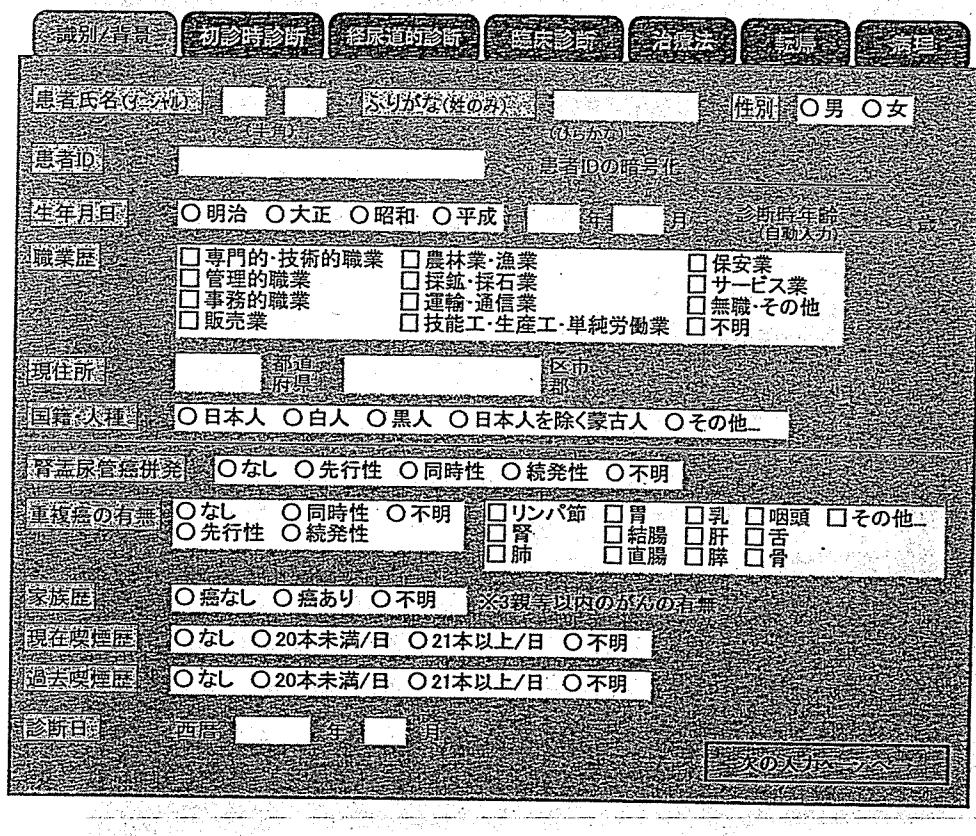
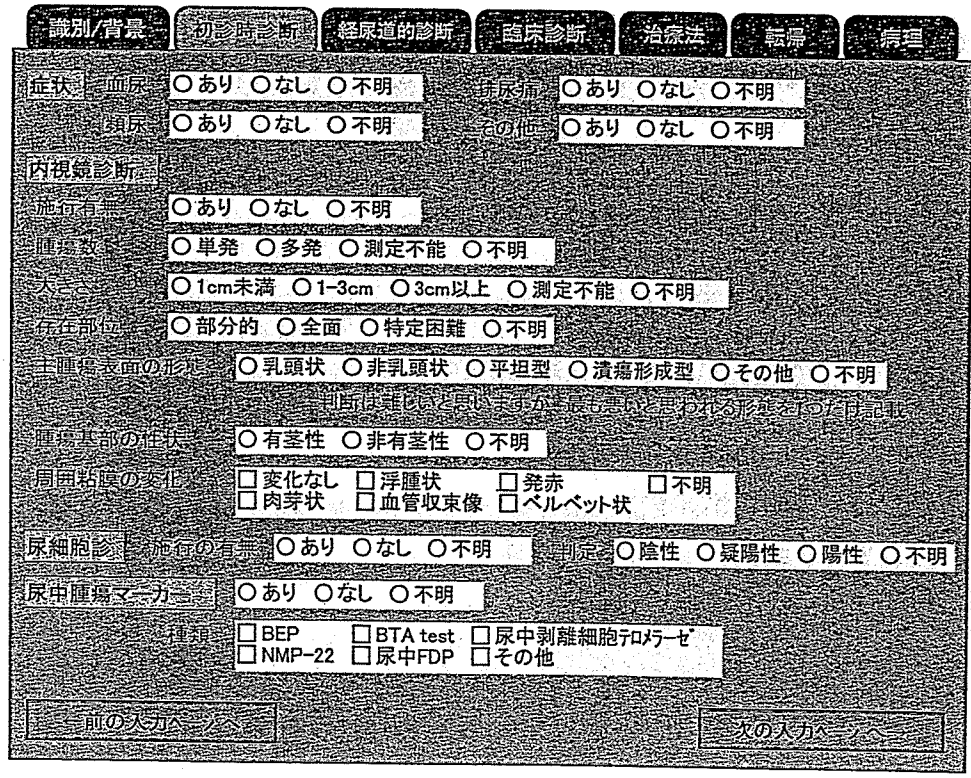
Institution	1999 Number of patients	2000 Number of patients	2001 Number of patients
Takatsuki Red Cross Hospital	–	–	8
Saiseikai Suita Hospital	–	–	14
Chibune Hospital	–	–	10
Osaka Second Police Hospital	–	–	5
Hyogo Prefecture			
Kobe University Graduate School of Medicine	–	32	21
Kobe National Hospital	–	–	9
Itami City Hospital	–	8	19
Takasago Municipal Hospital	–	0	–
Miki City Hospital	–	13	16
Kakogawa Municipal Hospital	–	4	–
Hyogo Prefectural Rihabilitaton Center	–	–	0
Nara Prefecture			
Nara National Hospital	–	4	5
Takanohara Central Hospital	9	–	–
Hirao Hospital	9	–	–
Kokuho Central Hospital	4	–	–
Nara Prefectural Mimuro Hospital	–	20	–
Saiseikai Nara Hospital	–	7	–
Takai Hospital	–	9	–
Nara Prefectural Hospital	–	–	24
Wakayama Prefecture			
Wakayama Medical University	–	49	–
Wakayama Rosai Hospital	8	13	19
Koyo Hospital	2	11	3
Hidaka General Hospital	–	16	–
Kinan General Hospital	–	6	8
Tottori Prefecture			
Yonago Medical Center	–	–	9
Shimane Prefecture			
Shimane University School of Medicine	–	17	26
Okayama Prefecture			
Okayama University Medical School	10	–	–
Kawasaki Medical School	–	29	–
Kurashiki Medical Center	–	27	24
Konkou Hospital	3	11	12
Matsuda Hospital	–	7	7
Okayama Central Hospital	–	–	34
Mizushima Hospital	–	–	4
Hiroshima Prefecture			
Hiroshima University	–	–	20
Kobatake Hospital	–	18	13
Kajikawa Hospital	–	–	2

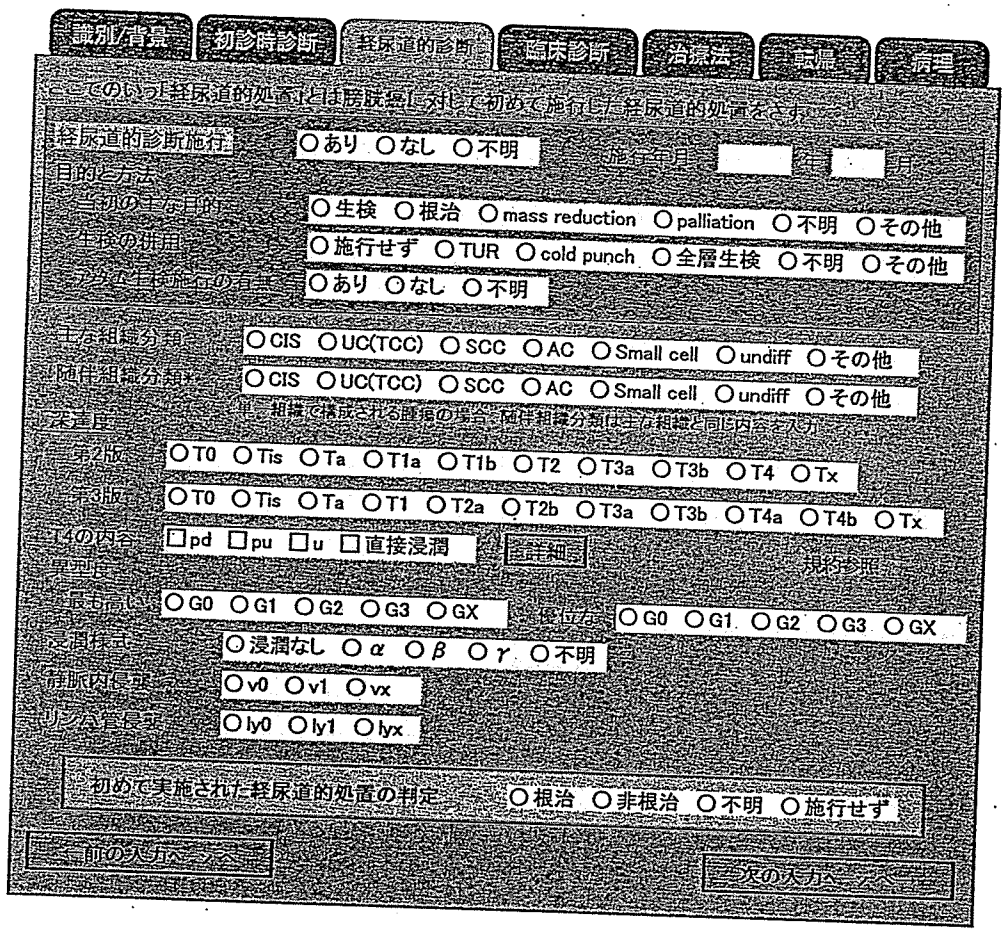
Institution	1999 Number of patients	2000 Number of patients	2001 Number of patients
Takanobashi Central Hospital	–	–	9
Harada Hospital	–	–	0
Yamaguchi Prefecture			
Yamaguchi University Hospital	–	15	13
National Shimonoseki Hospital	–	0	–
Onoda Municipal Hospital	–	–	5
Shimonoseki Kosei Hospital	–	–	10
Hikari Municipal Hikari General Hospital	–	–	6
Tokushima Prefecture			
Anan Central Hospital of The Medical Association	–	10	–
Jinshinkai Kamei Hospital	–	–	2
Kagawa Prefecture			
National Zentsuji Hospital	–	7	6
Takamatsu Municipal Hospital	5	–	–
Kagawa Prefectural Central Hospital	–	–	13
Ehime Prefecture			
Ehime University Hospital	31	15	11
National Shikoku Cancer Center	17	21	20
Ehime Prefectural Central Hospital	19	–	–
Matsuyama Red Cross Hospital	22	21	17
Shikoku Central Hospital	–	6	5
Kochi Prefecture			
Kochi Municipal Central Hospital	–	–	7
Kochi Prefectural Aki Hospital	–	–	5
Kitajima Hospital	–	–	3
Fukuoka Prefecture			
Kyushu University Hospital	13	16	20
University of Occupational and Environmental Health	16	–	24
Ohomuta City General Hospital	18	–	26
Harasanshin General Hospital	71	84	95
Kitakyushu City Yahata Hospital	3	3	8
Chikushi Hospital Fukuoka University	14	–	–
Fukuoka Prefectural Yanagawa Hospital	–	7	–
Fukuoka Prefectural Hepato-gastroenterological Center	–	10	–
Shinyukuhashi Hospital	–	9	–
Takayama Hospital	–	7	–
Tagawa Municipal Hospital	–	11	–
Chikugo City Hospital	–	–	6
Kano Hospital	–	25	13
Kawanami Hospital	–	–	4
Asakura Kensei Hospital	–	–	2
Nagasaki Prefecture			
Nagasaki University Hospital	–	12	23

