from equal aspirated volume group. (P<0.01)
全身系への抗がん剤漏出量は有意差 (p<0.01) をもってNIPPのほうがIPPより減少した。また、5%NIPPより10%NIPPのほうが有意差 (p<0.01) をもってさらに減少した。

1.2. 動物実験でのNIPPの投与回数による影響

15匹のブタを用いてIn-out flow rate差を20ml/minに定め、CDDP(5mg/kg)の投与回数を1－3回に分けて骨盤内CDDP濃度および全身系へのleakageを測定した。また、コントロールとして静脈内投与（3回投与）実験を5匹行った。
Group A (NIPP, 1 bolus)、Group B (NIPP, 2 boluses)、Group C (NIPP, 3 boluses)、 Group D (systemic, 3 boluses as control)

結果と考察）投与回数が少ないほど骨盤内抗がん剤濃度は優位に高いが骨盤外への抗がん剤漏出量も多くなることが判明した。患者の腎機能等の状態に応じて投与方法を変える必要があると考えられた。なお、同量の抗がん剤を用いた場合NIPP療法での骨盤内抗がん剤濃度は全身化学療法の約3倍となり、全身血（末梢血）は5分の1以下となることが判明した。

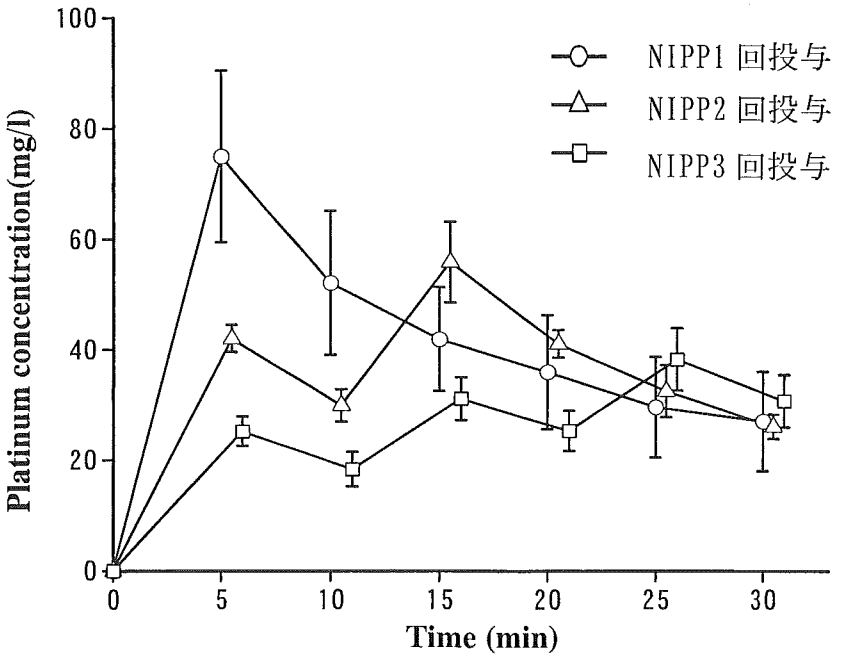

Figure 3. NIPP投与回数別 シスプラチン血中濃度の推移(動脈血)

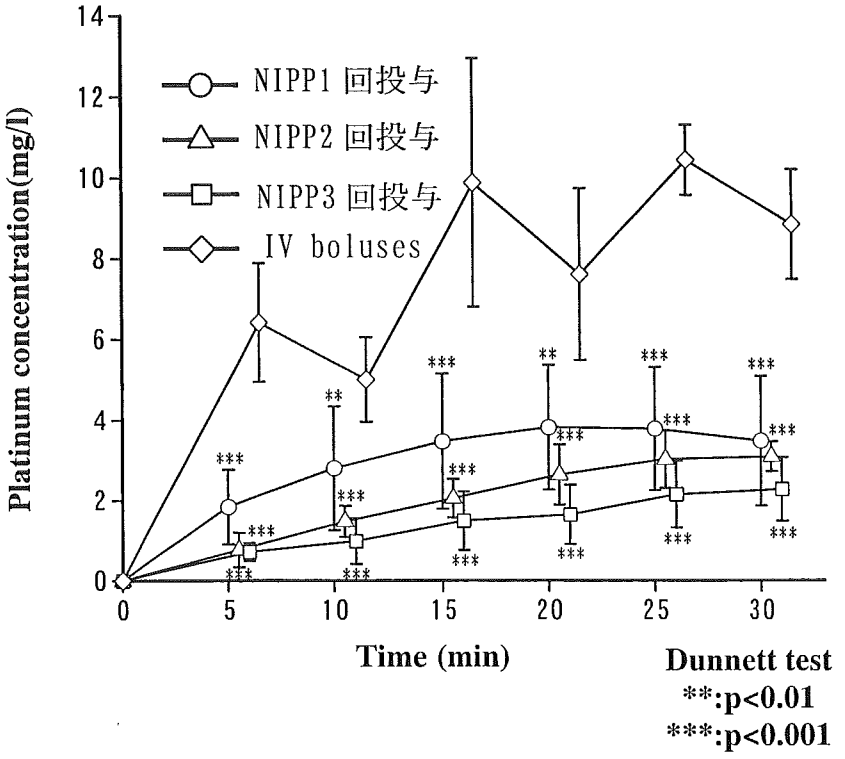

Figure 4. NIPP投与回数別 シスプラチン血中濃度の推移

1.3. CDDP 投与方法における骨盤内組織内濃度差と腎組織内への CDDP 漏出量

21 匹のブタに CDDP (5mg/kg) 投与後 30 分に開腹し各組織を摘出して CDDP 濃度を測定。5 通りの投与方法による組織内濃度の比較を試みた（最終的には各々5 匹の計 25 匹を行う予定)。

