は，1996-1998PCS（53.6％），1999-2001PCS（51.8％）ではほとんど変化がなかったが，2003-2005PCSでは，69.6％と増加していた．術後照射に関しては，その割合は大きな変化はなかった．一方，2003-2005PCSでは，内分泌療法抵抗・再燃前立腺癌に対して放射線治療が施行された症例は36例（6.1％）のみであり，1996-1998PCS（18.6％），1999-2001PCS（18.2％）と比較して，割合が低下している．PCSは各施設にて各疾患ごとにランダムに選択された10～20症例を調査するため，疾患全体数の変化はわからないが，おそらく根治的外照射例が増加したことにより，相対的に内分泌療法抵抗・再燃前立腺癌の割合が低下したものと推測される．

根治照射症例（外部照射），根治照射症例（小線源療法），アジュバント・救済照射症例については，別項で詳細に解説される．以下に，内分泌療法抵抗・再燃例についてPCSで得られた結果について述べる．

1 内分泌療法抵抗・再燃例への放射線治療

前立腺はアンドロゲン依存性の臓器であり，前立腺癌の大部分がアンドロゲン依存性を示すため，アンドロゲン作用を遮断する内分泌療法は，前立腺癌にきわめて有効である．遠隔転移やリンパ節転移を伴う進行前立腺癌には内分泌療法は第一選択であり，限局性前立腺癌の場合にもネオアジュバント・アジュバント療法などとして重要な治療手段の1つとなっている．欧米では，早期前立腺癌への第一選択としての内分泌療法単独は，心血管障害や糖尿病などのリスクの上昇の可能性から一般的ではなく，むしろ生存率を下げる可能性が指摘されている[4]．しかし，日本においては，早期の場合にも内分泌療法単独が行われることも多い．実際，日本泌尿器科学会による前立腺癌全国登録プログラムでの2000年の調査結果では，遠隔転移を伴わないT1-3N0M0の場合でも内分泌療法単独は46％と最も多く施行されていた[5]．また，J-CaP（Japan study group of Prostate Cancer）研究会からの報告では，2001年から2003年までに登録された2万6,272例のうち，1万9,409例（74％）が初回に内分泌療法が施行されていた[6]．

内分泌療法は著明な初期効果を示すことが多いが，そのまま継続した場合腫瘍はアンドロゲン依存性を喪失して再増殖を始め，再燃となる．内分泌療法に抵抗・再燃の場合で，局所・所属リンパ節のみの病変として認められる場合には放射線治療が選択枝の1つとなる[7]．しかし，欧米においては，限局性の内分泌療法再燃・抵抗前立腺癌に対する放射線治療成績の報告は少なく[8~9]，その詳細は不明であった．

上記に述べたように，わが国には，限局性前立腺癌においても内分泌療法単独で治療されることも多かったという背景があり，世界的に見ても多くの内分泌療法抵抗・再燃例に対する放射線治療が実施されており[10~13]，前立腺PCSのデータは貴重なものと考えられる．

2 方　法

調査対象は，1996～1998年，1999～2001年，2003～2005年に放射線治療が開始された，遠隔転移を伴わない前立腺癌で，過去に放射線治療歴がないこと，他に悪性腫瘍の既往がないことである．無作為に抽出されたA施設（大学病院・がんセンター），B施設（その他の国公立病院）より，最終的に前立腺癌1,431例の臨床データが集積された．そのうち，内分泌療法抵抗・再燃例は190例（13.3％）であった．

前立腺癌取扱い規約では，内分泌療法が奏効せず，引きつづき進行する状態を抵抗，内分泌療法が一時奏効したものが再び増悪する状態を再燃と定義するが，ここでは，両者をあわせて解析した．また，各グループ間の検定にはカイ二乗検定を用いた．

結　果

1）患者背景

患者背景を表2に示す．年齢の中央値は各調査年で異なるが，73～76歳であった．組織型

表2　患者背景

	1996～1998年	1999～2001年	2003～2005年	p value
Age (years)				0.400
Median	73	73	76	
Range	55～86	51～94	49～85	
Differentiation				0.003
Well	6(11%)	10(13%)	4(16%)	
Moderate	31(56%)	27(35%)	8(32%)	
Poor	18(33%)	40(52%)	13(52%)	
Gleason score				0.448
2～6	3(30%)	4(17%)	4(21%)	
7	4(40%)	4(17%)	4(21%)	
8～10	3(30%)	15(66%)	11(58%)	
T stage				0.407
T1	0(0%)	2(3%)	1(3%)	
T2	8(15%)	19(25%)	6(20%)	
T3	27(49%)	38(49%)	15(50%)	
T4	20(36%)	18(23%)	8(27%)	
N stage				0.304
N0	32(68%)	61(81%)	27(87%)	
N1	15(32%)	14(19%)	4(13%)	
Pretreatment PSA (ng/ml)				0.814
<10	4(11%)	10(15%)	2(6%)	
10～20	5(15%)	8(11%)	4(13%)	
20≦	26(74%)	51(74%)	26(81%)	
PSA before RT (ng/ml)				0.014
<10	16(35%)	46(52%)	26(72%)	
10～20	12(27%)	19(21%)	7(19%)	
20≦	17(38%)	24(27%)	3(9%)	

* 欠損データがあるため，合計は各群の総数と必ずしも一致していない．

は，全体的に低分化腺癌の比率が高く，Gleasonスコアはデータ欠損が多いものの，Gleasonスコア8-10の割合が高かった．T因子に関してはT3-4が全体の80%程度を占めており，局所進行前立腺癌の割合が多い．N因子では年々比率は低下しているものの，10～30%程度にリンパ節転移が認められている．全治療前のPSA値は，70%以上が20 ng/ml以上の高値を示している．特記すべきは放射線治療前のPSA値であり，1996～1998年では≧20 ng/mlが38%であったが，2003～2005年にはわずか9%と減少する一方で，<10 ng/mlの比率が35%から72%と上昇している．すなわち，内分泌療法抵抗・再燃となった場合，PSA値の低い時点から放射線治療が開始されるようになっていることがわかる．

2）内分泌療法

内分泌療法の内訳を表3に示す．内分泌療法は，LH-RHアナログ，抗アンドロゲン剤が主であり，去勢術の割合が経年的に低下してきている．エストラサイトを含む化学療法は20～30%に施行されていた．また，内分泌療法から放射線治療開始までの期間の中央値は，2～3年であった．

3）放射線治療

前立腺に対する総線量を図1に示す．総線量の中央値は，1996～1998年60 Gy, 1999～2001年66 Gy, 2003～2005年68 Gyと経年的に増加していた．内分泌療法抵抗・再燃例においては，60 Gy以上の根治的な線量を投与された群と，55 Gy未満の緩和的な線量が投与された群に分かれていた．しかし，2003～2005年では，55 Gy未満の群は少なくなっており，一方で70 Gy以上が投与される割合が高くなっている．これは，内分泌療法抵抗・再燃例であっても，緩和ではなく，根治的に治療される傾向になっていることを意味している．骨盤リンパ節領域への照射施行率は，1996～1998年には67%であったが，2003～2005年には39%と低下している（表4）．また，1996～1998年には前後対向2門にて照射されている例が17%あったが，2003～2005年はまったくなくなり，3門以上の多門照射または回転照射にて治療されるようになっている．

