きだせば，国立がんセンターはがん予防に積極的に乗りだすことになり，かつがん予防に関する国の中心的な拠点として，従来十分でなかった機能が強化されることになる。現在，その実現に向けて懸命に努力しているところである。

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Cancer Therapy & Host

癌治療と宿主

——別　刷——

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巻頭言

癌治療と遺伝子多型

垣添忠生

国立がんセンター総長

遺伝子多型，特に一塩基多型(single nucleotide polymorphism；SNP)は，ゲノム上のわずかな個人差に相当する．数百塩基対から1000塩基対に1カ所ほど存在し，全体ではひとりに数百万個はあるのではないかと推定されている．このSNPが，癌のかかりやすさ，抗癌剤の効果や副作用の出方などに関係している．したがって，SNPを解明することは，宿主ごとに対応した個別化した医療，いわゆるオーダーメード医療につながる可能性から，現在，癌だけでなく，糖尿病や高血圧といった生活習慣関連病も含め，熱い期待が寄せられ，研究が盛んである．

この，いわば個人の体質差を決める遺伝子解読を求め，2002年10月29日，ワシントンで開かれた日米英中加5カ国による国際会議で，国際共同研究として解読を進めることが合意されたという．日本は米国に次いで2番目に多い全体の25％の解読を分担する．2004年までに全体の90％の解読を目指す．重要な点は，その結果は公開し，特許の取得は考えないとのことで，SNPは人類の共通財産という整理がされたのだろう．

SNPの解読が進み，特定の癌や疾患との関係が明らかにされていくと，SNP情報の扱いには取り分け注意深い対応が必要である．個人がSNP情報による社会的差別を受けたりすることがないよう，個人情報の秘匿，解析にあたってのインフォームド・コンセントの重要性など，慎重な倫理的対応が求められている．

SNP情報がもっと集積されてくると，癌の診断も，治療も，予防も一変する可能性が高い．医療は，人類がかつて経験したことのない世界に入っていく可能性が高い．慎重かつ大胆な取り組みが望まれる．

がん分子標的治療

別刷

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メディカルレビュー社

Basic Science

早期診断法の開発と課題

Early detection of cancer

垣添　忠生
Tadao Kakizoe

国立がんセンター総長

Summary

がんの早期診断は，遺伝子診断や新しいマーカーの開発によるハイリスクの人たちの絞り込みと，画像診断の組み合わせで達成される。前者はゲノミクス，プロテオミクスなどの成果に期待される。後者は現状でもかなりの達成がなされているが，検診を前提とした場合，さらに被験者の負担と危険性が少なくて，精度の高い方法の開発が望まれる。

国立がんセンターでは，平成15年度中に，がん予防・検診研究センターを立ち上げるべく現在懸命な取り組みが進められている。このセンターは，がん検診実施部門，検診技術開発部門，がん情報部門，がん予防部門の４部門で構成され，がんの一次，二次予防に総合的に取り組む国の拠点と位置づけている。この活動の鍵の１つが早期診断法である。

Key words

●早期診断　●がん検診　●がん予防　●個別医療

はじめに

21世紀のがん診療の基本戦略は，キーワードで語ると「予防」,「治癒」,「個別医療」の3つだろうか。「予防」には，がんにならない，すなわちがんの一次予防と，がんになっても死なない，すなわち早期発見，検診を含めたがんの二次予防，のバランスのよい発展が重要である。「治癒」は，現在のがんの治癒率が大略50%であるのを，70〜80%に高めること，つまり，がんを克服し，人々ががんでは死ななくすること。「個別医療」は，がんの遺伝子診断などに基づき，1人1人の患者に最適の診療が行われることにより，治療後のQOLをできるだけ高く保つこと，を指す。

本特集では，私はこの3つのキーワードのいずれにも関係する「早期診断法の開発と課題」について記す。早期診断法の開発は，検診に最も深く関わるが，早期発見，早期治療を受けた人の大部分が救命されることから，治癒にも関連する。また，早期発見されたがんの治療の選択肢は多くなるため，患者の希望を生かした個別医療も可能となる。

Ⅰ 発がん過程の考察

ヒトの遺伝子は3〜4万個あり，そのうちがんに関連する遺伝子が300個ほどあるのでは，と考えられている。核内で，がん遺伝子の活性化，がん抑制遺伝子の不活化など，遺伝子異常が6〜8段階，つまり多段階に積み重なることにより，正常細胞ががん細胞に変わる，と考えられている。がん細胞が増殖して10^9個程度に達すると，直径約1cmの腫瘤となり，画像診断により臨床的に認識される存在となる。これがさらに大きく増殖すると，周囲臓器に浸潤したり，遠隔臓器に転移したりする。この過程がきわめてゆっくりと進むがん，普通の速度で進むがん，急速に進行するがん，おおよそこの3つの型に大別される。時間経過とがんの増殖を二次元で表現すると，図1のように模式化される。この過程に医療が介入するのは，予防，検診，診療，緩和医療が考えられる。早期発見が最も意味をもつのは，通常の速度で増殖するがんの場合である。きわめてゆっくり増殖するがんの場合や，潜在がんの場合には，がんを発見したことが患者に新たな問題を提起する場合もありうる。また，きわめて増殖速度の速いがんの場合には，早期発見自体が困難な状況も想定され，あっという間に緩和医療に達してしまう場合もある。それぞれの場合に，的確な対応が求められるが，個人ごとの遺伝子解析は，いずれこうした増殖速度の予測もできる可能性がある。また，画像診断技術の進歩により，発見される病巣の大きさがどんどんと小さくなり，直径1cm以下の病巣でみつかることもまれでなくなった。遺伝子異常の起こりはじめから，臨床的病巣の認識までの期間がさらに短縮されていく可能性がある。これは診断という観点からすると未知の領域である。

Ⅱ がん早期発見に向けた現在の取り組み

現在のがん検診の対象臓器と，その診断に使われている方法を列記しよう。胃がんに対しては，間接胃二重造影法，子宮頸がんに対しては擦過細胞診，大腸・直腸がんは便潜血反応，肺がんは胸部X線撮影と喀痰細胞診，乳がんは視触診によっている。前立腺がんに対しては，一部の熱心な医療機関が前立腺特異抗原