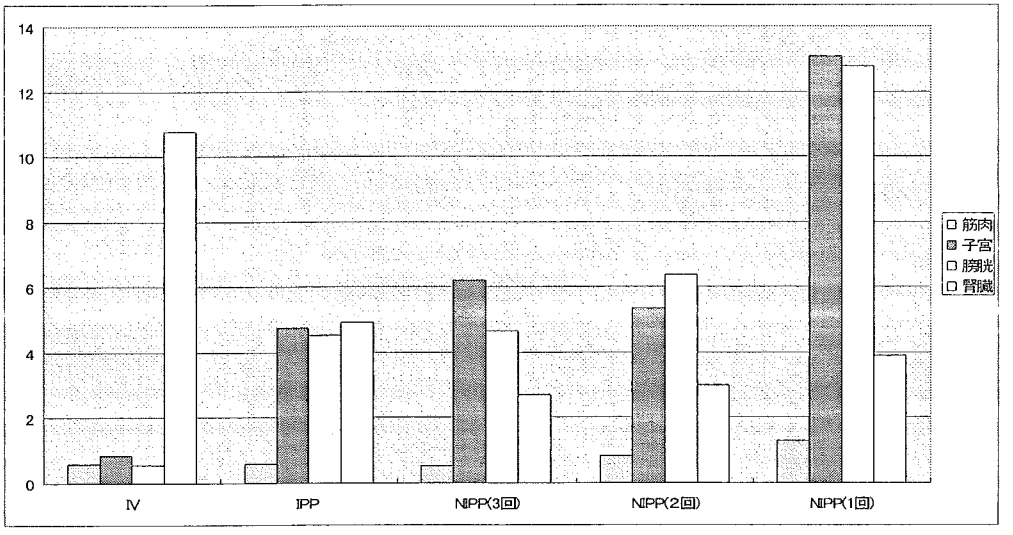

Figure 5. 投与方法による組織内抗がん剤濃度の推移。
Group A (systemic, 3 boluses as control), Group B (IPP, 3 boluses), Group C (NIPP, 3 boluses), Group D (NIPP, 2 boluses), Group E (NIPP, 1 bolus)

抗がん剤投与回数を減少させることで標的組織の組織内抗がん剤濃度が高まる傾向にあるが同時に腎の組織内抗がん剤濃度も高まった。組織内抗がん剤濃度に関してはさらに検討していく必要性がある。

2. 臨床試験

2.1. Pilot study

1999 年 12 月から 2004 年 10 月までに, NIPP を 72 人の骨盤部進行がん患者に対し 108 回施行した。この内、直腸がん術後再発または dissemination のため curative resection を行えなかった直腸がん患者は 38 人で経過観察を途中で断念した 7 人を除いた 31 人で評価を行った。男性 22 人、女性 9 人で年齢は 58（44-80）歳であった。NIPP は合計 51 回施行した。
再発が確認されてからの 1 年、2 年、3 年、4 年および 5 年生存率は、おのおの 94 %、 65 %、29 %、26 %および 16 %であった。

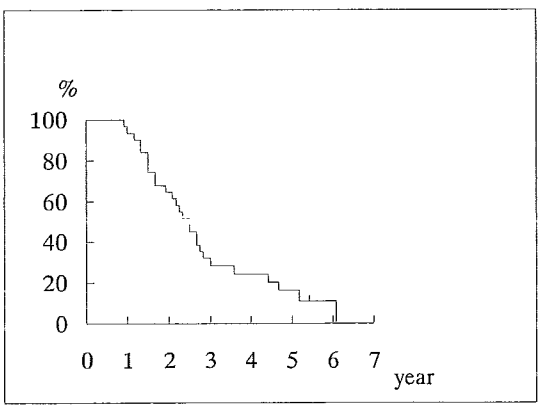

Figure 5. The survival rates of recurrent rectal cancer
The 1-, 2-, 3-, 4- and 5-year survival rates calculated as starting from the date of the diagnosis were 93.6%, 64.5%, 28.7%, 24.6% and 16.4%, respectively.

2.2. Phase I study

CDDP 投与量は 150 mg/m^2 から始めて 240 mg/m^2 に達しているが腎機能障害、末梢神経障害、耳鳴り等の聴器障害においては Grade 1 の毒性も認められず、また腎機能障害のある患者に対しても増悪は認められなかった。しかし、消化器症状においては NIPP 治療翌日に嘔気・

嘔吐を訴える患者が 27 人中 20 人にみられたが何れも軽症で投与した抗癌剤投与量とは有意な関係は認められていない。

II. 肝腫瘍に対する低侵襲的抗がん剤灌流療法の基礎的研究。

当療法中での血圧降下は軽度で灌流システムも機能した。また、肝・腎・消化管（大腸・小腸）の障害の有無を病理学的に評価した結果、肝・腎には有意な障害は見られなかったが小腸において軽度の浮腫が認められた。

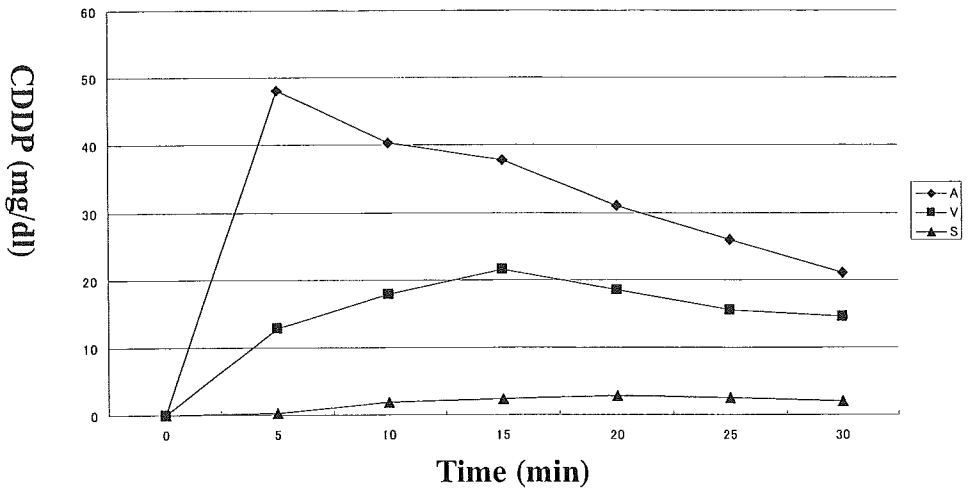

Table 1. Platinum concentrations in the isolated liver perfusion

D. 考察

1) 我々の開発した NIPP 療法は高濃度の抗がん剤を局所に曝露させ、全身系への抗がん剤漏出を抑える非常に優れたドラッグデリバリーシステム（DDS）であると推測された。臨床試験でも大量の抗がん剤を用いているにもかかわらず副作用の軽減を実現させている。生存率においても放射線治療と化学療法を組み合わせた治療成績を過去の論文と比較すると Wong ら(1998 年)の報告では 5 年生存率は 5 %、局所コントロール率は 7 %で、また、Lingareddy ら(1997 年)の報告では 3 年生存率は 14 %であった。何れの報告と比較しても NIPP 治療を施行した生存率は高く、randomized controlled trial にて予後の向上を確定したいと考えている。