3. 考　察

10年間にわたるPCSの調査にて，わが国における内分泌療法抵抗・再燃前立腺癌の放射線治療の実態が明らかとなった．照射開始時にはT3-4症例が多く，PSAは高値であり，低分化腺癌が多かった．照射線量は55 Gy未満と，60 Gy以上の2つの群に分かれたが，2003～2005年には，根治的と考えられる70 Gy以上の線量が投与されるようになっており，投与線量の中央値も経年的に増加している．

表3　内分泌療法内訳

	1996～1998年	1999～2001年	2003～2005年	p value
Orchiectomy	19(33%)	22(23%)	4(11%)	0.106
Estrogen agent	12(21%)	33(34%)	5(14%)	0.018
LH-RH analogue	42(72%)	80(83%)	29(81%)	0.215
Androgen blocker	36(62%)	73(76%)	31(86%)	<0.0001
Chemotherapy	19(33%)	19(20%)	9(25%)	0.302
Interval between HT & RT (months)				0.055
Median	22.7	27.7	38.6	
Range	0.4～103.4	0.4～168.4	5.3～145.4	

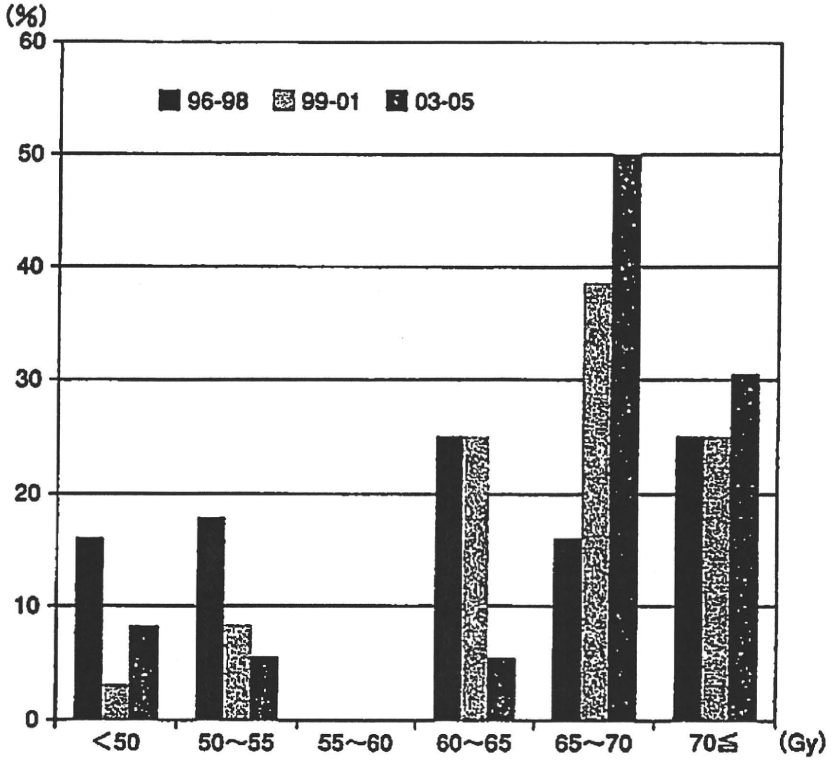

図1　放射線線量

放射線治療前のPSA値については，1996～1998年では，PSA値が高くなってから照射される傾向にあったが，一方，2003～2005年にはPSA値が低いうちに照射が開始されている症例の割合が増加している．内分泌抵抗・再燃限局性前立腺癌53例に対する放射線治療成績の解析では，放射線治療開始時のPSA値が高いものでは予後不良であったと報告されており[10]，内分泌療法に不応となった場合には，PSA値が低いうちに放射線治療を施行すべきであろう．

内分泌療法抵抗・再燃前立腺癌に対する適切な照射線量についてはよくわかっていない．今回の解析では，前述のように55 Gy未満と，60 Gy以上の2つの群に分かれた．緩和的目的ならば前立腺局所への40～50 Gy程度の照射で十分効果を上げるとされている[14]．また，症状のある内分泌療抵抗・再燃前立腺癌に対しては，27～38 Gyの線量で，11カ月以上の十分な局所コントロールが得られたとされている[15]．一方，たとえ内分泌不応であっても，3年局所コントロール率は60 Gy以上の線量で90%であったとする報告もあり[8]，根治的目的にて放射線治療を行うと

表4　照射方法

	1996～1998年	1999～2001年	2003～2005年	p value
Energy of X-ray (local)				0.616
<10 MV	8(19%)	21(24%)	5(16%)	
=>10 MV	34(81%)	67(76%)	26(84%)	
All fields treated each day				0.070
Yes	19(49%)	67(70%)	23(64%)	
Pelvic irradiation				0.005
Yes	39(67%)	41(43%)	14(39%)	
Conformal therapy				<0.0001
Yes	13(22%)	30(32%)	19(53%)	
Technique for local fields				0.093
AP/PA	7(17%)	4(5%)	0(0%)	
LR/RL	2(5%)	4(5%)	3(9%)	
≥ 3 fields	16(38%)	50(57%)	19(60%)	
Moving/Dynamic/Pendulum/Others	17(40%)	30(33%)	10(31%)	

きには，照射線量は増加させるべきであろう．

内分泌療法抵抗・再燃前立腺癌の放射線治療成績は，たとえ限局性であっても一般的に不良とされている．欧米からの報告は少ないものの，領域内に限局した内分泌療法抵抗・再燃前立腺癌に対し，中央値66 Gyの外照射を行った報告では，4年全生存率39%と不良であったとしている[8]．また，29例の同様の報告でも，放射線治療により良好な局所コントロールは得られるが，遠隔転移が高頻度であり，5年全生存率は28%と不良であったとされている[9]．

PCSでは予後調査も行うものの，訪問調査という研究の性格上，どうしても経過観察期間が短くなることが多い．その点を加味したうえで，われわれは，1996～1998年，1999～2001年に治療され，PCSで予後データのはっきりしている内分泌療法抵抗・再燃前立腺癌140例について解析した[12]．中央値66 Gyが照射され，50%に全骨盤照射が併用されていた．観察期間の中央値は20.7カ月とやや短いが，5年全生存率は48.1%，5年臨床的無再発生存率は36.7%と不良であった．しかし，再発例のうち，46例は遠隔転移であり，局所再発は6例のみであった．Grade 3以上の晩発性有害事象は6例のみに認められた．今回のわれわれの解析結果でも，欧米からの報告と同様な結果が得られている．