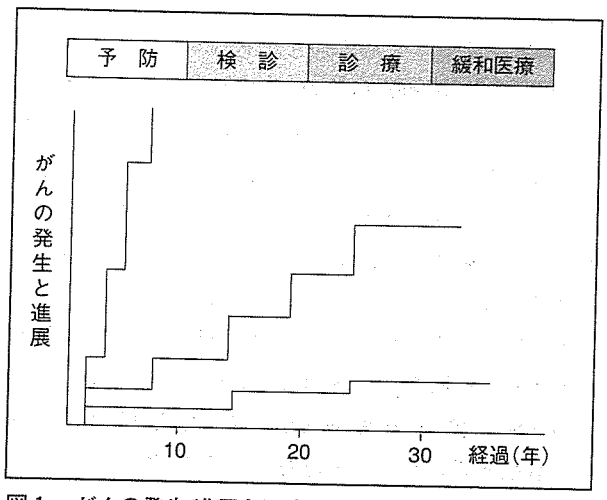

図1　がんの発生/進展と医療

(Prostate Specific Antigen；PSA)の血清診断を取り込んで研究的に進められている。このうち，胃がんに対する胃二重造影法，子宮頸がんに対する擦過細胞診，大腸・直腸がんに対する便潜血反応の有効性は，国際的にも認められている。肺がんに対する胸部X線撮影と喀痰細胞診の有効性は，わが国には有効とする報告が多いが[1]，国際的にはMayo Lung Program[2]以来，その有効性については懐疑的である。乳がんに対する視触診あるいは自己検診に関しては，最近，有効性は証明されなかった，とする大規模な臨床試験の結果が報告されている[3]。多くの国で50歳以上の女性に乳房撮影(Mammography；MMG)が取り入れられており，MMGの有効性が証明されている。前立腺がんに対するPSAの有効性は依然として激しい議論の対象とされている。

Ⅲ がん早期診断が意味するもの

がんの発見が遅すぎては，検査を受ける意味がないことは明らかである。一方，ヘリカルCTによる肺がん検診で経験しているように，あまりに早く，小さい病変をみつけても，それががんか否かを鑑別するのが難しい，という問題が起こる。つまり，がんの早期診断といっても，実は適時診断することが重要である。この視点をもちながら，がん早期診断技術の開発について述べる。この場合，考えなければならない因子としては，目的の点からすると，検診を前提とする場合と，診療を前提とする場合とがある。さらに，技術的にみると，画像診断法の開発と，遺伝子診断，マーカー診断法の開発がある。この4つの因子の組み合わせから考えると，遺伝子診断，マーカー診断によって被験者を絞り込み，画像診断により確定診断を得る。これは検診の場合も，診療の場合も変わらない。検診の場合は，集団検診であれ，個別検診であれ，無症状の人を対象とするのが普通だから，被験者に苦痛を与えたり検査に危険を伴うものは極力避けなければならない。医療を求めて医療機関を受診した人が対象であれば，有症状で，しかも治療を求めてきている人が対象だから，多少の危険性は事前にきちんとした説明を加えれば，インフォームド・コンセントは得られるはずである。

ここでは，主に検診を前提としたがんの早期診断について触れることにしたい。これは，現在新規のがん患者の約50%が亡くなっているが，その内容をよくみてみると，そのうちの半数は，もう少し早く受診していたら，つまり発見がもう少し早かったら何とか対応できた，と考えられる。現在，私どもはその詳細を検討中である。この人たちに対する検診の重要性が，がん治療成績の向上を求める最も大切な，具体的目標としてとりあげることができる。ちなみに，残る半数がいわゆる難治がんで，膵がんやスキルス胃がんなどがその代表である。これらのがんの治療成績を向上させるには基礎研究がきわめて重要で，研究所と，さらには企業との共同研究をダイナミックに展開する必要がある。

Ⅳ 各臓器がんの早期診断法の開発

1．食道・胃がん

胃の二重造影法による胃がんの発見率は，約0.1%である。二重造影法に代わって，細径内視鏡を使って観察のみを実施し，生検は行われない方式を検診として導入した場合，これによって発見される胃がんの率は約0.3%と想定されている。

2．乳がん

MMGを中心とするが，乳房の大きい人の場合，MMGと超音波検査の組み合わせが乳がんの発見に有効だった例がある。MMGのコンピュータによる自動診断が画像の一次スクリーニングとして導入される可能性もある。

3．肝胆膵がん

造影CT検査と超音波検査の組み合わせが最も有効な検査法であるが，検診に造影CTを導入するのは造影剤過敏症の可能性から問題がある。とりあえずは肝胆膵を超音波でスクリーニングすることから始めるのが妥当と思われる。

4．肺がん

マルチスライス・ヘリカルCTを使用して短時間に全肺をスキャンするのが有効と思われる。「東京から肺がんをなくす会」のデータによると，ヘリカルCTの導入によりⅠ期肺がんの発見率が飛躍的に増加することが示されている[4]。問題は，がんと鑑別の難しい小病変が多数描出されることで，このスクリーニングのためにコンピュータを利用した自動画像診断をとり込む必要も生じよう。二次スクリーニングを専門医が行う体制をとらないと，画像の量からいって対応不可能な状況がすぐに生まれることが予測される。すでに，十分に精度の高いコンピュータ・システムがつくられつつあると聞いている。

5．子宮頸がん

子宮頸部細胞診の有効性は確立済みであり，当面はこれで進むことになる。しかし，検体の採取が被験者にとって必ずしも快いものではない，という観点からすると，新しい検査方式の開発が望まれている領域である。

6．子宮体がん，卵巣がん

子宮体がんは日本で増加しつつあり，その診断に内膜肥厚を指標としたMRI診断の導入を考えている。MRIを実施するなら同時に卵巣の腫瘤性病変の有無を診ることも，当然研究として実施することになる。

7．大腸・直腸がん

内視鏡検査か注腸検査の選択ができる体制を考えている。これは検査手段の被験者への負担が必ずしも軽くないからである。

8．前立腺がん

PSAによる血清診断を行い，異常者は生検で精検する方式をとることになる。

Ⅴ がん予防・検診研究センター

国立がんセンターは創立以来，今年で40年を迎えた。当初より，その使命として診療，研究，研修に取り組み，多くの成果をあげてきたと自負している。最近はこれに，情報発信も加え，懸命に取り組んできた。

従来，がん予防，一次予防と二次予防に関しては，研究所で一次予防に関する基礎研究が進められてきたが，国立がんセンター全体としての予防に関する取り組みは必ずしも十分ではなかった。現在，この実現に向けて，わが国が取り組むべき戦略上の重要目標と位置づけ努力している。