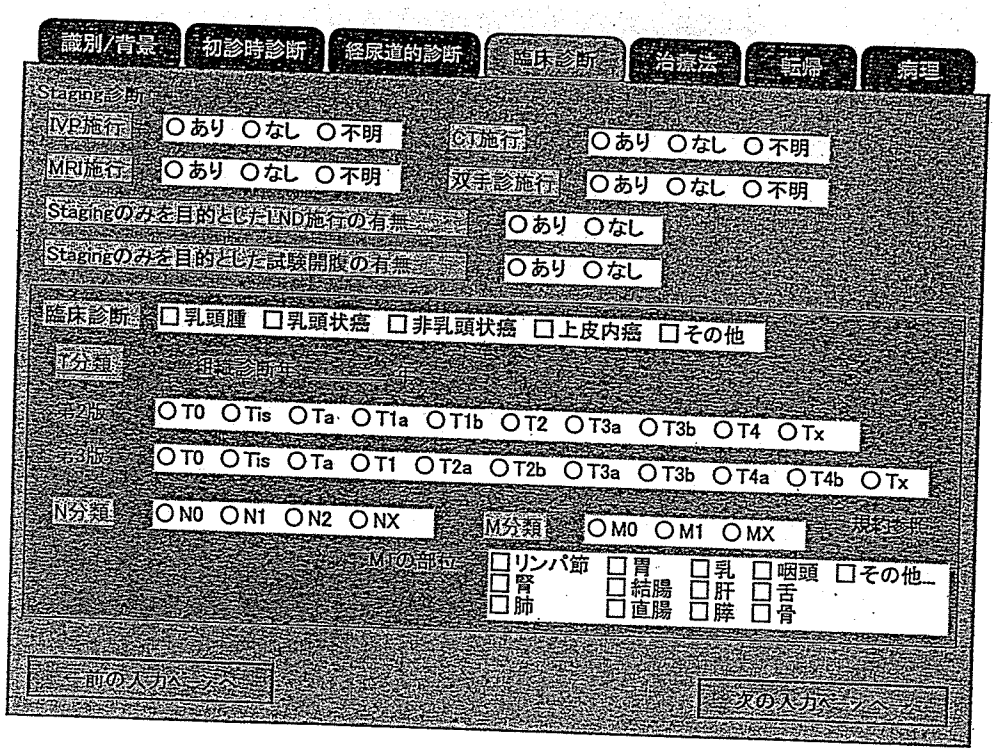
Institution	1999 Number of patients	2000 Number of patients	2001 Number of patients
Nagasaki Municipal Hospital	16	17	18
Kumamoto Prefecture			
Kumamoto University School of Medicine	–	21	–
Kawano Hospital	–	8	–
Saiseikai Kumamoto Hospital	–	–	5
Taragi Municipal Hospital	–	–	4
Oita Prefecture			
Oita University	–	–	16
Oita Medical Association Arumeida Hospital	5	–	–
Health Insurance Nankai Hospital	–	–	6
Miyazaki Prefecture			
Kushima City National Health Insurance Hospital	4	2	6
Kobayashi City Hospital	–	11	–
Yokoyama Hospital	–	3	–
Koga General Hospital	–	–	20
Kagoshima Prefecture	–	–	–
Kagoshima University Hospital	–	19	20
Kagoshima Prefectural Oshima Hospital	–	5	–
Kagoshima City Hospital	–	20	–
Soogunn-ishikairitu Hospital	–	4	8
Shimoinaba Hospital	–	10	12
Izumi Hospital	–	12	4
Satsumagun Ishikai Hospital	–	2	–
Akune Citizen Hospital	–	2	5
Saiseikai Sendai Hospital	–	10	5
Ibusuki National Hospital	–	–	13
Okinawa Prefecture			
University of the Ryukyus	–	10	7
Nakagami Hospital	7	14	14

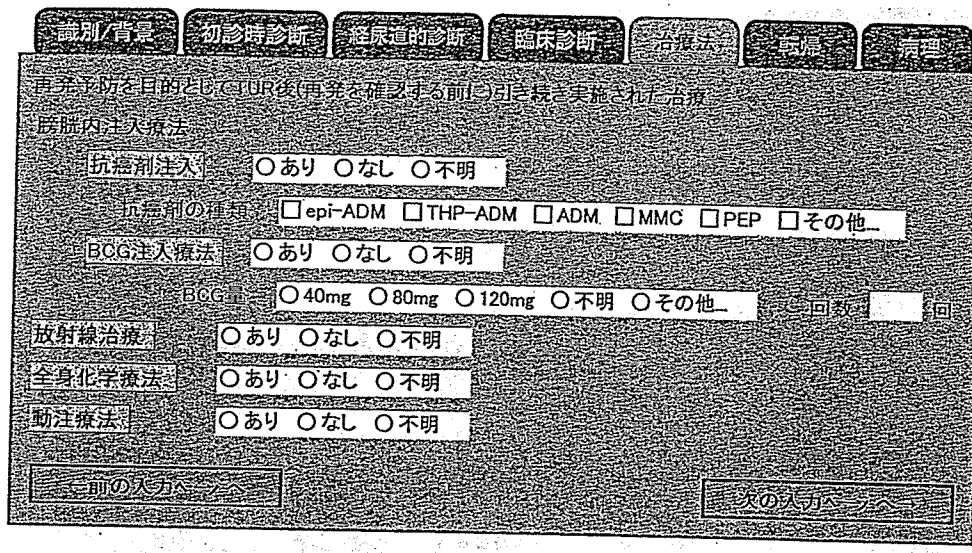
入力レイアウト

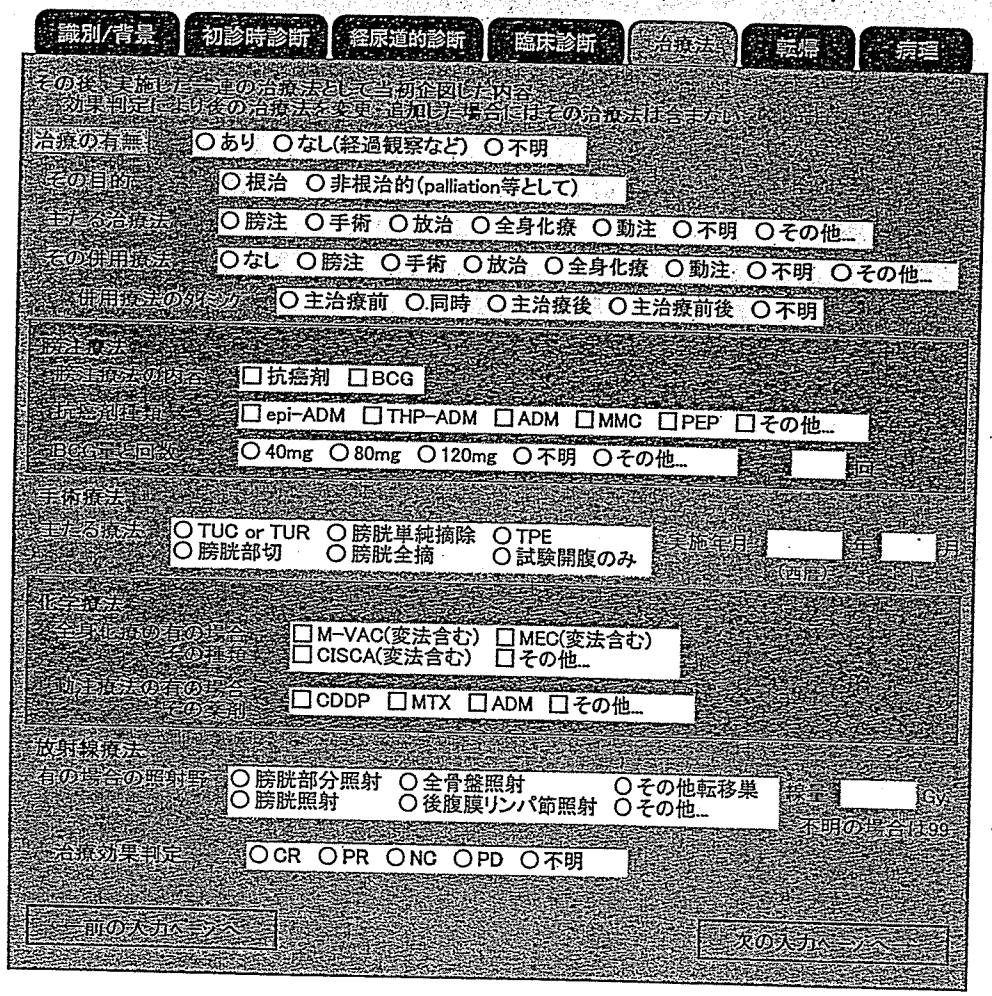

識別/背景
初診時診断
経尿道的診断
臨床診断
治療法
転帰
病理
患者氏名(イニシャル)
(半角)
ふりがな(姓のみ)
(全角)
性別 ○男 ○女
患者ID
患者IDの暗号化
生年月日 ○明治 ○大正 ○昭和 ○平成 年 月
診断時年齢 (自動入力)
職業歴
□専門的・技術的職業 □農林業・漁業 □保安業
□管理的職業 □採鉱・採石業 □サービス業
□事務的職業 □運輸・通信業 □無職・その他
□販売業 □技能工・生産工・単純労働業 □不明
現住所
都道府県
区市郡
国籍・人種 ○日本人 ○白人 ○黒人 ○日本人を除く蒙古人 ○その他
腎盂尿管癌併発 ○なし ○先行性 ○同時性 ○続発性 ○不明
重複癌の有無 ○なし ○同時性 ○不明 ○先行性 ○続発性
□リンパ節 □胃 □乳 □咽頭 □その他
□腎 □結腸 □肝 □舌
□肺 □直腸 □膵 □骨
家族歴 ○癌なし ○癌あり ○不明 ※3親等以内のがんの有無
現在喫煙歴 ○なし ○20本未満/日 ○21本以上/日 ○不明
過去喫煙歴 ○なし ○20本未満/日 ○21本以上/日 ○不明
診断日 西暦 年 月
次の入力ページへ