わが国では，比較的早期であっても高齢などが理由で，内分泌療法単独が施行されることも多い．前立腺PCSにて集積された前立腺癌1,431例の中で，内分泌療法抵抗・再燃例は190例(13.3%)であり，正確に比較するデータはないものの，この割合は欧米よりはるかに多いものと思われる．上記で述べたように，内分泌療法抵抗・再燃前立腺癌は，前立腺局所に関しては放射線治療により十分コントロールできる可能性があるが，遠隔転移をきたしやすく，予後は不良である．すなわち，内分泌療法に抵抗性になる前に放射線治療などの集学的治療を検討する必要であると思われる．

近年，局所進行前立腺癌において，継続的な内分泌療法単独よりも，継続的な内分泌療法に放射線治療を併用することで，生存率が改善する臨床試験の結果が相次いで発表された．局所進行前立腺癌875例を，MAB(Maximum androgen blockade)療法3カ月後にフルタミドを継続的に投与する群と，同療法に外部照射70 Gyを照射する群にランダム化した臨床試験では，10年での全死亡率は内分泌療法群で39.4%，外部照射併用群で29.6%と有意に低下した[16]．また，局所進行前立腺癌1,205例を去勢またはLHRH analogを継続的に施行する群と，同治療に65～69 Gyを併用する群にランダム化した臨床試験でも，放射線治療併用群が有意に死亡のリスクを改善している[17]．これらの臨床試験の報告から，

少なくとも局所進行前立腺癌においては，内分泌療法単独ではなく，内分泌療法に放射線治療を併用する治療が今後標準になっていくものと思われ，この治療方針が普及すれば，わが国においても内分泌療法抵抗・再燃前立腺癌の放射線治療症例の割合は減少するかもしれない．

まとめ

PCSにより得られたわが国の内分泌療法抵抗・再燃前立腺癌の医療実態について述べた．

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文　献

1) Viani GA, Stefano EJ, Afonso SL: Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 74: 1405–1418, 2009
2) 中村和正：前立腺がん術後症例に対する術後補助および救済放射線治療の考え方．医学のあゆみ 227: 800–804, 2008
3) Nakamura K, Ogawa K, Sasaki T, Onishi H, et al: Patterns of Radiation Treatment Planning for Localized Prostate Cancer in Japan: 2003–2005 Patterns of Care Study Report. *Jpn J Clin Oncol* 39: 820–824, 2009
4) Van Hemelrijck M, Garmo H, Holmberg L, et al: Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. *J Clin Oncol* 28: 3448–3456, 2010
5) 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* 12: 46–61, 2005
6) Hinotsu S, Akaza H, Usami M, et al: Current status of endocrine therapy for prostate cancer in Japan analysis of primary androgen deprivation therapy on the basis of data collected by J-CaP. *Jpn J Clin Oncol* 37: 775–781, 2007
7) 中村和正，桑原康雄：前立腺癌に対する緩和的医療としての放射線治療の役割．泌尿器外科 21: 1039–1042, 2008
8) Lankford SP, Pollack A, Zagars GK: Radiotherapy for regionally localized hormone refractory prostate cancer. *Int J Radiat Oncol Biol Phys* 33: 907–912, 1995
9) Sanguineti G, Marcenaro M, Franzone P, et al: Is there a "curative" role of radiotherapy for clinically localized hormone refractory prostate cancer? *Am J Clin Oncol* 27: 264–268, 2004
10) Akimoto T, Kitamoto Y, Saito J, et al: External beam radiotherapy for clinically node-negative, localized hormone-refractory prostate cancer: impact of pretreatment PSA value on radiotherapeutic outcomes. *Int J Radiat Oncol Biol Phys* 59: 372–379, 2004
11) Nakamura K, Teshima T, Takahashi Y, et al: Radiotherapy for localized hormone-refractory prostate cancer in Japan. *Anticancer Res* 24(5B): 3141–3145, 2004
12) Sasaki T, Nakamura K, Ogawa K, et al: Radiotherapy for patients with localized hormone-refractory prostate cancer: results of the Patterns of Care Study in Japan. *BJU Int* 104: 1462–1466, 2009
13) Ogawa K, Nakamura K, Sasaki T, et al: External beam radiotherapy for clinically localized hormone-refractory prostate cancer: clinical significance of Nadir prostate-specific antigen value within 12 months. *Int J Radiat Oncol Biol Phys* 74: 759–765, 2009
14) Kraus PA, Lytton B, Weiss RM et al: Radiation therapy for local palliative treatment of prostatic cancer. *J Urol* 108: 612–614, 1972
15) 川上　理，河合恒雄，米瀬淳二・他：ホルモン抵抗性 stage D2 前立腺癌の局所再燃に対する対症的放射線療法．日泌尿会誌 84: 1681–1684, 1993
16) Widmark A, Klepp O, Solberg A, et al: Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 373(9660): 301–308, 2009
17) Warde PR, Mason MD, Sydes MR. et al: Intergroup randomized phase III study of androgen deprivation therapy (ADT) plus radiation therapy (RT) in locally advanced prostate cancer (CaP) (NCIC-CTG, SWOG, MRC-UK, INT: T94-0110; NCT00002633). *J Clin Oncol* 28: 18s, 2010 (suppl)

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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

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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.

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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