まず，わが国のがんの実態の正確な把握で，これがすべての出発点である。国のがん予防の拠点にこの情報が集約されるシステムを作る必要がある。この情報が行政や医療従事者，国民に自由に使われることが望ましい。次に，がんの一次予防について，許可を得て生活習慣情報とゲノム情報を得た集団，あるいはハイリスクの人たちを対象とした化学予防の取り組み，行動科学的研究が想定される。二次予防については，5000人規模の集団を対象として，最新の手法を使ったがん検診の研究的実施が必要である。食道・胃がんは内視鏡で，乳がんはMMGと乳房超音波検査の組み合わせで，肝胆膵は腹部エコーで，肺がんはヘリカルCTで，子宮頸がんは細胞診で，体がん，卵巣がんはMRIで，大腸は注腸または内視鏡で検診することを考えている。これら全コースを受診した人に，オプションとしてPETを組み込んで検診におけるPETの意味の評価も行う。これらの集団は前述したようにあらかじめ同意を得て，生活習慣を分析し，ゲノム解析し，その後のフォローアップで発見されるがんとの関係を対比することにより，理想的ながん検診の研究を進める。また，検診技術をより苦痛が少なくて，精度の高いものにするべく，新しい技術開発が必要で，これは企業と共同研究を進めることになる。以上の業務を進めるには，がん検診実施部門，検診技術開発部門，がん情報部門，がん予防部門の4部門が必要である。すでに，国立がんセンター内にこのような目的で，がん予防・検診研究センターを設ける必要があることを検討会の答申としていただいている。また，この答申に沿って，平成14年度補正予算にて建物整備の予算化が行われている。このセンターが首尾よく動き出せば，国立がん

センターはがん予防に積極的にのり出すことになり，かつがん予防に関する国の中心的な拠点として，従来十分でなかった機能が強化されることになる。現在，その実現に向けて懸命に努力しているところである。

おわりに

早期診断法の開発と課題を，検診とからめて，その全体像に関する考えを述べた。新しい診断技術の開発と，その実践，評価，全国展開と，やらなければならない課題は山積みである。諸賢のご批判，ご支援を仰ぎながら最善を尽くしたい。

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Review

Reconstruction of the urinary tract after cystectomy for transitional cell carcinoma of the bladder

By

Tadao KAKIZOE

Review

Reconstruction of the urinary tract after cystectomy for transitional cell carcinoma of the bladder

By Tadao KAKIZOE

National Cancer Center, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045
(Communicated by Takashi SUGIMURA, M. J. A., Sept. 12, 2003)

Abstract: Transitional cell carcinoma (TCC) in the urinary tract is characterized by the development of multiple tumors in time and space. When cystectomy is performed, urinary tract is reconstructed by various options including a neobladder using patient's own intestine anastomosed to the urethra. This procedure assures normal voiding from the urethra even after cystectomy. Use of the urethra for preserving urethral voiding and function of a neobladder are reviewed from viewpoints of carcinogenesis and quality of life after cystectomy. Incidence of subsequent urethral cancer arising after cystectomy is relatively high, however, if high risk patients are appropriately excluded, a neobladder can be constructed safely from the oncologic standpoint and patient's quality of life.

Key words: Bladder cancer; renal pelvic cancer; ureteral cancer; urethral cancer; urinary diversion; neobladder.

Introduction. Mucosal surface of the urinary tract, i.e., renal pelvis, ureter, bladder and the greater part of the proximal urethra, is covered with urothelium or transitional cell epithelium being composed with three to seven cell layers thick.[1] Typical structure is composed with basal cells, intermediate cells and superficial cells. Superficial cells have the binucleated, flat, large characteristic shape being called umbrella cells.[1] Luminal surface of the umbrella cells is covered with asymmetric unit plasma membrane which is effective to protect the tissue from high osmotic pressure of the urine.[2]

More than 90% of cancers arising in the urinary tract are transitional cell carcinomas (TCC), the rest are squamous cell carcinomas and adenocarcinomas. Multiple tumor development in the entire urinary tract in time and space is a well-known biological phenomenon of TCC, particularly in the bladder.[3] Ureteral and urethral involvement of TCC needs serious consideration when cystectomy is necessary and urinary reconstruction is indicated. This phenomenon is explained as a result of "field cancerization"[4)-7)] in which the entire urothelium from the renal pelvis to the urethra is susceptible to carcinogens flowing down in the urine. On the other hand, TCC cells can be implanted to other sites of the urothelium,[8] so called "implantation". These two mechanisms make it difficult to determine whether a recurrent tumor represents an inadequately treated initial one, or implantation of cancer cells, or the effects of multifocal carcinogenesis. Molecular analysis of multiple cancers in the bladder or multiple cancers developed in the upper urinary tract and the bladder tells us as one possibility that those multiple cancers are monoclonal origin indicating the implantation of cancer cells from the original tumors.[9)-12)] It is likely that all of these mechanisms are relevant. In fact, Akaza *et al.*[13] reported the biphasic pattern of recurrences of the bladder cancers after transurethral resection (TUR), which may indicate the combination of early implantation and late new growth.

Urinary reconstruction after cystectomy has been conducted historically by uretero-sigmoidostomy, ileal conduit, cutaneous continent reservoir requiring self-catheterization and an orthotopic neobladder anastomosed to the urethra. An orthotopic neobladder assures normal voiding from the urethra. Each procedure has relation to cancer development in the reconstructed

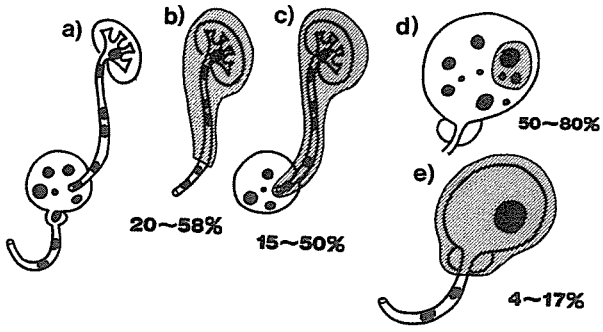

Fig. 1. Schematically illustrated multiple development of cancers in the urinary tract. The extreme left a) indicates a case having renal pelvic, ureteral, bladder and urethral cancers simultaneously. b) When ordinary nephrectomy is performed for the renal pelvic and/or ureteral cancer, subsequent ureteral cancer in the remaining ureter is 20-58%. c) Even though total nephroureterectomy is performed, subsequent bladder cancer occurs in 15-50%. d) When superficial bladder cancers are resected by transurethral procedure, subsequent bladder cancers arising in the normal appearing bladder mucosa are 50-80%. e) After complete removal of the bladder and prostate, incidence of subsequent urethral cancer is 4-17% (Ref.3)).

urinary tract.