2) 当療法の問題点は上腸間膜静脈からの血液のリターンを十分に全身系へ戻すことが困難であることだが新医療機材の開発に

より循環動態の安定を維持することが可能であった。一歩一歩、確実に新治療が実現されつつあるものと考えられた。

E. 結論

I. 我々の開発した NIPP 療法は高濃度の抗がん剤を局所に曝露させ、全身系への抗がん剤漏出を抑える非常に優れた DDS であると推測された。

II. 肝腫瘍に対する抗がん剤灌流療法システムは動物実験上ほぼ完成したと考えられた。今後はさらなる安全性の確立と臨床応用に向けた研究を進めたいと考えている。

F. 健康危険情報

特にないと考えられる。

(今後の研究計画)

「膵がんに対する閉鎖循環下抗がん剤灌流療法の開発」

肝腫瘍に対する抗がん剤灌流療法システムがほぼ完成したことから、この灌流システムの延長線上にある膵がんに対する抗がん剤灌流療法システムの開発は非常に現実味を帯びてきた。すでに考案している膵灌流システムを動物実験にて確立する予定である。

G. 研究業績

1．英語論文業績(2004-2006 年)

1) Murata S, Tajima H, Ichikawa K, Onozawa S, Wang J, Kumazaki T, Nomura K. Transcatheter oily chemoembolization combined with embolization using degradable starch microspheres in patients with cirrhosis and hepatocellular carcinoma. Liver International 2006 (in press).

2) Wang J, Murata S, Kumazaki T. Dynamic changes of the liver microcirculation after embolization of the hepatic artery with degradable starch microspheres: in vivo study with fluorescent microscopy. World J Gastroenterol. 2006 (in press).

3) Murata S, Tajima H, Fukunaga T, Nakazawa K, Onozawa S, Kumazaki T, Kuramoto K, Kuamochi M. Management of the pancreaticoduodenal artery aneurysms: Results of superselective transcatheter embolization. AJR Am J Roentgenol. 2006 (in press)

4) Murata S, Tajima H, Abe Y, Watari J, Uchiyama F, Kumazaki T. Successful embolization of the left gastric artery aneurysm obtained in preoperative diagnosis. Hepatogastroenterology. 2006 (in press)

5) Murata S, Tajima H, Abe Y, Onozawa S, Uchiyama F, Kumazaki T, Nomura K. Innovative therapeutic development of isolated liver perfusion: Applicability to the treatment of hepatic malignancy. J Nippon Med Sch. Feb;73 (1):48-50, 2006.

6) Tajima H, Murata S, Kumazaki T, Abe Y, Takano T. Pulmonary artery perforation repair during thrombectomy using microcoil embolization. Cardiovasc Intervent Radiol. 29(1):155-156, 2006.

7) Satake M, Tateishi U, Kobayashi T,

Murata S, Kumazaki T. Percutaneous transhepatic portal vein embolization: effectiveness of absolute ethanol infusion with balloon catheter in a pig model. Acta Radiol. Jul;46 (4):344-52, 2005.

8) Murata S, Tajima H, Kusakai G, Kumazaki T, Abe Y, Onozawa S, Komada Y, Kondo Y, Kimata R, Himeno S, Satake M. Reduction of drug leakage by negative-balance isolated pelvic perfusion: correlation between leakage and in-out flow rate in a pig model. J Cancer Res Clin Oncol. 131:575-580, 2005.

9) Murata S, Tajima H, Abe Y, Komada Y, Fukunaga T, Nakazawa K, Kumazaki T. Transcatheter management for multiple liver tumors after hepatic artery obstruction following reservoir placement. Hepatogastroenterology. May-Jun;52 (63):852-6, 2005.

10) Mohamad RA, Murata S, Kumazaki T. Assessment of the regularity of hepatic arterio-portal anastomosis exploiting in vivo microscopy. Radiat Med. Mar;23 (2):85-8, 2005.

11) Tajima H, Murata S, Kumazaki T, Nakazawa K, Ichikawa K, Yamamoto T, Tanaka K, Takano T. Recent advances in interventional radiology for acute massive pulmonary thromboembolism. J Nippon Med Sch. Apr;72 (2):74-84, 2005.

12) Murata S, Tajima H, Abe Y, Fukunaga T, Nakazawa K, Mohamad RA, Kumazaki T. Embolization under temporary hepatic venous occlusion for hepatocellular carcinoma with great arterio-hepatic vein shunts. AJR Am J Roentgenol. Feb; 184 (2):415-7, 2005.

13) Tajima H, Murata S, Kumazaki T, Nakazawa K, Abe Y, Komada Y, Niggemann P, Takayama M, Tanaka K, Takano T. Hybrid treatment of acute massive pulmonary thromboembolism: mechanical fragmentation with a modified rotating pigtail catheter, local fibrinolytic therapy, and clot aspiration followed by systemic fibrinolytic therapy. AJR Am J Roentgenol. Sep; 183:589-595, 2004.

14) Tajima H, Murata S, Kumazaki T, Nakazawa K, Kawamata H, Fukunaga T, Yamamoto T, Takayama M, Tanaka K, Takano T. Manual aspiration thrombectomy with a standard PTCA guiding catheter for treatment of acute massive pulmonary thromboembolism. Radiat Med. May-Jun; 22 (3):168-72, 2004.

15) Jian W, Tajima H, Murata S, Abe Y, Hakozaki K, Kumazaki T, Kasuga M, Takano T. Renal artery stenosis in a patient with Leriche syndrome: brachial artery access for stent placement. Radiat Med. Jan-Feb;22(1):49-51, 2004.