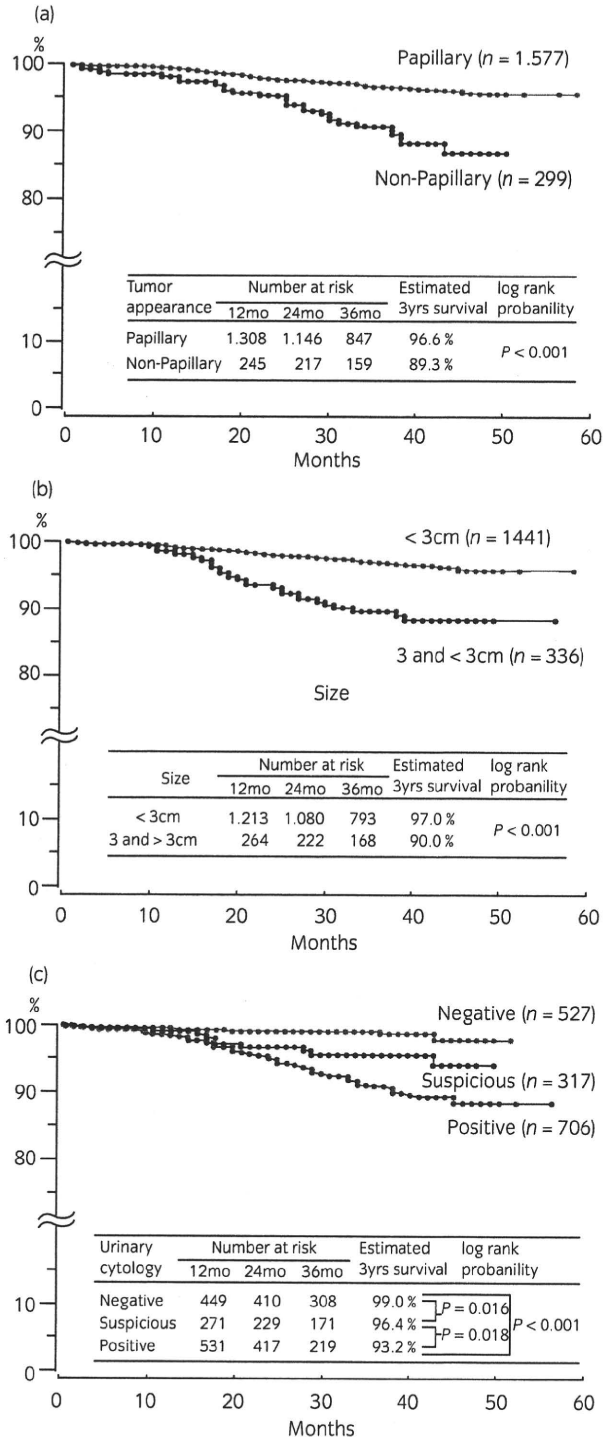

Fig. 1 Cause-specific survival (CSS) according to cystoscopic findings before transurethral resection. (a) CSS according to tumor appearance. Kaplan–Meier's survival estimation curve is shown here. Of the 1919 cases, 52 (2.7%) non-informative cases were excluded. (b) CSS according to tumor size. Kaplan–Meier's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

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Impact of Convenience Void in a Bladder Diary With Urinary Perception Grade to Assess Overactive Bladder Symptoms: A Community-Based Study

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Aim: Bladder diaries including bladder perception grade were analyzed to assess convenience void (CV) in community-dwelling women 40 years of age or older. **Methods:** A total of 310 women completed a 3-day bladder diary with a grade for bladder perception. The grade was defined on scores 0–5 as follows: 0 = No bladder sensation, 1 = Sensation of bladder filling without desire to void, 2 = Desire to void, 3 = Strong desire to void, 4 = Urgency without urge urinary incontinence (UUI), and 5 = Urge incontinence episode. CV was defined as void without desire to void: when the grade was 0, CV in a narrow sense, and when 0 or 1, CV in a broad sense. **Results:** The incidence of CV in the broad sense significantly decreased with age. Of the 310 women, 48 (15.5%) had overactive bladder (OAB) symptoms on the medical interview, including 37 (11.9%) without UUI (OAB-Dry) and 11 (3.5%) with UUI (OAB-Wet). Of the remaining 262 women, 111 (35.8%), who had urgency but a urinary frequency of 7 or less, and another 141 (48.7%) were classified into the Normal with Urgency and Normal without Urgency groups, respectively. The incidence of CV in a broad sense in the Normal without Urgency group was significantly greater than that in the Normal with Urgency and OAB-Wet groups. The mean voided volumes of CV in the broad sense in the OAB-Wet group were significantly smaller than those in the other three groups. **Conclusions:** The evaluation of CV may be a new tool in assessing storage condition and voiding dysfunction. *Neurourol. Urodynam. 29:1286–1289, 2010.* © 2010 Wiley-Liss, Inc.

Key words: bladder diary; bladder sensation; community-based study; convenience void; overactive bladder

INTRODUCTION

A bladder diary can record the important factors of voiding behavior including frequency of voiding, voided volumes, pad usage, fluid intake, 24-hr urine production, the grade of urgency, and the degree of incontinence.[1] The bladder diary is becoming a standard assessment tool for overactive bladder (OAB). The grade of bladder sensation during daily life can be evaluated by scoring the perception of urinary bladder fullness in a bladder diary.[2–5]

Recently, as De Wachter and Wyndaele described,[3] bladder sensation during daily life can be evaluated by scoring the grade of perception of fullness on frequency volume charts (FVCs). They concluded that frequency–volume charts with evaluation of perception of fullness might provide an initial non-invasive tool to study bladder sensation. Moreover, a relatively new term, convenience void (CV), which describes voiding episodes without a desire to void for social reasons, has been advocated to be considered for inclusion in the FVCs used in research.[6] In healthy volunteers including 38 women and 15 men with an average age of 38 years, Darling and Neilson[6] reported that CV was common in 72% of the participants, and represented 9.2% of the total number of voids. The numbers of CVs reported by male and female volunteers were 4.6 and 3.4 times weekly, respectively.[6]

At the time of CV, the bladder will be emptied for social reasons, such as before joining a meeting, before going out on a long journey, or before retiring to bed at night. We considered that for men or women with OAB, the frequency of CV might be an indicator of how they controlled their voiding behavior in order to avoid urgency.

The aim of this study was to assess CV by a bladder diary with bladder perception grades and to evaluate the relationship between CV and OAB in community-dwelling women 40 years of age or older examined during a mass-screening program in Japan.

MATERIALS AND METHODS

In July and August 2004 a total of 548 women (mean 60 years of age, range 40–86 years) was recruited for the purpose of a mass-screening program for general health in a community-based study in a rural town in Hokkaido Prefecture in Japan. 7.3% of all the women 40 years of age or older in the town participated. In this study, 80 women (14.6%) refused to fill in the bladder diary and 158 women (28.8%) failed to fill it in completely. Finally, 310 women (56.6%, mean 58 years of age, range 40–83 years) who decided to participate in the present study by self-selection out of the 548 participants of the mass-screening program completed a 3-day bladder diary, which included a grade for bladder perception. The Ethical Committee at our institutions approved this study, and written informed consent was obtained from all the participants. The grade of perception was defined by scores from 0 to 5 as follows; 0 = No bladder

Dirk De Ridder led the review process.
Conflicts of interest: none
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sensation, 1 = Sensation of bladder filling without desire to void (voiding can easily be delayed for more than 60 min), 2 = Desire to void (voiding can easily be delayed for more than 30 min), 3 = Strong desire to void (voiding cannot be delayed for more than 15 min), 4 = Urgent desire to void (voiding cannot be delayed for more than 5 min), and 5 = Urge incontinence episode. The perception grades 0–4 have been previously established, as proposed by De Wachter and Wyndaele.[3] We have modified the scale by adding a perception grade 5, in which the void is assessed as being of urge urinary incontinence (UUI). The grade scored at each void is entered in the bladder diary. How to complete the bladder diary with bladder perception was explained to the participants by means of both covering letter, and by word of mouth by nurses. The diaries were returned during the mass-screening program. The subjects with OAB were abstracted from the medical interview at the time of the mass-screening program by a definition of OAB of eight or more voids per day and one or more urgency episodes per week, as described in a previous epidemiological study in Europe, the United States, and Japan.[7–9] In this study, two definitions of CV were used, CV in the narrow sense and CV in the broad sense. CV in the narrow sense consisted of voids at perception grade 0, while CV in the broad sense consisted of voids at perception grades 0 and 1. Additionally, the incidence of CV was calculated by the frequency of CV in the narrow sense or the broad sense per day/24 hr urinary frequencies in each woman.