In this review, urinary reconstruction will be discussed in relation to cystectomy from the standpoints of multiple, tumor development in the entire urinary tract and the function of a neobladder.

Carcinogenesis in the urinary tract. *Characteristic patterns of transitional cell carcinoma (TCC).* TCC can be classified as papillary carcinoma, nodular carcinoma and carcinoma *in situ* (CIS) according to their gross and microscopic configuration. Papillary carcinomas usually develop in multiple forms and frequently recur elsewhere, however, these tumors usually remain superficial confining to the mucosal layer, and the prognosis of patients, even treated conservatively, is generally fair. On the other hand, nodular carcinomas are usually deeply invasive when first observed, and the clinical outcome, even after cystectomy, is poor. CIS is a flat lesion with or without reddy velvet-like appearance of the mucosal surface, and although initially CIS is confined to the mucosal layer, CIS easily starts to invade to the submucosal or deeper muscular layer. TCCs are a mixture of these three basic patterns.[15]

Multiple development of TCC in the urinary tract. Multiple development of TCC in the entire urinary tract has been well documented. For example, renal pelvic, ureteral, bladder and urethral cancers are sometimes observed in a single case (Fig. 1a). When ordinary nephrectomy is performed for the renal pelvic and/or ureteral cancer, TCC arising in the remnant ureter, i.e. about one third of the lower part of the ureter, is reported in 20-58% (Fig. 1b). Consequently, the established state of the art operation for TCC of the renal pelvis and/or ureter is total nephroureterectomy indicating removal of the kidney, total ureter with resection of the small part of the bladder. Even such an operation is performed, however, a 15 to 50% incidence of subsequent TCC in the bladder is reported (Fig. 1c). When superficial papillary TCC of the bladder is treated by transurethral resection (TUR), the subsequent development of tumors having a similar nature in the normal-appearing bladder mucosa is reported to be 50-80% (Fig. 1d). After cystoprostatectomy (removal of the bladder and prostate) for bladder cancer in men, a 4-17% incidence of cancer in the remaining urethra is reported[16] (Fig. 1e). In female patients, involvement of the urethra in relation to bladder cancer is reported to be 1.4-36%.[17]

Table I. Pathological findings of the subsequently and concurrently resected urethras

	No. Cases
Subsequently resected urethra	
Coexistence of papillary and *in situ* ca	3
Ca *in situ*	5
Papillary ca	3
Invasion to the corpus spongiosum and cavernosum	7
Concurrently resected urethra	
No cancerous tissue	17
Small foci of ca in the corpus spongiosum	1
Small area of dysplasia	1

These data should be taken into consideration when we perform nephroureterectomy (removal of the kidney and ureter) or cystectomy and for the follow-up plans of the upper and lower urinary tract and the contralateral urinary tract assuming them as a single unit from the renal pelvis to the urethra.

Selection of urinary reconstruction in relation to carcinogenesis. When a patient is indicated for cystectomy as the treatment of invasive bladder cancer, basically three different options of selecting 1 of 3 types of urinary reconstruction are provided to the patients and families as information: (1) an ileal conduit, (2) a cutaneous continent reservoir requiring self-catheterization, or (3) an orthotopic neobladder anastomosed to the urethra to ensure urethral voiding. Presently, type (2) is not commonly used because patients do not choose this type of reconstruction mainly because type (2) seems to be intermediate of types (1) and (3). From the carcino-

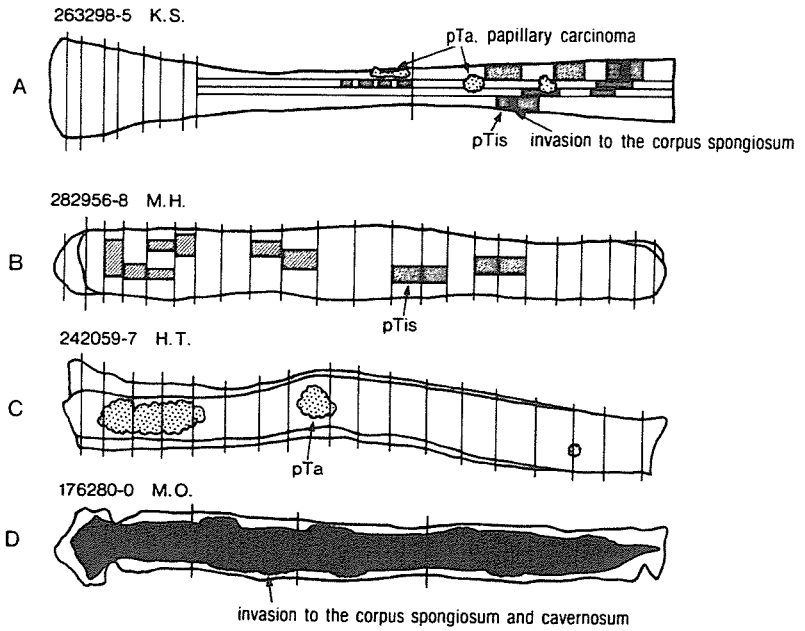

Fig. 2. Typical pathological findings in the resected urethra. Prostatic side is at left and meatus of urethra is at right side. Each specimen was examined by vertical or horizontal sections as indicated (Ref. 18). pTis indicates carcinoma *in situ* on the surface of the urethral mucosa. pTa indicates papillary superficial cancer without submucosal invasion.

geneic standpoint, an orthotopic neobladder anastomosed to the urethra is the biggest issue to be discussed. In male bladder cancer patients, urethral recurrence of TCC after cystoprostatectomy is reported to be 4-17% (Fig. 1e). In our series of patients analyzed by Tobisu *et al.*,[18] of 169 male patients who underwent cystectomy for bladder cancer, 18 (10.6%) demonstrated subsequent urethral cancer within 5 years after cystectomy. Risk factors for subsequent urethral cancer were analyzed in terms of the grade, stage, number, size, location and gross pattern of bladder cancers in the cystectomized specimens. Significant risk factors in bladder cancer relevant to the later development of cancer in the retained urethra were papillary cancers, multiple cancers, and tumors in the bladder neck, prostatic urethra and prostatic gland. On the other hand, 19 patients with concomitant CIS and/or multiple tumors in the bladder compatible to the above-mentioned risk factors underwent simultaneous prophylactic urethrectomy with cystectomy in the same observed period. Of them, 17 (89%) of 19 had no pathological lesion in the resected urethra (Table I). As is indicated in Fig. 2, pathological findings observed in the urethra subsequently resected after cystectomy were versatile but the urethra simultaneously resected with cystectomy exhibited almost no pathological lesions. Possible reason to explain this extreme difference may be that the urine stream is preserved in the latter cases until simultaneous removal of the bladder, prostate and urethra (cystoprostatourethrectomy). To support this hypothesis, urethral cancer development is not commonly observed and is not a serious problem for patients who undergo repeated TUR for multiple, frequent recurrences in the bladder. This hypothesis together with above mentioned risk factors for urethral cancer development in relation to bladder cancer supports our idea to reconstruct the urinary tract by anastomozing the neobladder to the urethra. Regarding urethral cancer after cystectomy, male patients are carefully analyzed, however, the incidence and characteristics of urethral involvement in female patients with bladder are not well documented. One reason for the very few amount of data may the principle of routine urethrectomy together with cystectomy is well established in female patients because the female urethra is short and easy to remove with the bladder. A 1.4% incidence of urethral involvement was observed during follow-up cystoscopy in 293 female patients with bladder cancer.[19] A few studies of bladder cancer were reported urethral involvement in cystourethrectomy specimens.[20),21] We reviewed 47 consecutive step-sectioned cys-

