Institutions that were registered

Institution	1999		2000		2001	
	Number	Number of patients	Number	Number of patients	Number	Number of patients
University Hospital	17	298	38	750	30	596
National Hospital	3	86	50	644	63	1003
General Hospital	52	754	57	800	78	955
Private Hospital, Clinic	0	0	7	115	10	124
Total	72	1138	152	2309	181	2678

Institution	1999	2000	2001
	Number of patients	Number of patients	Number of patients
Hokkaido			
Hokkaido University	12	14	–
Sapporo Medical University	18	–	27
Asahikawa Medical College Hospital	–	8	–
Otaru Municipal Hospital	20	24	42
Sanjukai Hospital	–	53	–
Sibetsu City Hospital	–	3	–
Hakodate Goryokaku Hospital	–	8	4
Furuya Hospital	–	14	–
Hakodate Hospital	–	–	6
Bibai Rousai Hospital	–	–	10
Kushiro Red Cross Hospital	–	–	7
Kutchan Kosei General Hospital	–	–	12
Teine Keijinkai Hospital	–	–	17
Furano Hospital	–	–	8
Hokkaido Social Insurance Hospital	–	–	12
Muroran City General Hospital	–	–	13
Megumino Hospital	–	–	4
Kohnan Hospital	–	–	7
Aomori Prefecture			
Aomori Prefectural Central Hospital	11	–	–
Towada Municipal Hospital	4	6	15
Oyokyo Kidney Institute, Hirosaki Hospital	–	5	–
Hachinohe Red Cross Hospital	–	–	16
Hachinohe-peace Hospital	–	–	1
Iwate Prefecture			
Iwate Medical University, School of Medicine	–	29	–
Iwate Prefectural Kuji Hospital	–	7	–
Iwate Prefectural Miyako Hospital	–	5	6
Miyagi Prefecture			
Miyagi Cancer Center	–	27	11
Tohoku Kosai Hospital	–	12	–
Akita Prefecture			

Institution	1999	2000	2001
	Number of patients	Number of patients	Number of patients
Ogachi Central Hospital	12	10	–
Yamagata Prefecture			
Yamagata University, School of Medicine	5	–	–
Kitamurayama Hospital	–	7	10
Fukushima Prefecture			
Ohta Atami Hospital	–	2	–
Fujita Public Hospital	–	–	15
Ibaraki Prefecture			
University of Tsukuba	22	22	25
Mito Kyodo Hospital	–	11	–
Mito Red Cross Hospital	–	16	8
Hakujuji General Hospital	–	3	5
Kitaibaraki Municipal General Hospital	–	–	9
Tochigi Prefecture			
Dokkyo University School of Medicine	–	26	–
Ashikaga Red Cross Hospital	23	–	–
Ohtawara Red Cross Hospital	–	–	6
Saiseikai Utsunomiya Hospital	–	–	29
Gunma Prefecture			
Gunma University Hospital	17	–	–
Tatebayashi Kosei Hospital	11	17	12
Saitama Prefecture			
Saitama Cancer Center	20	22	40
National Saitama Hospital	–	14	10
Kasukabe Municipal Hospital	20	–	25
Koshigaya Municipal Hospital	–	68	–
Kawaguchi Medical Center	–	28	–
Saitamaken Saiseikai Kurihashi Hospital	–	25	–
Fukaya Red Cross Hospital	–	–	16
Social Health Insurance Omiya General Hospital	–	–	5
Chichibu Municipal Hospital	–	–	18
Chiba Prefecture			
Ichikawa General Hospital, Tokyo Dental College	–	7	–
Matsudo Municipal Hospital	23	–	–
Yatsuhoken Hospital	–	6	5
SECOMEDIC Hospital	–	–	12
Tokyo			
Juntendo University, School of Medicine	22	–	–
Keio University School of Medicine	32	37	–
Teikyo University	–	18	–
Nippon Medical School	–	26	–
Tokyo University	–	12	–
Tokyo Medical University	–	35	41

Institution	1999	2000	2001
	Number of patients	Number of patients	Number of patients
Itabashi Hospital Nihon University School of Medicine	–	–	36
Nihon University Surugadai Hospital	–	–	15
Kyorin University	–	–	41
National Cancer Center Hospital	50	56	91
National Hospital Tokyo Disaster Medical Center	–	–	10
International Medical Center of Japan	19	–	–
Tokyo Industory Hospital	–	4	11
Toranomon Hospital	25	–	–
Sassa General Hospital	6	4	–
Inagi Municipal Hospital	7	6	–
Nagakubo Clinic	17	12	–
Tobu Chiiki Hospital	28	–	–
Nishikubo Hospital	–	15	12
Tokyo Electric Power Hospital	–	3	–
Akabane Central General Hospital	–	0	–
Self-defense Forces Central Hospital	–	–	1
Machida Municipal Hospital	–	–	21
Social Insurance Central General Hospital	–	–	15
JR Tokyo General Hospital	–	–	12
Towa Hospital	–	–	1
Mishuku Hospital	–	–	3
Kanagawa Prefecture			
St. Marianna University School of Medicine	–	11	10
St. Marianna University Yokohama City Seibu Hospital	–	4	7
Tokai University	–	43	32
National Sagamihara Hospital	–	–	17
Yokohama City Kowan Hospital	5	–	–
Chigasaki Municipal Hospital	17	–	–
Inada Noborito Hospital	9	–	10
Health Insurance Kawasaki Central Hospital	5	–	–
Odawara City Hospital	20	–	24
The International Goodwill Hospital	16	13	25
Kawasaki Municipal Kawasaki Hospital	–	21	20
Saiseikai Kanagawaken Hospital	–	26	26
Yokohama Sakae Kyosai Hospital	–	22	13
Yokosuka Hokubu Kyosai Hospital	–	5	9
Yokohama Rousai Hospital	–	35	–
Atsugi City Hospital	–	8	–
Yokosuka Kyosai Hospital	–	–	27
Social Insurance Yokohama Central Hospital	–	–	12
Kanagawa Prefectural School of Nursing and Midwifery	–	–	6
Niigata Prefecture			
Niigata Cancer Center Hospital	46	–	63

