shown in Table 2. We may overlook or ignore half

Table 3 Univariate and multivariate analysis using the Cox proportional hazard model

Parameter	Univariate			Multivariate (events: 51, $n = 1354$; 70.6%)		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Papillary	3.333	2.068–5.371	<0.001	2.167	1.192–3.937	0.011
Stalk	2.067	1.291–3.310	0.003			NS
Multiplicity						
Solitary	1.000					
Multiple	2.270	1.357–3.798	0.002			NS
Size						
<3 and 3 cm	1.000			1.000		
>3 cm	3.414	2.079–5.608	<0.001	2.717	1.553–4.753	*<0.001*
Cytology						
Negative	1.000			1.000		
Suspicious	3.502	1.197–10.246	0.002	5.803	1.229–27.388	0.026
Positive	7.812	3.113–19.607	<0.001	11.516	2.752–48.190	0.001
Worst grade						
1	<0.001	0–>1000	0.958			
2	0.559	0.362–0.862	0.009			
3	1.000					
Predominant grade						
1	1.000					
2	5.249	1.635–16.853	0.005			NS
3	8.622	2.596–28.637	<0.001			
Infiltration type						
α	1.000					
β	5.631	1.589–19.955	0.007		Not analyzed	
γ	7.643	1.710–34.159	0.008			
Age	1.418	0.857–2.344	0.174			

CI, confidence interval; NS, not significant.

Table 4 Distribution of initially planned treatment after transurethral resection

	All ($n = 1919$)	CD ($n = 76$)	Survivors ($n = 1843$)
Surveillance	633 (33.0%)	15 (19.7%)	618 (33.5%)
Intravesical chemotherapy	601 (31.3%)	15 (19.7%)	586 (31.8%)
BCG	301 (15.7%)	13 (17.1%)	288 (15.6%)
TUC or TUR	34 (1.8%)	3 (3.9%)	31 (1.7%)
Radical cystectomy	95 (5.0%)	9 (11.8%)	86 (4.7%)
Intra-arterial chemotherapy	22 (1.1%)	1 (1.3%)	21 (1.1%)
Systemic chemotherapy	16 (0.8%)	2 (2.6%)	14 (0.8%)
Radiation	8 (0.4%)	1 (1.3%)	7 (0.4%)
Others	176 (9.2%)	15 (19.7%)	161 (8.7%)
Unknown/blank	33 (1.7%)	2 (2.6%)	31 (1.7%)

Others include oral anti-cancer agents, laparotomy, simple cystectomy, partial cystectomy, combination of two or more modalities.
BCG, bacillus Calmette–Guerin; TUC, transurethral coagulation; TUR, transurethral resection.

of these CD cases if we start from T1G3. When assessing risk criteria in T1 bladder cancer, it is necessary to include all histological grades and treatment strategies to distinguish the characteristics of CD cases in the data registry.

Here, three significant limitations of this analysis should be noted. First, when assessing risk factors, the very important confounding factor of plans after the initial TUR was not considered. As there were still various strategies for T1

bladder cancer in the years 1999–2001, as shown in Table 4, it was difficult to analyze and draw conclusions on the impact of plans after the initial TUR on CD. When using the Cox proportional hazard model in particular, the data require more events (CD cases) for the inclusion of more factors (plans after TUR) in multivariate analysis. However, when we look at the mortality rate for each plan, surveillance includes only CD 2.5%, intravesical instillation of chemotherapeutic agents 2.8%, intravesical BCG instillation (alone) 4.3%, and radical cystectomy (alone) 9.2%. These data do not indicate at all that the choice of cystectomy caused an increase in the incidence of CD. Clinically, we chose high-risk cases and used more invasive, but more effective, therapy options to achieve longer survival. Although the details are not included here, the background to these cases is different from the plans for other cases.

The second limitation is related to the high number of incomplete registrations, especially in terms of the infiltration type. When carrying out pathological diagnosis of bladder cancer, the infiltration type should be described in the report, because it is a well-known risk factor in malignant behavior. With a complete data set, the infiltration type might have been identified as a risk factor by multivariate analysis.

The third limitation is a lack of central pathological review. There were 164 cases registered as T1 with "no invasion" as the infiltration type in the initial data set. In addition, as mentioned earlier, the infiltration type was not properly reported.

Finally, it should be mentioned again that these data were not produced by a cohort study.

The period of registration in the present study was from 1999 to 2001, although strategies for diagnosis and treatment have recently been modified. Some new chemotherapy drugs and regimens (such as taxanes and gemcitabine[19,20]) have proved to be effective in survival prolongation and have become widely used in clinical practice.[21] New molecular markers[22–28] and diagnostic tools[29,30] have also been developed. We hope that these recent advances will be applied in future registrations.

As a further consideration, this registry might not represent all bladder cancer cases. In Japan, the number of patients with bladder cancer was estimated at over 14 000 in 1999 and 13 700 in 2000, and the estimated number of newly diagnosed bladder cancer patients is 8000–9000 a year (a 6–7 occurrence rate per 100 000 people[31]). In this registry, the data covers only a quarter of the estimated number of new cases. In other words, the registration system misses three quarters of all bladder cancer cases in Japan. This could be one of the reasons why the proportion of T1 cases in the registry is higher (38% of all bladder cancer cases) than previous reports.

Despite the small proportion of CD cases among T1 bladder cancer patients (<5%) and the fact that a 3-year survival rate of 95% is a favorable result for a malignant tumor,[31] 76 of the 1919 T1 cases diagnosed with non-muscle-invasive bladder cancer died within 3 years of the initial diagnosis, some of whom underwent immediate cystectomy. Because the data collected covered only a quarter of the estimated number of new cases, the number of CD patients with initial diagnosis of T1 bladder cancer per year in Japan can be estimated to be more than 100 by simple calculation. A figure of more than 100 deaths a year is not something that should be ignored.

To prevent treatment failure in T1 bladder cancer treatment, we sought a way to distinguish CD cases within the registry data. Through multivariate analysis, we determined that the risk factors associated with CD are non-papillary tumor appearance, a tumor size greater than 3 cm and positive urinary cytology, but not worst or predominant histological grade tumors. If we start from T1G3 to deal with life-threatening high-risk conditions, we will miss nearly half of all CD cases. We should include not only T1G3, but also T1 cases with these two grades of tumor.