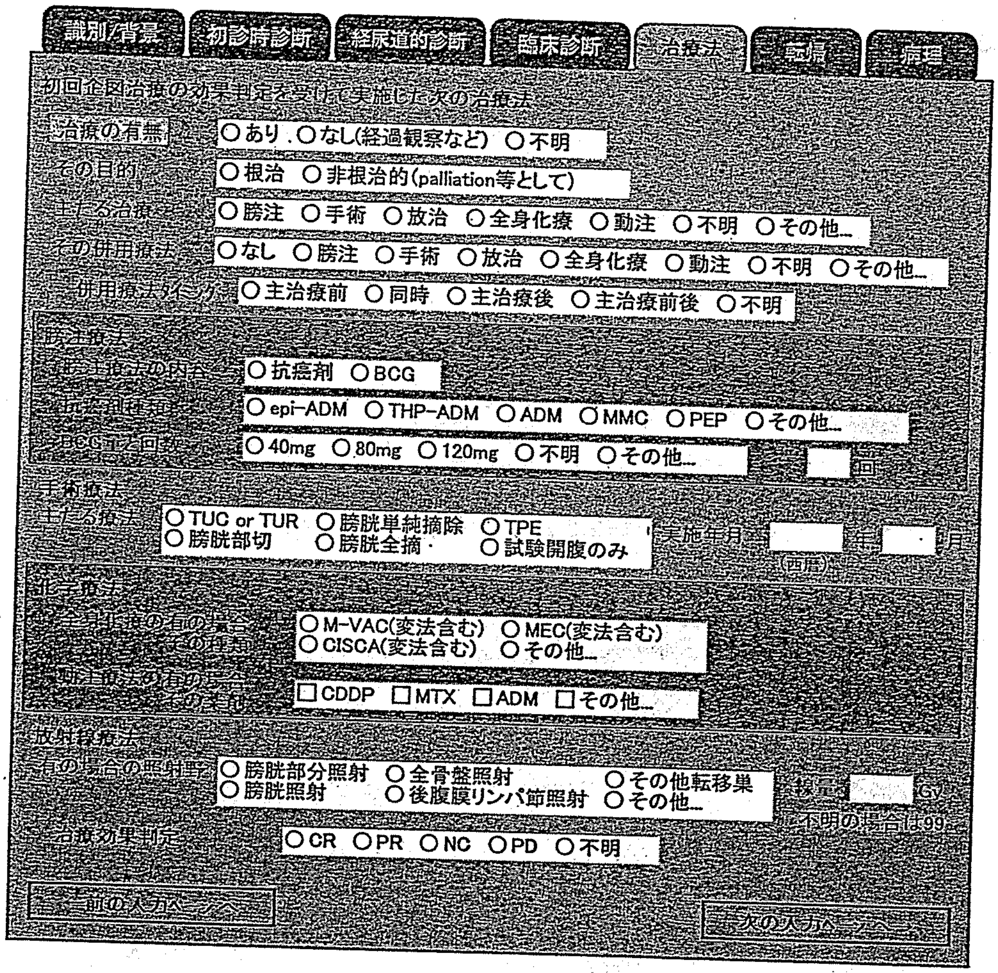

識別/背景
初診時診断
経尿道的診断
臨床診断
治療法
転帰
病理
症状 血尿 ○あり ○なし ○不明
頻尿 ○あり ○なし ○不明
排尿痛 ○あり ○なし ○不明
その他 ○あり ○なし ○不明
内視鏡診断
施行有無 ○あり ○なし ○不明
腫瘍数 ○単発 ○多発 ○測定不能 ○不明
大きさ ○1cm未満 ○1-3cm ○3cm以上 ○測定不能 ○不明
存在部位 ○部分的 ○全面 ○特定困難 ○不明
主腫瘤表面の形態 ○乳頭状 ○非乳頭状 ○平坦型 ○潰瘍形成型 ○その他 ○不明
判断は難しいとは思いますが一番当てはまると思われる形態をひとつ選択
腫瘍基部の性状 ○有茎性 ○非有茎性 ○不明
周囲粘膜の変化 □変化なし □浮腫状 □発赤 □不明
□肉芽状 □血管収束像 □ベルベット状
尿細胞診 施行の有無 ○あり ○なし ○不明 判定 ○陰性 ○疑陽性 ○陽性 ○不明
尿中腫瘍マーカー ○あり ○なし ○不明
種類 □BEP □BTA test □尿中剥離細胞テロメラーゼ
□NMP-22 □尿中FDP □その他
前の入力ページへ
次の入力ページへ


識別/背景
初診時診断
経尿道的診断
臨床診断
治療法
転帰
病理
ここでいう「経尿道的処置」とは膀胱に対して初めて施行した経尿道的処置をさす。
経尿道的診断施行
○あり ○なし ○不明
施行年月
年
月
目的と方法
この主な目的
○生検 ○根治 ○mass reduction ○palliation ○不明 ○その他
生検の併用
○施行せず ○TUR ○cold punch ○全層生検 ○不明 ○その他
フォロー生検施行の有無
○あり ○なし ○不明
主な組織分類
○CIS ○UC(TCC) ○SCC ○AC ○Small cell ○undiff ○その他
随伴組織分類
○CIS ○UC(TCC) ○SCC ○AC ○Small cell ○undiff ○その他
単一組織で構成される腫瘍の場合、随伴組織分類は主な組織と同じ内容で入力
深達度
第2版
○T0 ○Tis ○Ta ○T1a ○T1b ○T2 ○T3a ○T3b ○T4 ○Tx
第3版
○T0 ○Tis ○Ta ○T1 ○T2a ○T2b ○T3a ○T3b ○T4a ○T4b ○Tx
T4の内訳
□pd □pu □u □直接浸潤
詳細
規約参照
最も高い
○G0 ○G1 ○G2 ○G3 ○GX
異型度
○G0 ○G1 ○G2 ○G3 ○GX
脈管侵襲
○浸潤なし ○α ○β ○γ ○不明
静脈内侵襲
○v0 ○v1 ○vx
リンパ管侵襲
○ly0 ○ly1 ○lyx
初めて実施された経尿道的処置の判定
○根治 ○非根治 ○不明 ○施行せず
前の入力ページへ
次の入力ページへ


識別/背景
初診時診断
経尿道的診断
臨床診断
治療法
転帰
病理
Staging診断
IVP施行
○あり ○なし ○不明
CT施行
○あり ○なし ○不明
MRI施行
○あり ○なし ○不明
双手診施行
○あり ○なし ○不明
Stagingのみを目的としたLND施行の有無
○あり ○なし
Stagingのみを目的とした試験開腹の有無
○あり ○なし
臨床診断
□乳頭腫 □乳頭状癌 □非乳頭状癌 □上皮内癌 □その他
T分類
組織診断年
年
第2版
○T0 ○Tis ○Ta ○T1a ○T1b ○T2 ○T3a ○T3b ○T4 ○Tx
第3版
○T0 ○Tis ○Ta ○T1 ○T2a ○T2b ○T3a ○T3b ○T4a ○T4b ○Tx
N分類
○N0 ○N1 ○N2 ○NX
M分類
○M0 ○M1 ○MX
規約参照
M1の部位
□リンパ節 □胃 □乳 □咽頭 □その他
□腎 □結腸 □肝 □舌
□肺 □直腸 □膵 □骨
前の入力ページへ
次の入力ページへ


識別/背景
初診時診断
経尿道的診断
臨床診断
治療法
転帰
病理
再発予防を目的として TUR後(再発を確認する前に)引き続き実施された治療
膀胱内注入療法
抗癌剤注入 ○あり ○なし ○不明
抗癌剤の種類 □epi-ADM □THP-ADM □ADM □MMC □PEP □その他...
BCG注入療法 ○あり ○なし ○不明
BCG ○40mg ○80mg ○120mg ○不明 ○その他... 回数 回
放射線治療 ○あり ○なし ○不明
全身化学療法 ○あり ○なし ○不明
動注療法 ○あり ○なし ○不明
一つ前の入力へ
次の入力へ


識別/背景
初診時診断
経尿道的診断
臨床診断
治療法
転帰
病理
その後、実施した一連の治療法として当初企図した内容。
効果判定により後の治療法を変更・追加した場合にはその治療法は含まない。
治療の有無 ○あり ○なし(経過観察など) ○不明
その目的 ○根治 ○非根治的(palliation等として)
主たる治療法 ○膀注 ○手術 ○放治 ○全身化療 ○動注 ○不明 ○その他...
その併用療法 ○なし ○膀注 ○手術 ○放治 ○全身化療 ○動注 ○不明 ○その他...
併用療法のタイミング ○主治療前 ○同時 ○主治療後 ○主治療前後 ○不明
膀注療法
膀注療法の内容 □抗癌剤 □BCG
抗癌剤種類 □epi-ADM □THP-ADM □ADM □MMC □PEP □その他...
BCG ○40mg ○80mg ○120mg ○不明 ○その他... 回
手術療法
主たる術式 ○TUC or TUR ○膀胱単純摘除 ○TPE ○膀胱部切 ○膀胱全摘 ○試験開腹のみ
実施年月 年 月 (西暦)
化学療法
全身化療の有の場合その種類 □M-VAC(変法含む) □MEC(変法含む) □CISCA(変法含む) □その他...
動注療法の有の場合その薬剤 □CDDP □MTX □ADM □その他...
放射線療法
有の場合の照射野 ○膀胱部分照射 ○全骨盤照射 ○その他転移巣 ○膀胱照射 ○後腹膜リンパ節照射 ○その他...
線量 Gy 不明の場合は99
治療効果判定 ○CR ○PR ○NC ○PD ○不明
一つ前の入力へ
次の入力へ


識別/背景
初診時診断
経尿道的診断
臨床診断
治療法
転帰
病理
初回企図治療の効果判定を受けて実施した次の治療法
治療の有無
○あり ○なし(経過観察など) ○不明
その目的
○根治 ○非根治的(palliation等として)
主たる治療
○膀注 ○手術 ○放治 ○全身化療 ○動注 ○不明 ○その他...
その併用療法
○なし ○膀注 ○手術 ○放治 ○全身化療 ○動注 ○不明 ○その他...
併用療法タイミング
○主治療前 ○同時 ○主治療後 ○主治療前後 ○不明
○抗癌剤 ○BCG
○epi-ADM ○THP-ADM ○ADM ○MMC ○PEP ○その他...
○40mg ○80mg ○120mg ○不明 ○その他...
回
手術療法
主たる療法
○TUC or TUR ○膀胱単純摘除 ○TPE
○膀胱部切 ○膀胱全摘 ○試験開腹のみ
実施年月
年
月
(西暦)
化学療法
○M-VAC(変法含む) ○MEC(変法含む)
○CISCA(変法含む) ○その他...
□CDDP □MTX □ADM □その他...
放射線療法
有の場合の照射野
○膀胱部分照射 ○全骨盤照射 ○その他転移巣
○膀胱照射 ○後腹膜リンパ節照射 ○その他...
Gy
不明の場合は99
治療効果判定
○CR ○PR ○NC ○PD ○不明
前の入力ページへ
次の入力ページへ

識別/背景 | 初診時診断 | 経尿道的診断 | 臨床診断 | 治療法 | 転帰 | 病理

その後の経過中に再発等により実施した治療法(尿路癌に対してのみ)
同じ内容の治療が繰り返された場合には主たる治療を入力してください。
再発等がない場合あるいは不明の場合は予後・転帰のみを入力してください。