Institution	1999	2000	2001
	Number of patients	Number of patients	Number of patients
Niigata City General Hospital	–	–	33
Niigata Kobari Hospital	–	–	15
Toyama Prefecture			
Toyama Medical and Pharmaceutical University	–	–	16
Takaoka Hospital	15	–	–
Saiseikai Toyama Hospital	–	–	8
Ishikawa Prefecture			
Kanazawa University	–	17	–
National Kanazawa Hospital	–	11	17
Public Central Hospital of Matto Ishikawa	–	17	9
Kaga Central Public Hospital	–	6	15
Komatsu Municipal Hospital	–	–	8
Fukui Prefecture			
Fukui Prefectural Hospital	11	4	–
Fukuiken Saiseikai Hospital	–	–	32
Yamanashi Prefecture			
University of Yamanashi	–	24	–
Otsuki Municipal Central Hospital	–	–	4
Nagano Prefecture			
Shinshu University School of Medicine	16	24	14
Saku Central Hospital	15	16	15
Omachi General Hospital	10	7	–
Iida Municipal Hospital	–	17	23
Ina Central Hospital	–	–	11
Okaya Municipal Hospital	–	–	13
Showa-inan General Hospital	–	–	8
Gifu Prefecture			
Gifu University, School of Medicine	–	15	15
Gifu Red Cross Hospital	–	–	9
Shizuoka Prefecture			
Hamamatsu University School of Medicine	10	–	–
Hamamatsu Medical Center	18	15	–
Shimada Municipal Hospital	20	24	–
Hamamatsu Red Cross Hospital	–	6	–
Hamaoka Municipal Hospital	–	2	4
Shizuoka Municipal Shimizu Hospital	–	6	25
Numazu City Hospital	–	–	25
Fuji City General Hospital	–	–	20
Aichi Prefecture			
Nagoya University	–	11	5
Aichi Medical University	–	12	–
Fujita Health University Hospital	–	23	18
Red Cross Nagoya First Hospital	29	–	36

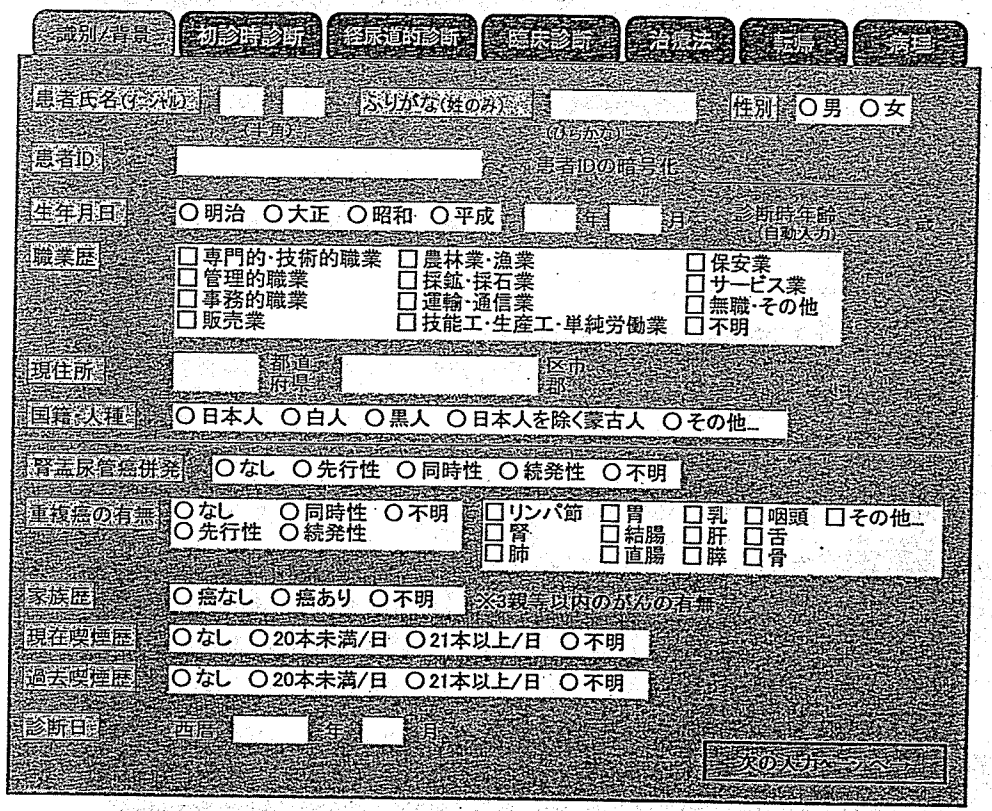
Institution	1999	2000	2001
	Number of patients	Number of patients	Number of patients
Meijo Hospital	12	12	12
Chukyo Hospital	–	33	14
Komaki City Hospital	–	10	10
TOYOTA Memorial Hospital	–	–	12
Anjo Kosei Hospital	–	–	37
Nagoyacity Jouhoku Municipal Hospital	–	–	12
Toyokawa City Hospital	–	–	21
Nagoya Urology Hospital	–	–	32
Mie Prefecture			
Mie University	8	20	31
Mie Chuo National Hospital	–	11	11
Ise Municipal Hospital	–	4	–
Matsusaka Chuo General Hospital	–	–	11
Shiga Prefecture			
Shiga University School of Medicine	15	11	–
Social Insurance Shiga Hospital	–	–	8
Omihachiman City Hospital	–	–	13
Kyoto			
Kyoto University, Faculty of Medicine	37	–	–
Kyoto Prefectural University of Medicine	–	20	24
Meiji University of Oriental Medicine	–	6	–
Kansai Medical University Otokoyama Hospital	–	–	5
Fukuchiyama City Hospital	–	8	7
Kyoto First Red Cross Hospital	–	–	16
Maizuru Red Cross Hospital	–	–	4
Osaka			
Kinki University	–	8	–
Osaka City University	–	32	–
Kansai Medical University	–	–	21
Osaka Police Hospital	29	24	–
Osaka Kosei-nenkin Hospital	11	26	17
Osaka Seamen's Insurance Hospital	9	11	7
Yodogawa Christian Hospital	14	31	12
Bobath Memorial Hospital	1	0	2
Ohno Memorial Hospital	5	1	4
Hanwa Sumiyoshi Hospital	5	–	8
Osaka Red Cross Hospital	–	35	–
Hoshigaoka Koseinenkin Hospital	–	28	–
Izumisano City Hospital	–	19	22
Tane General Hospital	–	16	–
Komatsu Hospital	–	2	–
Saiseikai Tondabayashi Hospital	–	12	–
Saikeikai Hospital and Clinics	–	7	–