The present analysis omitted consideration of a very important confounding factor (i.e. plans after the initial TUR), its data lacked a central pathology review and the proportion of incomplete data was large; accordingly, we hope it will be possible to achieve better analysis and results from registered data in the future.

References

1 Skinner EC. The best treatment for high-grade T1 bladder cancer is cystectomy. *Urol. Oncol.* 2007; **25**: 523–5.
2 Sanchez-Carbayo M, Cordon-Cardo C. Molecular alterations associated with bladder cancer progression. *Semin. Oncol.* 2007; **34**: 75–84.
3 Schned AR, Andrew AS, Marsit CJ, Kelsey KT, Zens MS, Karagas MR. Histological classification and stage of newly diagnosed bladder cancer in a population-based study from the Northeastern United States. *Scand. J. Urol. Nephrol.* 2008; **42**: 237–42.
4 Gardmark T, Bladstroem A, Hellsten S, Maimstroem PU, Members of The Swedish National Bladder Cancer Registry. Analysis of clinical characteristics, management and survival of patients with Ta T1 bladder cancer in Sweden between 1997 and 2001. *Scand. J. Urol. Nephrol.* 2006; **40**: 276–82.
5 Margel D, Tal R, Goian S, Kedar D, Engeistein D, Baniel J. Long-term follow-up of patients with Stage T1 high-grade transitional cell carcinoma managed by Bacille Calmette-Guerin immunotherapy. *Urology* 2007; **69**: 78–82.
6 Lerner SP, Tangen CM, Scharew M, Wood D, Vrawford ED. Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high-risk non-muscle invasive tumor. *Urol. Oncol.* 2009; **27**: 155–159.
7 Dalbagni G. The management of superficial bladder cancer. *Nat. Clin. Pract. Urol.* 2007; **4**: 254–60.

8 Lambert EH, Pierorazio PM, Olsson CA *et al.* The increasing use of intravesical therapies for stage T1 bladder cancer coincides with decreasing survival after cystectomy. *BJU Int.* 2007; **100**: 33–6.

9 Kulhami GS, Finelli A, Fleshner NE *et al.* Optimal management of high-risk T1G3 bladder cancer: a decision Analysis. *PLoS Med.* 2007; **4**: 1538–49.

10 Okuyama A, Kohri K, Akaza H *et al.* The report of clinical statistical studies on registered bladder cancer patients in Japan 1999–2001. *Nippon Hinyokika Gakkai Zasshi* 2006; **97**: NP2–31 (in Japanese).

11 Japanese Urological Association, The Japanese Society of Pathology. *General Rule for Clinical and Pathological Studies on Bladder Cancer*, 2nd edn. Kanehara & Co. Ltd, Tokyo, 1993.

12 Japanese Urological Association, The Japanese Society of Pathology. *General Rule for Clinical and Pathological Studies on Bladder Cancer*, 3rd edn. Kanehara & Co. Ltd, Tokyo, 2001.

13 Sylvester RJ, van der Meijden AP, Oosterilimck W *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur. Urol.* 2006; **49**: 466–75.

14 Denzinger S, Otto W, Fritsche HM *et al.* Bladder sparing approach for initial T1G3 bladder cancer: do multifocality, size of tumor or concomitant carcinoma in situ matter? A long-term analysis of 132 patients. *Int. J. Urol.* 2007; **14**: 995–9.

15 Fernandez-Gomez J, Soisona E, Unda M *et al.* prognostic factors in patients with non-muscle invasive bladder cancer treated with Bacillus Calmette-Guerin: multivariate analysis of data from randomized CUETO trials. *Eur. Urol.* 2008; **53**: 992–1002.

16 Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Boehle A, Palou-Redolta J. EAU guidelines on non-muscle invasive urothelial carcinoma of the bladder. *Eur. Urol.* 2008; **54**: 303–314.

17 Denzinger S, Fritsche HM, Otto W, Blana A, Wieland WF, Burger M. Early versus deferred cystectomy for initial high-risk pT1G3 urothelial carcinoma of the bladder: do risk factors define feasibility of bladder-sparing approach? *Eur. Urol.* 2008; **53**: 146–52.

18 Gupta A, Lotan Y, Bastian PJ *et al.* Outcomes of patients with clinical T1 grade 3 urothelial cell bladder carcinoma treated with radical cystectomy. *Urology* 2008; **71**: 302–7.

19 Sternberg CN, Calabrò F, Pizzocaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer* 2001; **92**: 2993–8.

20 Fechner G, Siener R, Reimann M, Kobalz L, Albers P, German Association Of Urologic Oncology (Auo) Bladder Cancer Study Group. Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). *Int. J. Clin. Pract.* 2006; **60**: 27–31.

21 Takahashi T, Higashi S, Nishiyama H *et al.* Biweekly paclitaxel and gemcitabine for patients with advanced urothelial cancer ineligible for cisplatin-based regimen. *Jpn J. Clin. Oncol.* 2006; **36**: 104–8.

22 Andius P, Johansen SL, Holmaeng S. Prognostic factors in stage T1 bladder cancer: tumor pattern (solid or papillary) and vascular invasion more important than depth of invasion. *Urology* 2007; **70**: 758–62.

23 Burger M, Denzinger S, Hartmann A, Wieland WF, Stoehr R, Obermann EC. Mcm2 predicts recurrence hazard in stage Ta/T1 bladder cancer more accurately than CK20, Ki37 and histological grade. *Brt J. Cancer* 2007; **96**: 1711–15.

24 Erdemir F, Ozcan F, Kilicasian I, Pariaktas BS, Uluocak N, Gokce O. The relationship between the expression of E-cadherin and tumor recurrence and progression in high-grade stage T1 bladder urothelial carcinoma. *Int. Urol. Nephrol.* 2007; **39**: 1031–7.

25 Dalbagni G, Parekh DJ, Ben-Porat L, Potenzoni M, Herr HW, Rueter VE. Prospective evaluation of p53 as a prognostic marker in T1 transitional cell carcinoma of the bladder. *BJU Int.* 2007; **99**: 281–5.