16) Tajima H, Murata S, Kumazaki T, Ichikawa K, Tajiri T, Yamamoto Y. Successful Interventional Treatment of Acute Internal Jugular Vein Thrombosis. AJR Am J Roentgenol. Feb;182

(2):467-469, 2004.
17) Niggemann P, Murata S, Naito Z, Kumazaki T. A comparative study of the microcirculatory changes in the developing liver cirrhosis between the central and peripheral parts of the main lobe in mice. Hepatology Research 28:41-48, 2004.

特許出願(2004-2006 年)

１）医療用ガイドワイヤー
発明者：村田　智
出願日：平成 16 年 6 月 3 日（特願 2004-194727）

２）血流灌流回路
発明者：村田　智
出願日：平成 16 年 7 月 21 日（特願 2004-233787）

３）血管閉塞器具
発明者：村田　智
出願日：平成 17 年 7 月 14 日（特願 2005-233726）

厚生労働科学研究費補助金（第3次対がん総合戦略研究事業）
分担研究報告書

がん治療のための革新的新技術の開発研究

分担研究者 公文裕巳

研究要旨
新規の癌抑制遺伝子である REIC/Dkk-3 を治療遺伝子として前立腺癌を標的とする遺伝子治療の開発基礎研究を実施し、REIC/Dkk-3 遺伝子発現アデノウイルスベクターを用いた遺伝子治療の臨床応用可能性が示された。

A. 研究目的

岡山大学において単離・同定された癌関連遺伝子で、発癌において抑制的に機能する REIC/Dkk-3 を治療遺伝子として前立腺癌を標的とする遺伝子治療の開発研究を実施する。

B. 研究方法

REIC/Dkk-3 遺伝子発現アデノウイルスベクター（ヒト、マウス）を用いて前立腺癌細胞（ヒト、マウス）へのアポトーシス誘導作用を in vitro, in vivo で確認しその作用機序を分子生物学的手法を用いて解析した。

今回あらたにマウス REIC 遺伝子を発現するアデノウイルスベクターを作成し治療実験に供した。マウス前立腺にマウス前立腺癌細胞である RM-9 を 5000 個/15μ注入し一週間後（Day7）に直径３ｍｍの腫瘍形成を確認しアデノウイルスベクターを $1.2x10^8$PFU 注入した。経時的な腫瘍サイズの変化はわれわれが開発したマウス経直腸的超音波法（Prostate. 47(2):118-24,2001）を用いて計測した。

C. 研究結果

1）REIC/Dkk-3 によるアポトーシス誘導の機序解明：

平成 16 年度において確認されたヒト前立腺癌細胞への REIC/Dkk-3 遺伝子導入による選択的アポトーシス誘導作用は c-jun N 末端 Kinase（JNK）の活性化に起因する Bax のミトコンドリア移行と Bcl-2 のダウンレギュレーションによることを明らかにした。

平成 16 年度より実施してきた一連の研究成果は Cancer Research,65:9617-9622,2005 に掲載された。

2）マウス同所移植モデルを用いた遺伝子治療実験

平成 16 年度に実施した動物実験はヌードマウス皮下移植モデルを用いたが、平成 17 年度はマウス前立腺癌細胞（RM-9）—immune competent mouse（C57 マウス）による同所移植モデルを用いた治療実験を行った。その結果、治療群は対照群に比して有意に腫瘍重量の低下を認め（$p<0.003$）、さらに生存期間の有意な延長を認めた（Logrank $P<0.0001$）。（投稿準備中）

3）REIC/Dkk-3 遺伝子の機能解析：

REIC/Dkk-3 遺伝子の正常細胞での生理的機能、ならびに、発癌への関与についてより詳細に機能解析に供するため Stable transfectant 作成に向けて検討を行った。Stable transfectant については、Lipofection 法により REIC/Dkk-3 を RM-9 に導入、3 種類の stabel clone を得たので、現在解析中である。

D. 考察

REIC/Dkk-3 は、岡山大学でヒト正常線維芽細胞の不死化に伴って発現が低下する遺伝子として同定され、一連の研究結果より我々は REIC/Dkk-3 を新規の癌抑制遺伝子として提唱した。今回、前立腺癌を対象に REIC/Dkk-3 遺伝子発現アデノウイルスベクターによる強制発現によるアポトーシス誘導作用について詳細な検討を行った。その結果、REIC/Dkk-3 遺伝子は前立腺癌の治療標的遺伝子となることが明らかとなり、アデノウイルスベクターを用いた遺伝子治療の有効性が確認され具体的な臨床応用の実現可能性が示唆された。

選択的アポトーシス誘導機構として、c-jun N 末端 Kinase（JNK）の活性化に起因する Bax のミトコンドリア移行と Bcl-2 のダウンレギュレーションが直接的に関与することを独自に実証したことは、JNK に関連した様々な分子機構（ストレス応答機構など）の関与も示唆されるという点において興味深い。

REIC/Dkk-3 はほぼ全てのヒト前立腺癌組織で発現の減弱が認められ、悪性度の高い癌では完全に消失がみられることも明らかになっており（Cancer Research, 65:9617-9622,2005）、REIC/Dkk-3 を治療の標的基盤とする全く新しい前立腺癌医療の体系化の可能性が示唆された。

E. 結論

REIC/Dkk-3 遺伝子は前立腺癌に対する有力な治療標的遺伝子であり、遺伝子治療として具体的な臨床応用が可能である。

F． 健康危険情報

該当せず

G． 研究発表

1． 論文発表

Abarzua, F., Sakaguchi, M., Takaishi, M., Nasu, Y., Kurose, K., Ebara, S., Miyazaki, M., Namba, M., Kumon, H. and Huh, NH: Adenovirus-mediated overexpression of REIC/Dkk-3 selectively induces apoptosis in human prostate cancer cells through activation of JNK. Cancer Research,65: 9617-9622, 2005