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(ペンネーム)
(半角)
ふりがな(姓のみ)
(ひらがな)
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
区市町村郡
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
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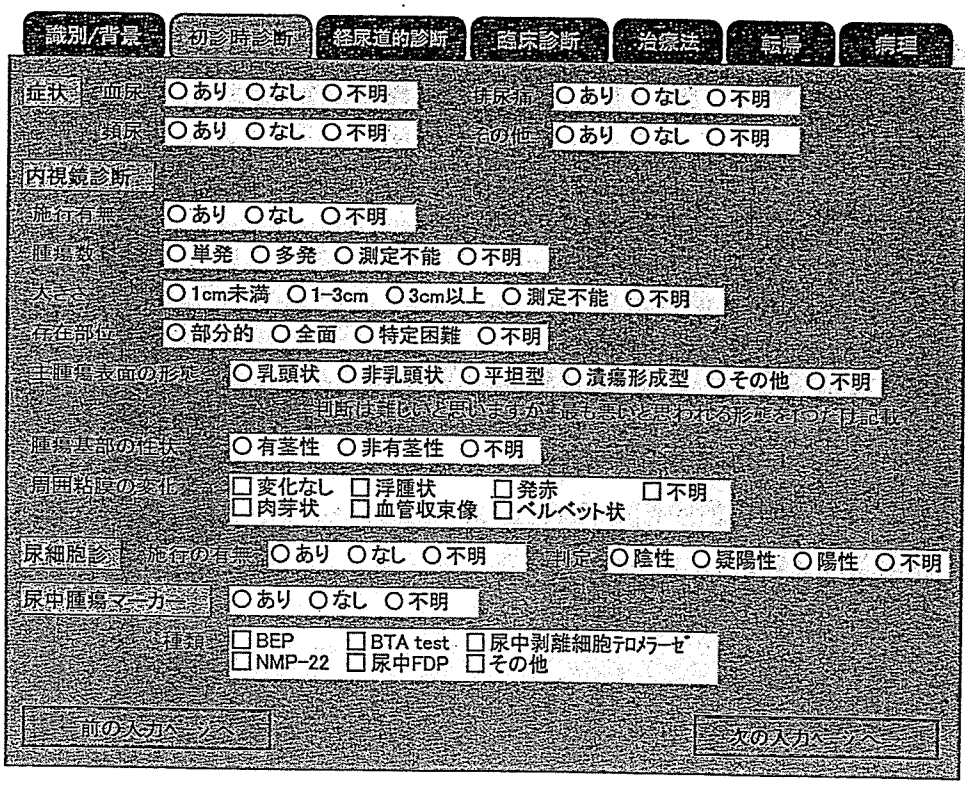
識別/背景
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臨床診断
治療法
転帰
病理
症状 ○あり ○なし ○不明
肉眼尿
頻尿 ○あり ○なし ○不明
排尿痛 ○あり ○なし ○不明
その他 ○あり ○なし ○不明
内視鏡診断
施行有無 ○あり ○なし ○不明
腫瘍数 ○単発 ○多発 ○測定不能 ○不明
大きさ ○1cm未満 ○1-3cm ○3cm以上 ○測定不能 ○不明
存在部位 ○部分的 ○全面 ○特定困難 ○不明
主腫瘍表面の形態 ○乳頭状 ○非乳頭状 ○平坦型 ○潰瘍形成型 ○その他 ○不明
←判断は難しいと思いますが最も悪いと思われる形態をつけ記載
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
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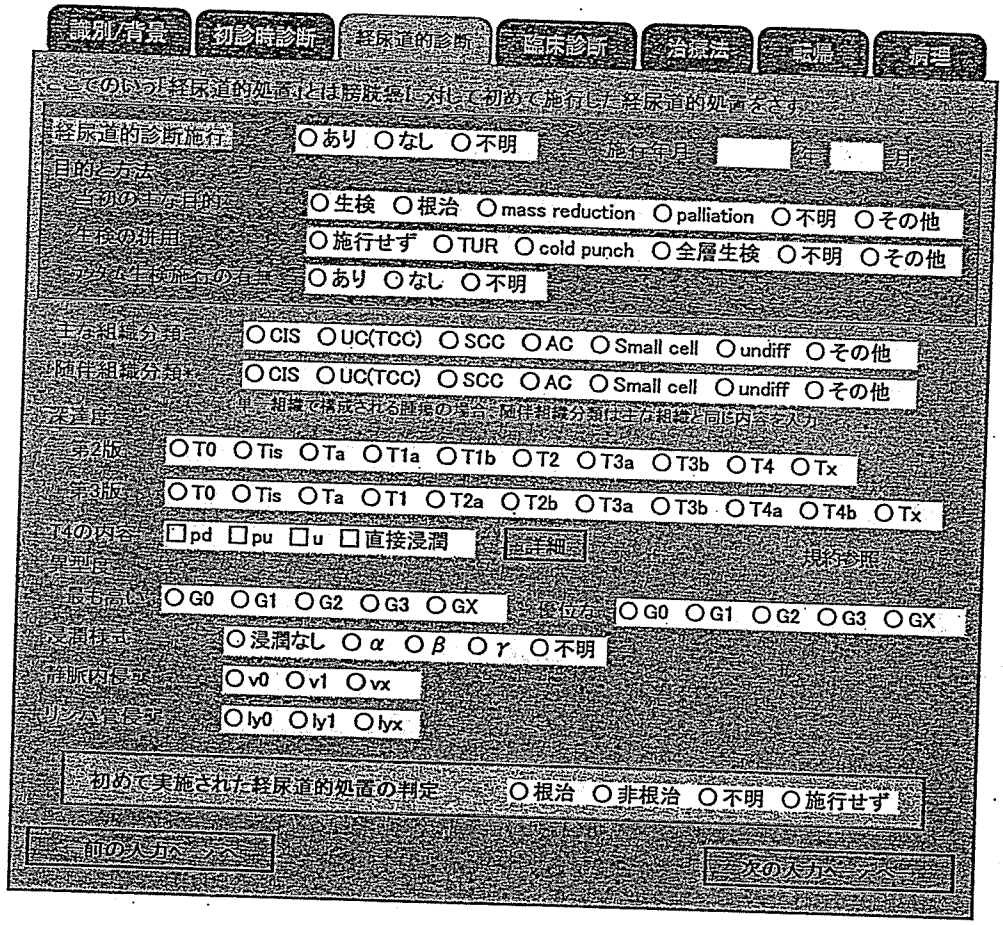
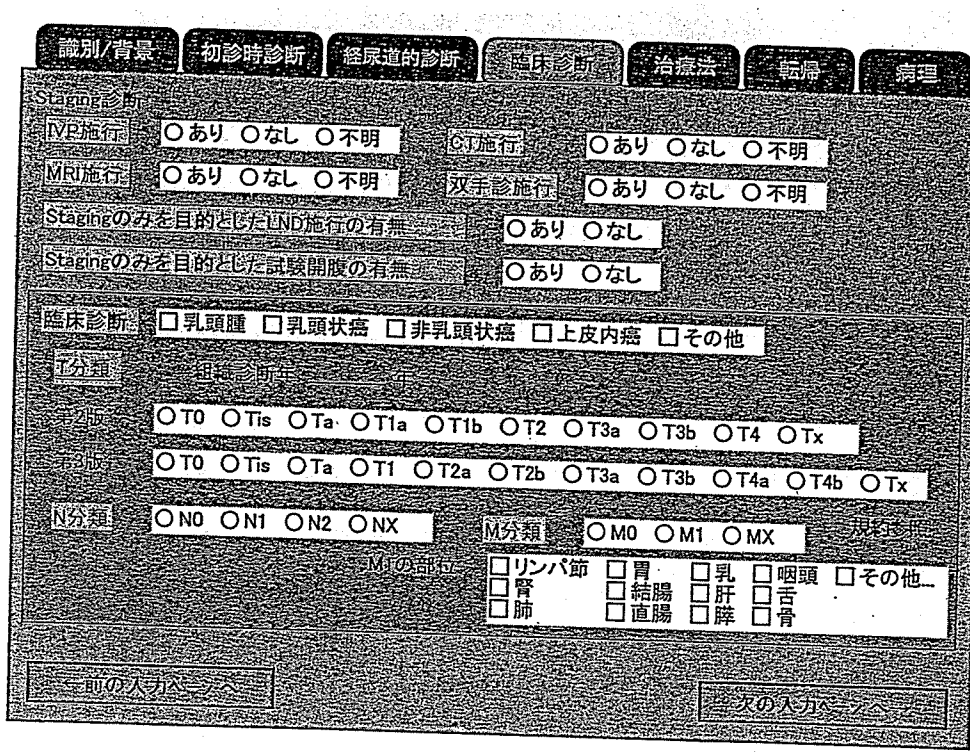
次の入力ページへ