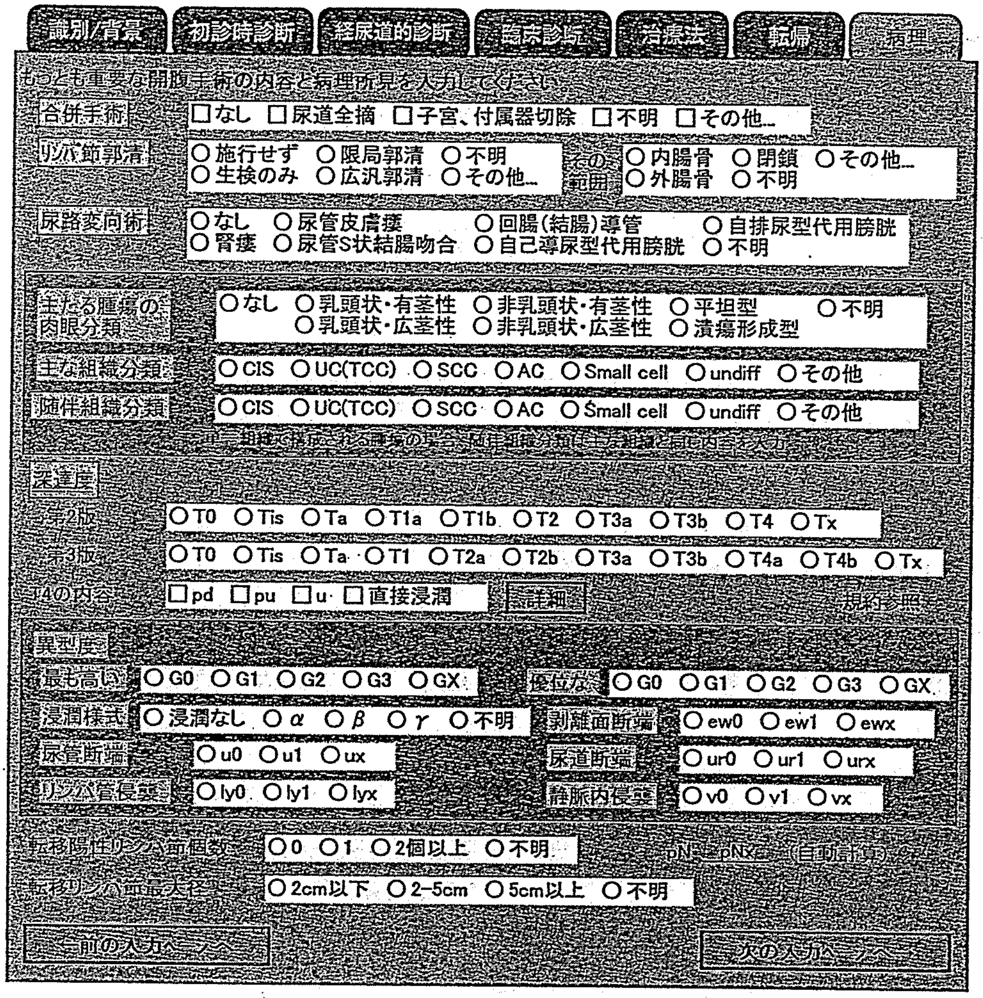
再発・転移 ○膀胱内再発 ○局所再発 ○遠隔転移 ○上部尿路再発 ○その他...
確認年月 年 月
実施治療 ○経過観察 ○内視鏡手術 ○膀胱全摘 ○放射線療法 ○動注療法 ○膀注 ○膀胱部分切除 ○TPE ○全身化学療法 ○その他...
その目的 ○根治 ○維持 ○姑息的 ○不明 効果 ○CR ○PR ○NC ○PD ○不明

再発・転移 ○膀胱内再発 ○局所再発 ○遠隔転移 ○上部尿路再発 ○その他...
確認年月 年 月
実施治療 ○経過観察 ○内視鏡手術 ○膀胱全摘 ○放射線療法 ○動注療法 ○膀注 ○膀胱部分切除 ○TPE ○全身化学療法 ○その他...
その目的 ○根治 ○維持 ○姑息的 ○不明 効果 ○CR ○PR ○NC ○PD ○不明

再発・転移 ○膀胱内再発 ○局所再発 ○遠隔転移 ○上部尿路再発 ○その他...
確認年月 年 月
実施治療 ○経過観察 ○内視鏡手術 ○膀胱全摘 ○放射線療法 ○動注療法 ○膀注 ○膀胱部分切除 ○TPE ○全身化学療法 ○その他...
その目的 ○根治 ○維持 ○姑息的 ○不明 効果 ○CR ○PR ○NC ○PD ○不明

予後・転帰
確認年月 年 月 ←追跡が可能であった日までを入力
生死 ○生存 ○死亡 死亡原因 ○癌死 ○他因死
生存の内容 ○癌なし生存 ○癌あり生存 ○癌の有無不明生存
○局所再発 ○膀胱内再発 ○膀胱内＋腎盂尿管再発 ○転移 ○腎盂・尿管再発 ○その他

前の入力ページへ 次の入力ページへ


識別/背景
初診時診断
経尿道的診断
治療法
転帰
病理
もっとも重要な開腹手術の内容と病理所見を入力してください。
合併手術
□なし □尿道全摘 □子宮、付属器切除 □不明 □その他...
リンパ節郭清
○施行せず ○限局郭清 ○不明 ○生検のみ ○広汎郭清 ○その他...
その範囲
○内腸骨 ○閉鎖 ○その他... ○外腸骨 ○不明
尿路変向術
○なし ○尿管皮膚瘻 ○回腸(結腸)導管 ○自排尿型代用膀胱 ○腎瘻 ○尿管S状結腸吻合 ○自己導尿型代用膀胱 ○不明
主たる腫瘍の肉眼分類
○なし ○乳頭状・有茎性 ○非乳頭状・有茎性 ○平坦型 ○不明 ○乳頭状・広茎性 ○非乳頭状・広茎性 ○潰瘍形成型
主な組織分類
○CIS ○UC(TCC) ○SCC ○AC ○Small cell ○undiff ○その他
随伴組織分類
○CIS ○UC(TCC) ○SCC ○AC ○Small cell ○undiff ○その他
深達度
第2版
○T0 ○Tis ○Ta ○T1a ○T1b ○T2 ○T3a ○T3b ○T4 ○Tx
第3版
○T0 ○Tis ○Ta ○T1 ○T2a ○T2b ○T3a ○T3b ○T4a ○T4b ○Tx
T4の内容
□pd □pu □u □直接浸潤
詳細
規約参照
異型度
最も高い
○G0 ○G1 ○G2 ○G3 ○GX
優位な
○G0 ○G1 ○G2 ○G3 ○GX
浸潤様式
○浸潤なし ○α ○β ○γ ○不明
剥離面断端
○ew0 ○ew1 ○ewx
尿管断端
○u0 ○u1 ○ux
尿道断端
○ur0 ○ur1 ○urx
リンパ管侵襲
○ly0 ○ly1 ○lyx
静脈内侵襲
○v0 ○v1 ○vx
転移陽性リンパ節個数
○0 ○1 ○2個以上 ○不明
pN = pNx (自動計算)
転移リンパ節最大径
○2cm以下 ○2-5cm ○5cm以上 ○不明
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The significance of the expression of dihydropyrimidine dehydrogenase in prostate cancer

Yongnan Li, Yoichi Mizutani, Takumi Shiraishi, Terukazu Nakamura, Kazuya Mikami, Natsuki Takaha, Koji Okihara, Akihiro Kawauchi, Toshiyuki Sakai* and Tsuneharu Miki

*Department f Urology and *Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Kyoto, Japan*

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OBJECTIVE

To measure dihydropyrimidine dehydrogenase (DPD), an enzyme involved in the metabolism of 5-fluorouracil (5-FU), expression in prostate cancer and determine whether 5-chloro-2,4-dihydroxypyridine (CDHP), a potent inhibitor of DPD, enhances the antitumoral activity of 5-FU against prostate cancer.

PATIENTS, MATERIALS AND METHODS

In all, 44 prostate tissue specimens were obtained from men who had a radical prostatectomy alone for prostate cancer, and 38 specimens from men who had had neoadjuvant hormonal therapy. We analysed the cancerous tissue and normal prostate tissue for DPD expression using immunohistochemistry, and determined its prognostic significance. In cultured human prostate cancer lines (DU145 and LNCaP), we compared the cytotoxicity of 5-FU/CDHP with that of 5-FU alone. Finally, in experiments on immunodeficient mice, we studied the effect of oral administration of tegafur, a pro-drug for 5-FU, with or without CDHP on the growth of tumours introduced by injection of DU145 cells.

RESULTS

The expression of DPD was significantly higher in cancerous than normal prostate tissue; 36 of 44 (82%) specimens of prostate cancer expressed DPD, whereas only 25 of 44 (57%) specimens of normal prostate tissue expressed DPD. For men with prostate cancer who had radical prostatectomy alone, men with negative DPD expression tended to have a longer recurrence-free survival than those with positive expression; there were no recurrences in men with prostate cancer and negative DPD expression in the 5-year follow-up. DPD expression was significantly lower in men with prostate cancer who received neoadjuvant hormonal therapy. In vitro treatment of human prostate cancer cell lines with 5-FU/CDHP showed more cytotoxicity than with 5-FU treatment alone. Finally, DU145 tumours in mice treated with tegafur and CDHP were significantly smaller than in mice given tegafur alone.

CONCLUSION

The present study showed that DPD expression is elevated in prostate cancer, and indicate that DPD inhibitors might enhance the antitumour activity of 5-FU against prostate cancer.

KEYWORDS

DPD, prostate cancer, immunohistochemistry, 5-FU

INTRODUCTION

Dihydropyrimidine dehydrogenase (DPD), an important enzyme in the pyrimidine degradation pathway [1–6], is the rate-limiting enzyme responsible for converting thymine to dihydrothymine [7,8]. Early analyses of human tumour cell xenografts showed a wide range of DPD enzymatic activity among various solid and haematopoietic tumours [9–11]. As DPD is responsible for the degradation of 5-fluorouracil (5-FU), intratumoral DPD activity was investigated in clinical studies in patients with head-and-neck [12] and colorectal [13] cancers treated with 5-FU. DPD activity varies among individual tumours, and increased DPD activity is correlated with a poor clinical response to 5-FU-based chemotherapy [12,13]. Recently, immunohistochemistry was used to evaluate DPD protein expression *in situ* using paraffin-embedded blocks of specimens [14–16]. Like DPD activity, high levels of DPD expression were associated with a poor clinical response to 5-FU in nude mice with gastric cancer xenografts, and in patients with colorectal cancer [17].

To our knowledge, nothing is known about the expression of DPD in prostate cancer, or about its roles in prostate cancer. In the present study we investigated DPD expression by immunohistochemistry in prostate cancer tissue and in normal prostate tissue, and determined its prognostic significance. The effect of 5-chloro-2,4-dihydroxypyridine (CDHP), a DPD inhibitor, on 5-FU cytotoxicity against prostate cancer was also examined.

PATIENTS, MATERIALS AND METHODS

In all, 44 prostate cancer specimens with adjacent normal prostate tissue were obtained from the surgical pathological files of Kyoto Prefectural University of Medicine between 1997 and 2004. None of the patients had had preoperative androgen-deprivation therapy or radiotherapy. The cases were selected to represent the full spectrum of pathological stage and grade. The mean (range) age of the patients was 66 (53–75) years. The 2002 TNM system was used for pathological staging, and the final pathological stages included 30 cases of T2 and 14 of T3; 38 men with prostate cancer who had had neoadjuvant hormonal therapy (NHT) were also examined. The study was performed after approval by a local Human

Investigations Committee, and informed consent was obtained from each patient.

For immunohistochemistry, serial 5-μm sections were cut from formalin-fixed, paraffin wax-embedded slices of the specimens. The sections were de-waxed in xylene, rehydrated with graded alcohols, and antigen retrieved by microwave heating for 15 min. Endogenous peroxidase was blocked by incubating samples in 3% H_2O_2 in methanol. After washing three times in PBS, samples were placed in 10% normal equine serum (Cosmo Bio Co. Ltd, Tokyo, Japan) in PBS for 30 min to reduce nonspecific staining. The sections were then incubated with polyclonal antibody against DPD (Second Cancer Research Laboratory, Taiho Pharmaceutical Co. Ltd, Saitama, Japan) at 4 °C overnight. After washing three times in PBS, slides were incubated with Histofine Simplestain MAX-PO® (Nichirei Corporation Co. Ltd, Tokyo, Japan) at room temperature for 1 h. Immunohistochemical reactions were revealed with a solution of 3, 3′-diaminobenzidine tetrahydrochloride. The sections were then counted randomly at ×200.