26 Karam JA, Lotain Y, Ashfaq R, Sagalowsky AI, Shariat SF. Surviving expression in patients with non-muscle invasive urothelial cell carcinoma of the bladder. *Urology* 2007; **70**: 482–6.

27 Mhawech-Faucegrlia P, Fischer G, Alyarez Y Jr, Ahmed A, Hermann FR. Predicting outcome in minimally invasive (T1a and T1b) urothelial bladder carcinoma using a panel of biomarkers: a high throughput tissue microarray analysis. *BJU Int.* 2007; **100**: 1182–7.

28 Svatek RS, Karam J, Karakiewiccz PI *et al.* Role of urinary cathepsin B and L in the detection of bladder urothelial cell carcinoma. *J. Urol.* 2008; **179**: 478–84.

29 Kausch I, Doehn C, Jocham D. Recent improvements in the detection and treatment of non-muscle-invasive bladder cancer. *Expert Rev. Anticancer Ther.* 2006; **6**: 1301–11.

30 Denzinger S, Wieland WF, Otto W, Filbeck T, Knuechel R, Surger M. Does photodynamic transurethral resection of bladder cancer? A long-term follow-up of a randomized study. *BJU Int.* 2008; **101**: 566–9.

31 Marugame T, Kamo K, Katanoda K *et al.* Cancer incidence and incidence rates in Japan in 2000: estimates based on data from 11 population-based cancer registries. *Jpn J. Clin. Oncol.* 2006; **36**: 668–75.

厚生労働科学研究費補助金
(分担研究報告書)

平成２４年度厚生労働科学研究費補助金がん臨床研究事業
「がん登録からみたがん診療ガイドラインの普及効果に関する研究
- 診療動向と治療成績の変化－」
皮膚悪性腫瘍の登録体制とガイドライン評価体制

(研究分担者　岩月啓氏・岡山大学大学院医歯薬学総合研究科　皮膚科学分野・教授)

研究要旨
皮膚リンパ腫診療ガイドライン2011年改訂版を作成し、その英語版を学術雑誌へ掲載した。本ガイドラインをもとに皮膚リンパ腫国際学会（ベルリン、2013年2月）演題が採択され、海外研究者と意見交換をする。悪性黒色腫と皮膚リンパ腫の疫学調査と登録体制を強化し、他の皮膚癌の登録も順次進める予定である。

A．研究目的
皮膚悪性腫瘍診療ガイドラインの「皮膚リンパ腫」と「メラノーマ・上皮系皮膚悪性腫瘍」の両者を改訂し、可能な疾患から英語版の作成を行い国際的情報共有を目指す。改訂版ガイドラインの普及と評価を実施し、拠点施設における患者登録システムを検討する。

B．研究方法
平成24年度-26年度の研究計画を図１に示す。平成24年度は、皮膚悪性腫瘍ガイドライン改訂版を順次上梓し、英語版ガイドラインを掲載し、国際的情報共有することを目標設定した。また、従来のメラノーマ・皮膚リンパ腫全国登録を継続し、拠点施設におけるコホート研究を整備し、診療動向と治療成績を評価する体制作りに日本皮膚悪性腫瘍学会とともに取り組む。

(倫理面への配慮)
臨床統計調査は日本皮膚科学会学術委員会倫理委員会の了解を得て実施している。個人情報は各施設で管理し、臨床疫学統計には連結不可能な情報を用いた。利益相反に関する施設規約を遵守している。

C．研究結果
平成24年度は、「皮膚リンパ腫診療ガイドライン2011年改訂版」（菅谷誠ほか）を作成し、日本皮膚科学会雑誌　122管第6号1513－1531に簡略版を掲載し、日本皮膚科学会ＨＰにはガイドライン完全版を掲載した。本ガイドラインの英語版（研究発表参照）としてJournal of Dermatologyに電子版が掲載された。このガイドライン英語版を国際学会において紹介し、海外の研究者と意見交換する（国際皮膚リンパ腫学会：ベルリンにて）。

メラノーマ、有棘細胞癌、基底細胞癌、乳房外パジェット病を対象疾患とする「皮膚悪性腫瘍診療ガイドライン改訂版」は原稿がほぼ完成し、日本皮膚科学会学術委員会でのパブリックコメント取得準備中である。本ガイドラインと、上記の皮膚リンパ腫ガイドライン改訂版を合本化し、「皮膚悪性腫瘍ガイドライン」とする予定。

メラノーマと皮膚リンパ腫の全国登録調査を2007年から毎年実施し、毎年、学会報告をしてきた（表1，2、図2）

D．考察
両ガイドラインは、日本癌治療学会がん診療ガイドライン委員会での審査・評価を経て公開し、ＭＩＮＤＳへの公開も同時に進める予定である。さらに、平成25年度には、診療従事者に対して本ガイドラインのアンケート調査を行い、普及度、利用率、評価を調査するためのアンケート用紙を準備した（表3）

E．結論
皮膚悪性腫瘍診療ガイドラインの改訂作業を進めた。皮膚リンパ腫は英語版ガイドラインを発表した。次年度はこれらの普及・評価のためのアンケートを実施予定である。症例登録体制の強化を準備中である。

F．健康危険情報　　該当なし。

G．研究発表
1．論文発表
Sugaya M, Hamada T, Kawai K, Yonekura K, Ohtsuka M, Shimauchi T, Tokura Y, Nozaki K, Izutsu K, Suzuki R, Setoyama M, Nagatani T, Koga H, Tani M, Iwatsuki K. Guidelines for the management of cutaneous lymphomas (2011): A consensus statement by the Japanese Skin Cancer Society - Lymphoma Study Group. J Dermatol. 2012 [Epub ahead of print]

２．学会発表
Sugaya M, Iwatsuki K et al. Guidelines for the management of cutaneous lymphomas (2011): A consensus statement by the Japanese Skin Cancer Society - Lymphoma Study Group.(2013年2月6日－9日, Berlin:演題採択)