Statistical analyses used were ANOVA and Student's *t*-test. Data analyses were performed with statistical software packages (JMP 6, SAS, NC). A *P*-value of less than 0.05 was defined as statistically significant. Data were shown as the mean ± standard deviation.

RESULTS

A total of 5,709 voids were obtained, with complete voided volumes and bladder perception grades entered in the 3-day bladder diaries. Of the total of 5,709 voids, 404 (7.1%) were graded 0 and 822 (14%) were graded 1, resulting in CV in the narrow sense of 7.1%, and CV in the broad sense of 21% of all voids. There were no significant differences between the incidence of CV in the narrow sense and age groups, while the incidence of CV in the broad sense significantly decreased with age groups ($P < 0.001$) (Table I).

The mean voided volumes of grade 0 and grade 1 were 141 and 185 ml, respectively. The voided volumes in grade 0 were significantly less than those in grade 1 ($P < 0.000001$). The mean voided volume of both grades 0 and 1 together (CV in the broad sense) was 170 ml.

Of the 310 women, 48 (15.5%) had OAB symptoms, including 37 (11.9%) without urge incontinence (OAB-Dry), and 11 (3.5%) with urge incontinence (OAB-Wet), according to the definition of OAB by medical interview, in which the subjects had both eight or more voids per day and one or more urgency episodes per week. The other 262 women were classified into the Normal group. In the analysis of bladder perception grades in the Normal group, 111 (35.8%) women had voids at grades 4 or 5 that indicated urgency (Normal with Urgency group), while 151 (48.7%) did not (Normal without Urgency group).

The mean age of the OAB-Wet group was significantly ($P < 0.01$) higher than in any other group (Table II). There were no significant differences in the incidence of CVs in the narrow sense among the four groups, while the incidence of CV in the broad sense in the Normal without Urgency group was significantly greater than those in the Normal with Urgency ($P = 0.0014$) and OAB-Wet groups ($P = 0.032$).

The relationships between the CV and the mean voided volume from the 3-day bladder diaries were also shown in the Table II. There were no statistical differences in the mean voided volume of CV in the narrow sense among the four groups. On the contrary, in the analysis of CV in the broad sense, the mean voided volumes in the Normal without Urgency group were significantly larger than those in the other three groups, and the volumes in the OAB-Wet group were significantly smaller than those in the other three groups, although there were no significant differences in the volumes between the Normal with Urgency and the OAB-Dry groups.

DISCUSSION

CV (void without desire to void, or void with lack of sensation of bladder fullness), is a relatively new term for research.[6] In analysis of 1-week FVCs in 53 healthy volunteers, Darling and Neilson[6] reported CV occurred at a short interval and with a small volume. In their study, the participants were instructed to highlight voids when they did not have the desire to pass urine but did so out of convenience. Several healthy volunteers stated that the decision to void was made when there was absolutely no need to void, but after the cycle was set in motion the mere act of thinking about it triggered the sensation of bladder fullness.[6] Hence, reliable recording of CV episodes was difficult to assess with the addition of a simple request to participants regarding the clear determination of CV on each void in FVC, if the questionnaire lacked an objectively quantified grade of perception of urinary bladder fullness at each time of void. In the 3-day bladder diary with a grade of bladder perception from 0 to 5, which we used, CV could be determined when the void was made with a lack of sensation of bladder fullness or without a desire to void.

In the present study, the incidences of CV were 7.1% in the narrow and 21.0% in the broad sense, with an average age of 60 years. Darling and Neilson[6] reported CV occurred in 9.2% of the total number of voids in healthy volunteers with an average age of 38 years. The incidence of voids at grade 0 (CV in the narrow sense) was 18.7%, and at grades 0 and 1 (CV in

TABLE I. Age Groups and Voids With Grades of Perception From 0 to 5

Age group	40–49 (n = 57)	50–59 (n = 113)	60–69 (n = 101)	≥70 (n = 39)	*P*-value
Incidence of CV (%)					
Narrow sense	8.9 ± 13.4	8.7 ± 14.5	5.6 ± 12.7	4.5 ± 8.1	0.127
Broad sense	29.8 ± 28.6	23.7 ± 22.3	20.5 ± 26.7	10.2 ± 12.5	0.001

The grade is defined on scores 0–5 as follows: 0 = No bladder sensation, 1 = Sensation of bladder filling without desire to void, 2 = Desire to void, 3 = Strong desire to void, 4 = Urgency without urge urinary incontinence, and 5 = Urgency with urge urinary incontinence.

TABLE II. Distribution of CVs in Comparison Between the Normal and the OAB Groups, Including Normal Without Urgency, Normal With Urgency, OAB-Dry and OAB-Wet

	Normal without Urgency	Normal with Urgency	OAB-Dry	OAB-Wet
Number (%)	151 (48.7)	111 (35.8)	37 (11.9)	11 (3.6)
Mean age (years)	58.0 ± 9.6	58.4 ± 9.2	57.2 ± 9.7	67.9 ± 10.8**,##,††
Incidence of CV (%)				
Narrow sense	7.3 ± 14.5	7.4 ± 12.7	6.6 ± 9.1	6.3 ± 8.1
Broad sense	27.3 ± 29.9	17.6 ± 17.7**	17.7 ± 17.2	14.7 ± 13.7*
Voided volume at CV (ml)				
Narrow sense	152.0 ± 100.8	133.6 ± 76.8	123.7 ± 76.3	100.0 ± 57.3
Broad sense	182.7 ± 106.9	155.5 ± 88.8**	157.7 ± 93.7*	106.7 ± 63.8**,#,†

*$P < 0.05$, compared with Normal without Urgency.
**$P < 0.01$, compared with Normal without Urgency.
#$P < 0.05$, compared with Normal with Urgency.
##$P < 0.01$, compared with Normal with Urgency.
††$P < 0.01$, compared with OAB-Dry.
†$P < 0.05$, compared with OAB-Dry.

the broad sense) was 65% in young female healthy volunteers with an average age of 21 years.[3] In this study, the incidence of CV in a broad sense decreased with age, being 30%, 24%, 21%, and 10% in women in their 40s, 50s, 60s, and 70s or older, respectively ($P = 0.001$). These outcomes indicated that the incidence of CV could correlate with age-related pathogenesis. One explanation is that CV principally occurred due to social intention to void by the will of the individual. Accordingly, it may be probable that the episodes of CV in younger persons are more frequent than those in older ones due to differences in social activity. On the other hand, Pfisterer et al.[10] reported that bladder sensation diminished significantly with age. In this study, the finding of an age-associated decrease in bladder sensation was observed in spite of increasing volumes at first desire to void and at strong desire to void in cystometry. Pfisterer et al. suggested that the larger the volume at which a person realizes the need to go to the bathroom, the shorter is the period of warning during which she can void at her convenience. Additionally, Neoemova et al.[11] reported that there is no good correlation between data from cystometry and data on voiding diaries. Further studies are needed to clarify the relationship between aging and CV in bladder diaries.