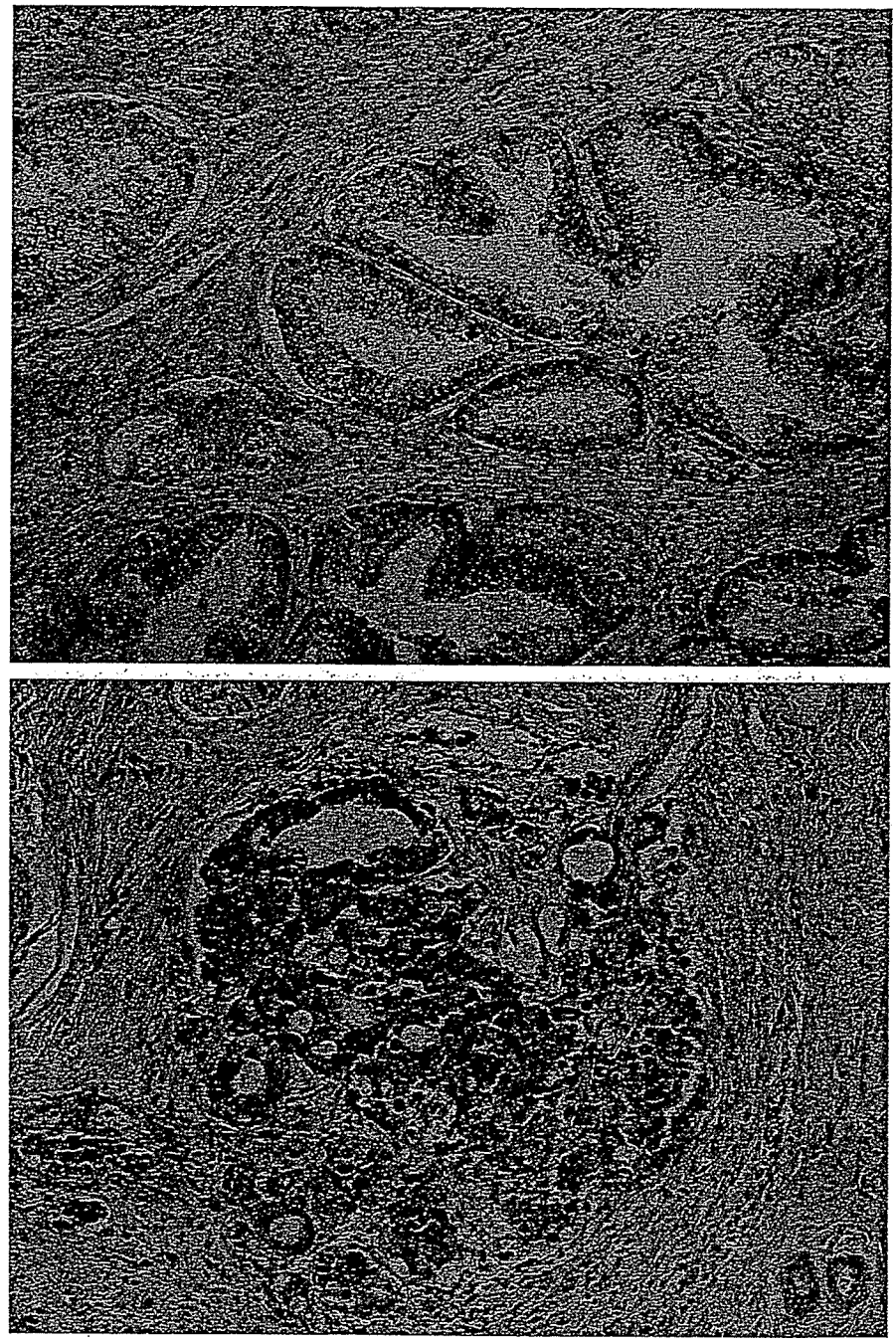
The intensity of DPD immunoreactivity was evaluated in normal prostate tissue and prostate cancer from the same slide for each case. The microscopic fields with the most immunoreactivity were chosen for analysis; [3] 1000 cells were analysed in each case. DPD was localized in the cytoplasm of both normal prostate tissue and prostate cancer cells. DPD expression was determined by a pathologist (Fig. 1); the intensity was graded from (–) to (+++). Samples with <10% positive cells were designated as negative (–), with 10–25% positive as +, 25–50% positive as ++, and >50% positive as +++.

The DU145 and LNCaP human prostate cancer cell lines were maintained in RPMI 1640 (Life Technologies Inc., Gaithersburg, MD, USA) supplemented with 100 units/mL penicillin and 100 μg/mL streptomycin (Life Technologies Inc.) and 10% fetal bovine serum (Bio-cult, Glasgow, Scotland, UK) at 37 °C in a 5% CO_2 atmosphere.

Male severe combined immunodeficiency (SCID) mice (8–9 weeks of age) were purchased from CLEA Japan (Osaka, Japan), and housed in a specific pathogen-free animal facility. The mice were fed irradiated mouse chow and autoclaved water treated by reverse osmosis. The Committee for Animal Research, Kyoto Prefectural University of Medicine approved the experimental procedure.

5-FU (Lot no. 308033) was kindly supplied by Kyowa Hakkou Co. Ltd, Tokyo, Japan. Tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil, FT], CDHP and potassium oxonate (OXO) were donated by Taiho Pharmaceutical Co. Ltd, Tokyo, Japan. FT, which is a prodrug of 5-FU, functions as an effector; OXO, which inhibits the conversion of 5-FU to 5-fluorouridine 5-monophosphate by

FIG. 1. Expression of DPD in prostate cancer and normal prostate tissue. Specimens were fixed in formalin, embedded in paraffin wax, and immunostained with DPD monoclonal antibody. Pictures were reduced from ×200. A, DPD-negative normal prostate tissue. B, Arrow *indicates DPD-positive prostate cancer.*



Cell type, n (%)	Staining intensity grade			
	−	+	++	+++
Normal prostate	19 (43)	16 (36)	9 (21)	0
Prostate cancer*	8 (18)	21 (48)	11 (25)	4 (9)

*The staining intensity in prostate cancer was significantly higher than in normal prostate ($P = 0.02$, chi-square for independence test).

TABLE 1. Intensity of cells with DPD immunostaining in 44 RP specimens.

orotate phosphoribosyltransferase, is mainly distributed in the gastrointestinal tract after oral administration in mice, and relieves the gastrointestinal tract toxicity induced by 5-FU.

For the cytotoxicity assay, a microculture tetrazolium dye (MTT) assay was used to determine cell lysis as previously [18]. Briefly, 100 μL of target cell suspension (2×10^4 cells) was added to each well of 96-well flat-bottom microtitre plates (Corning Glass Works, Corning, NY, USA), and each plate was incubated for 24 h at 37 °C in a humidified 5% CO_2 atmosphere. After incubation, the supernatants were aspirated, and cells were washed three times with RPMI-1640 medium, and 200 μL of drug solution or medium (control) were distributed in the 96-well plates. Each plate was incubated for 24 h at 37 °C. After incubation, 200 μL of MTT working solution (5 mg/mL, Sigma Chemical Co., St. Louis, MO, USA) was added to each well, and the cultures were incubated for 4 h at 37 °C in a humidified 5% CO_2 atmosphere. The medium was removed from the wells and replaced with 100 μL of isopropanol (Sigma) supplemented with 0.05 M HCl. The absorbance of each well was measured with a microculture-plate reader (Immunoreader, Japan Intermed Co. Ltd, Tokyo, Japan) at 540 nm. The percentage cytotoxicity was calculated as [1 − (absorbance of experimental wells/absorbance of control wells)] × 100.

For the *in vivo* study with the DU145 cell line, 6×10^6 DU145 cells with a mixture of 50 μL Matrigel (Becton-Dickinson, NJ, USA) and 50 μL RPMI 1640 with no antibiotics or serum were injected s.c. into the right flanks of SCID mice; 13 days later, the DU145 tumour size was ≈120 mm^3. The mice were assigned to three groups of eight mice: control mice received saline orally; tumour-bearing mice were treated with FT/OXO, (8.3/8.3 mg/kg/day) or FT/CDHP/OXO (8.3/2.4/8.3 mg/kg/day) for 18 consecutive days. The tumours were measured at 3-day intervals until 18 days after the initial treatment; the diameter was scaled with a digital calliper and the volume calculated as $a \times b^2/2$, where a is the long diameter and b the short diameter.

Data were analysed by Student's t-test and chi-square test. Biochemical recurrence was defined as a postoperative serum PSA level of ³ 0.1 ng/mL [19]. Postoperative recurrence-free survival rate was determined using the Kaplan–Meier method. All P-values were two-sided, and $P < 0.05$ was considered to indicate significance.

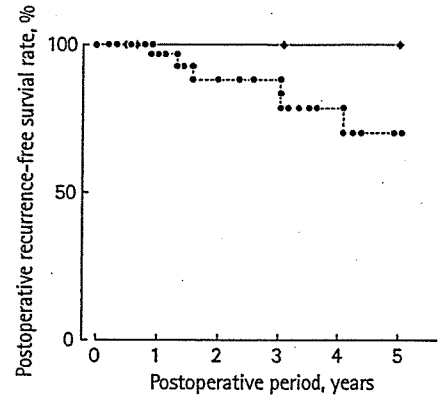
RESULTS

In specimens from men treated with radical prostatectomy (RP) alone, DPD expression was detected in 36 of 44 (82%) cancer samples ($P < 0.05$) compared to 25 of 44 (57%) specimens of normal prostate tissue. The staining was also significantly more intense in cancer cells than in normal prostate cells ($P = 0.02$; Table 1). However, there was no correlation between DPD expression and the stage/grade of the cancer (data not shown).

For men with prostate cancer who had RP alone, the recurrence-free survival was determined by Kaplan–Meier analysis. In the 5-year follow-up, men with negative DPD expression tended to have a longer recurrence-free survival than those with positive DPD expression, but the difference was not statistically significant ($P = 0.1$; Fig. 2). There were no recurrences in men with prostate cancer and negative DPD expression.

The expression of DPD in men with prostate cancer was higher in men treated with RP alone (82%; 36 of 44) than men treated with NHT (53%; 20 of 38; $P < 0.001$). For T2 cancer, DPD expression was lower in men treated with NHT (48%; 14 of 29) than with RP alone (80%, 24 of 30; $P < 0.001$). However, for stage T3 cancer, there was no significant difference in DPD expression between men treated with NHT (six of nine) or RP alone (12 of 14).

FIG. 2. Relationship between DPD expression and postoperative recurrence-free rate in men with prostate cancer. Postoperative recurrence-free rate of men with prostate cancer undergoing RP alone was determined by the Kaplan–Meier method. Men with prostate cancer were classed as those with positive DPD expression and those with negative expression. Men with prostate cancer with negative expression had a higher recurrence-free rate than those with positive expression in the 5-year follow-up ($P = 0.1$). Solid line, eight men with negative DPD expression; dashed line, men with positive DPD expression.



For well and moderately differentiated prostate cancer, DPD expression in men with RP alone (81%; 34 of 42) was significantly higher than in men treated with NHT (52%, 14 of 27; $P < 0.001$). However, for poorly differentiated prostate cancer, there was no significant difference in expression between men treated with RP alone (two of two) or NHT (five of 11).