H．知的財産権の出願・登録状況
(予定を含む。)
1．特許取得　　該当なし。
2．実用新案登録　　該当なし。
3.その他　　該当なし。

図１．皮膚悪性腫瘍の登録体制とガイドライン評価体制：研究計画

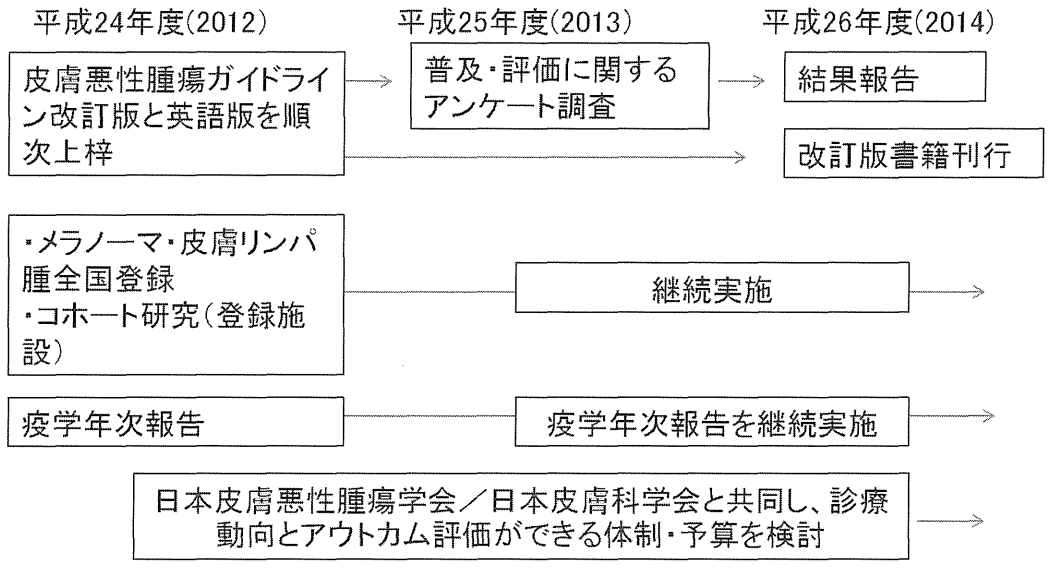


表1　日本皮膚悪性腫瘍学会における「皮膚がん予後統計委員会」

皮膚悪性腫瘍学会が主導する疫学研究事業
(2007年から実施中)

皮膚がん予後統計委員会

a. **メラノーマに関する臨床疫学調査**
- 全国約160の主要施設に対して不定期に行う全国症例調査
- 指定した26施設において定期的に症例の予後調査を行う追跡調査
- 症例数　2,126例
- 症例情報は各施設での登録時に匿名化され収集
- 筑波大学医学部皮膚科教室が業務を担当し，データ管理・運用

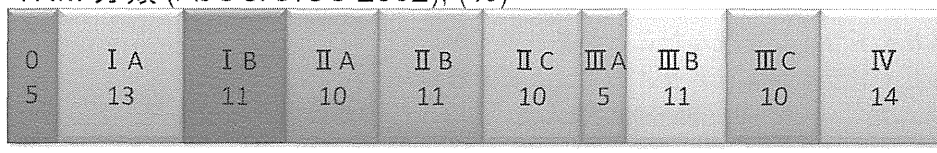
b. **皮膚リンパ腫に関する臨床疫学調査**
- 日本皮膚科学会認定の主研修施設（約100施設）と一般認定施設（約500施設）が参加
- 個人情報に抵触しないミニマム エッセンシャルの情報提供
- 症例数　1,544例
- 岡山大学医学部皮膚科教室が業務担当し，データを管理・運用

図２．メラノーマに関する臨床疫学調査結果

メラノーマに関する臨床疫学調査

Total no.	2126
Male/Female ratio	981:1142(1:1.16)
Age	Average 62.7/ Median 65
Follow up(months)	0~170 (Average17.6)

TNM 分類 (AJCC/UICC 2002), (%)



