厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
肛門扁平上皮癌に対する新規化学放射線療法の確立

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研究要旨
稀少疾患である臨床病期 II/III 期肛門管扁平上皮癌に対する根治的化学放射線療法の多施設共同臨床試験において、放射線治療の内容の精度評価・品質管理を行い、臨床試験の質の保証を図っている。本試験は我が国初の肛門管扁平上皮癌に対する根治的化学放射線療法の臨床試験であるためが、放射線治療品質保証に関する資料が提出された 36 例の放射線治療内容の評価では、遵守 83.3%と品質保証活動によって治療の質を保つことができている。さらなるプロトコール遵守率の増加のために、施設への逸脱内容のフィードバックと全参加施設への定期的な放射線治療規定の確認の連絡が重要である。

A．研究目的

本研究の目的は、稀少疾患である臨床病期 II/III 期肛門管扁平上皮癌に対する根治的化学放射線療法の多施設共同臨床試験において、放射線治療の内容の精度評価・品質管理を行い、臨床試験の質を保証することである。放射線治療内容の均一化を目指し、経時的にプロトコール遵守率を上げ、臨床試験の質を高め、保証することを目標とする。

B．研究方法

研究方法は、「臨床病期 II/III 期肛門管扁平上皮癌に対する S-1+MMC を同時併用する根治的化学放射線療法の臨床第 I/II 相試験：JCOG0903」において、放射線治療の品質保証活動を行うことである。本試験は我が国初の肛門管扁平上皮癌に対する根治的化学放射線療法の臨床試験であるため、プロトコール作成段階において、参加施設予定の放射線治療担当医と臨床試験の内容及び放射線治療規定に関して意思統一を図り、プロトコール本文に明確な放射線治療規定を記載している。試験開始後、登録例において、放射線治療内容の評価に必要な各種診断画像、治療計画情報、位置照準画像、放射線治療照射記録等の資料を登録施設から提出してもらい、放射線治療規定の遵守の程度につき、登録例毎に判定を行う。問題点があれば、登録施設にフィードバックする。

（倫理面への配慮）

本臨床試験は、「臨床研究に関する倫理指針」およびヘルシンキ宣言などの国際的倫理原則に従って遂行している。 説明同意文書を作成し、JCOG プロトコール審査委員会と国立がん研究センター倫理委員会において審査承認された文書で登録前に患者本人に対して十分な説明を行い、文書で同意を得て症例登録を行う。データの取り扱い上、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報（プライバシー）保護を厳守する。JCOG に所属する研究班は共同で、Peer review と外部委員審査を併用した第三者的監視機構としての各種委員会を組織しており、本研究も、JCOG のプロトコール審査委員会、効果・安全性評価委員会、監査委員会、放射線治療委員会などによる第三者的監視を受けることを通じて、倫理性の確保に努めている。

C．研究結果

今年度は本試験に登録された第II相試験のうち、放射線治療品質保証に関する資料が提出された18例について放射線治療内容の確認、評価をした。全例3次元放射線治療計画を施行し、放射線治療規定通り1回線量1.8 Gy、総線量59.4 Gyで治療されていた。標的体積設定において、全例原発巣と転移リンパ節の囲みは適切であった。総合判定は、遵守15例（83.3%）、逸脱3例（16.7%）であった。逸脱の内容は、2例が所属リンパ節領域の予防照射の囲み、1例が予防照射線量に関するものであった。前者の1例は直腸間膜（傍直腸リンパ節領域）の囲みが一部不足しており、もう1例は頭側のリンパ節領域として総腸骨リン

パ節領域までを含めており、規定よりも広めの領域に予防照射範囲を設定していた。また、後者の1例の逸脱は鼠径リンパ節領域への予防照射線量が規定の36.0 Gyよりも多く照射されていた。第I相試験と合わせた36例の総合判定として、遵守30例（83.3%）、逸脱6例（16.7%）であり、違反例は認めていない。逸脱例に関しては、逸脱内容について登録施設へフィードバックをした。また、重要な周知事項についてはメーリングリストを通じて全参加施設の放射線治療責任者に連絡し、情報共有をした。JCOG大腸がんグループの班会議にても、本試験の放射線治療品質保証活動の進捗状況を報告した。