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
ここでのいう経尿道的処置とは膀胱癌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
当初の主な目的
○生検 ○根治 ○mass reduction ○palliation ○不明 ○その他
生検の術用
○施行せず ○TUR ○cold punch ○全層生検 ○不明 ○その他
カテなし生検後の有無
○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
深達度
*1つの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を入力
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
最も高い
○G0 ○G1 ○G2 ○G3 ○GX
低分化
○G0 ○G1 ○G2 ○G3 ○GX
浸潤様式
○浸潤なし ○α ○β ○γ ○不明
静脈内皮
○v0 ○v1 ○vx
リンパ管内皮
○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
一つ前の入力へ
次の入力へ


識別/背景
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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
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
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

再発予防を目的としてTUR後(再発を確認する前)つ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

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量と回数 ○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

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...

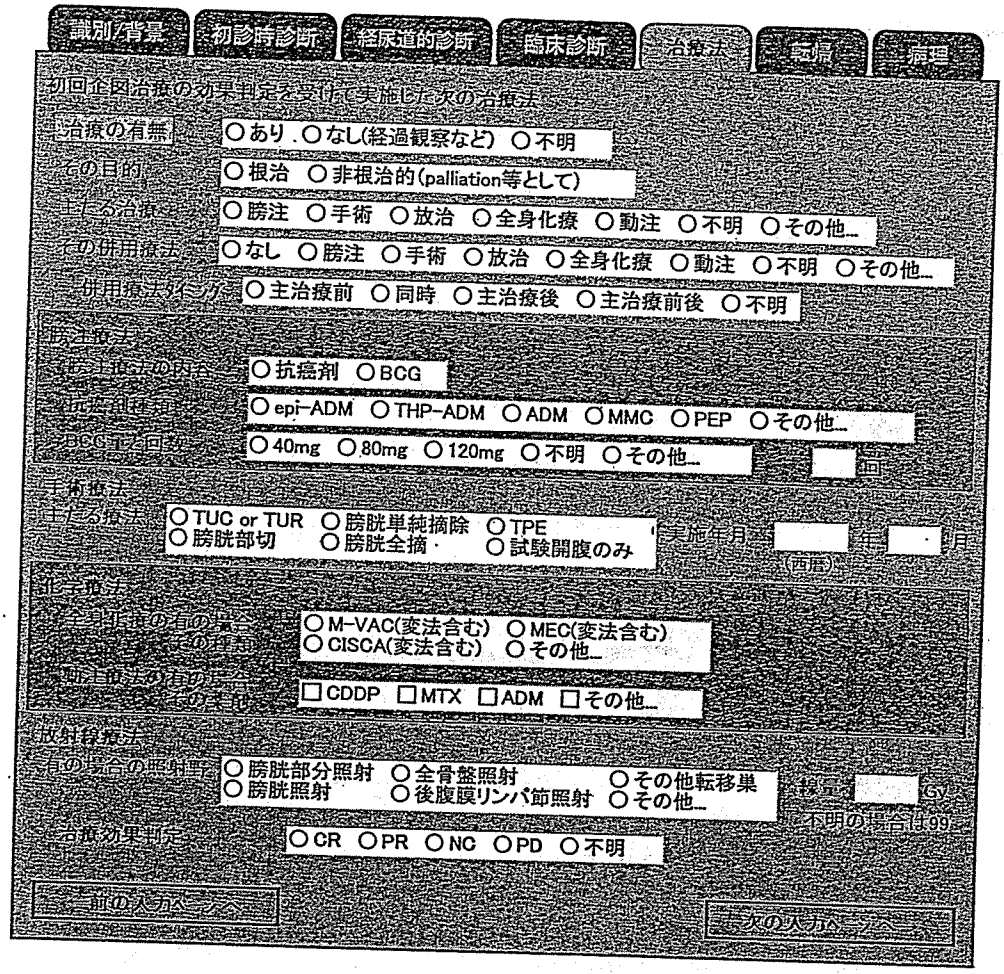
動注療法の有の場合 その種類 □CDDP □MTX □ADM □その他...