The clinical impact of CV on OAB remained unknown, although CVs in the healthy volunteers appeared on the FVC and were analyzed in the previous reports. In the present study, incidence of CV in a broad sense in the OAB-Wet group was significantly less than that in the Normal without Urgency group, while that in the OAB-Dry group was 10% less compared with the Normal without Urgency group although the difference was not statistically significant. In our previous study there were no significant differences in the incidence of voids at other grades among the four groups. As for the voided volume, the mean voided volumes of CV in a broad sense significantly differed between the Normal without Urgency (182.7 ml), OAB-Dry (157.7 ml), and OAB-Wet (106.7 ml) groups. These results are thought to be connected to the characteristics of OAB. Persons with OAB feel urinary sensation suddenly even when there is only a small storage volume. Accordingly, the voided volume at CV, which is defined as voiding with a lack of sensation of bladder fullness, is smaller than that in normal persons. On the other hand, they were thought to know their own timing of urinary sensation and to go to toilet early, but urgency may cause sudden urinary sensation resulting in voids with urinary sensation, which led to a decreased incidence of CV. Consequently, the incidence of CV in a broad sense in women with OAB may be less than that in normal women.

The analysis of the Normal with Urgency group, which included women with urgency and frequency of urination of seven or less per day, is interesting. In this group, the incidence and the mean voided volume of CV in a broad sense were very similar to those in the OAB-Dry group, but different from those in the Normal without Urgency group. The nature of the Normal with Urgency group may be similar to that of the OAB-Dry group but not the Normal without Urgency group. Although OAB is defined as urgency, with or without urgency incontinence, usually with frequency and nocturia,[1] the condition in the Normal with Urgency group may be classified as OAB but unusually without frequency. If so, the incidence of this group of 35.8% is very high and never "unusual." In our previous study, the 24 hr voided volume and voiding frequency in the Normal with Urgency group were significantly less than those in the OAB-Dry group,[12] but similar to those in the Normal without Urgency group. This increase of daily urine output may cause frequency in the OAB-Dry group. Thus, the analysis of CV might clarify the difference between the Normal with and without Urgency groups, while the difference between the Normal with Urgency and OAB-Dry groups might be evaluated by the analysis of the 24 hr voided volume as well as 24 hr voiding frequency. Further study is necessary to confirm these hypotheses.

In the present study, two definitions for CV were used; a narrow and a broad sense. Neoemova et al.[13,14] analyzed voiding patterns between continent and incontinent women using a 3-day sensation-related bladder diary, which defined the CV as no desire to void. Their definition of CV is nearly the same as our definition of CV in the broad sense. In our study, significant differences were observed in comparisons in age related frequency, the incidence of CV, and mean voided volume between classified groups, only when CV in a broad sense was used. Accordingly, CV in a broad sense is thought to be suitable for use in the clinical setting.

The usefulness of a 3-day sensation-related bladder diary has been reported by Neoemova et al.[13] in continent and incontinent women. The study revealed, however, that there were no significant differences in the mean voided volume of CV between healthy volunteers and the women with UUI, while the mean voided volume of CV in a broad sense in the OAB-Wet group was significantly less than that in the other three groups including the Normal without Urgency group in

the present study. The reasons why the results were different are unclear. On the other hand, those researchers did not analyze the incidence of CV, while the incidence of CV in the Normal without Urgency group was significantly greater than that in the Normal with Urgency and OAB-Wet groups in our study. Thus, not only the voided volume of CV but also the incidence of CV was useful for the assessment of OAB using a bladder diary with bladder perception grade.

The analysis of voided volume and incidence of CV in the broad sense from the bladder diary with urinary perception grade was therefore thought to be useful for the evaluation of OAB. The analysis of CV may be important because it can change the analysis of "sensation-related voids."

CONCLUSIONS

The incidence of CV decreased with age. The incidence and voided volumes of CV in the broad sense were significantly related to existing urgency or OAB. The evaluation of CV may be a new tool in assessing the storage condition and voiding dysfunction. Further studies will be necessary to evaluate the true efficacy of the bladder diary with bladder perception grade and CV for assessment of storage and voiding symptoms.

REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: Report from the Standardization Subcommittee of the International Continence Society. Neurourol Urodyn 2002;21:167–78.
2. Abrams P, Klevmark B. Frequency volume charts: An indispensable part of lower urinary tract assessment. Scand J Urol Nephrol Suppl 1996;179: 47–53.
3. De Wachter C, Wyndaele JJ. Frequency-volume charts: A tool to evaluate bladder sensation. Neurourol Urodyn 2003;22:638–42.
4. Chapple CR, Artibani W, Cardozo LD, et al. The role of urinary urgency and its measurement in the overactive bladder symptom: Current concepts and future prospects. BJU Int 2005;95:335–40.
5. Cardozo L, Coyne KS, Versi E. Validation of the urgency perception scale. BJU Int 2005;95:591–6.
6. Darling R, Neilson D. Convenience voids: An important new factor in urinary frequency volume chart analysis. J Urol 2005;173:487–9.
7. Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760–6.
8. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20: 327–36.
9. Homma Y, Yamaguchi O, Hayashi K. Neurogenic Bladder Society Committee: An epidemiological survey of overactive bladder symptoms in Japan. BJU Int 2005;96:1314–8.
10. Pfisterer MH, Griffiths DJ, Schaefer W, et al. The effect of age on lower urinary tract function: A study in women. J Am Geriatr Soc 2006;54: 405–12.
11. Neoemova I, Meel TV, De Wachter S, et al. Does sensory bladder function during cystometry differ from that in daily life? A study in incontinent women. Neurourol Urodyn 2009;28:309–12.
12. Honjo H, Kawauchi A, Ukimura O, et al. Analysis of bladder diary with urinary perception to assess overactive bladder symptoms in community-dwelling women. Neurourol Urodyn 2009;28:982–5.
13. Neoemova I, De Wachter S, Wuyts FL, et al. Reliability of the 24-h sensation-related bladder diary in women with urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:955–9.
14. Neoemova I, De Wachter S, Wyndaele JJ. Comparison of sensation-related voiding patterns between continent and incontinent women: A study with a 3-day sensation-related bladder diary (SR-BD). Neurourol Urodyn 2008;27: 511–4.