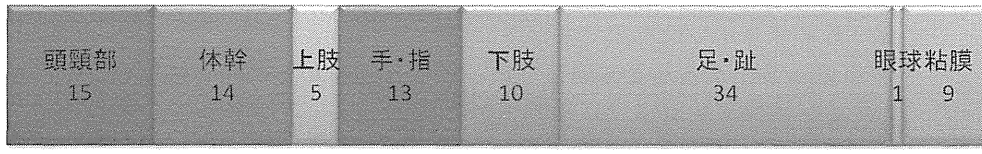


表２．皮膚リンパ腫に関する臨床疫学調査結果

皮膚リンパ腫に関する臨床疫学調査

結果1. 全国症例数調査　概要

	2010年						2007-2009年					
	No. Cases	Incidence rate	Age (y)			M/F	No. Cases	Incidence rate	Age (y)			M/F
			Range	Mean	Median				Range	Mean	Median	
Mature T- and NK-cell neoplasms	**305**	**80.1%**	**16-100**	**63.6**	**66.0**	**1.3/1.0**	**932**	**80.1%**	**5-97**	**61.0**	**-**	**1.3/1.0**
Mycosis fungoides/Sézary syndrome	143	37.5%	19-91	61.6	63.0	1.4/1.0	483	41.5%	17-95	60.9	62.5	1.4/1.0
Mycosis fungoides	133	34.9%	19-91	61.3	63.0	1.4/1.0	457	40.2%	17-95	60.6	62.0	1.3/1.0
Sézary syndrome	10	2.6%	37-79	65.4	68.0	2.3/1.0	16	1.4%	41-89	69.3	69.5	7/1
Adult T-cell leukemia/lymphoma	79	20.7%	38-88	67.2	68.0	1.2/1.0	170	14.6%	19-93	67.5	69.0	1.3/1.0
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	33	8.7%	18-83	60.0	65.0	1.5/1.0	128	11.0%	8-97	55.4	60.5	1.3/1.0
Primary cutaneous anaplastic large cell lymphoma	21	5.5%	22-83	62.0	68.0	2.0/1.0	82	7.1%	12-97	53.6	59.0	1.7/1.0
Lymphomatoid papulosis	12	3.1%	18-73	58.5	62.5	1.0/1.0	42	3.6%	8-84	49.1	48.0	0.9/1.0
Peripheral T-cell lymphoma, not otherwise specified	17	4.5%	43-99	73.5	75.0	3.3/1.0	62	5.3%	5-91	61.5	66.5	0.9/1.0
Primary cutaneous gamma-delta T-cell lymphoma	4	1.0%	16-69	42.5	42.5	1.0/1.0	1	0.1%	78	-	-	0/1
Primary cutaneous CD4 positive small/medium T-cell lymphoma §	4	1.0%	38-74	62.8	69.5	1.0/1.0	19	1.6%	14-93	60.8	62.0	0.9/1.0
Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma §	0	0.0%	-	-	-	-	8	0.5%	6-93	54.2	54.5	1.5
Subcutaneous panniculitis-like T cell lymphoma	8	2.1%	36-76	53.1	50.5	0.3/1.0	19	1.6%	17-76	53.1	55.0	0.7/1.0
Extranodal NK/T cell lymphoma, nasal type	7	1.8%	31-94	69.7	73.0	0/7	18	1.5%	38-82	64.7	65.0	0.8/1.0
Angioimmunoblastic T-cell lymphoma	5	1.3%	64-82	74.0	72.0	0.7/1.0	13	1.1%	43-75	65.3	68.0	0.5/1.0
Anaplastic large cell lymphoma, ALK negative	3	0.8%	40-90	66.3	65.0	0.5/1.0	5	0.4%	32-80	59.2	75.0	4/1
Anaplastic large cell lymphoma, ALK positive	0	0.0%	-	-	-	-	4	0.3%	28-73	51.5	52.5	3/1
Mature B-cell neoplasms	**71**	**18.6%**	**0-92**	**69.5**	**72.0**	**1.3/1.0**	**195**	**16.8%**	**0.3-97**	**66.1**	**-**	**1.0/1.0**
Primary cutaneous follicle centre lymphoma	10	2.6%	58-86	71.0	70.0	4.0/1.0	20	1.7%	26-88	65.3	68.5	1.9/1.0
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	16	4.2%	42-83	64.3	62.5	0.8/1.0	30	2.6%	20-94	57.2	55.5	0.9/1.0
(Primary cutaneous) MALT lymphoma	13	3.4%	42-83	65.5	63.0	1.2/1.0	28	2.4%	20-94	57.1	55.5	0.9/1.0
Diffuse large B-cell lymphoma, not otherwise specified	36	9.4%	45-92	74.6	75.5	1.3/1.0	122	10.5%	0.3-97	71.7	76.0	0.8/1.0
Primary cutaneous diffuse large B-cell lymphoma, leg type	16	4.2%	52-91	76.8	80.0	1.0/1.0	27	2.3%	48-90	74.8	77.0	0.6/1.0
Intravascular large B-cell lymphoma	2	0.5%	55-79	67.0	67.0	2/0	9	0.8%	53-77	63.8	62.0	8/1
Follicular lymphoma	2	0.5%	56-65	60.5	60.5	1.0/1.0	9	0.8%	24-84	59.9	60.0	0.8/1.0
Blastic plasmacytoid dendritic cell neoplasm	**5**	**1.3%**	**60-80**	**71.2**	**74.0**	**4.0/1.0**	**16**	**1.4%**	**34-86**	**74.8**	**77.5**	**4.3/1.0**
Others	0	0.0%	-	-	-	-	20	1.7%	-	-	-	-
Total	**381**	**100.0%**	**0-100**	**64.8**	**67.0**	**1.3/1.0**	**1,163**	**100.0%**	**0.3-97**	**62.1**	**-**	**1.2/1.0**

§：暫定病名

表３　アンケート用紙の様式　（2013年8月9日、10日　実施案）

皮膚悪性腫瘍ガイドラインの利用状況についてのアンケートのお願い

2013年8月9日　日本皮膚悪性腫瘍学会（甲府市）
企画代表　皮膚悪性腫瘍ガイドライン委員会　委員長　岩月啓氏　（岡山大学）

エビデンスに基づく皮膚悪性腫瘍の標準的診療を推進するためにガイドラインが作成されました。ガイドラインの利用状況とあり方について先生方の御意見を拝聴したく、以下のアンケートにご回答くださいますようお願い申し上げます。（マークシートの１－１２行をお使いください。該当する数字を塗りつぶしてください。）

A.　皮膚悪性腫瘍ガイドラインを読んだことがありますか。

1.　皮膚悪性腫瘍ガイドラインⅠ（メラノーマ、上皮系腫瘍）
　１：一通り読んだ　　２：部分的に読んだ　　３：調べたい項目を読んだ
　４：存在は知っているが読んでいない　　５：存在を知らない

2.　皮膚悪性腫瘍ガイドラインⅡ（皮膚リンパ腫）
　１：一通り読んだ　　２：部分的に読んだ　　３：調べたい項目を読んだ
　４：存在は知っているが読んでいない　　５：存在を知らない

B.　皮膚悪性腫瘍ガイドラインⅠ（メラノーマ、上皮系腫瘍）について

3.　患者への説明にガイドラインをご利用ですか？
　１：いつも利用　２：しばしば利用　３：たまに利用　４：ほとんど利用せず　５．利用しない

4.　治療計画などの立案にガイドラインは有用ですか？
　１：有用　２：やや有用　３：どちらともいえない　４：どちらかと言えば無用　５．無用

5.　（総合的に）ガイドラインは日常診療に役立ちますか？
　１：有用　２：やや有用　３：どちらともいえない　４：どちらかと言えば無用　５．無用

C.　皮膚悪性腫瘍ガイドラインⅡ（皮膚リンパ腫）について

6.　患者への説明にガイドラインをご利用ですか？
　１：いつも利用　２：しばしば利用　３：たまに利用　４：ほとんど利用せず　５．利用しない

7.　治療計画などの立案にガイドラインは有用ですか？
　１：有用　２：やや有用　３：どちらともいえない　４：どちらかと言えば無用　５．無用

8.　（総合的に）ガイドラインは日常診療に役立ちますか？
　１：有用　２：やや有用　３：どちらともいえない　４：どちらかと言えば無用　５．無用

D.　皮膚悪性腫瘍ガイドラインの改訂・公開・関連セミナーについて

9.　ガイドライン全面改訂はいつ行うべきとお考えですか？
　１：定期的改訂　２：新薬・新技術開発時　３．診療報酬改正時　４．海外ガイドラインと連動
　５：その他　　（具体的に：　　）
　＊具体的内容は本紙へご記入ください。