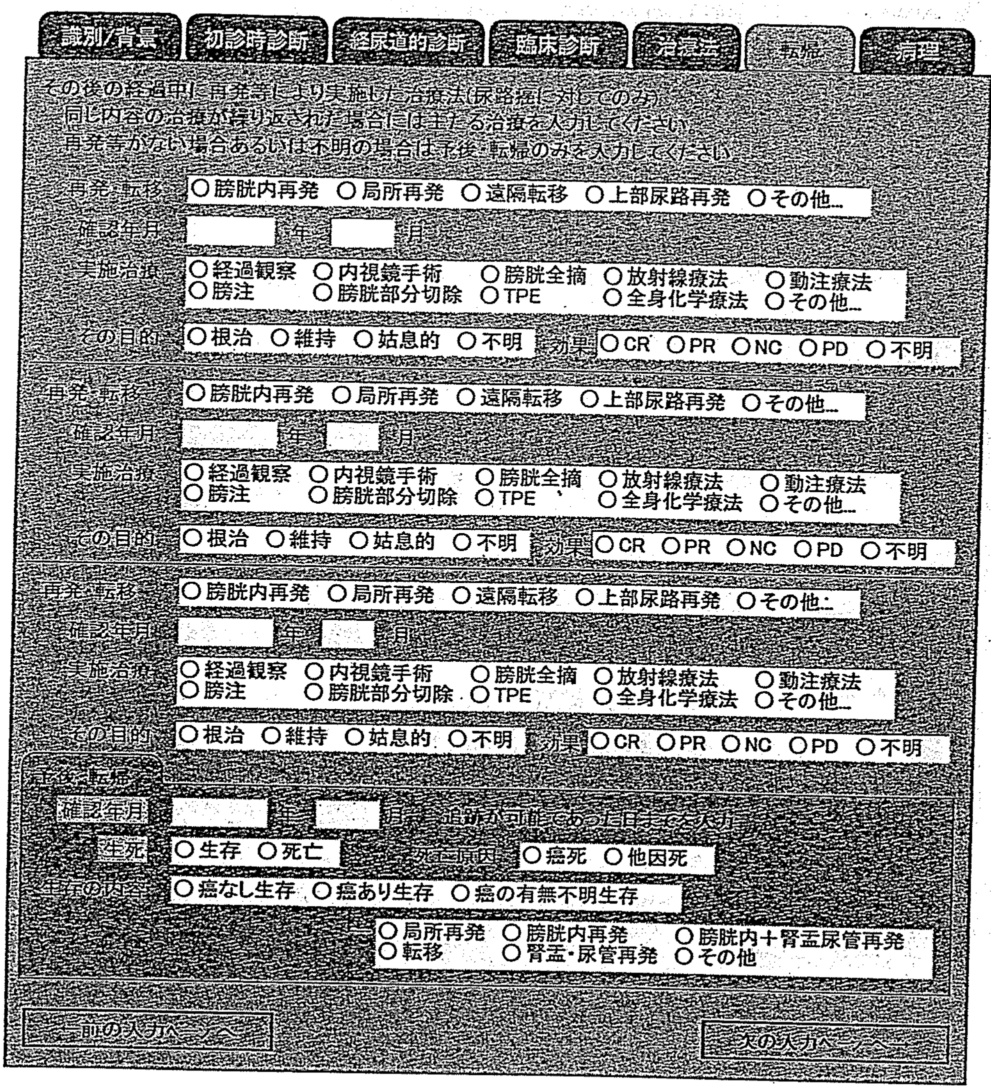
放射線療法

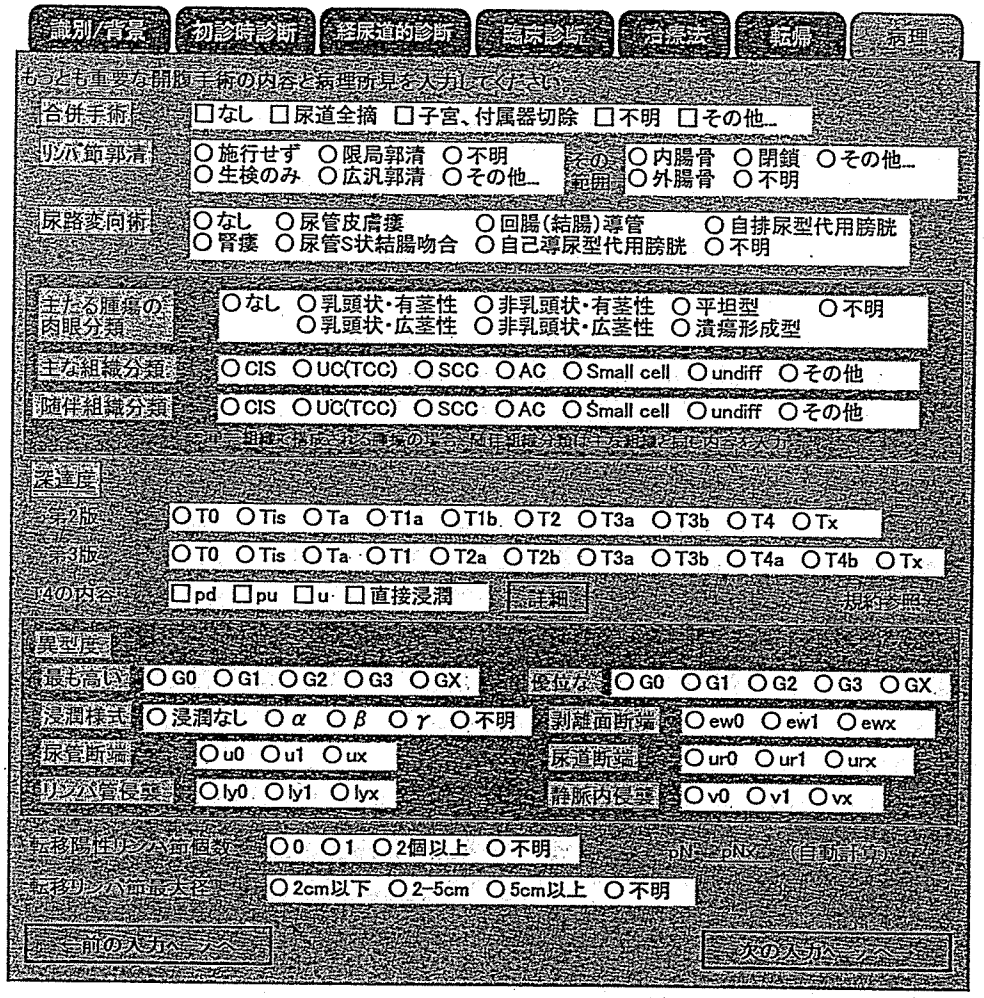
有の場合の照射野 ○膀胱部分照射 ○全骨盤照射 ○その他転移巣 ○膀胱照射 ○後腹膜リンパ節照射 ○その他... 線量 Gy 不明の場合は99