D．考察

多施設共同で実施する放射線治療を用いるがん臨床試験において、放射線治療内容の格差は臨床試験の結果に影響を及ぼすため、試験内容の質を保証することを目的とした放射線治療の品質保証活動は重要である。本試験でもプロトコール作成段階から品質保証活動を施行している。平成 25 年度の放射線治療内容について、評価した 18 例の遵守率は平成 24 年度に続き、80%以上を維持しており、品質保証活動が機能しているものと考えられた。逸脱の 3 例については、臨床的に問題とならない内容であったが、臨床試験の結果をより正確に評価するためにもさらなる放射線治療内容の質の保持を図る努力が必要である。そのために逸脱した登録施設に逸脱内容のフィードバックを施行し、登録施設の次の登録例には放射線治療規定が遵守できるようにしている。今後も経時的にプロトコール遵守率が上がるように、放射線治療の品質保証活動を継続していく予定である。

E．結論

本試験は稀少疾患である肛門管扁平上皮癌に対して多施設共同で実施している臨床試験であるため、放射線治療の品質保証活動が重要である。現在までに登録例の放射線治療内容の質は保たれている。

F．健康危険情報

なし

G．研究発表

1．論文発表

伊藤芳紀、稲葉浩二、村上直也、師田まどか、角美奈子、吉尾浩太郎、高橋加奈、関井修平、北口真由香、原田堅、小林和馬、伊丹純．コンツーリングを学ぼう　肛門管癌．臨床放射線 58:1848-1855, 2013.

2．学会発表

該当なし

H．知的財産権の出願・登録状況

1．特許取得　該当なし
2．実用新案登録　該当なし
3．その他　該当なし

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書
肛門扁平上皮癌に対する新規化学放射線療法の確立

分担研究者　　唐澤 克之　　がん・感染症センター都立駒込病院放射線科　部長

研究要旨
JCOG0903 非適格の肛門扁平上皮癌に対して、その放射線治療の照射技法を IMRT に変えて行い、その Feasiblity をチェックした。その結果 IMRT は安全に施行可能で、有害事象を軽減している可能性が考えられた。また海外でも肛門扁平上皮癌に対して IMRT を用いた化学放射線療法を用いて良好な治療成績をあげている。将来的に本邦でも検討されるべき照射技法と考えられた。

A．研究目的
JCOG0903 の症例登録を支援するとともに、放射線治療の技術的検討を行い、欧米ですでにルーチン化して用いられている、肛門扁平上皮癌に対する IMRT の研究を行い、本研究を側面から支える。

B．研究方法
JCOG0903 の適応例に対しては、JCOG0903 へのエントリーを優先させて登録し、照射技法は通常の 3 次元原体照射法(3DCRT)を用いるが、適応を満たさない症例に関しては、照射技法に IMRT を用いて、その Feasibility を評価した。その際 Dose-volume histogram(DVH)を用いて、通常の 3DCRT との比較を行った。

また、国内外での本疾患の IMRT での治療状況に関する調査のため、ASCO-GI シンポジウムを始めとした各種学会に出席して、演者と情報交換を行い、情報の収集に当たった。

（倫理面への配慮）
IMRT は、一定の施設基準を満たせば、限局性の固形腫瘍に対しては適応が認められているため、当院にはその基準を満たしているので、日常臨床として用いている。IMRT については、治療計画とその検証が重要であるが、検証作業に関しては専任の医学物理士の確認と装置が毎回治療前に確認用の CT を必ず撮像しているため、治療の誤差は最小限に抑えられる。また必ず治療前に IC を文書にて取得している。