2. 学会発表

なし

H． 知的財産権の出願・登録状況

出願特許：

名称：前立腺癌細胞のアポトーシス誘発剤

発明者：公文裕巳、許 南浩、那須保友、阪口正清

出願番号： 特願２００５－７３８０７

特願２００５－８４４９５

研究成果の刊行に関する一覧表

刊行書籍名	刊行書店名	刊行年	執筆者氏名
Recent advances in radiology for the diagnosis of gastric carcinoma IN The Diversity of Gastric Carcinoma. Pathogenesis, Diagnosis, and Therapy, M.Kaminishi, K,Takubo, M. Mafune (Eds.), pp. 221-232	Splinger-Verlag Tokyo	2005	Iinuma G, Tomimatsu H, Muramatsu Y, Moriyama N, Kobayashi T, Saito H, Maeda T, Miyakawa K, Wakao F, Satake M, and Arai Y
Surgical resection of the stomach with lymph node dissection. In: Upper Gastrointestinal Surgery, Fielding, J.W.L, Hallissey, M.R, eds., pp.335-347	Springer-Verlag, London	2005	Sasako, M, Fukagawa, T, Katai, H and Sano, T

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
野村　和弘	悪性脳腫瘍治療の新しい展開：診断と治療の変遷	癌と化学療法	32	432-436	2005
野村　和弘	脳腫瘍取扱い規約の概要 in 脳腫瘍の診断と治療	日本臨床	63巻増刊号9	195-203	2005
野村　和弘	本邦および世界における脳腫瘍の発症に関する疫学的動向　in 脳腫瘍の診断と治療―最新の研究動向―	日本臨床	63巻増刊号9	9-15	2005
中村　亮一、村垣　善浩、伊関　洋	術中MRI手術環境	医科器械学	75	248-255	2005
Kobayashi T, et al.	A flexible endoscopic surgical system: first report on a conceptual design of the system validated by experiments	Jpn J Clin Oncol	35	667-671	2005
Iinuma G, Kobayashi T et al.	Vascular virtual endoluminal visualization of invasive colorectal cancer on MDCT colonography	Am J Roentgenol	184	1194-1198	2005

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
小林　寿光 土田　敬明 金子　昌弘	肺腫瘍のＣＴガイド下気管支鏡検査	からだの科学増刊「高度先進医療」	12	13-15	2005
菅原　明彦 土田　敬明 金子　昌弘 小林　寿光	ＣＴガイド下極細径気管支鏡検査	呼吸器科	8	353-357	2005
菅原　明彦 小林　寿光	磁気を応用した微細鉗子・内視鏡の開発	日本臨牀	64	353-357	2006
荻野　尚	肺がん治療における陽子線・重イオン線治療	臨床と研究	82	277-281	2005
Nishio T, Sato T, Kitamura K, Murakami K Ogino T	Distribution of ß+ decayed nuclei generated in the CH2 and H2O targets by the target nuclear fragment reaction using therapeutic MONO and SOBP proton beam	Med Phys	32	1070-1082,	2005
Kawashima M, Furuse J, Nishio T, Konishi M, Ishii H, Kinoshita T, Nagase M, Nihei K, Ogino T	Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma	J Clin Oncol	23	1839-1846	2005
荻野　尚:	陽子線がん治療の現状と展望 ―国立がんセンター東病院における臨床実績を中心に	Isotope News	9	2-6	2005
荻野　尚	粒子線治療	臨床消化器内科	21	275-281	2006

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nihei K, Ogino T, Ishikura S, Kawashima M, Nishimura H, Arahira S Onozawa M	Phase II feasibility study of high-dose radiotherapy for prostate cancer using proton boost therapy: First clinical trial of proton beam therapy for prostate cancer in Japan	Jpn J Clin Oncol	35	745-752	2005
Nishio T, Kataoka S, Tachibana M, Matasumura K, Uzawa N, Saito H, Sasano T, Yamaguchi M, Ogino T	Development of simple control system for uniform proton dose distribution in a dual-ring double scattering method	Phys Med Biol	51	1249-1260	2006
Ikarashi, Y., Iizuka, A., Heike, Y., Yoshida, M., Takaue, Y. Wakasugi, H.	Cytokine production and migration of in vitro-expanded NK1.1^{-} invariant V α 14 natural killer T (V α 14i NKT) cells usin α-galactosylceramide and IL-2.	Immunol. Lett.	101	160-167	2005
Uchida, T., Baba, S Irie, A., Soh, S., Masumori, N., Tsukamoto, T., Nakatsu, H., Fujimoto, H., Kakizoe, T., Ichikawa, T.et al.,	Transrectal high-intensiuty focused ultrasound in the treatment of localized prostate cancer: a multicenter study	Acta Urol. Jpn.	51	651-658	2005
藤元 博行	局所進行性前立腺癌に対するホルモン療法と手術療法の併用療法.	日本臨床	63	271-278	2005
藤元 博行	本邦、前立腺癌症例に対する根治的前立腺全摘除術の可能性と限界	臨床放射線	50	593-601	2005

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Etoh, T, Katai, H, Fukagawa, T, Sano, T, Oda, I, Gotoda, T, Yoshimura K, Sasako M	Treatment of early gastric cancer in the elderly patient: Results of EMR and gastrectomy at a national referral center in Japan	Gastrointestinal Endoscopy	62	868-871	2005
Saka, M, Mudan, S.S, Katai, H, Sano, T, Sasako, M Maruyama, K	Pancreaticoduodenectomy for advanced gastric cancer	Gastric Cancer	8	1-5	2005
森谷 宜皓	進展様式に基づいた消化器癌手術のこつと工夫 -7.進展様式に基づく直腸癌術式の選択と手術のコツ-	日外会誌	106	302-330	2005
森谷 宜皓, 上原 圭一, 山本 聖一郎, 赤須 孝之, 藤田 伸	骨盤内臓全摘術 （total pelvic exenteration,TPE）	手術	59	833-840	2005
藤田, 山本 赤須、森谷	側方郭清,予防的側方郭清と治療的側方郭清	外科治療	28	799-805	2005
上原, 山本, 赤須, 藤田, 森谷	仙骨合併骨盤内臓全摘術	手術	59	1149-1153	2005
森谷 宜皓,	最新のがん手術 -特集対がん戦略最前線-	Ever 遥か	2	7-10	2005
太田,山本, 藤田 赤須、森谷	腹腔鏡下結腸切除後に肺塞栓症をきたした１例 -症例報告-	日本内視鏡外科学会誌	10	566-570	2005
Yamamoto S, Fujita S, Akasu T, Moriya Y.	Safety of laparoscopic intracorporeal rectal transection with double-stapling technique anastomosis	Surg Oncol Clin N Am	15	70-74	2005