治療効果判定 ○CR ○PR ○NC ○PD ○不明

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
初回全身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)
上記治療
○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
膀注療法
膀注療法の内容
○抗癌剤 ○BCG
抗癌剤種別
○epi-ADM ○THP-ADM ○ADM ○MMC ○PEP ○その他_
BCG注入回数
○40mg ○80mg ○120mg ○不明 ○その他_
回
手術療法
上記療法
○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
(西暦)
年
月
化学療法
上記療法の内容
○M-VAC(変法含む) ○MEC(変法含む)
○CISCA(変法含む) ○その他_
上記療法の有の場合
□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1回
治療効果判定
○CR ○PR ○NC ○PD ○不明
一つ前の入力ページへ
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
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
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
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
※二組織で構成、それ以外の場合、随伴組織分類は主な組織と同じ内容を入力
深達度
→2版
○T0 ○Tis ○Ta ○T1a ○T1b ○T2 ○T3a ○T3b ○T4 ○Tx
3版
○T0 ○Tis ○Ta ○T1 ○T2a ○T2b ○T3a ○T3b ○T4a ○T4b ○Tx
4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
最も低い
○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
→N-→pNX-（自動計算）
転移リンパ節最大径
○2cm以下 ○2-5cm ○5cm以上 ○不明
前の入力へ
次の入力へ

The significance of the expression of dihydropyrimidine dehydrogenase in prostate cancer

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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.

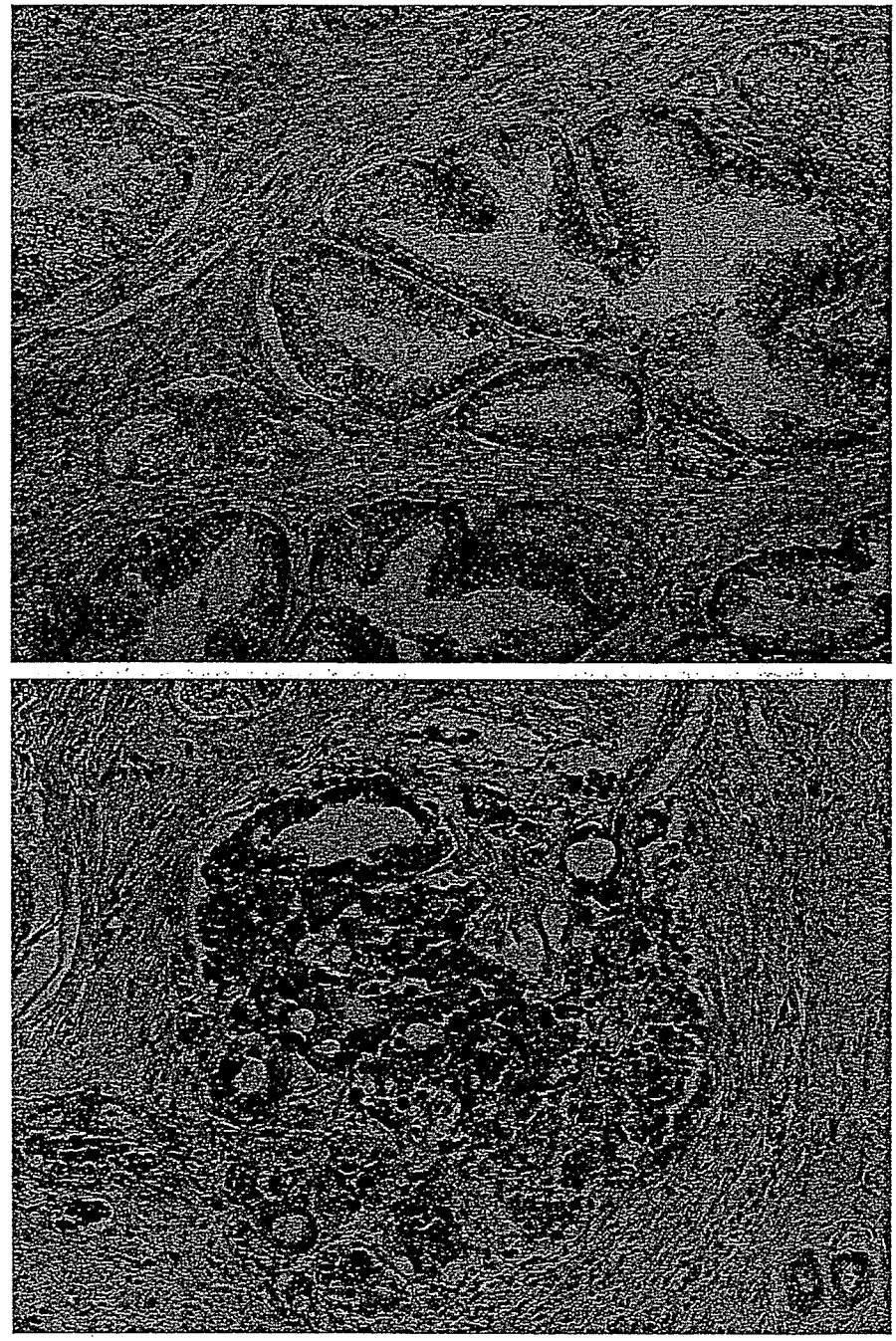
For immunohistochemistry, serial 5-μm sections were cut from formalin-fixed, paraffin wax-embedded slices of the specimens. The sections were de-waxed in xylene, rehydrated with graded alcohols, and antigen retrieved by microwave heating for 15 min. Endogenous peroxidase was blocked by incubating samples 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.

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.*



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

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.