C．研究結果
この 1 年間に JCOG0903 の非適格な肛門扁平上皮癌は 4 例あり、いずれも IMRT を用いた（化学）放射線治療（1 例は放射線治療単独）にて治療を施行した。いずれの症例も有害事象は軽微で、治療の休止無く治療を終了した。DVH 上では明らかに 3DCRT に比較し、正常臓器の高線量域の体積を減らしており、有害事象の軽減の理由であることが示唆された。

ASCO-GI シンポジウムでは、肛門扁平上皮癌の発表は主にポスターに限られたが、IMRT を用いることにより、治療の完遂率は向上し、生存率は再現性をもって 80%を超えて来ていることが確認できた。その他ヨーロッパの施設からも同様の報告を聴いた。

D．考察
以前より、我が国の放射線治療が欧米に比較して遅れを取っているということが問題となってきているが、高精度放射線治療に関する研究会などが、頻繁に開催されるようになり、徐々にではあるが、肛門扁平上皮癌に対しても IMRT が行われるようになってきている。現在のところ局所制御率に関しては、長期の成績が出されていないが、これからそれらデータも出されて来ると考えられる。有害事象は明らかに低減できていることが、海外でも証明されているので、現在施行されている JCOG0903 の次の臨床試験では、IMRT が放射線治療のオプションとしてでも使われるように、放射線治療の技術の進歩、普及に関与していく予定である。

E．結論
肛門扁平上皮癌に対し、IMRT は安全に施行可能で、有害事象を軽減している可能性が考えられた。局所制御に関しては今後のさらなる検討が必要であ

る。

F．健康危険情報
なし

G．研究発表
1.　論文発表
唐澤克之．肛門管癌に対する放射線治療ガイドライン　大腸癌 Frontier5(2)，137-142，2012
唐澤克之．肛門癌　放射線治療計画ガイドライン 2012　157-160，金原出版社，2012
唐澤克之．特集：大腸癌の最新療法　放射線療法．日本臨床　第 72 巻・第一号 127-133、2014

2.　学会発表
唐澤克之　肛門管癌に対する化学放射線療法　第 48 回日本医学放射線学会秋季臨床大会教育講演、平成 24 年 9 月 28 日長崎

H．知的財産権の出願・登録状況
1.　特許取得
なし

2.　実用新案登録
なし

3.　その他
なし

Ⅲ.　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
該当なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Komori K, Kanemitsu Y, Kimura K, Sano T, Ito S, Abe T, Senda Y, Shimizu Y.	Detailed stratification of TNM stage III rectal cancer based on the presence/ absence of extracapsular invasion of the metastatic lymph nodes.	Diseases of the Colon & Rectum	56	726-732	2013
Komori K, Kimura K, Kinoshita T, Sano T, Ito S, Abe T, Senda Y, Misawa K, Ito Y, Uemura N, Shimizu Y.	Sex Differences Between cT4b and pT4b Rectal Cancers.	International Surgery	98	200-204	2013
Inomata M, Akagi T, Nakajima K, Etoh T, Shiraishi N, Tahara K, Matsumoto T, Kinoshita T, Fujii K, Shiromizu A, Kubo N, Kitano S	Prospective Feasibility Study to Evaluate Neoadjuvant synchronous S-1 + RT for Locally Advanced Rectal Cancer: A Multicenter Phase II Trial	Jpn J Clin Oncol	43 (3)	321-3	2013
伊藤芳紀、稲葉浩二、村上直也、師田まどか、角美奈子、吉尾浩太郎、高橋加奈、関井修平、北口真由香、原田 堅、小林和馬、伊丹 純.	コンツーリングを学ぼう 肛門管癌	臨床放射線	58	1848-1855	2013
唐澤克之	特集：大腸癌の最新療法　放射線療法	日本臨床	第72巻・第1号	127-133	2014

Ⅳ.　研究成果の刊行物・別刷り

ORIGINAL CONTRIBUTION

Detailed Stratification of TNM Stage III Rectal Cancer Based on the Presence/Absence of Extracapsular Invasion of the Metastatic Lymph Nodes

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Tsuyoshi Sano, M.D. • Seiji Ito, M.D. • Tetsuya Abe, M.D. • Yoshiki Senda, M.D.
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BACKGROUND: The presence/absence of extracapsular invasion in metastatic lymph nodes has been reported as being significantly correlated with the prognosis in a wide variety of cancers. However, the influence of extracapsular invasion in the metastatic lymph nodes on the prognosis in patients with stage III rectal cancer has not yet been investigated.