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Procedure

Technique for a hybrid system of real-time transrectal ultrasound with preoperative magnetic resonance imaging in the guidance of targeted prostate biopsy

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Abstract: Diagnostic magnetic resonance imaging (MRI) for prostate has achieved increasingly higher levels of accuracy. Because real-time MR-guided targeted biopsy is still a complicated and expensive procedure, there is considerable interest in a technique of MR/transrectal ultrasound (TRUS) hybridized image-guided biopsy. However, because the 3-D shapes of the prostate at the time of image-acquisition at preoperative MRI are likely to be different from the intra-operative TRUS images, the precise registration of each 3-D volume data is critical. To reduce the potential errors in registration of TRUS with MRI, we introduce new procedural techniques in a rigid image fusion technique. First, preoperative MR images were obtained with a specifically-made plastic outer-frame, with exactly the same shape as the real TRUS probe, placed in the rectum, in order to simulate the deformation of the prostate caused by the absence or presence of a TRUS probe during the acquisition of MR or TRUS images. Second, instead of using a single plane of longitudinal image, we applied biplane TRUS images to be shown in parallel on a multiplanar display with corresponding reconstructed MRI, in order to register both horizontal and longitudinal images of the prostate simultaneously, thereby achieving improved 3-D anatomical matching.

Key words: image registration, magnetic resonance imaging, prostate biopsy, prostate cancer, transrectal ultrasound.

Introduction

Although diagnostic magnetic resonance imaging (MRI) is accurate in the diagnosis of prostate cancer,[1–3] it is too expensive for urologists to use MR-guidance for lesion-targeted biopsy and intervention, because an interventional MR-system is costly and requires MRI-compatible non-metallic instruments and expertise.[4,5] Because the actual needle placement is regularly visualized by real-time transrectal ultrasound (TRUS), the recently emerging integration of TRUS with MRI is a highly attractive technology, especially for targeting the lesions detectable only by MRI.[6–10] The improvement of MR/TRUS hybrid technology would give us credible information to reclassify a MRI suspected lesion as a biopsy proven cancer lesion. In the present study, we proposed new techniques potentially improving registration in the hybrid system of TRUS with MRI.

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Technique

The present clinical study was authorized by the institutional review board of the Committee for Clinical Research on Human Subjects at our institution. After obtaining informed consent, 10 patients with elevated prostate-specific antigen and suspicious lesions on 3T-MRI underwent prostate biopsy. TRUS biopsy was carried out using the transperineal approach under local anesthesia with the hybrid technology of real-time virtual sonography (Hitachi Medical, Kashiwa, Japan), which allows real-time biplane TRUS images and corresponding multiplanar reconstructed MRI images to be shown in parallel on a display. Figure 1 shows the configuration of the hybrid system.

All MR images were obtained with a 3.0T clinical scanner (Gyroscan Achieva 3.0Tesla X-series; Philips, DA Best, the Netherlands) with a 5-channel phased array body coil before biopsy. In order to minimize the difference in deformation of the prostate with and without a TRUS probe, a specially-made plastic outer-frame for the TRUS probe was placed in the rectum during MR acquisitioning. The special plastic outer-frame is shown in Figure 2. Thus, the shape of the prostate in the preoperative MRI simulated a deformation similar to the prostate shape with the TRUS probe inserted in the rectum (Fig. 3).

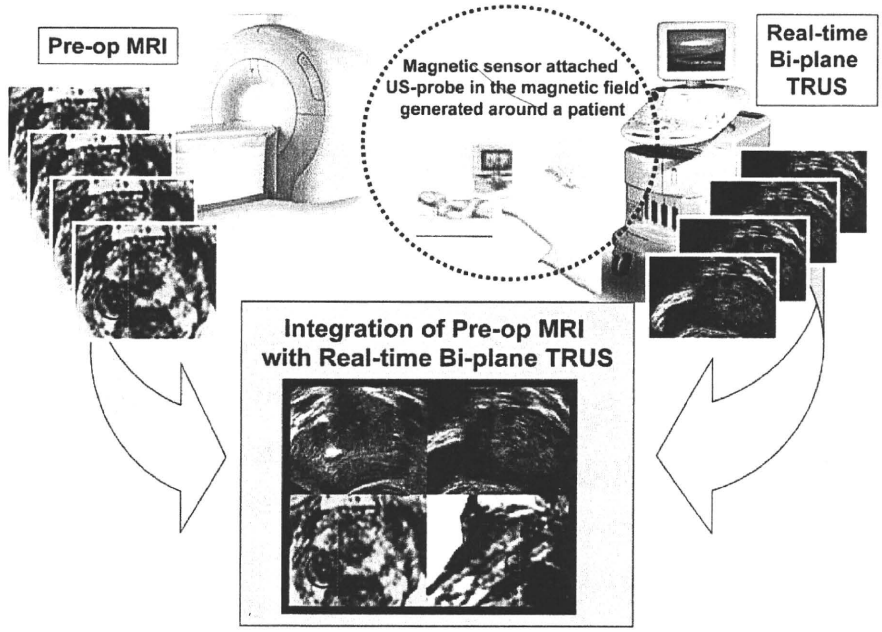

Fig. 1 Configuration of the hybrid system of real-time transrectal ultrasound (TRUS) with magnetic resonance imaging (MRI), which consists of (i) a magnetic field generator to be placed near the patient; (ii) an ultrasound (US) machine and TRUS-probe with a electromagnetic sensor (model 800 sensor; Ascension, Burlington, VT, USA) attached; (iii) a magnetic positioning sensor unit (3-D guidance trakSTAR; Ascension); and (iv) a computer workstation with display. The electromagnetic sensor, which is attached on the handling part of the TRUS probe, can communicate the position of the TRUS probe with the workstation in real-time. Pre-op, preoperative.

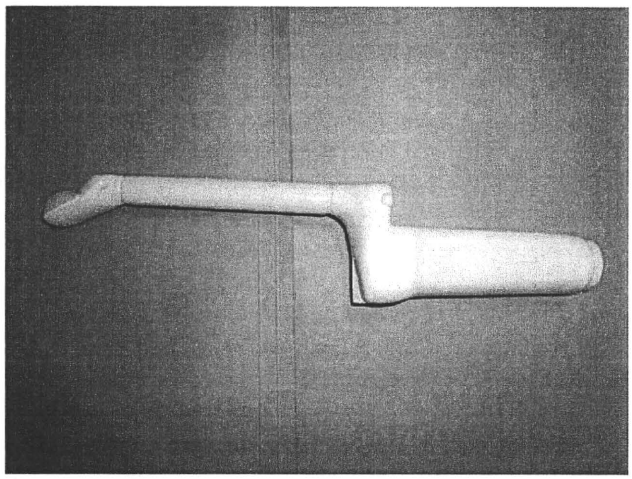

Fig. 2 The plastic outer-frame of the transrectal ultrasound (TRUS) probe, which consists only of plastic, and contains no metal, so as to be suitable for a magnetic resonance imaging (MRI) examination, in order to simulate the possible deformation of the prostate that might be caused by the presence or absence of a TRUS probe between TRUS and MRI.

The MRI volume data were transferred to the computer workstation by CD with Digital Imaging and Communication in Medicine data. Preoperative MR data sets were acquired and the data of the most informative functions were selected. The magnetic positioning sensor unit is connected to the workstation to obtain information on the spatial position and angle of the TRUS probe. The workstation can display two biplane vertical MR tomograms that are reconstructed according to the real-time information of the spatial position and angle of the TRUS probe.