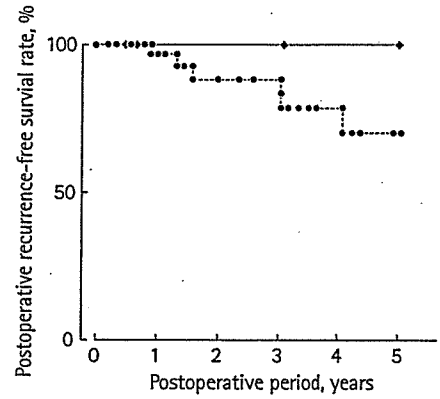
RESULTS

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).*

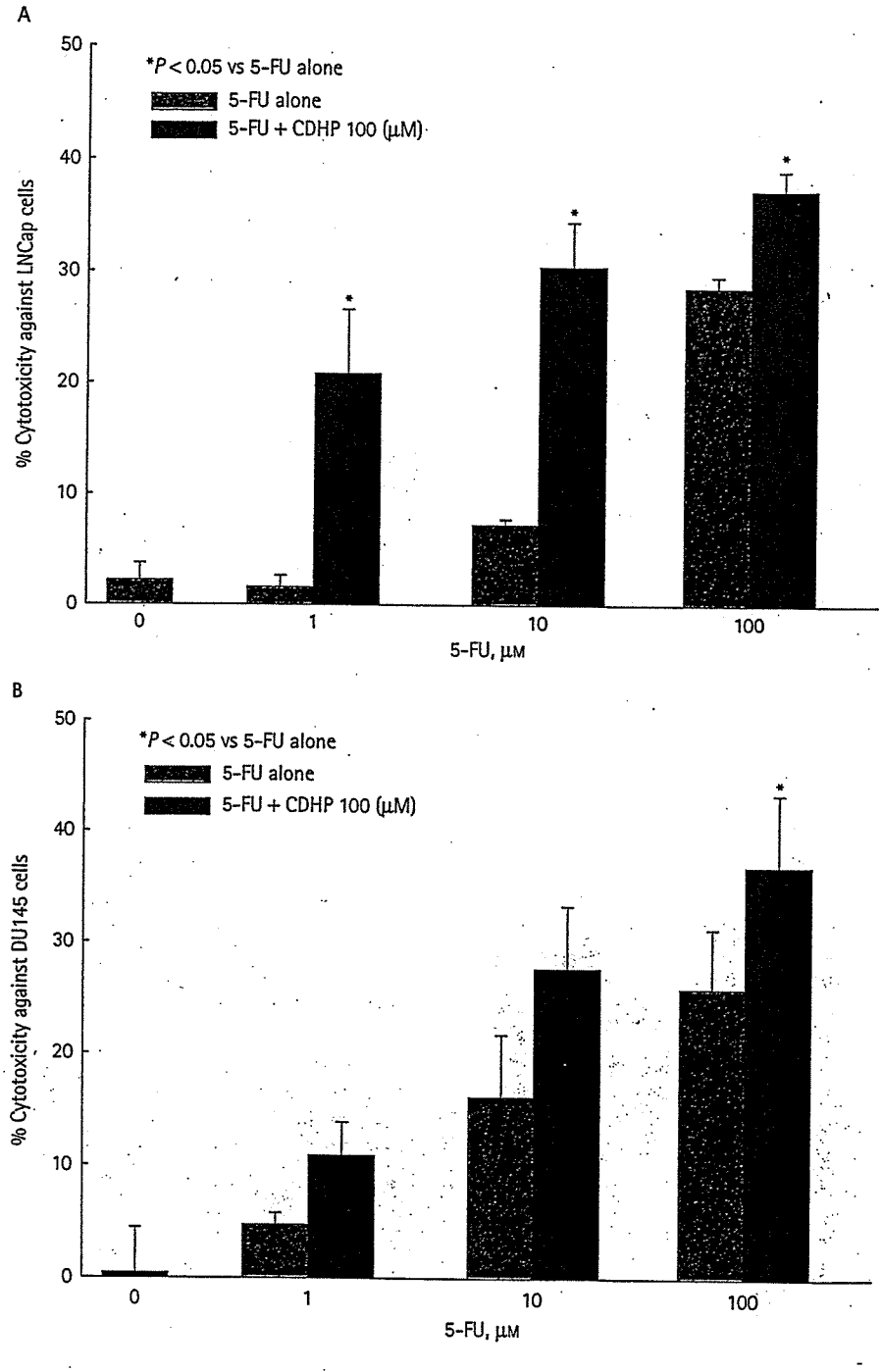
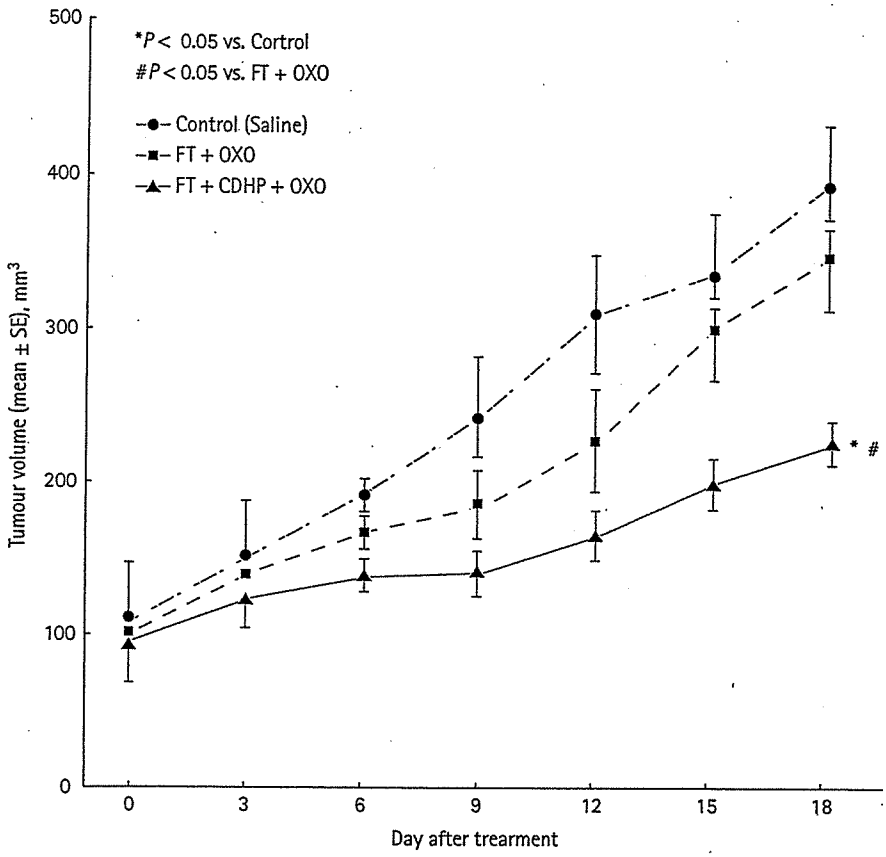