OBJECTIVE: We investigated the presence/absence of extracapsular invasion in the metastatic nodes of the relevant main/lateral lymph node group in patients with rectal cancer to determine the usefulness of this parameter for stratifying the prognosis of patients with stage III rectal cancer.

DESIGN: This was a single-institution study.

SETTINGS: This study was conducted at a single institution.

PATIENTS: We enrolled 101 consecutive patients with stage III rectal cancer who had undergone curative surgery with extended lymph node dissection and investigated the presence/absence of extracapsular invasion in the regional metastatic lymph nodes to determine the usefulness of such stratification for a more precise prediction of the patient prognosis.

MAIN OUTCOME MEASURES: The main outcomes measured were the disease-free and overall survival rates.

RESULTS: Univariate analysis revealed a significantly poorer prognosis, in terms of both the disease-free survival rate ($p = 0.003$) and overall survival rate ($p = 0.008$), of the pN3-extracapsular invasion-positive cases in comparison with the pN3-extracapsular invasion-negative cases. Multivariate analysis revealed the presence/absence of extracapsular invasion in the metastatic lymph nodes as the only variable that was statistically significantly associated with the disease-free survival rate ($p = 0.011$).

LIMITATIONS: This was a retrospective study in a small number of patients from a single institution. There were no comparator groups.

CONCLUSIONS: Detailed stratification of pN3 cases based on the presence/absence of extracapsular invasion in metastatic lymph nodes has the potential to contribute significantly to more available prediction of the prognosis of patients with stage III colorectal cancer.

KEY WORDS: Extracapsular invasion; Stage III; Rectal cancer.

Lymph node metastatic status is known as one of the most important factors influencing the prognosis in patients with rectal carcinoma. For cases with TNM stage III rectal cancer, systemic adjuvant chemotherapy with regimens including oxaliplatin, such as folinic acid, oxaliplatin, and fluorouracil, has been established as the standard.[1] However, patients who have TNM stage III rectal cancer have come to be recognized as a heterogeneous group, and not all patients require strong adjuvant chemotherapy regimens, including folinic acid, oxaliplatin, and fluorouracil. Some of these patients have a good prognosis, similar to that of patients with stage II disease,

Financial Disclosures: None reported.

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Dis Colon Rectum 2013; 56: 726–732
DOI: 10.1097/DCR.0b013e318286c518

whereas others have a poor prognosis. Among the factors defining the lymph node metastatic status, the number of metastatic lymph nodes has been reported as one of the most important factors influencing the prognosis in patients with TNM stage III rectal cancer. Furthermore, both the number of lymph nodes retrieved and the number of positive nodes have been reported as important prognostic factors, and it has been recommended that at least a 12-node threshold should be met to improve the predictive accuracy.[2] However, in Japan, the regional lymph node group involved has also long been included as an important consideration for staging.[3]

Recently, the presence of extracapsular invasion (ECI) of the metastatic lymph nodes has been reported as being significantly related to the prognosis in a wide variety of cancers.[4–7] However, although most reports have indicated the malignant potential of ECI in the metastatic lymph nodes, there have been no reports on the significance of the location of the metastatic lymph nodes showing ECI in terms of the regional lymph node group involved.

We investigated the presence/absence of ECI in the relevant main/lateral lymph node group in cases with TNM stage III rectal cancer to determine the usefulness of patient stratification based on this parameter for a more accurate prediction of the prognosis.