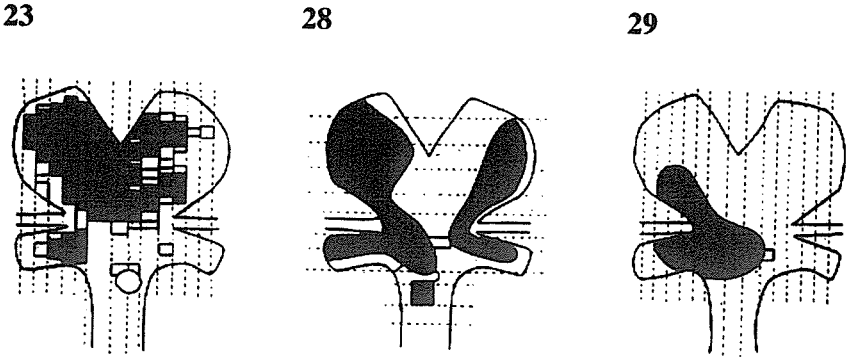

Fig. 3. Urethral involvement in 47 cystourethrectomy specimens in female bladder cancer (Ref.17)). Bladders are sagittally opened and lower part of the diagram indicates the urethra.

tourethrectomy specimens of bladder cancer in female patients to determine the incidence and characteristics of bladder cancer with the involvement of the urethra.[17] Of the 47 cases, 10 (23%) were papillary, 9 (21%) papillonodular that is intermediate between papillary and nodular carcinoma and 18 (42%) nodular carcinoma, and 6 (14%) primary or secondary CIS. There were 23 cases (54%) of invasive carcinoma of more than stage pT1 and 27 (63%) were grade 3 lesions. Urethral cancer was observed in only 3 cases (Fig. 3): 1 stage pT4, grade 3 papillonodular carcinoma developed widely in the bladder and, overriding the bladder neck and proximal urethra, stage pTa, grade 2 papillary cancer, was detected, while in 2 with nodular invasive lesions of the bladder including bladder neck, urethral cancer was detected either as a direct invasive extension via urethral CIS or as an intralymphatic spread without urethral mucosal change. These findings indicate the necessity for prophylactic urethrectomy in cases of papillary or papillonodular carcinoma encroaching on the bladder neck, and nodular invasive carcinoma infiltrating the bladder neck and trigone. Based on those analyses, by only removing the bladder, we successfully treated the first female bladder cancer patient by a neobladder anastomozing to the retained urethra.[22] Later, a large series of orthotopic neobladder for female bladder cancer patients including our series of patients were reported.[23]

Ureteral involvement in association with bladder cancer such as in a manner of spread of CIS is well documented. Consequently, it is a routine to examine the proximal end of the ureters by frozen section during cystectomy whether there is any CIS or cancerous lesions in the cut end of the ureters. Margin-free ureters must be used for ileal conduit or various forms of neobladder. In addition to this, when urinary tract is reconstructed after cystectomy via ileal conduit or neobladder, the incidence of appearing subsequent cancers in the remaining renal pelvis and/or ureter is reported to be 2-4%.[24] Bilateral involvement of the renal pelvis and ureter (synchronous or metachronous) occurs in 2-5%[25] of sporadic cases. Although the possibility is low, we have to be careful and always bear in mind this possibility.

Reconstruction of the urinary tract after cystectomy. Reconstruction of the urinary tract, particularly after cystectomy, must be planned from the two points, i.e., carcinogenic nature of remaining urinary tract, and postoperative function of the urinary tract and quality of life (QOL) of patients.

History. In 1852, Simon[26] performed the first continent urinary diversion in a patient with ectopic bladder using ureterorectal anastomosis. In 1911, Coffey[27] reported a physiologic implantation of the ureters to the sigmoid colon and in 1913, Lamoine[28] reported the first use of the true rectal bladder i.e., implanting both ureters to the rectum using the rectum as a bladder. Since 1913 ureterosigmoidostomy, implanting both ureters to the sigmoid colon, has been utilized as a major means of continent urinary diversion. With increased clinical experience, problems associated with ureterosigmoidostomy, such as recurrent pyelonephritis due to ureteral reflux, hyperchloremic acidosis, and the possibility of later colonic cancer development,[29] have become apparent. Development of mainly adenocarcinoma, occasionally TCC has been reported near the site of anastomosis between the ureters and sigmoid colon. Leadbetter[30] reported 45 cases arising cancer after ureterosigmoidostomy during 50 years. Physical irritation by fecal stream is thought to be one reason and the risk of developing this sort of cancer in patients who underwent ureterosigmoidostomy is 500 times higher than nor-

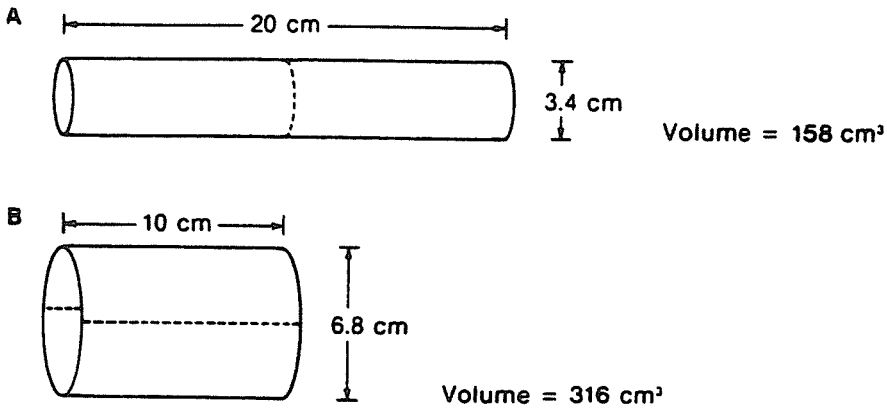

Fig. 4. Comparison of calculated capacities of (A) an intact 20 cm tube having 3.4 cm diameter and of (B) same segment opened lengthwise and folded upon itself (Ref. 38)).