FIG. 4. In vivo *antitumoral effects of FT/CDHP/OXO on DU145 cells. Mice bearing tumour with a starting volume of 120 mm³ were treated with oral administration of saline, FT/OXO (8.3/8.3 mg/kg), or FT/CDHP/OXO (8.3/2.4/8.3 mg/kg) daily; eight mice per group.* *P < 0.05 *vs control*, #P < 0.05 *vs FT/OXO.*



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.

REFERENCES

1 **Ezzeldin H, Johnson MR, Okamoto Y, Diasio RB.** Denaturing high performance liquid chromatography analysis of the DPYD gene in patients with lethal 5-fluorouracil toxicity. *Clin Cancer Res* 2003; **9**: 3021–8
2 **Ezzeldin HH, Lee AM, Mattison LK, Diasio RB.** Methylation of the DPYD promoter: an alternative mechanism for dihydropyrimidine dehydrogenase deficiency in cancer patients. *Clin Cancer Res* 2005; **11**: 8699–705
3 **Mizutani Y, Wada H, Fukushima M *et al.*** The significance of dihydropyrimidine dehydrogenase (DPD) activity in bladder cancer. *Eur J Cancer* 2001; **37**: 569–75
4 **Wei X, McLeod HL, McMurrough J, Gonzalez FJ, Fernandez-Salguero P.** Molecular basis of the human dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity. *J Clin Invest* 1996; **98**: 610–5
5 **Johnson MR, Diasio RB.** Importance of dihydropyrimidine dehydrogenase (DPD) deficiency in patients exhibiting toxicity following treatment with 5-fluorouracil. *Adv Enzyme Regul* 2001; **41**: 151–7
6 **Kobayashi H, Koike T, Nakatsuka A *et al.*** Dihydropyrimidine dehydrogenase expression predicts survival outcome and chemosensitivity to 5-fluorouracil in patients with oral squamous cell carcinoma. *Oral Oncol* 2005; **41**: 38–47
7 **Canellakis ES.** Pyrimidine metabolism. I. Enzymatic pathways of uracil and thymidine degradation. *J Biol Chem* 1956; **221**: 315–22
8 **Fink RM, Fink K, Henderson RB.** Beta-amino acid formation by tissue slices incubated with pyrimidines. *J Biol Chem* 1953; **201**: 349–55
9 **Naguib FN, el Kouni MH, Cha S.** Enzymes of uracil catabolism in normal and neoplastic human tissues. *Cancer Res* 1985; **45**: 5405–12
10 **Ho DH, Townsend L, Luna MA, Bodey GP.** Distribution and inhibition of dihydrouracil dehydrogenase activities in human tissues using 5-fluorouracil as a substrate. *Anticancer Res* 1986; **6**: 781–4
11 **Queener SF, Morris HP, Weber G.** Dihydrouracil dehydrogenase activity in normal, differentiating and regenerating liver and hepatomas. *Cancer Res* 1971; **31**: 1004–9
12 **Etienne MC, Cheradame S, Fischel JL *et al.*** Response to fluorouracil therapy in cancer patients: the role of tumoral dihydropyrimidine dehydrogenase activity. *J Clin Oncol* 1995; **13**: 1663–70
13 **McLeod HL, Sludden J, Murray GI *et al.*** Characterization of dihydropyrimidine dehydrogenase in human colorectal tumours. *Br J Cancer* 1998; **77**: 461–5
14 **Huang CL, Yokomise H, Kobayashi S, Fukushima M, Hitomi S, Wada H.** Intratumoral expression of thymidylate synthase and dihydropyrimidine dehydrogenase in non-small cell lung cancer patients treated with 5-FU-based chemotherapy. *Int J Oncol* 2000; **17**: 47–54
15 **Horiguchi J, Takei H, Koibuchi Y *et al.*** Prognostic significance of dihydropyrimidine dehydrogenase expression in breast cancer. *Br J Cancer* 2002; **86**: 222–5
16 **Oi K, Makino M, Ozaki M *et al.*** Immunohistochemical dihydropyrimidine dehydrogenase expression is a good

prognostic indicator for patients with Dukes' C colorectal cancer. *Anticancer Res* 2004; **24**: 273–9

17 **Ishikawa Y, Kubota T, Otani Y *et al.*** Dihydropyrimidine dehydrogenase activity and messenger RNA levels may be related to the antitumor effect of 5-fluorouracil on human tumor xenografts in nude mice. *Clin Cancer Res* 1999; **5**: 883–9

18 **Mizutani Y, Wada H, Yoshida O *et al.*** Significance of thymidylate synthase activity in renal cell carcinoma. *Clin Cancer Res* 2003; **9**: 1453–60

19 **Babaian RJ, Troncoso P, Bhadkamkar VA, Johnston DA.** Analysis of clinicopathologic factors predicting outcome after radical prostatectomy. *Cancer* 2001; **91**: 1414–22

20 **Takechi T, Fujioka A, Matsushima E, Fukushima M.** Enhancement of the antitumour activity of 5-fluorouracil (5-FU) by inhibiting dihydropyrimidine dehydrogenase activity (DPD) using 5-chloro-2,4-dihydroxypyridine (CDHP) in human tumour cells. *Eur J Cancer* 2002; **38**: 1271–7

21 **Nozawa H, Tsukui H, Nishida K, Yakumaru K, Nagawa H, Sekikawa T.** Dihydropyrimidine dehydrogenase expression in preoperative biopsy and surgically resected specimens of gastric carcinoma. *Cancer Chemother Pharmacol* 2002; **49**: 267–73

22 **Tuchman M, O'Dea RF, Ramnaraine ML, Mirkin BL.** Pyrimidine base degradation in cultured murine C-1300 neuroblastoma cells and *in situ* tumors. *J Clin Invest* 1988; **81**: 425–30

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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.