PATIENTS AND METHODS

We enrolled 101 consecutive patients with TNM stage III rectal cancer who had undergone curative surgery with extended lymph node dissection at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, between January 1979 and December 2001. Cases with the rectosigmoid as the primary cancer site were excluded. None of the patients had received any chemotherapy or radiation therapy before the surgery. Complete dissection of all the regional lymph nodes with mesorectal excision was performed in all cases. In Japan, lateral lymph node dissection is generally indicated if the lower margin of the primary cancer is located below the peritoneal reflection or anal canal with invasion into the muscularis propria or beyond.[8] There were no cancer cells in the circumferential margin of resection in any of the cases.

According to the location of the lymph nodes, we classified the lymph node involvement into 3 groups, ie, involvement of the perirectal lymph nodes, intermediate lymph nodes, or the main/lateral lymph nodes, according to the Japanese Classification of Colorectal Carcinoma, Second English Edition: pN1 is defined as metastasis to 1 to 3 pericolic/perirectal or intermediate lymph nodes, pN2 as metastasis to 4 or more pericolic/perirectal or intermediate lymph nodes, and pN3 as metastasis to the main/lateral lymph nodes. The main lymph nodes consist of the ileocolic root nodes, right colic root nodes, middle colic root nodes, and the nodes along the inferior mesenteric artery proximal to the origin of the left colic artery, and the lateral lymph nodes refer to those along the internal iliac artery, common iliac artery, obturator vessels and nerves, and external iliac artery. In this study, there were 52 cases with pN3 and 49 cases with pN2 (with metastasis to 4 or more pericolic/perirectal or intermediate lymph nodes) disease. pN2 status in the TNM classification is further subclassified as pN2a (metastasis to 4–6 regional lymph nodes) and pN2b (metastasis to 7 or more regional lymph nodes); there were 32 patients with pN2a disease and 16 patients with pN2b disease in this study.

FIGURE 1. Extracapsular invasion was defined as extracapsular growth of the tumor cells, invasion of the perinodal fat, or extranodal location of tumor cells continuously, not discontinuously (red arrow).

The resected lymph nodes were fixed in 10% formalin for several days, and sections were prepared across the maximum diameter of the nodes and stained with hematoxylin and eosin (H & E), with no specific immunostaining. The slides were then evaluated by simple light microscopy.

The ECI status was classified according to the distribution patterns of the cancer cells in the lymph nodes as the presence of ECI or absence of ECI. Extracapsular invasion was defined as extracapsular growth of tumor cells, invasion of the perinodal fat, or extranodal location of the tumor cells continuously. Although Ueno et al[9] reported extranodal cancer deposits as a prognostic factor, histological evidence of the lymph node structure in their study was based on routinely processed lymphadenectomy specimens, namely, discontinuous tumor cells. We categorized cases showing ECI in at least 1 node as "ECI-positive" (Fig. 1).

Then, patients showing ECI in at least one of the metastatic lymph nodes in the main lymph node and lateral lymph node groups were classified as pN3-ECI-positive, and those without ECI in any of the nodes in the main or lateral lymph node groups were classified as pN3-ECI-negative. After the operation, all pN3 cases

were administered oral chemotherapy with drugs such as oral 5-fluorouracil, 5′-doxifluridine, carmofur, or uracil-tegafur with leucovorin, as the most commonly used drugs, for approximately 6 to 12 months.[1,10,11]

We conducted a review of the hospital records to obtain clinicopathological information about the patients, including the sex and age (median, 58 years), lesion location, macroscopic configuration of the tumor, maximum tumor size (median size, 5 cm), greatest depth of invasion of the tumor (pT1 + pT2 vs pT3 + pT4), histological type of the tumor, presence/absence of lymphatic invasion and venous invasion, and the number of metastasis-positive lymph nodes. Adenocarcinomas of the rectum are graded predominantly on the basis of their glandular appearance and are classified as well or moderately differentiated or others, according to the World Health Organization histopathological classification of tumors of the colon and rectum, and the Japanese Classification of Colorectal Carcinoma.