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Matsushita H, Matsumura Y, Moriya Y, Akasu, T, et al.	A new method for isolating colonocytes from naturally evacuated feces and its clinical application to colorectal cancer	Gastroebterology	129	1918-1927	2005
Moriya Y, Akasu T, Fujita S, Ymamoto S. :.,	Total pelvic exeteration with distal sacrectomy for fixed recurrent rectal cancer	Surg Oncol Clin N Am	14:, 2005	225-238	2005
Yamamoto S, Fujita S, Akasu T, Moriya Y	Postsurgical surveillance for recurrence of UICC stage I colorectal carcinoma: Is follow-up by CEA justified?	Hepato-gastroenterology	52	444-449	2005
Murata S, Tajima H, Abe Y, Komada Y, Fukunaga T, Nakazawa K, Kumazaki T.	Transcatheter management for multiple liver tumors after hepatic artery obstruction following reservoir placement.	Hepatogastroenterology	52	852-856	2005.
Murata S, Tajima H, Kusakai G, Kumazaki T, Abe Y, et al.	Reduction of drug leakage by negative-balance isolated pelvic perfusion: correlation between leakage and in-out flow rate in a pig model	J Cancer Res Clin Oncol.	131	:575-580,	2005.
Abarzua, F., Sakaguchi, M., Takaishi, M., Nasu, Y., Kurose, K., Ebara, S., Miyazaki, M., Namba, M., Kumon, H.,Huh, NH	Adenovirus-mediated overexpression of REIC/Dkk-3 selectively induces apoptosis in human prostate cancer cells through activation of JNK.	Cancer Res	65	9617-9622	2005

Recent Advances in Radiology for the Diagnosis of Gastric Carcinoma

Gen Iinuma[1], Hideto Tomimatsu[1], Yukio Muramatsu[1], Noriyuki Moriyama[1], Toshiaki Kobayashi[2], Hiroshi Saito[2], Tetsuo Maeda[3], Kunihisa Miyakawa[3], Fumihiko Wakao[3], Mitsuo Satake[3], and Yasuaki Arai[3]

Introduction

Radiographic diagnosis of gastric carcinoma [1] was first introduced in the 1960s in Japan, which led the world in the early diagnosis of gastric carcinoma by double-contrast method using film-screen systems (FSS) [2,3]. Qualitative diagnostics, including diagnosis of the depth of tumor invasion, were explored thoroughly in the 1970s, and it could be claimed that the radiographic diagnosis of gastric carcinoma was completely established by the beginning of the 1980s [4]. Gastric radiography has now become a standard examination modality in the screening and preoperative staging of gastric carcinoma and is widely used across the globe. The mortality rate from gastric carcinoma is especially high in Japan, and gastric radiography has made a substantial contribution to the detection of gastric carcinoma in mass screening. With recent advances in endoscopic techniques, the primary role in the diagnosis of gastric carcinoma, including its early diagnosis, has been inherited by endoscopy, but it is also a fact that radiography is still widely used in clinical diagnosis in screening and preoperative staging [5]. The demand for computerization of medical information grew in the 1980s, and against a background of advances in image engineering, the digitalization of medical images has proceeded apace [6,7]. In gastric radiography, too, digitalization via digital radiography (DR) using high-resolution charge-coupled device (CCD) cameras (CCD-DR) has been established and disseminated rapidly, and we also have reported its usefulness in the diagnosis of gastric carcinoma [8]. Meanwhile, a recent major development in the field of radiology has been the emergence of multidetector row computed tomography (CT) (MDCT) [9]. With the advent of MDCT in the second half of the 1990s, CT has achieved increased efficiencies and improved image quality in a revolutionary scanning modality [10]. In the preoperative staging of gastric carcinoma, it is now possible to accurately evaluate local inva-

[1]Cancer Screening Division, Research Center for Cancer Prevention and Screening, [2]Cancer Screening Technology Division, Research Center for Cancer Prevention and Screening, [3]Diagnostic Radiology Division, National Cancer Center Hospital, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: giinuma@gan2.ncc.go.jp

sion and small metastases, and three-dimensional (3D) MDCT imaging (MDCT gastrography) has arrived on the scene as a new diagnostic tool for primary lesions.

In this chapter, we describe the present status of radiologic diagnosis of gastric carcinoma using CCD-DR at our center, report our experience of MDCT gastrography in the preoperative staging of gastric carcinoma, and discuss the future prospects for radiographic diagnosis of gastric carcinoma using these new diagnostic techniques.

Advanced Digital Radiographic Systems for Gastric Diagnosis

In our hospital, images yielded by radiography of the gastrointestinal tract became completely digitalized with the adoption of CCD-DR (DR-2000H; Hitachi Medical, Tokyo, Japan) in 1999. At present, hard copies of diagnostic images are prepared for interpretation, but monitor-based diagnosis is yet to become a reality. Our radiographic investigations of the gastrointestinal tract use three CCD-DR systems: one C-arm type, one over-tube type, and one under-tube type. Each CCD-DR is connected by a DR network to two laser printers and an image server, and in parallel with the scanning procedure, reference images are forwarded to the hospital information system via a gateway after DICOM (digital imaging and communication in medicine) conversion at the same time as the diagnostic images are processed. After DICOM