10.　ガイドラインの公開方法はどれが適当ですか？（複数回答可）
　１：会員限定 HP　２：一般公開 HP　３：学術雑誌（online 含む）　４：書籍
　５：その他　（具体的に　　）

11.　ガイドラインをテーマとした講習会・教育講演は有用ですか？
　１：有用　２：やや有用　３：どちらともいえない　４：どちらかと言えば無用　５．無用

E.　皮膚科医・形成外科医としての背景

12.　皮膚科専門医または形成外科専門医ですか？　（複数回答可）
　１：皮膚科専門医　２：形成外科専門医　３：非専門医　４：皮膚悪性腫瘍指導専門医
　５：がん治療認定医

ご協力いただきありがとうございました。

	J D E	1 6 3 9	B	Dispatch: 24.7.12	Journal: JDE	CE: Sangeeta
	Journal Name	Manuscript No.		Author Received:	No. of pages: 13	PE: Priyadharsini

doi: 10.1111/j.1346-8138.2012.01639.x *Journal of Dermatology* 2012; 39: 1–13

REVIEW ARTICLE

Guidelines for the management of cutaneous lymphomas (2011): A consensus statement by the Japanese Skin Cancer Society – Lymphoma Study Group

Makoto SUGAYA,[1] Toshihisa HAMADA,[2] Kazuhiro KAWAI,[3] Kentaro YONEKURA,[4] Mikio OHTSUKA,[5] Takatoshi SHIMAUCHI,[6] Yoshiki TOKURA,[6] Koji NOZAKI,[7] Koji IZUTSU,[8] Ritsuro SUZUKI,[9] Mitsuru SETOYAMA,[10] Tetsuo NAGATANI,[11] Hiroshi KOGA,[12] Mamori TANI,[13] Keiji IWATSUKI[2]

[1]*Department of Dermatology, Faculty of Medicine, University of Tokyo, Tokyo,* [2]*Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama,* [3]*Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences,* [4]*Department of Dermatology, Imamura Bun-in Hospital, Kagoshima,* [5]*Department of Dermatology, Fukushima Medical University School of Medicine, Fukushima,* [6]*Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu,* [7]*Department of Gastrointestinal, Breast and Endocrine Surgery, The University of Tokyo Hospital,* [8]*Department of Hematology, Toranomon Hostapital, Tokyo,* [9]*Department of Hematopoietic Stem Cell Transplantation Data Management/Biostatistics, Nagoya University Graduate School of Medicine, Nagoya,* [10]*Department of Dermatology, Faculty of Medicine, University of Miyazaki, Miyazaki,* [11]*Department of Dermatology, Tokyo Medical University Hachioji Medical Center, Tokyo,* [12]*Department of Dermatology, School of Medicine, Shinshu University, Matsumoto, and* [13]*Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan*

ABSTRACT

In 2010, the first Japanese edition of guidelines for the management of cutaneous lymphoma was published jointly by the Japanese Dermatological Association (JDA) and the Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group. Because the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: (i) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as mycosis fungoides/Sézary syndrome; and (ii) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal natural killer/T-cell lymphoma, nasal type. References that provide scientific evidence for these guidelines have been selected by the JSCS – Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system.

Key words: adult T-cell leukemia/lymphoma, cutaneous lymphoma, guideline, mycosis fungoides, Sézary syndrome.

INTRODUCTION

A number of guidelines on the management of cutaneous lymphoma have already been published in Europe and North America. However, the prevalence and clinical types of cutaneous lymphoma vary among different ethnic groups, and medical systems vary from country to country. As a result, the unmodified European/US guidelines may not be well-suited for use in Japan. We wanted to provide a "best treatment" consensus on clinical practice guidelines for cutaneous lymphoma, based on the actual situation in Japan.

In these guidelines, the diagnosis of cutaneous lymphoma is based on classifications from the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer, Cutaneous Lymphomas Task Force (EORTC),[1] and on the 4th edition of the WHO classification published in 2008.[2] The staging and classification of mycosis fungoides (MF)/Sézary syndrome (SS) are based on the tumor

Correspondence: Keiji Iwatsuki, M.D., Ph.D., Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, 700-8558, Japan. Email: keijiiwa@cc.okayama-u.ac.jp

Conflict of interest: none

Received 22 June 2012; accepted 26 June 2012.

-node-metastasis (TNM) staging from the International Society for Cutaneous Lymphomas (ISCL) group.[3] For cutaneous lymphomas other than MF/SS, we decided to use the TNM staging system proposed by the ISCL[4] rather than the conventional Ann Arbor classification system.

The British group,[5] EORTC[6] and European Society for Medical Oncology (ESMO)[7] each issued treatment guidelines for MF/SS. In 2009, using published work and overseas guidelines for references, we published the first edition of guidelines based on the actual situation of cutaneous lymphoma in Japan.[8] Because the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: (i) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as MF/SS; and (ii) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal natural killer (NK)/T-cell lymphoma (ENKL), nasal type. References that provide scientific evidence for these guidelines have been selected by the Japanese Skin Cancer Society (JSCS) - Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system. The evidence level and degree of recommendation used for the current version are shown in Table 1.

BASIS FOR THE CURRENT GUIDELINES

The cutaneous lymphomas listed in the present guidelines are basically in accordance with the WHO-EORTC classification (2005),[1] but it is difficult to precisely define "primary cutaneous" lymphoma. Ordinarily, a condition is defined as "primary cutaneous" lymphoma if appropriate procedures show no extracutaneous lesions at the time of diagnosis. The present guidelines include lymphomas and hematopoietic malignancies with marked affinity for the skin (Fig. 1, Table 2). The diagnostic nomenclature follows the 4th edition of the WHO classification (2008).[2]

To describe the skin lesions of cutaneous lymphoma, typically MF/SS, uniform terminology is needed. Without consistent terminology, accurate disease staging is impossible, and inconsistencies may develop in prognostic analysis. The ISCL/EORTC group has defined terminology for MF/SS.[9] Those definitions are adopted in the present guidelines (Table S1), and representative clinicopathological findings of various types of cutaneous lymphoma are provided in supporting information (Figs S1–S7).