Rectal cancer is defined as a tumor whose lowest border is located between the anal verge and the sacral promontory. Lesions are classified as upper or lower rectal cancers depending on their location with respect to the peritoneal reflection. The tumors are classified into 2 types on the basis of their macroscopic appearance: mass type or diffuse type. The mass type includes the superficial, polypoid, and ulcerated types of tumors with a clear margin, and the diffuse type includes the ulcerated type with infiltration, diffuse infiltrating, and unclassified types. The number of positive lymph nodes was categorized as less than 3 or more than 4.

All data are expressed as the mean ± SD. The Fisher exact probability text, univariate logistic regression, and multivariate stepwise logistic regression analysis were subsequently performed to identify factors that might influence ECI-positive lymph node metastasis. The log-rank test was used to evaluate the differences in the overall survival rate and the disease-free survival rate between groups. Statistical significance was set at $p < 0.05$.

RESULTS

Table 1 shows the relationship between the ECI status and clinicopathological findings. No significant differences were observed in relation to the sex, age, tumor location, tumor macroscopic configuration, tumor size, greatest depth of tumor invasion, tumor histological type, presence/absence of lymphatic or venous invasion, or the number of positive lymph nodes in pN3 rectal cancer.

Table 2 shows the results of the univariate analysis performed to identify factors that might be correlated with the disease-free survival rate. Although no significant differences in the disease-free survival rate were observed in relation to the age, tumor location, tumor macroscopic configuration, tumor size, greatest depth of tumor invasion, tumor histological type, presence/absence of lymphatic or venous invasion, or the number of positive lymph nodes in pN3 rectal cancer, the rate differed significantly depending on the sex and pN3-ECI status. Male patients, in comparison with female patients, and pN3-ECI-positive patients, in comparison with the pN3-ECI-negative patients, showed significantly poorer prognoses in terms of the disease-free survival rates ($p = 0.024$ and $p = 0.003$).

TABLE 1. The relationship between the ECI status and clinicopathological findings

	pN3-ECI positive (n = 19)	*pN3-ECI negative (n = 33)*	*p*
Sex			
Male	11(57.9)	18(54.5)	0.523
Female	8(42.1)	15(45.5)	
Age			
<58	9(47.4)	16(48.5)	0.584
≥58	10(52.6)	17(51.5)	
Location			
Upper rectum	2(10.5)	6(18.2)	0.378
Lower rectum	17(89.5)	27(81.8)	
Macroscopic configuration			
Massive	14(73.7)	29(87.9)	0.178
Diffuse	5(26.3)	4(12.1)	
Tumor size			
<5 cm	12(63.2)	18(54.5)	0.379
≥5 cm	7(36.8)	15(45.5)	
Greatest depth invasion			
pT1+pT2	4(21.1)	6(18.2)	0.536
pT3+pT4	15(78.9)	27(81.8)	
Histological type			
W/M	15(78.9)	27(81.8)	0.536
Others	4(21.1)	6(18.2)	
Lymphatic invasion			
Present	14(73.7)	25(75.8)	0.560
Absent	5(26.3)	8(24.2)	
Venous invasion			
Present	11(57.9)	21(63.6)	0.452
Absent	8(42.1)	12(36.4)	
No. of positive LNs			
<3	6(31.6)	14(42.4)	0.318
≥4	13(68.4)	19(57.6)	

Values shown are n (%).
W/M = well and moderately differentiated adenocarcinoma; LNs = lymph nodes; ECI = extracapsular invasion.