mal controls.[31] This risk is evaluated as 5% for 6-50 years after ureterosigmoidostomy. Hydronephrosis appearing in patients who underwent ureterosigmoidostomy must be carefully checked bearing in mind the possibility of carcinoma near the ureteral anastomoses. In 1950, Bricker[32] first reported reconstruction of the urinary tract using an ileal conduit. This technique is widely accepted as the major procedure for urinary tract reconstruction. In 1951,[33] Couvelaire reported the first clinical use of bladder substitution, a kind of neobladder from the present meaning, through an anastomosis of the isolated ileum to the urethra. In 1985, Camey[34] used an isolated U-shaped ileum anastomosis to the urethra as a continent urinary diversion in more than 150 patients. Unfortunately, nocturnal incontinence due to increased pressure of the ileal segment resulting from ileal peristalsis occured. For a long time this type of procedure was used sporadically. In 1982, Kock *et al.*[35] reported on their pioneering use of a detubularized ileal segment i.e., opening the lumen of ileal tube and to use it as a ileal plate, a continent reservoir. With this breakthrough, an almost explosive interest in continent urinary reconstruction using cutaneous and urethrally anastomosed forms occurred throughout the world.

Theoretical considerations. The neobladder procedure involved postcystectomy construction using a segment of the patient's own intestine to form a new almost natural-like bladder. Ideally this neobladder must achieve high compliance, i.e., low pressure in neobladder, continence, and nonrefluxing reservoirs that allow adequate capacity and preservation of upper urinary tract function. The purpose of bladder replacement with an internal reservoir is not to improve survival of patients after cystectomy for bladder cancer but to improve quality of life. The status of continence and upper urinary tract function are evaluated by a normal micturition pattern, 24-hour continence, serum creatinine levels, and intravenous pyelography. QOL and functional comparison among various procedures of urinary tract reconstruction[36),37] have been reported.

The basic principles of a neobladder, including configuration of reservoir, accommodation, viscoelasticity and contractility have been thoroughly reviewed by Hinman[38] from the standpoints of physics, mathematics, and hydraulics. The configuration, and studies of the volume of the reservoir (height × radius^2) showed that the detubularized, folded pouch had almost twice the volume of the original ileal segment (Fig. 4). Interestingly, accommodation, volume to mural tension and viscoelasticity or compliance depend on the physical characteristics of the reservoir wall, and contractility depends on the motor functions of the bowel.

The clinical success of a neobladder is principally related to its reservoir geometry. The selected bowel segments are opened (detubularized) along the antimesenteric border and refashioned into various shapes, such as a U, S, M or W resembling to the shape of alphabet. Different reservoir shapes produce different characteristics in length and location of selected bowel, radius, and volume of the reservoir.

Quality of life after reconstruction of the urinary tract. Ileal conduit is the time-honored procedure since 1950[32] and significant number of patients underwent this surgery all over the world. In principle, this surgical procedure needs to apply urine-collecting pouch to the stoma where the distal end of ileal conduit is anastomosed to the skin. This pouch must be changed to the new one every 5 to 10 days. Patients must discard the

urine from pouch when it is full, 5-6 times a day. If the urine extravasates to the space between the stoma and pouch, severe dermatitis around the stoma occurs. Unexpected urine leakage may sometimes occur from the stoma. Renal pelvic stones may arize. These are the main clinical issues associated with ileal conduit. With neobladder, when successfully constructed, patients can enjoy almost normal life by voiding the urine from the urethra even after cystectomy. However, this procedure is relatively new compared to ileal conduit, we have only 10 to 15 years observation period after construction. About 10-15% of patients suffer from incontinence, particularly while sleeping, and approximately 10-15% of patients cannot void necessitating intermittent self-catherization indicating to introduce a catheter from the urethra to the neobladder. As a long-term sequelae, stone formation in the neobladder is known and hyperchloremic acidosis by absorbing the electrolytes in the urine stored in the neobladder, or excretion of calcium resulting in osteoporosis, particularly elderly female patients are also known. Consequently, both procedures have characteristic merits and demerits, respectively.

In summary, urinary reconstruction after cystectomy should be considered from the carcinogenic standpoint and the function of reconstructed urine flow route.

As was stated earlier, the variety of cancerous changes observed in the 18 patients with urethral recurrence is in sharp contrast to the simultaneously resected urethras of 19 patients with almost no cancerous changes (Table I, Fig. 2). The shedding of cancer cells from malignant urethral tissue by urine flow appears to be an important mechanism when considering the very low incidence of urethral recurrence in the large numbers of patients who undergo repeated transurethral resections for multiple papillary bladder cancers (unpublished). Shed bladder cancer cells spilled in the urethra during cystectomy procedure are left intact in the remnant urethra because there is no urine flow after cystectomy. They are harvested in the urethra during the months or years after cystectomy. This mechanism may explain the difference shown in Table I. In addition, recent molecular evidence[9)-12)] indicates that the implantation of cancer cells may provide an explanation for the multiple development of TCC in the urinary tract.

For a support of this hypothesis, we are seeking molecular evidence to prove the same molecular changes in the bladder cancer and the urethral cancer. However, we are so far unsuccessful to obtain appropriate specimens to analyze. Should this be the case, subsequent urethral cancer development may not be a hindrance to neobladder construction when patients at high risk for urethral cancer are excluded.

Conclusion. Urinary reconstruction after cystectomy for bladder cancer has a long history. Modern surgical technique revolutionalized the procedure of reconstructions using patient's own intestine for a neobladder. Theoretical consideration must be added to construct the neobladder from the standpoints of the function of neobladder, selection of the bowel, shape and size of the reservoir in terms of length and radius. At the same time, when neobladder is anastomosed to the urethra to assure voiding from the urethra after cystectomy, carcinogenic risk factors of developing subsequent cancers in the urethra both in male and female patients must be seriously considered. In this respect, contribution from Japan was great as was reviewed in this article. QOL and cure of the disease are two most important factors when cystectomy is indicated for a patient with bladder cancer. Highest QOL and/or function of the neobladder and the lowest risk of the subsequent carcinogenesis must be compromised reasonably for each patient.