Registration between the real-time biplane TRUS image and the reconstructed virtual MR images out of the previously acquired MR 3-D volume data was carried out with biplane image-to-image-registration. First, the midline longitudinal view, as well as the maximum prostatic horizontal view of the MR images, was obtained out of the MR 3-D volume data, using the multiplanar display function. This can visualize the entire urethra with the urethral orifice opened at the bladder neck in the midline longitudinal view and also the maximum horizontal tomogram of the prostate, respectively. Next, the TRUS probe was manipulated in order to make both longitudinal and horizontal ultrasound (US) images match the already obtained, corresponding longitudinal and horizontal tomograms of MRI, respectively. This combined use of biplane US images to match simultaneously both longitudinal and horizontal MR tomograms facilitated the 3-D spatial registration, instead of using a single longitudinal plane for image-to-image registration, which is likely to cause unsatisfactory matching in the horizontal direction.

If clinicians still find unsatisfactory matching between MR and TRUS, a further detailed re-adjustment function is still available, to match the ultrasonically well-recognized anatomical landmarks (such as the prostate boundary or transition zone boundary, calcification and the concerned lesion) with the corresponding anatomical landmarks in MRI. In the initial setting of MR volume data, the software has a function to highlight the targeted lesion by a red circle. According to the manipulation of the TRUS probe, the size of the red circle can be changed. Obtaining the exact plane with the highlighted red circle maximized in diameter shows the optimal plane for targeting the center of the lesion, and facilitates precise targeting, which potentially maximizes sampling of the cancer core length and/or percentage (Fig. 4).

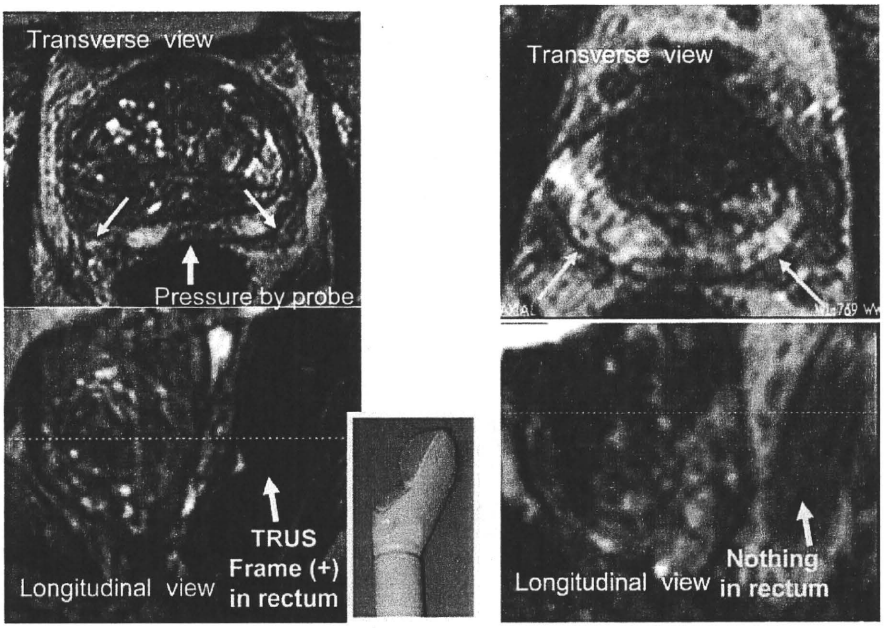

Fig. 3 Typical change in prostatic shape caused by the pressure of the presence (in the left case) or absence (in the right case) of the plastic outer frame of the transrectal ultrasound probe in the rectum. The top-part of the plastic outer frame is shown in the middle, as imaged in the left case, inserted in the rectum The prostatic deformation caused by the probe was typically evident in the posterior rim as well as the posterior-lateral edges of the prostate, as shown by the arrows.

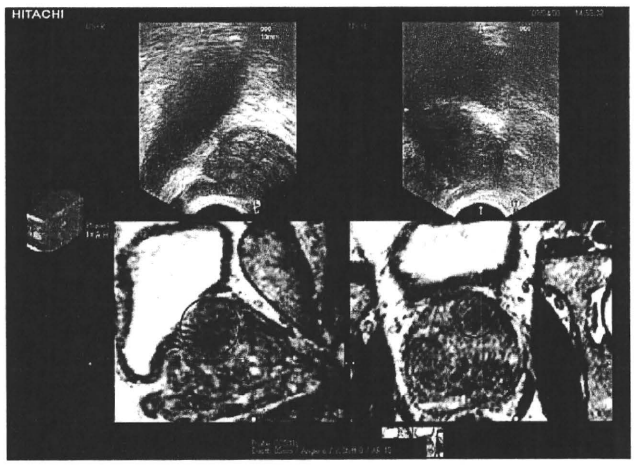

Fig. 4 The hybrid system allowed excellent anatomical visualization of biplane transrectal ultrasound and corresponding magnetic resonance imaging (MRI) image in parallel in the display, to visualize and navigate targeting to transition zone cancer foci (highlighted by red circle), which are detectable only in MRI. A white dotted line in each display of the longitudinal or horizontal MR view shows the line with which another plane (horizontal or longitudinal plane, respectively) is currently in accord.

Discussion

Two important techniques for registration of MRI with TRUS were proposed. One is to register image-to-image using biplane views, such as longitudinal and horizontal views of TRUS, with each MRI. Therefore, targeting to suspected lesions can be confirmed with greater confidence than in the use of a single longitudinal plane. Another new original technique is that we specifically made a plastic outer-frame for the TRUS probe (containing no metal) in order to insert it into the rectum at the time of MRI acquisition, to avoid the possible deformation caused with and without the TRUS probe. There is a critical issue of how to reduce the difference in the deformation of the targeted organ, which might happen between the different conditions at each image acquisition when we need to register the two imaging modalities.[9–12] In the present study, we found that the plastic outer frame of the TRUS probe, inserted at the MR acquisition, could minimize such possible deformation by simulating the condition at the TRUS biopsy. The pressure of the probe in the rectum is likely to cause typical deformation in the posterior-lateral parts of the prostate. It is conceivable that the achieved simulation of the possible differences between MRI and TRUS is essential for and would enhance the precision of the biopsy-targeting and targeted treatment, because cancer is likely to occur in such posterior-lateral parts of the prostate.

In conclusion, the study showed new technical procedures for the hybrid of biplane TRUS with MRI. The use of the hybrid system is available at a significantly lower cost, using regular metallic instruments (including the biopsy needle, automated biopsy equipment and the therapeutic ablative needle), and a currently clinically available MRI machine. The MR/TRUS hybrid system could play an essential role as the guidance tool for precise MR-detected lesion-targeted biopsy, as well as potentially enhancing the precision of targeted focal therapy.

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