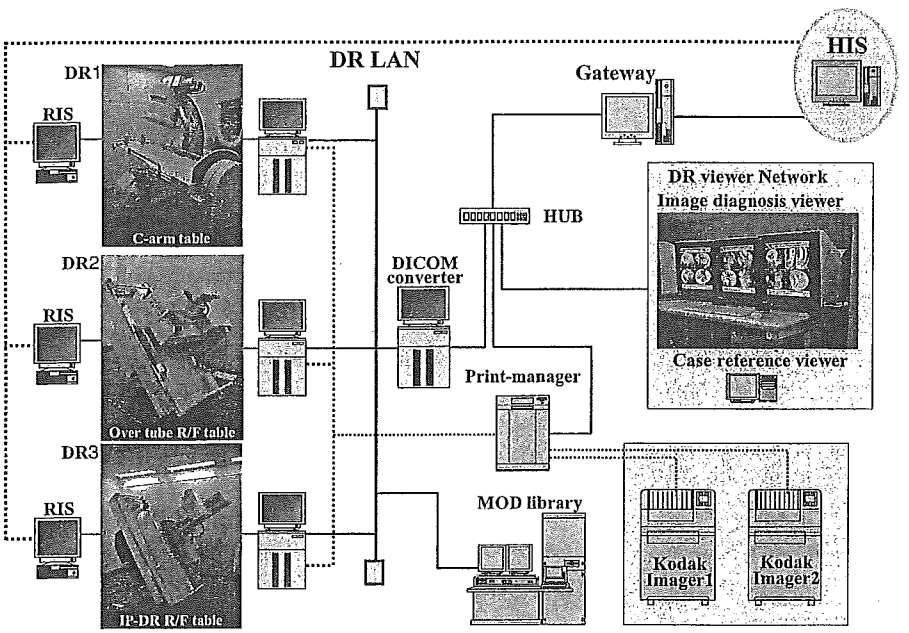

FIG. 1. Advanced digital radiography system for gastric diagnosis. Three charge-coupled device-digital radiography (CCD-DR) units are routinely used for gastric examinations in our hospital. Each unit connects with a DR network, and the images can be diagnosed on an image workstation

conversion, the images are accessible for monitor diagnosis at an image workstation with three viewers (Fig. 1).

The Status of CCD-DR-Based Radiographic Examination of Gastric Carcinoma

At our center, we use 250–300 ml barium at a 130–140 w/v% concentration in gastric radiographic studies. The scanning methods employed are the filling method, double-contrast radiography, and the compression method, but the core diagnostic technique in radiographic diagnosis of gastric carcinoma is double-contrast imaging obtained with barium (positive contrast medium) and gas (negative contrast medium). After barium is swallowed, the patient is given 5 g of a foaming agent, and by distending the stomach via the CO_2 gas so produced, we are able to easily obtain double-contrast images. The barium contained in the gas-distended stomach moves with changes in posture, and double-contrast images of excellent quality are obtained by ensuring that the barium adheres uniformly to the mucosal surfaces. Unlike the filling and compression methods, double-contrast imaging is indispensable for the visualization of early gastric carcinoma, which is characterized by few irregularities of the mucosal surfaces (Fig. 2). With gastric radiography based on the double-contrast method, we can easily identify the macroscopic types of gastric carcinomas, their exact extensions and locations in the stomach (Figs. 3–6). However, viewing double-contrast images obtained with contrast provided by gas and barium requires a broad dynamic range. The dynamic range for CCD-DR images adequately covers the image quality required for gastric radiography, and the image quality matches that in conventional FSS. Additionally, CCD-DR digital images also enable the optimization of image quality via image processing after scanning and, compared with FSS, are relatively well matched image by image and allow standardized diagnostic images to be obtained.

Comparative Evaluation of FSS and CCD-DR in the Diagnosis of Gastric Carcinoma

We conducted a prospective study to evaluate the difference in diagnostic accuracy between FSS and CCD-DR, and reported in a publication of *Radiology* [8]. From January to February 1997, we randomly assigned patients scheduled for gastric radiography to either FSS or CCD-DR; 112 patients were examined by FSS and 113 by CCD-DR. Six radiologists who were blinded to the clinical details assessed the films for each patient with a six-level confidence rating for the presence or absence of gastric carcinoma. The CCD-DR images in this study were prepared as hard copies for diagnosis. The diagnoses for each patient were rated against those produced by three other radiologists who conducted the actual radiographic examinations and were aware of all clinical data, such as endoscopic findings and the pathology of biopsy specimens. The sensitivity and specificity of FSS and CCD-DR for gastric carcinoma were determined from the assessments obtained, the difference between the two modalities was statistically analyzed, and a comparison was performed by receiver-operating characteristic (ROC) analysis. The study yielded a diagnosis of gastric carcinoma by FSS in 24 patients and by CCD-DR in 27 patients; the sensitivity for diagnosing the presence of gastric carcinoma was 64.6% and 75.3%, respectively

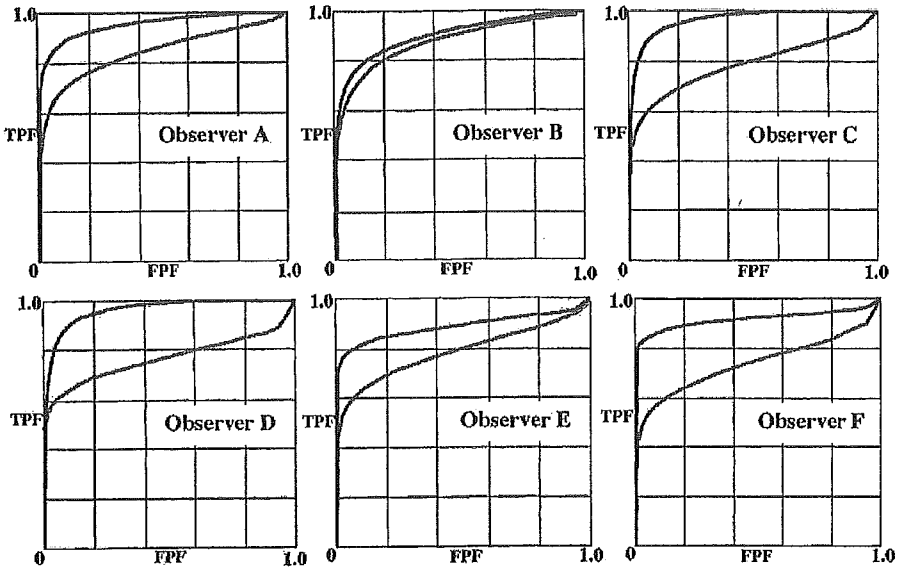

FIG. 7. Receiver operating characteristic (ROC) curves obtained from six observers. All observers achieved more accurate results with CCD-DR than with conventional radiography. Diagnostic accuracy of CCD-DR is clearly superior to that of conventional radiography. (Used with permission from Radiological Society of North America)

($P = 0.278$), and the specificity was 84.5% and 90.5%, respectively ($P = 0.011$). The ROC analysis [11] also showed that the diagnostic performance of CCD-DR was clearly superior (Fig. 7).