Various inhibitors of DPD were developed in *in vitro* studies to increase the anticancer effects of 5-FU [20]; CDHP is a potent DPD inhibitor with no anticancer activity by itself. We examined whether CDHP enhanced the cytotoxic activity of 5-FU against prostate cancer cells *in vitro*. 5-FU/CDHP had a significant cytotoxic effect against both hormone-sensitive LNCaP (Fig. 3A) and hormone-resistant DU145 (Fig. 3B) cells compared with 5-FU alone.

FT/OXO and FT/CDHP/OXO were orally administered for 18 days to SCID mice bearing the DU145 cancer. No mice had died by 18 days. On day 18, mice given FT/CDHP/OXO

had significantly smaller tumours than mice given PBS ($P = 0.01$) or FT/OXO ($P = 0.03$; Fig. 4).

DISCUSSION

This is the first report that DPD expression is higher in prostate cancer than in normal prostate tissue; furthermore, men with prostate cancer and positive DPD expression had a higher recurrence rate than men with negative DPD expression during the 5-year follow-up. Thus, positive DPD expression might be associated with a worse prognosis, and DPD might be a molecular therapeutic target in prostate cancer.

The present data indicate that DPD expression in prostate cancer is significantly higher than in normal prostate tissue; ≈43% of normal prostate tissue lacked DPD expression, while most prostate cancer specimens expressed DPD. We previously reported that DPD activity in bladder cancer tissue is twice that in normal bladder tissue [3]. Horiguchi et al. [15] reported that 59 of 119 (50%) patients had positive immunostaining for DPD in breast cancer, and clarified the prognostic significance of the DPD expression in breast cancer. DPD expression, as estimated by immunohistochemical analysis in the preoperative biopsy, was comparable to that in resected gastric carcinoma [21]. The level of DPD activity in malignant cell lines was related to malignant behaviour [22]. These studies indicate that the expression of DPD in various cancers is significantly higher than in normal tissue.

Sensitivity to 5-FU can be enhanced by using a DPD inhibitor like CDHP [20], and DPD inhibition is a major goal in the strategy for the development of 5-FU treatment. Several authors reported that DPD activity and DPD mRNA expression are inversely correlated with chemosensitivity to 5-FU *in vitro* and in patients with cancer. Thus, DPD is not only a key modulator of 5-FU pharmacokinetics, but also a good predictor of responsiveness to 5-FU [20]. In the present study, CDHP enhanced 5-FU cytotoxicity in prostate cancer cells *in vitro*, and oral administration of CDHP enhanced the antitumour activity of 5-FU against prostate cancer cells in SCID mice. DPD appears to be important in regulating 5-FU sensitivity in prostate cancer. Accordingly, we consider it valuable to establish a simple and reliable method to assess DPD expression in prostate cancer. In addition, combined therapy with 5-FU and DPD inhibitors might be effective against prostate cancer.

In the present study, DPD expression was significantly higher in prostate cancer, and positive-DPD expression was associated with a worse prognosis. These findings suggest that assessing DPD expression might be useful for the management of prostate cancer. As DPD expression might be used as a prognostic indicator in men with prostate

*FIG. 3. Enhancement of the sensitivity of prostate cancer cells to 5-FU by CDHP. LNCaP (A) and DU145 (B) cells were treated with 5-FU (1–100 μM) in combination with CDHP (100 μM) for 24 h and the cytotoxicity was assessed by a 1-day MTT assay. Results from three different experiments are expressed as the mean (SD). *P < 0.05 vs 5-FU alone. White bar, 5-FU alone; black bar, 5-FU + CDHP (100 μM).*

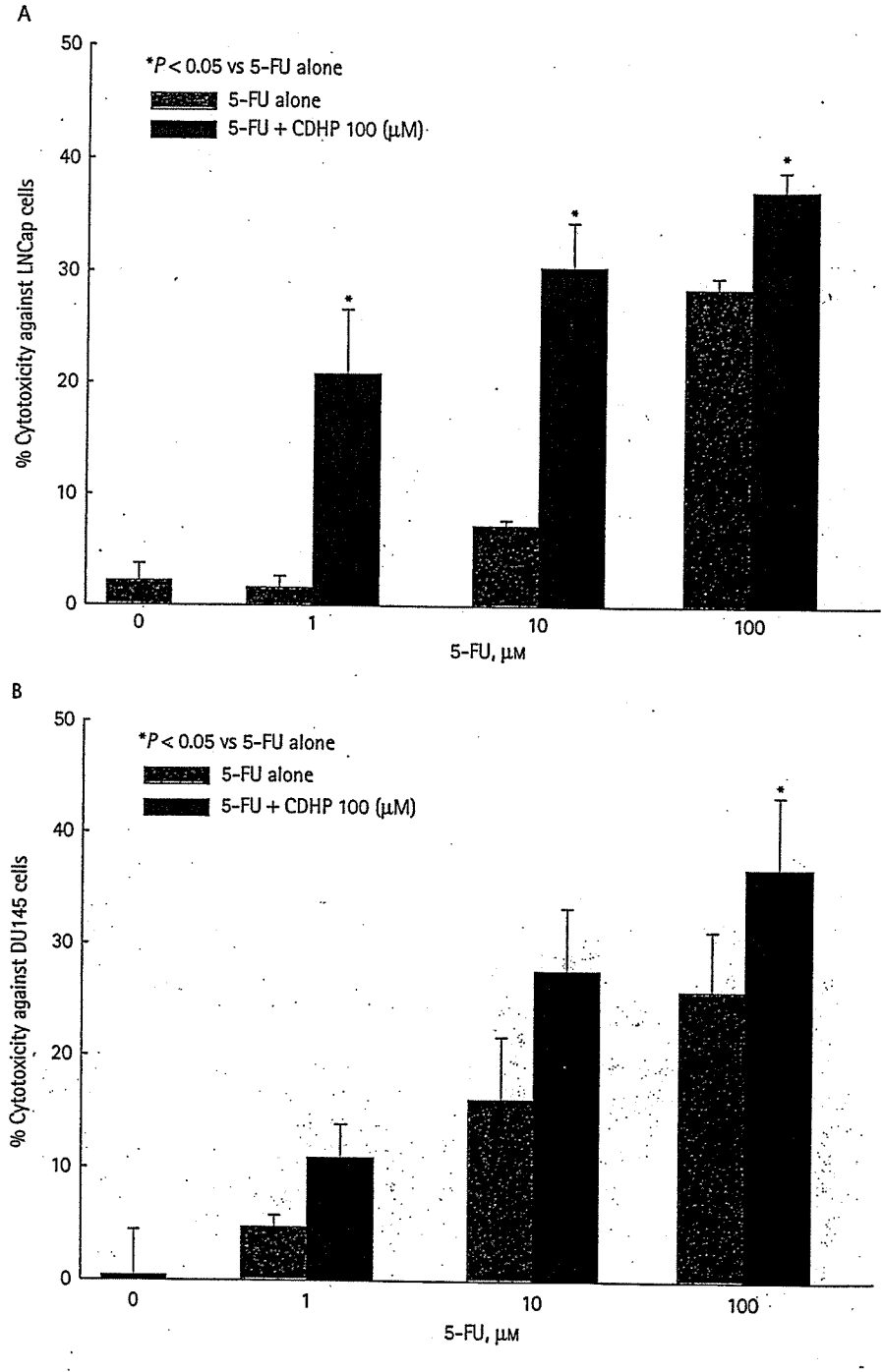
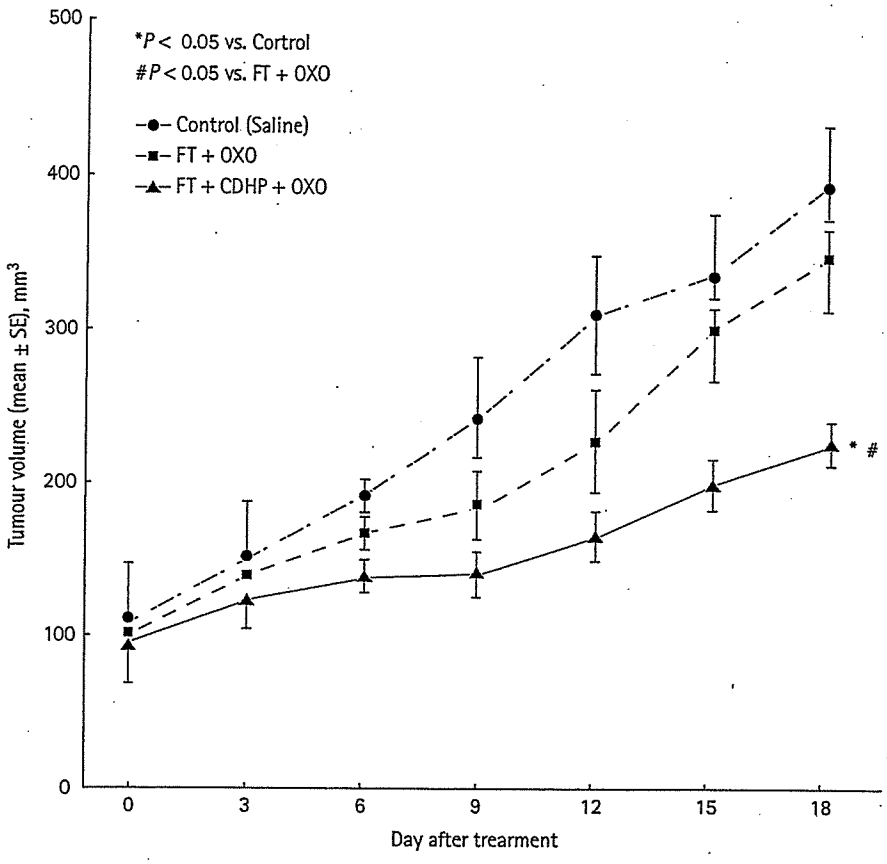


FIG. 4. In vivo *antitumoral effects of FT/CDHP/OXO on DU145 cells. Mice bearing tumour with a starting volume of 120 mm³ were treated with oral administration of saline, FT/OXO (8.3/8.3 mg/kg), or FT/CDHP/OXO (8.3/2.4/8.3 mg/kg) daily; eight mice per group. *P < 0.05 vs control, #P < 0.05 vs FT/OXO.*



cancer, the accurate prognosis might help doctors to decide upon more intensive therapeutic approaches in combination with DPD inhibitors. However, further studies are required for confirmation.

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CONFLICT OF INTEREST

None declared.

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Correspondence: Yoichi Mizutani, Department of Urology, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-Ku, Kyoto 602–8566, Japan.
e-mail: ymizutan@koto.kpu-m.ac.jp

Abbreviations: **DPD**, dihydropyrimidine dehydrogenase; **5-FU**, 5-fluorouracil; **CDHP**, 5-chloro-2, 4-dihydroxypyridine; **OXO**, potassium oxonate; OPRT, orotate phosphoribosyltransferase; **FT**, 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur); **SCID**, severe combined immunodeficiency; **MTT**, microculture tetrazolium dye; **RP**, radical prostatectomy.

ELSEVIER

RUNNING SUTURE FOR VESICOURETHRAL ANASTOMOSIS IN MINILAPAROTOMY RADICAL RETROPUBIC PROSTATECTOMY

TSUNEHARU MIKI, KOJI OKIHARA, OSAMU UKIMURA, SOH USIJIMA, KIMIHIKO YONEDA, YOICHI MIZUTANI, AKIHIRO KAWAUCHI, MINORU KOGA, AND MASAMI TAKEYAMA

ABSTRACT

Introduction. We used a running suture method for vesicourethral anastomosis in patients undergoing minilaparotomy radical retropubic prostatectomy.