Table 3 shows the results of univariate analysis performed to identify factors that might be correlated with the overall survival rate. Although no significant differences in the overall survival rate were observed in relation to the age, tumor location, tumor macroscopic configuration, greatest depth of tumor invasion, tumor histological type, presence/absence of lymphatic or venous invasion, or the number of positive lymph nodes, the rate differed significantly depending on the sex, tumor size, and pN3-ECI status. Male patients, patients with a tumor diameter of greater than 5 cm, and pN3-ECI-positive patients showed

TABLE 2. Univariate analysis of the disease-free survival rates in pN3 cases

	n (%)	*p*
Sex		
Male	29(55.8)	0.024
Female	23(44.2)	
Age		
<58	25(47.4)	0.686
≧58	27(52.6)	
Location		
Upper rectum	8(15.4)	0.139
Lower rectum	44(84.6)	
Macroscopic configuration		
Massive	43(82.7)	0.574
Diffuse	9(17.3)	
Tumor size		
<5 cm	30(80.8)	0.253
≧5 cm	22(19.2)	
Greatest depth invasion		
pT1+pT2	10(19.2)	0.309
pT3+pT4	42(80.8)	
Histological type		
W/M	42(80.8)	0.219
Others	10(19.2)	
Lymphatic invasion		
Present	39(75.0)	0.180
Absent	13(25.0)	
Venous invasion		
Present	32(61.5)	0.378
Absent	20(38.5)	
No. of positive LNs		
<3	20(38.5)	0.072
≧4	32(61.5)	
pN3-ECI		
Positive	19(36.5)	0.003
Negative	33(63.5)	

W/M = well and moderately differentiated adenocarcinoma; LNs = lymph nodes; ECI = extracapsular invasion.

TABLE 3. Univariate analysis of the overall survival rates in pN3 cases

	n (%)	*p*
Sex		
Male	29(55.8)	0.021
Female	23(44.2)	
Age		
< 58	25(47.4)	0.185
≧ 58	27(52.6)	
Location		
Upper rectum	8(15.4)	0.265
Lower rectum	44(84.6)	
Macroscopic configuration		
Massive	43(82.7)	0.934
Diffuse	9(17.3)	
Tumor size		
<5 cm	30(80.8)	0.047
≥5 cm	22(19.2)	
Greatest depth invasion		
pT1+pT2	10(19.2)	0.243
pT3+pT4	42(80.8)	
Histological type		
W/M	42(80.8)	0.272
Others	10(19.2)	
Lymphatic invasion		
Present	39(75.0)	0.589
Absent	13(25.0)	
Venous invasion		
Present	32(61.5)	0.765
Absent	20(38.5)	
No. of positive LNs		
<3	20(38.5)	0.129
≥4	32(61.5)	
pN3-ECI		
Positive	19(36.5)	0.008
Negative	33(63.5)	

W/M = well and moderately differentiated adenocarcinoma; LNs = lymph nodes; ECI = extracapsular invasion.

significantly poorer prognoses in terms of the overall survival rate in comparison with the female patients, patients with a tumor diameter of less than 5 cm, and pN3-ECI-negative patients ($p = 0.024$, $p = 0.047$, and $p = 0.008$).

Table 4 shows the results of multivariate analysis performed to identify variables that might be independently correlated with the overall and disease-free survival rates. pN3-ECI was identified as the only variable found to show a statistically significant correlation with the disease-free survival rate ($p = 0.011$), whereas none of the examined factors were statistically significantly correlated with the overall survival rate.

Figure 2 shows the disease-free survival rates in the patients enrolled in the study. No significant differences in the disease-free survival rate were observed among the pN2a, pN2b, and pN3 cases overall (left side). However, when the pN3 patients were stratified further according to the presence/absence of ECI in the main/lateral groups of lymph nodes, ie, pN3-ECI-positive/pN3-ECI-negative, the disease-free survival rate was statistically significantly lower in the pN3-ECI-positive cases in comparison with that in the pN2b cases ($p = 0.034$). The disease-free survival rate also differed significantly between the pN3-ECI-positive and pN3-ECI-negative cases ($p = 0.003$).

Figure 3 shows the overall survival rates in the patients enrolled in this study. No significant differences in the overall survival rate were observed among the pN2a, pN2b, and pN3 cases overall (left side). However, when the

TABLE 4. Multivariate analysis of the overall survival rates and disease-free survival rates

	HR	*95% CI*	*p*
Disease-free survival rates			
Sex	0.509	0.244–1.0063	0.072
pN3-ECI	0.411	0.206–0.816	0.011
Overall survival rates			
Sex	0.481	0.229–1.009	0.053
Tumor size	0.756	0.518–1.103	0.147
pN3-ECI	0.503	0.244–1.037	0.603

ECI = extracapsular invasion.