Usefulness of Radiography of Gastric Carcinoma by CCD-DR

The diagnostic performance of CCD-DR for gastric carcinoma is adequately comparable to that of FSS, indicating that the digitalization of images in gastric radiography is entirely feasible. The future adoption of diagnosis by monitor display will make possible the real-time display and optimization of diagnostic images and enable greater ease of image storage and retrieval. Capitalizing on these advantages of digitalization promises to yield an efficient and effective diagnostic environment for screening and preoperative staging, as compared with the conventional FSS modality.

Preoperative Evaluation of Gastric Carcinoma Using MDCT

To date, the role of radiographic CT studies in the preoperative staging of gastric carcinoma has primarily involved evaluating invasion of surrounding organs or metastasis to lymph nodes or other organs, and it was rare for it to be used for evaluation of the primary tumor itself [12,13]. However, the advent of MDCT has made possible the arrival of full-scale volume scans, facilitating high-speed, detailed image acquisition over an extensive area. The degree of resolution of CT images has improved

dramatically with MDCT, enabling the detailed evaluation of local lesions and the detection of small metastases, even in ordinary axial images [14]. Moreover, workstations that are capable of processing the massive quantities of image data produced by MDCT have been developed, and the three-dimensional CT visualization of gastric lesions, which is called MDCT gastrography, has become straightforward. This trend is fairly flourishing in the diagnosis of colorectal cancer as MDCT colonography, which is considered to have a great potential of being a modality for colorectal cancer screening [15–17].

Three-Dimensional Visualization of the Stomach by MDCT Gastrography

To visualize gastric lesions in three dimensions using MDCT, it is necessary to distend the gastric lumen with a foaming agent (CO_2 gas). As a consequence of the contrast between the gas and the inner gastric surface, owing to the substantial difference in density, it is possible to effortlessly prepare 3D images of the inner gastric surface. MDCT gastrography employs two methods for visualization, virtual endoscopic views and 3D gas insufflation views, obtained by 3D processing of the CT image data (Fig. 8).

Evaluation of the Detectability of Gastric Carcinoma by MDCT Gastrography

In the 3-month period between March and June 2003, we evaluated 4-row MDCT (Aquilion; Toshiba Medical Systems, Tokyo, Japan) in 84 gastric carcinoma patients who underwent MDCT for preoperative staging. Each scan was performed with the standard abdominal scan parameter settings for preoperative staging using automatic exposure control [18]. We prepared virtual endoscopic and 3D gas insufflation views from the image data obtained for each patient by MDCT volume scans, and two radiologists prepared responses on the basis of all clinical data for each patient, including gastroscopic findings, and the detectability of gastric carcinoma was evaluated by consensus for each display method. Eighty-six gastric carcinoma lesions (44 early and 42 advanced lesions) were diagnosed in the 84 patients. The detectability by virtual endoscopic and 3D gas insufflation views by MDCT gastrography was 47.7% and 40.9%, respectively, for early lesions (Table 1), and 59.5% and 76.2% for advanced lesions (Table 2). Hence, the detectability was less than 50% for early lesions, but about 60%–70% for advanced lesions of gastric carcinoma [19]. Especially in early lesions, all protruded-type lesions could be recognized, while less than half of depressed-type lesions, which is a common type of early gastric carcinoma, were missed (Figs. 9, 10).

TABLE 1. Detectability for 44 early gastric carcinomas by multidetector row computed tomography (MDCT) gastrography

	Protruded type	Flat elevated type	Depressed type	Total
Virtual endoscopic views	100% (2/2)	50.0% (1/2)	45.0% (18/40)	47.7% (21/44)
Three-dimensional gas insufflation views	100% (2/2)	50.0% (1/2)	37.5% (15/40)	40.9% (18/44)

TABLE 2. Detectability for 42 advanced gastric cancers by MDCT gastrography

	Borrman I type	Borrman II type	Borrman III type	Borrman IV type	Total
Virtual endoscopic view	0% (0/1)	84.6% (11/13)	68.8% (11/16)	25.0% (3/12)	59.5% (25/42)
Three-dimensional gas insufflation view	0% (0/1)	76.9% (10/13)	68.8% (11/16)	91.7% (11/12)	76.2% (32/42)

MDCT gastrography is presently inadequate for the detection of gastric carcinoma and its potential for clinical application is low.

Potential for MDCT Gastrography in Preoperative Staging for Gastric Carcinoma

MDCT gastrography is simpler and less invasive than endoscopy and radiography, and permits evaluation of the stomach overall in an examination of short duration. Detection of early lesions is challenging, and although it therefore has low potential as a screening method, it is capable of detecting lesions that are advanced to a certain extent, and also of simultaneously detecting lesions in other organs of the abdomen. In preoperative staging, as for radiography, it is capable of objectively ascertaining the position and overall picture of the primary lesion, and of diagnosing the relations between the degree of extramural invasion and surrounding organs. With the axial images of MDCT, representing a quantum leap in resolution compared with normal CT, it was possible to also diagnose correctly lymph node metastasis. Because MDCT itself is an examination method required for the preoperative diagnosis of local spread or remote metastasis of gastric carcinoma, it is highly likely at present that it can partially replace the role of radiography or ultrasound endoscopy. As well, because the image data of MDCT is digitalized density information, it is possible to selectively visualize 3D information in a manner that is effective for diagnosis, and has a great potential of being a modality for computer-aided diagnosis [20]. By digitally combining the 3D view of the primary lesion and the 3D image data of diagnosed lymph node metastasis, it will be possible to provide surgeons with effective preoperative 3D views of gastric carcinoma (Fig. 11).

Conclusions

As a result of future advancements in image engineering and computer technology, digital radiographic systems and MDCT systems will continue to evolve, and it can be predicted that new diagnostic methods that utilize the advantages of digitalization in the radiological diagnosis of gastric carcinoma will also be developed. MDCT gastrography has little potential at present as a diagnostic method for the primary lesions of gastric carcinoma. However, with further advances in MDCT, higher-speed examinations, improved image quality, and optimization of exposure dose, it appears certain that MDCT gastrography will gradually replace radiography, endoscopy, and ultrasound endoscopy.