Technical Considerations. The vesicourethral anastomosis using a single knot at the 6:30-o'clock position is created with two steps of semicircular running suture. A total of 21 consecutive patients underwent this running suture method using the Endostitch in the hands of a single surgeon (T.M.) between March and November 2004. The running suture procedure was completed in 15 minutes on average. After surgery, no urinary leakage at the anastomotic site was found. Satisfactory continence was achieved in the short term in 100% (0 to 1 pad per day) of cases. However, dilation at the anastomosis using a metal dilator was required in 2 patients immediately after surgery.

Conclusions. The running suture method is considered a feasible alternative in minilaparotomy radical retropubic prostatectomy. UROLOGY **67:** 410–412, 2006. © 2006 Elsevier Inc.

Minilaparotomy radical prostatectomy is reportedly a favorable procedure compared with standard radical prostatectomy in terms of reducing incisional pain and hastening recovery.[1] From March 2004, we have used a 6-cm lower abdominal midline incision for minilaparotomy radical prostatectomy. A minimal incision sometimes makes the anastomosis suture difficult, because the needle driver cannot be handled effectively with the small operative exposure. To manage the anastomosis suture successfully, we have applied a running suture method using the Endostitch and two braided absorbable sutures.

SURGICAL TECHNIQUE

After minilaparotomic removal of the prostate has been accomplished, the bladder neck is everted to ensure a mucosa-to-mucosa anastomosis. Before starting the running suture, two 2-0 braided absorbable sutures (Polysorb 2-0, 120) are tied together at their tail ends (Fig. 1A, upper). The vesicourethral anastomosis is created with two steps of semicircular running suture (a clockwise suture from the 6:30-o'clock to 12-o'clock positions and an anticlockwise suture from the 5:30-o'clock to 12-o'clock positions).

The first needle is passed from outside to inside the urethra at the 6:30-o'clock position (Fig. 1A, lower) using a needle holder (Endostitch) and then from inside the bladder to the outside (Fig. 1B, upper). After passing at the 6:30-o'clock position between the urethra and bladder, a knot is made at the 6:30-o'clock position on the urethra (Fig. 1B, lower).

The needle is repeatedly passed from the urethra (outside to inside) to the bladder neck (inside to outside) in a clockwise and semicircumferential manner to the 12-o'clock position (Fig. 1C, upper).

The surgeon then changes to a second needle and manipulates the same Endostitch device. The needle is passed in the same way but rotating counterclockwise (Fig. 1C, lower). Before reaching the 1-o'clock position, a 20F Foley catheter is placed into the bladder. The balloon on the catheter is filled with 20 mL water. When the running stitch is achieved, gentle traction is exerted on the Foley catheter to bring the bladder in contact with the urethra. Then the operator pulls up each thread gently to attach the urethra

From the Department of Urology, Kyoto Prefectural University of Medicine, Kyoto, Japan; and Department of Urology, Kenporen Osaka Central Hospital, Osaka, Japan

Reprint requests: Koji Okihara, M.D., Ph.D., Department of Urology, Kyoto Prefectural University of Medicine, Kawaramachi Hirokoji, Kyoto 602-8566, Japan. E-mail: okiharakoji@hotmail.com

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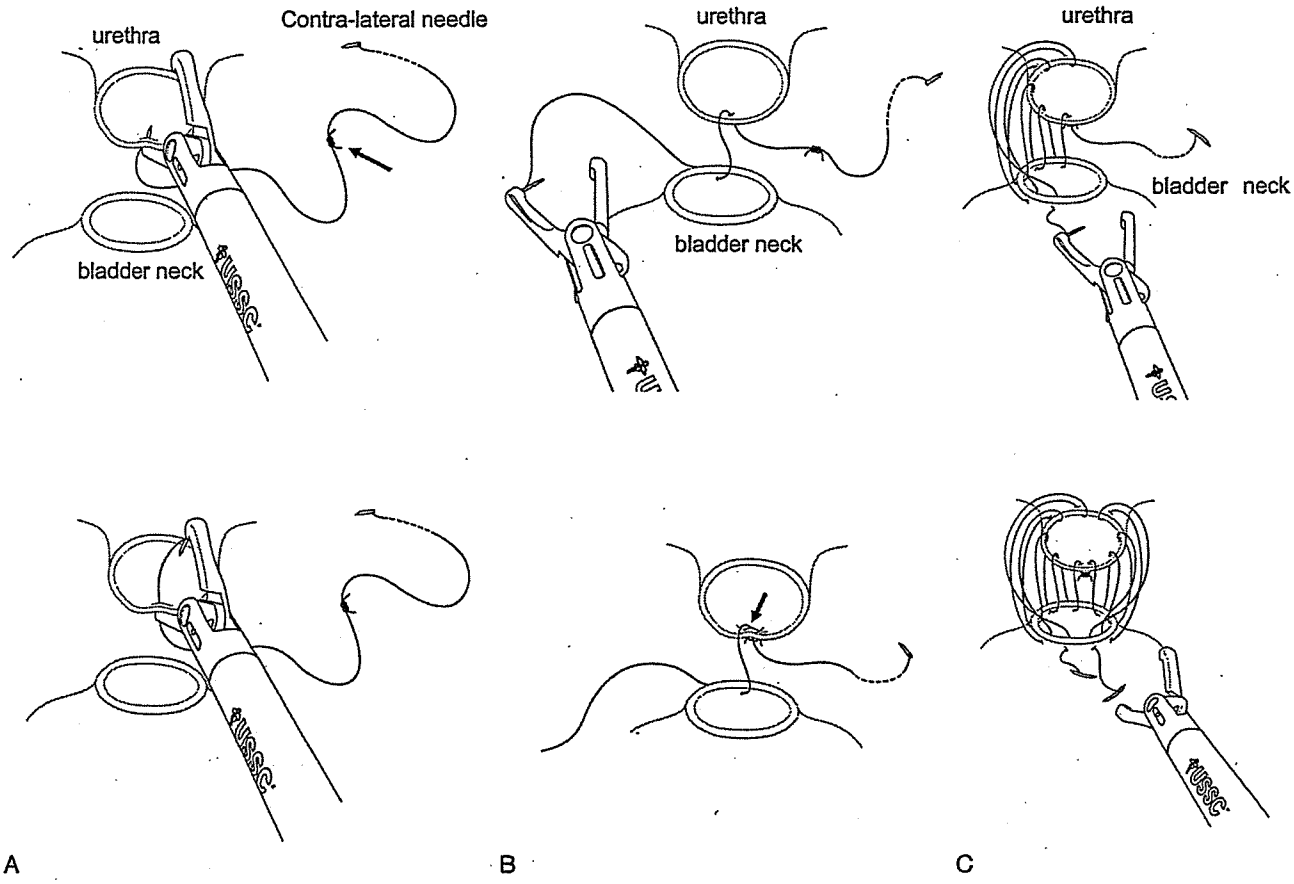

FIGURE 1. *(A) Two 2-0 absorbable monofilaments (Polysorb 2-0, 120) were sutured at the edge of each filament (arrow). We routinely do not leave any stitches in the urethra before excision of prostate (upper). First needle passed from outside to inside of urethra at 6-o'clock position (lower). (B) Needle passed from inside bladder to outside at 6-o'clock position (upper). After passing at 6-o'clock position between urethra and bladder, knot tied at 6-o'clock position on urethra (lower). (C) Needle repeatedly passed from urethra (outside to inside) to bladder neck (inside to outside) in clockwise and semicircumferential manner to 12-o'clock position (upper). Needle passed in same way with anticlockwise rotation (lower).*

and bladder neck mucosa to mucosa. Next, a single suture is made at the 12-o'clock position using knotting forceps. Finally, the bladder is filled with 150 mL saline to test the integrity of the anastomosis.

RESULTS

In the 21 cases in this series, it took between 12 and 20 minutes (average 15) to complete the running suture. Before catheter removal 5 days after surgery, contrast cystography revealed no obvious leakage in any of the patients. The urethral catheter was removed 6 to 7 days after surgery. Without exception, no urinary leakage occurred at the anastomotic site. In the outpatient referral unit, the operating surgeon interviewed the patients regarding the number of pads used per day. During follow-up of at least 3 months, satisfactory continence, defined as 0 (n = 19) to 1 pad (n = 2), was achieved in all patients in this study. Only the initial 2 patients complained of mild urinary dysuria immediately after removal of the catheter. Anastomosis stricture was diagnosed by retrograde urethrography in these 2 patients. Dilation at the anastomosis using a metal dilator was performed successfully in both patients without endoscopic dilation.

COMMENT

Before using the running suture vesicourethral anastomosis, we performed standard minilaparotomy radical retropubic prostatectomy with a 7-cm midline incision using a retractor with specially designed blades. A technique using a special retractor to achieve good exposure was also reported by LaFontaine *et al.*[1] They applied five 2-0 absorbable interrupted sutures for the anastomosis. In their report, four initial sutures were placed in each quadrant of the urethra and one suture was placed at the 6-o'clock position before complete division of the urethra. Leaving the stitches in the urethra made the anastomosis easy, specifically in the minilaparotomic procedure. However, in this method, stitches sometimes become entangled in the urethra immediately before the anastomosis.

TABLE I. *Current reports of running suture for urethrovesical anastomosis in radical prostatectomy*

Reference	RP	Patients (n)	Method for RS	Time Required for RS* (min)	Continence Rate (%)	Urinary Leakage (%)
Hoznek *et al.*,[2] 2000	LRP	30	First RS from 3-o'clock to 9-o'clock position Second RS from 2-o'clock position	23–39 (31)	84 (6 mo)	10
Abbou *et al.*,[4] 2000	LRP	33	Two-step semicircumferential RS	NA	84 (1 mo)	0
van Velthoven *et al.*,[3] 2003	LRP	122	Single knot at 12-o'clock position	14–48 (35)	NA	0
Lee *et al.*,[5] 2004	Ro-RP	100	Single knot at 12-o'clock position (same as Ref. 3)	NA	NA	NA
Menon *et al.*,[6] 2004	Ro-RP	120	First RS from 4-o'clock to 12-o'clock position, two-step RS	5–34 (13)	96 (3 mo)	20

Key: RP = radical prostatectomy; RS = running suture; LRP = laparoscopic RP; Ro-RP = robotic-assisted RP; NA = not available.
** Mean in parentheses.*

To avoid having to disentangle stitches, we routinely leave no stitches in the urethra before excision of the prostate.

LaFontaine *et al.*[1] also reported that in minilaparotomy radical prostatectomy the urethral catheter (18F Foley) was left in place for at least 2 weeks. Similar to their procedure, we started minilaparotomy radical prostatectomy using an interrupted suture for vesicourethral anastomosis in 2001. In our initial series, we left the urethral catheter in place for 10 to 14 days, following their experience. Thereafter, we decided to reduce the time the catheter was indwelling to 6 to 7 days.