STAGING

Staging for MF/SS (ISCL/EORTC 2007, modified in 2011)

For the staging of MF/SS, we previously used the categories developed by Bunn *et al.*[10] and Sausville *et al.*[11] In 2007, a new staging system was proposed by the ISCL/EORTC group,[3] which was modified in 2011 (Tables S2 and S3).[12]

In the ISCL/EORTC staging system, peripheral blood findings are classified into three categories: B_0 (atypical lymphocytes accounting for $\leq 5\%$ of peripheral blood lymphocytes), B_1 (atypical lymphocytes accounting for >5% of peripheral blood lymphocytes, but <1000/μL), and B_2 (atypical lymphocyte

Table 1. Standards for the determination of evidence level and degree of recommendation

Classification of evidence level	
I	Systematic review and/or meta-analysis Staging/classification proposal and treatment recommendation or consensus paper from WHO, EORTC and ISCL
II	One or more randomized comparative studies
III	Non-randomized comparative studies
IV	Analytical epidemiology studies (cohort research and case–control studies) Case series studies (≥ 5 cases)
V	Descriptive studies (case reports and case series studies [<5 cases])
VI	Opinions of expert committee and individual specialists*
Degree of recommendation classification†	
A	Strongly recommended for implementation (efficacy shown by at least 1 report providing level I or high-quality level II evidence)
B	Recommended for implementation (efficacy shown by ≥ 1 reports providing low-quality level II, high-quality level III, or very high-quality level IV evidence)
B-C1	Recommended for implementation, but less strongly supported than B
C1	Implementation can be considered, but evidence‡ is insufficient (low-quality III–IV, high-quality multiple V, or committee-approved VI evidence)
C2	No evidence‡; cannot be recommended (no evidence of effectiveness, or evidence available of ineffectiveness)
D	Recommended not to implement (high-quality evidence of ineffectiveness or harmfulness)

*Data from basic research and theories derived from such data are placed at this level. †Some of the "degree of recommendation" statements in these guidelines are not in complete agreement with the above table. ‡"Evidence" refers to knowledge from clinical trials and epidemiological research. This is because these "degree of recommendation" grades were based on a consensus among the committee members, taking feasibility into account. This consensus was reached after due consideration of the shortage of evidence internationally on the treatment of skin cancer and the fact that the evidence from overseas is not directly applicable in Japan.

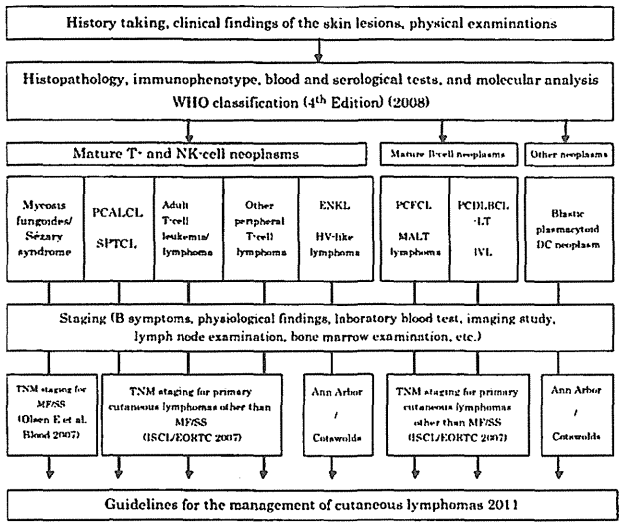


Figure 1. Diagnostic and staging algorithm for cutaneous lymphomas. DC, dendritic cell; ENKL, extranodal T/NK-cell lymphoma, nasal type; HV, hydroa vacciniforme; IVL, intravascular large B-cell lymphoma; MALT lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type; MF/SS, mycosis fungoides/Sézary syndrome; PCALCL, primary cutaneous anaplastic large cell lymphoma; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; PCFCL, primary cutaneous follicle center lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; TNM, tumor-node-metastasis; WHO, World Health Organization.

count of $\geq 1000/\mu L$ with a positive clone). Additional parameters that meet the B_2 criteria include the following: CD4/CD8 ratio of 10 or more, $CD4^+CD7^-$ of 40% or more, and $CD4^+CD26^-$ of 30% or more.[3,12,13] Cases with erythroderma who meet the B_2 criteria are defined as SS, or stage IVA_1 (Table S3 and Fig. S1). Erythrodermic MF of the B_0 or B_1 category is classified as stage IIIA or IIIB.

If lymphoma cells replace all or large portions of the lymph node structure, the condition is diagnosed as N_3 and is classified as stage IV_2 (Table S3). Even if the lymph node is infiltrated by atypical cells, a diagnosis of N_3 is not made as long as the foci are small and nodal architecture is preserved.[3,12]

TNM classification of cutaneous lymphoma other than MF/SS (ISCL/EORTC 2007)

No TNM classification appropriate for the evaluation of cutaneous lesions was available for primary cutaneous lymphoma categories other than MF/SS. In 2007, the ISCL and EORTC proposed a new TNM classification system (Table S4).[4] Although the TNM classification reflect the extent of lesions, an adequate staging system has not been established yet. Moreover, the classification does not indicate prognoses for some disease types.[14] The category of "non-MF/SS" covers many types of cutaneous lymphoma, and new staging systems are needed for each disease type, based on the collected clinical data and prognostic analysis.

Table 2. Classification of cutaneous lymphomas

Cutaneous T/NK cell lymphoma
Mycosis fungoides: MF
Variants
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome: SS
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Hydroa vacciniforme-like lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
Primary cutaneous $CD4^+$ small/medium T-cell lymphoma*
Peripheral T-cell lymphoma, not otherwise specified
Cutaneous B-cell lymphomas
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Hematological precursor cell neoplasm
Blastic plasmacytoid dendritic cell neoplasm

*Provisional. Representative clinicopathological features of MF/SS, anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, subcutaneous panniculitis-like T-cell lymphoma, extranodal NK/T cell lymphoma, hydroa vacciniforme-like lymphoma, blastic plasmacytoid dendritic cell neoplasm have been shown in Figs S1–S7.