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Phase I Study of Autologous Tumor Vaccines Transduced with the GM-CSF Gene in Four Patients with Stage IV Renal Cell Cancer in Japan: Clinical and Immunological Findings

Kenzaburo Tani,[1,2,*] Miyuki Azuma,[3] Yukoh Nakazaki,[1,2] Naoki Oyaizu,[1] Hidenori Hase,[1] Junko Ohata,[1] Keisuke Takahashi,[1] Maki OiwaMonna,[1] Kisaburo Hanazawa,[4] Yoshiaki Wakumoto,[4] Kouji Kawai,[5] Masayuki Noguchi,[5] Yasushi Soda,[1] Reiko Kunisaki,[1] Kiyoshi Watari,[1] Satoshi Takahashi,[1] Utako Machida,[1] Noriharu Satoh,[1] Arinobu Tojo,[1] Taira Maekawa,[1] Masazumi Eriguchi,[1] Shinji Tomikawa,[1] Hideaki Tahara,[1] Yusuke Inoue,[1] Hiroki Yoshikawa,[1] Yoshitsugu Yamada,[1] Aikichi Iwamoto,[1] Hirofumi Hamada,[6] Naohide Yamashita,[1] Koh Okumura,[7] Tadao Kakizoe,[8] Hideyuki Akaza,[5] Makoto Fujime,[4] Shirley Clift,[9] Dale Ando,[9] Richard Mulligan,[10] and Shigetaka Asano[1]

[1]*Advanced Clinical Research Center, The Institute of Medical Science, University of Tokyo, Tokyo 108-8639, Japan*
[2]*Department of Advanced Molecular and Cell Therapy, Division of Molecular and Clinical Genetics, Department of Molecular Genetics, Medical Institute of Bioregulation, Kyushu University, Fukuoka 812-8582, Japan*
[4]*Department of Urology* [7]*and Department of Immunology, Juntendo University School of Medicine, Tokyo 113-8421, Japan*
[5]*Department of Urology, University of Tsukuba School of Medicine, Ibaraki 305-8575, Japan*
[3]*Department of Molecular Immunology, Division of Oral Health Sciences, Graduate School, Tokyo Medical & Dental University, Tokyo 123-8519, Japan*
[6]*Department of Molecular Medicine, Sapporo Medical University, Sapporo 060-8556, Japan*
[8]*Department of Urology, National Cancer Center Hospital, Tokyo 104-0045, Japan*
[9]*Cell Genesys, Inc., South San Francisco, CA 94080, USA*
[10]*Division of Molecular Medicine, Children's Hospital, Department of Genetics, Harvard Medical School, Boston, MA 02115, USA*

**To whom correspondence and reprint requests should be addressed at the Department of Advanced Molecular and Cell Therapy, Division of Molecular and Clinical Genetics, Department of Molecular Genetics, Medical Institute of Bioregulation, Kyushu University, 3-1-1, Maidashi, Higashi-Ku, Fukuoka-shi, Fukuoka 812-8582, Japan. Fax: 81 92 642 6444. E-mail: taniken@bioreg.kyushu-u.ac.jp.*

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We produced lethally irradiated retrovirally GM-CSF-transduced autologous renal tumor cell vaccines (GVAX) from six Japanese patients with stage IV renal cell cancer (RCC). Four patients received GVAX ranging from 1.4×10^8 to 3.7×10^8 cells on 6 –17 occasions. Throughout a total of 48 vaccinations, there were no severe adverse events. After vaccination, DTH skin tests became positive to autologous RCC (auto-RCC) in all patients. The vaccination sites showed significant infiltration by $CD4^+$ T cells, eosinophils, and HLA-DR-positive cells. The kinetic analyses of cellular immune responses using peripheral blood lymphocytes revealed an enhanced proliferative response against auto-RCC in four patients, and cytotoxicity against auto-RCC was augmented in three patients. T cell receptor β-chain analysis revealed oligoclonal expansion of T cells in the peripheral blood, skin biopsy specimens from DTH sites, and tumors. Western blot analysis demonstrated the induction of a humoral immune response against auto-RCC. Two of the four patients are currently alive 58 and 40 months after the initial vaccination with low-dose interleukin-2. Our results suggest that GVAX substantially enhanced the antitumor cellular and humoral

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immune responses, which might have contributed to the relatively long survival times of our patients in the present study.

Key Words: GM-CSF, renal cell cancer, $CD4^+$ T cell, $CD8^+$ T cell, T cell repertoire

INTRODUCTION

Each year, approximately 3000 people die of renal cell cancer (RCC) in Japan [1]. Conventional treatments, such as surgery, chemotherapy, radiotherapy, and cytokine therapies, have not been established for stage IV RCC. Approximately 25% of RCC patients have metastatic disease at the time of diagnosis, and RCC sufferers have a reported 2-year survival rate of less than 20% [2]. As RCC is considered an immunogenic tumor, various types of antitumor immunotherapy have been reported that use cytokines, such as interleukin-2 (IL-2) and interferon-α; cell therapy with LAK; or nonmyeloablative stem cell transplantation. As all of these therapies have their limitations, the introduction of more specific antitumor immunotherapy with less toxicity is required [2–8].

Granulocyte–macrophage colony-stimulating factor (GM-CSF)-secreting cancer cell vaccines, which are generated from cancer cells by *ex vivo* gene transfer, have been shown to elicit tumoricidal antitumor immune responses in a variety of animal models and in human clinical trials [9–11]. Irradiated GM-CSF-secreting cancer cell vaccines are thought to induce antitumor immune responses by recruiting antigen-presenting cells, such as dendritic cells (DCs), to the site of immunization. DCs, which are the most potent immunostimulatory antigen-presenting cells, are known to activate antigen-specific $CD4^+$ and $CD8^+$ T cells, by priming them with oligopeptides that are processed from the lethally irradiated dying cancer cells. The antitumor immune reaction induced by GM-CSF-transduced tumor cells has been reviewed previously [11].