To reduce the midline incision by 1 cm inevitably causes difficulty in handling the needle driver if no stitches are to be left in the urethra. To solve this problem, we have applied a laparoscopic instrument for open surgery. The advantage of using the Endostitch is that inserting a hand at the anastomotic site is not required. Moreover, the time needed is significantly shorter with a running suture than with an interrupted suture. The evidence can be found in the Results section. Some clinical investigators have reported a running suture method for laparoscopic radical prostatectomy and robotic-assisted laparoscopic radical prostatectomy[2–6] (Table I). Our technique for the running suture is almost the same as that reported by van Velthoven *et al.*[3] They applied a single-knot method (two semicircles blocked by a knot at the 6-o'clock position and tightened by a single knot at the 12-o'clock position). The difference between their study and ours is the location of the primary knot at the 6-o'clock position (on the urethral side in our series). Compared with other series using laparoscopic surgery, the time required for the running suture in our series is almost similar. In addition, the continence rate in our study was 90% (19 of 21) 3 months after surgery. These results are also similar to those in other reports.

Two of our patients experienced anastomotic stenosis. In laparoscopic radical prostatectomy, Hoznek *et al.*[2] demonstrated that stenosis does not occur at the urethrovesical anastomosis created with running sutures, because the Foley catheter prevents any narrowing of the anastomosis circumference. The reason for the anastomotic stenosis in our series may have been because the suture line was tighter than it is in laparoscopic surgery. We suggest that paying attention to the degree of tightness at the suture line may help avoid anastomotic stenosis in minilaparotomy radical prostatectomy. To assess the incidence of anastomotic stenosis in the running suture method accurately, it will be necessary to have experience with a larger number of cases.

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ELSEVIER

COMPLEXED PSA IMPROVES PROSTATE CANCER DETECTION: RESULTS FROM A MULTICENTER JAPANESE CLINICAL TRIAL

KOJI OKIHARA, OSAMU UKIMURA, TERUKAZU NAKAMURA, SOH USHIJIMA, YOICHI MIZUTANI, AKIHIRO KAWAUCHI, YOSHIO NAYA, MUNEKADO KOJIMA, AND TSUNEHARU MIKI

ABSTRACT

Objectives. To compare the distribution of total and complexed prostate-specific antigen (cPSA) in men with and without prostate cancer with another studied population and to ascertain whether cPSA could enhance the detection of prostate cancer in Japanese men.

Methods. A total of 760 men whose serum total PSA (tPSA) values ranged from 1.0 to 100 ng/mL were enrolled. Serum samples for tPSA and cPSA (ADVIA Centaur) were obtained in all cases. The area under the curve was calculated for comparison of the tPSA and cPSA values. We calculated the number of cancers missed and false-positive results at various cutoff values of cPSA compared with the conventional tPSA threshold of 4.0 ng/mL.

Results. Prostate cancer was detected in 268 (35.3%) of 760 patients. cPSA was greater than 8.3 ng/mL (equivalent to 10.0 ng/mL tPSA) in 46.6% of the men with cancer. The area under the curve for cPSA (0.741) was significantly better than that for tPSA (0.721, $P < 0.001$). At a sensitivity of 85% to 95%, significant differences were found in the corresponding specificity between tPSA and cPSA. cPSA at a 3.0-ng/mL threshold detected an identical number of cancers as a tPSA cutoff of 4.0 ng/mL; however, it decreased the false-positive results by 28 cases.

Conclusions. To our knowledge, this is the first report of the distribution of cPSA in Japanese men using a urologic referral population. cPSA can be an alternative to tPSA as the first screening test. A substantial number of men in Japan with prostate cancer are currently diagnosed with a tPSA value greater than 10.0 ng/mL. UROLOGY **67:** 328–332, 2006.

In 1998, a novel assay for complexed prostate-specific antigen (cPSA), which avoided the use of antibodies to α_1-antichymotrypsin (ACT),[1] was developed. The Bayer cPSA assay can measure PSA-ACT and other immunoreactive fractions of PSA. Since the first reports, several retrospective and prospective studies focusing on the clinical usefulness of cPSA with European and American populations have been reported. Most of these studies have concluded that cPSA could enhance prostate cancer detection in men with a serum total PSA (tPSA) level between 4 and 10 ng/mL,[2,3] as well as at levels of 4.0 ng/mL or less.[4–7] Recently, the usefulness of cPSA as a screening tool was assessed in African-American men.[8] Considering the potential ethnic differences in cPSA, we conducted the first study of the new cPSA assay (Bayer ADVIA Centaur cPSA) in Japanese men.[9] The Bayer cPSA assay could replace tPSA as a first screening test and could enhance cancer detection compared with tPSA. The aims of this study were to confirm the established cutoff value of cPSA and to compare the distributions of cPSA in benign and malignant disease in Japanese men with those from an American and European multicenter clinical trial.[10]

MATERIAL AND METHODS

Between January 1999 and August 2004, we archived serum samples collected from outpatients referred to the Kyoto Prefectural University of Medicine (Kyoto), Matsushita Memorial

From the Department of Urology, Kyoto Prefectural University of Medicine, Kyoto, Japan; Department of Urology, Matsushita Memorial Hospital, Osaka, Japan; and Department of Urology, Nagoya Urology Hospital, Nagoya, Japan

Reprint requests: Koji Okihara, M.D., Department of Urology, Kyoto Prefectural University of Medicine, Kawaramachi Hirokoji, Kyoto 602-8566, Japan. E-mail: okiharakoji@hotmail.com

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Hospital (Osaka), and Nagoya Urologic Hospital (Nagoya). The samples were collected before any prostatic manipulation and were assayed retrospectively. Participants with a personal history of prostate cancer or symptoms of acute prostatitis and/or urinary tract infection were excluded from this study. Between January 1999 and December 2002, 214 men underwent eight-core transperineal ultrasound-guided prostate needle biopsy (conventional sextant and far lateral portion of the peripheral zone: one core each from the right and left sides).[9] Thereafter, an additional 585 consecutive biopsies were performed in the same manner. The institutional distribution of biopsies was 300 from Kyoto, 295 from Nagoya, and 204 from Osaka. The indication for prostate biopsy was either a tPSA level (Hybritech Tandem-R assay) greater than 4.0 ng/mL or abnormal digital rectal examination (DRE) findings, regardless of the tPSA value.

A blood sample was drawn to measure tPSA (Hybritech Tandem-R assay) and cPSA (Bayer ADVIA Centaur cPSA). As previously described,[9] the Bayer ADVIA Centaur cPSA assay is a simultaneous sandwich immunoassay that uses magnetic particles as the solid phase. In the Centaur assay, a light reagent with polyclonal goat anti-PSA antibody with acridinium eater is applied.

All serum samples were drawn before DRE. Within 24 hours of collection, all samples were centrifuged and stored at −70°C. The minimal specimen volume was 0.7 mL.

The chi-square test was used for each statistical comparison between two specificities at the same sensitivity. For continuous variables, a *t* test or analysis of variance was used to compare groups. Receiver operating characteristic curves were generated by plotting the sensitivity versus (1 − specificity). All statistical calculations were performed using the Statistical Analysis Systems (SAS Institute, Cary, NC) or Statistical Package for Social Sciences, version 10.0 (SPSS, Chicago, Ill) software package. $P < 0.05$ was taken as the level of statistical significance.

RESULTS

Of the 799 men with a complete sample collection, 307 (38%) had positive biopsy results for prostate cancer, and 9 (1.1%) had prostatic intraepithelial neoplasia. In the 799 men, the tPSA value ranged from 1.0 to 6820 ng/mL (median 7.4). The tPSA value was greater than 100.0 ng/mL in 39 men (4.9%). Similar to the recent studies,[8,10] the 39 men were omitted from analysis as outliers for descriptive and comparison purposes. Consequently, we enrolled 760 consecutive men undergoing a first-time prostate biopsy; of these, 268 (35.2%) had histologically confirmed prostate cancer. In the 131 patients with a tPSA value of 4.00 ng/mL or less, prostate biopsies were performed because of abnormal DRE results; of these men, cancer was detected in 18 (13.8%). Of the 268 men with cancer, 77 (29%) were diagnosed with clinical Stage T3 disease. Of the 77 men with Stage T3 disease, 60 (78%) had a tPSA level of 10.01 ng/mL or more. The biopsy Gleason score was less than 7 in 64 (24%) and 7 in 172 (64%) of 268 men.

Of the 760 men, 300 (39.5%) had suspicious DRE findings suggestive of prostate cancer by the supervising urologists at each institution. Of the 760 men, 568 (74.7%) answered the International

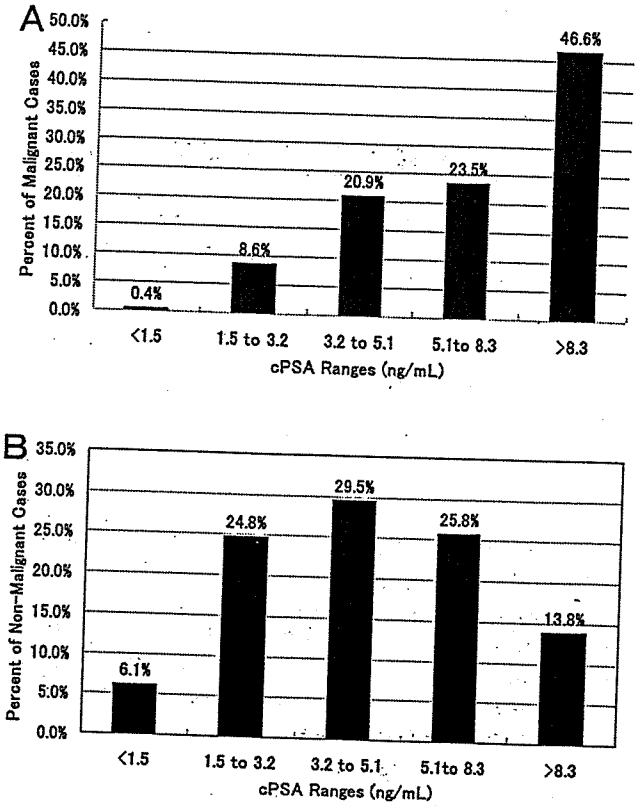

FIGURE 1. *Distribution of cPSA in men (A) with and (B) without biopsy proven prostate cancer.*

Prostate Symptom Score questionnaire before prostate biopsy. The total International Prostate Symptom Score was 0 to 7 (mild symptoms), 8 to 19 (moderate), and 19 to 35 (severe symptoms) for 238 (42.0%), 228 (40.2%), and 102 men (17.8%), respectively. The average patient age for men with cancer was 71.0 ± 7.5 years (median 71), and they were significantly older than the men without cancer (67.2 ± 7.7 years, median 68, $P < 0.001$). Comparing the patient populations from each institution, no significant differences were found in mean age (Kyoto, 67.5 ± 8.0 years; Osaka, 66.9 ± 7.8; and Nagoya, 65.1 ± 9.4) or the incidence of cancer (Kyoto, 38.3% [107 of 279]; Osaka, 35.1% [70 of 199]; and Nagoya, 32.2% [91 of 282]).

The median tPSA for the cancer group was significantly more than that for the benign group (10.0 ng/mL versus 6.1 ng/mL, $P < 0.001$). Similarly, the cPSA levels were greater in the cancer group (median 7.74 ng/mL, range 0.71 to 65.2) than in the noncancer group (median 5.69 ng/mL, range 0.87 to 51.2, $P < 0.001$). In addition, the 25th and 75th quartiles of cPSA in the cancer group and noncancer group were 4.61 and 16.67 ng/mL and 2.88 and 6.24 ng/mL, respectively.

To determine the equivalency values for cPSA and tPSA, we used the ranges reported by Partin *et al.*[10] The equivalent tPSA value for a cPSA value of 0 to 1.5, 1.5 to 3.2, 3.2 to 5.1, 5.1 to 6.8, 6.8 to 8.3, and greater than 8.3 ng/mL was 0 to 2.0, 2.0 to 4.0,