Staging of other cutaneous lymphomas and hematopoietic malignancies

Shimoyama and colleagues have provided a widely-used classification of adult T-cell leukemia/lymphoma (ATLL): acute, lymphoma, chronic and smoldering types.[15] According to Shimoyama's criteria, ATLL patients with cutaneous lesions only are usually classified into the smoldering group. It is not appropriate to stage ATLL patients with the TNM system proposed by Kim *et al.*[4] because of the presence of minimal hematological disease. Furthermore, for other hematological malignancies such as ENKL, nasal type, and blastic plasmacytoid dendritic cell neoplasm, the Ann Arbor or Cotswolds staging (Table S5)[16] has been widely adopted in Japan because of hematological and extracutaneous spreading of the illness.

EPIDEMIOLOGY OF CUTANEOUS LYMPHOMA

In line with the WHO classification (3rd edn), the incidence of all types of lymphomas was reported by pathologists in Japan.[17] The data were distinct from those in Western countries and similar in several ways to other data from Asia, although the relatively high rate of ATLL was attributed to the geographical difference in the etiologic factor, human T-lymphotropic virus

type 1 (HTLV-1). The JSCS – Lymphoma Study Group has conducted a nationwide survey of cutaneous lymphoma annually since 2007 (www.okayama-hihuka.jp/pdf/kekka2010.pdf). MF/SS account for approximately 51% of all cutaneous lymphomas, followed by ALCL and ATLL at approximately 9–8% each. B-cell lymphoma accounts for approximately 15% of all cutaneous lymphoma in Japan, so it is less frequent than in Europe or North America. ENLK, nasal type, accounts for only approximately 2%, which is nearly always associated with Epstein–Barr virus (EBV) infection. The NK-cell type is dominant in Japan.

PROGNOSTIC ANALYSIS

Prognostic analyses of patients with cutaneous lymphoma are limited.[18–21] In the present guidelines, we have highlighted the prognoses of MF/SS, ATLL, and ENLK, nasal type, the latter two of which preferentially occur in Japan. For the other types of cutaneous lymphoma, we have used reports from other countries (Table 3).[22–26]

MF/SS

Previous researchers already contributed to disease staging and prognostic analysis for MF/SS.[27] Since the new staging was advocated in 2007, prognostic analyses have been reported from Japan and the UK (Table 3).[18,22] The survival rates of Japanese patients with MF/SS were similar to those shown in previous studies conducted in the USA and Europe. The prognoses of patients with skin tumor (stage IIB) and extracutaneous involvement (stage IV) were significantly worse than those of patients with early-stage disease (stages IA–IIA). Erythrodermic MF patients without blood involvement (stage IIIA) showed excellent survival. Independent prognostic factors in multivariate analyses were higher age and the presence of either skin tumor or extracutaneous disease.[18] Although findings in Japan showed the prognosis for stage IIIA to be quite favorable, a British analysis indicated that it was similar to the prognosis for stage IIb,[22] this may have occurred because the two reports did not use the same diagnostic criteria for erythrodermic lymphoma, resulting in differences in patient characteristics.

ATLL

A recent observation in Japan indicated that the patch and plaque types of ATLL were associated with better survival rates.[19] Multivariate analysis demonstrated that the hazard ratios of the erythrodermic and nodulotumoral types were significantly higher than that of the patch type, and that the eruption type is an independent prognostic factor for ATLL. The overall survival worsened as the T stage became more advanced: the multipapular type and T2 were comparable, and the purpuric type had a significantly poorer prognosis than T1 (Fig. S3).[19]

ENKL

Suzuki *et al.*[20] have reported the prognosis of a total 150 patients with ENKL, nasal type, consisting of 123 nasal and 27 extranasal (16 cutaneous, nine hepatosplenic, one intestinal and one nodal) lymphomas. We focused on patients with the cutaneous type of ENKL, and re-examined their prognoses. Patients with stage I disease (determined by the Ann Arbor staging system) showed a favorable prognosis in 5-year overall survival of 75%, but the prognoses deteriorated in the advanced stages (Table 3). Unlike a previous study on $CD56^+$ hematological neoplasms with or without EBV infection in Europe,[28] our data highlighted that ENKL is usually associated with EBV infection, and assessed the prognoses of "nasal" and "cutaneous" ENKL separately.

TREATMENT GUIDELINES

Treatment guidelines for MF/SS

Mycosis fungoides/Sézary syndrome is the oldest defined form of cutaneous lymphoma, and is more common than other primary cutaneous lymphomas (Tables 4–11). At present, no treatment based on high-level evidence is available for this condition. In many cases, the clinical course may extend for 10 years or more. Therefore, the success or failure of therapeutic intervention may be difficult to determine. Moreover, ethical issues may complicate the implementation of randomized placebo-controlled studies. Only four randomized studies have compared the effectiveness of different treatment methods[29–32] and only one randomized placebo-controlled study has been conducted.[33] These guidelines give substantial weight to consensus among the committee members. The "B" recommendation level has been given to first-line therapies for daily clinical practice.

An additional problem is that far fewer treatment options are available for MF/SS in Japan than in Western countries. In the present guidelines, we have included information on treatment modalities that have not been approved by the Japanese National Health Insurance system. Experimental therapies not yet approved overseas or in Japan have been omitted from these guidelines.

CQ1: Is monitoring the clinical course without treatment recommended for MF?
Degree of recommendation: C1 (stage IA only), C2 (other than stage IA).
Recommendation: In stage IA of MF, one acceptable option is to monitor the clinical course without treatment. For stages beyond IA, monitoring the clinical course without treatment is generally not recommended (Data S1).

CQ2: Are topical steroids recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Topical steroid therapy is recommended at all stages of MF/SS (Data S1).

CQ3: Is topical chemotherapy recommended for MF/SS?
Degree of recommendation: C1.
Recommendation: Mechlorethamine/nitrogen mustard (HN2) or carmustine (BCNU) topical chemotherapy is currently used in Europe and North America, and is recommended for early-stage MF (stage IA through IIA). These agents are not yet approved or available in Japan. Nimustine hydrochloride (ACNU) is currently used topically in some facilities in Japan,