Since the initial clinical report on the use of a GM-CSF gene-transduced tumor vaccine [10], there have been a number of clinical studies applying this technology to the treatment of melanoma, renal cell carcinoma, prostate cancer, pancreatic cancer, and non-small-cell lung cancer. All of these clinical studies were performed without any severe adverse events [12–22]. In a clinical study examining RCC, Simons *et al.* reported a randomized, double-blind dose-escalation study with equivalent doses of autologous, irradiated RCC vaccine cells, with or without *ex vivo* human GM-CSF gene transfer. GM-CSF gene-transduced vaccines were equivalent in toxicity to nontransduced vaccines up to the feasible limits of autologous tumor vaccine yield. There was no dose-limiting toxicity, no evidence of autoimmune disease, and no replication-competent retrovirus encountered in 18 patients receiving full follow-up care. This phase I study demonstrated the feasibility, safety, and bioactivity of autologous GM-CSF gene-transduced tumor vaccines for RCC patients. An objective partial response was observed in one of the three patients who received 1.2×10^8 GM-CSF gene-transduced cells and showed the largest delayed-type hypersensitivity (DTH) conversion [13,14]. However, the optimum number of GM-CSF-transduced autologous renal tumor cell vaccine (GVAX) cells for use in vaccination and boosting and the optimum frequency of cell administration remain to be determined.

To determine more precisely whether GM-CSF-secreting RCC vaccines can be used safely to induce antitumor immunity in advanced RCC patients, we conducted a clinical trial of this treatment strategy. Our clinical protocol consisted of tumor resection by nephrectomy, the establishment of primary RCC cultures, and *ex vivo* gene transfer, which was carried out in our own cell-processing facility [23]. The minimum dosage of the vaccine cells was set according to the previous report on RCC by Simons *et al.* [14], and the booster schedule was based on a previous report on non-small-cell lung cancer by Soiffer *et al.* [16]. This was the first clinical trial of human gene therapy for cancer patients approved by the Japanese government and performed in Japan. The results of the present study indicate that this novel RCC immunotherapeutic regimen, which features vaccination with GM-CSF-secreting, irradiated autologous RCC tumor cells, is feasible, safe, and capable of eliciting systemic immune responses against RCC tumor cells. Furthermore, these patients, some of whom also received systemic low-dose IL-2 therapy, have been followed up on an outpatient basis.

RESULTS

Case Presentations

Forty patients suffering from either primary RCC with or without metastases or postoperative relapsed RCC were evaluated at our hospital between July 1998 and March 2001. Of these, 6 preoperative patients with stage IV RCC (UICC classification 1997) with metastatic lesions were allowed to participate in the present clinical study by our ethics committee, based on clinical condition and eligibility criteria listed under Patients and Methods. As

TABLE 1: Patient characteristics and clinical response to GVAX

	Patient			
	1	2	3	4
Age (years)/sex	60/male	71/male	57/female	50/male
Tumor site				
Primary	Right RCC	Right RCC	Left RCC	Left RCC
Metastases	Lung, liver	Sacral bone	Liver, lung	Lung
Previous therapy	None	Sacral irradiation	None	None
GM-CSF production[a] (ng/10^6 cells/24 h)	49	98	51	116
No. of GVAX treatments	10	17	15	6
Vaccinated total cell number	2.2×10^8	3.7×10^8	3.2×10^8	1.4×10^8
Adverse events				
Systemic	Low-grade fever	Low-grade fever	None	None
Local	Erythema, pruritis	Erythema, pruritis	Erythema, pruritis	Erythema, pruritis, blister
Eosinophil number[b] (/μl; mean ± SD)	718 ± 76	437 ± 306	226 ± 283	390 ± 150
Clinical response	PD	SD	PD	PD, MR
Survival (months from first vaccination)	7.5[c]	>62	45[c]	>44

PD, progressive disease; SD, stable disease; MR, mixed response.
[a] GM-CSF production rate from each autologous GM-CSF-transduced RCC.
[b] Eosinophil number was measured 48 h after vaccination.
[c] Patient passed away.

2 patients, a 48-year-old Japanese man having right RCC with multiple lung metastases and a 58-year-old Japanese man having right RCC with metastases to the right clavicle, bilateral lung, and liver, were excluded from this study because their GM-CSF-transduced RCC cells did not produce enough GM-CSF to satisfy the eligibility criteria as described under Autologous Vaccine Yield and Gene Transfer, 4 patients received GVAX.

The first patient (Case 1), a 60-year-old Japanese man, was diagnosed in August 1998 with RCC of the right kidney with multiple lung and liver metastases. His largest metastatic tumor, which was located in the right hilar region, was calculated volumetrically as 135 ml by computed tomography (CT) scan. The vaccine preparation used, his clinical course, and the autopsy findings have been reported previously [24]. Furthermore, he received a total of 2.2×10^8 GVAX cells over 10 subcutaneous injections. The adverse events he experienced during vaccination are summarized in Table 1. He received gamma knife irradiation for his brain metastases and was initiated with low-dose (700,000–140,000 IU) recombinant IL-2 (rIL-2; Imunace, 350,000 IU/vial; Shionogi, Osaka, Japan), which was administered intravenously according to the patient's request. One week after the start of the rIL-2 treatment, the patient's right hilar mass lesion became smaller and decreased by 30% of the total volume within 1 month (Fig. 1A). Unfortunately, this patient died of multiple RCC metastases on July 8, 1999, 10 months after nephrectomy and 7 months after the start of GVAX vaccination (Fig. 2A).

The second patient (Case 2), a 71-year-old Japanese man, was diagnosed in December 1998 with a sacral tumor that metastasized from RCC of the right kidney. He received a total dose of 30 Gy of irradiation of the sacral metastasis in February 1999 for severe pain, which was followed up with spinal anesthesia and oral morphine sulfate. The patient was nephrectomized on April 6, 1999, 43 days after the local irradiation, and pathology showed clear cell carcinoma. He received a total of 3.7×10^8 GVAX cells in 17 subcutaneous injections from June 3, 1999, to February 3, 2000. The adverse events he experienced during vaccination are summarized in Table 1. His pain at the sacral area disappeared completely after the 5th vaccination, and oral morphine sulfate was discontinued. He experienced mechanical ileus due to nephrectomy after the 13th vaccination, which resolved after a few days of iv fluid treatment. The ileus was not related to the vaccination, and no recurrence of the ileus was noted after 4 further vaccinations. During the course of vaccination, the growth rate of the sacral tumor was stable as assessed by CT scan. His clinical course with the change in tumor size is described in Fig. 2B. The serum level of the nonspecific tumor marker immunosuppressive acidic protein returned from double the normal level to normal after the 6th vaccination, and a thallium scan showed decreased uptake of thallium at the tumor site on completion of the vaccination protocol (data not shown). Eleven months after the start of vaccination, pathological examination of the biopsied sacral bone specimen showed no RCC. This patient had been doing well without any treatment, with a performance status of zero, until he experienced a dull pain in his right femoral area in late November of 2001, 29 months after the 1st vaccination. He was diagnosed as having a 1-cm lytic metastasis in the right femoral bone. He received local