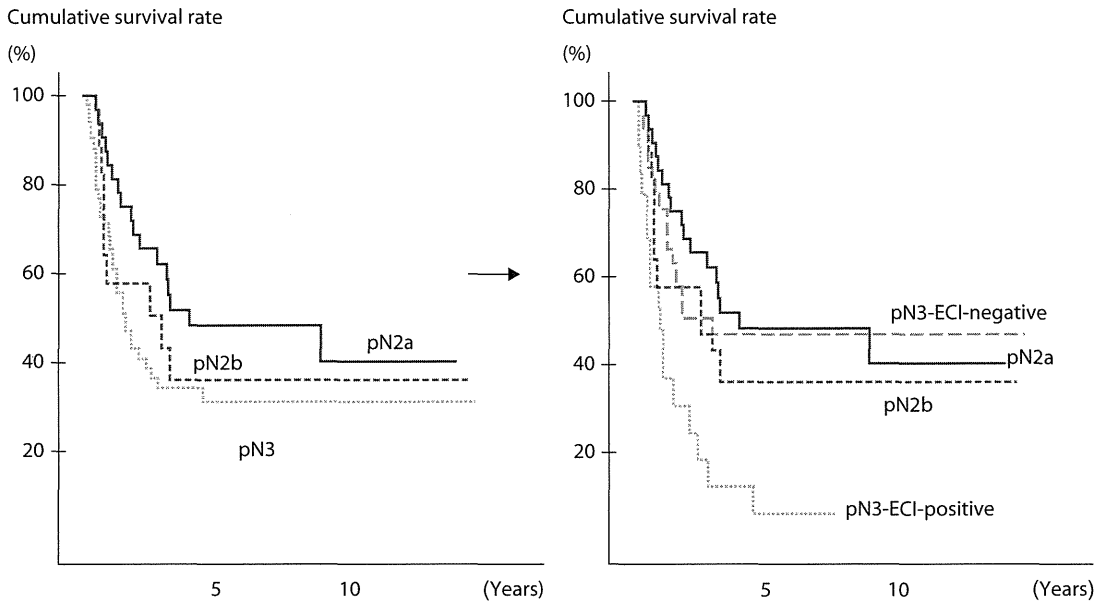

FIGURE 2. Disease-free survival rates in the enrolled patients. Left, pN2a, pN2b, and pN3 cases. Right, pN2a, pN2b, pN3-ECI-positive, and pN3-ECI-negative cases. ECI = extracapsular invasion.

pN3 patients were stratified further according to the presence/absence of ECI in the main/lateral groups of lymph nodes, ie, pN3-ECI-positive/pN3-ECI-negative, the overall survival rate was lower in the pN3-ECI-positive cases in comparison with that in the pN2b cases ($p = 0.077$). The overall survival rate also differed significantly between the pN3-ECI-positive and pN3-ECI-negative cases ($p = 0.008$).

DISCUSSION

Patients with TNM stage III colorectal cancer constitute a heterogeneous population with respect to the prognosis, with some showing a better prognosis than others. The patients have been divided into pN1, pN2, and pN3 cases according to the Japanese Classification of Colorectal Carcinoma, Second English Edition; pN1 cases have a more favorable prognosis than the pN2 or pN3 cases. In the present study, we demonstrated the absence of any significant differences in the overall or disease-free survival rates between the pN2 and pN3 cases.

Several previous studies have reported the presence of ECI in the metastatic lymph nodes as a poor prognostic factor in a variety of cancers.[4–7] It is significant that Fujii et al[12] reported that the presence of ECI in the metastatic lymph nodes may be a useful marker to identify patients with colorectal cancer who are at a high risk for disease recurrence in the short term. Furthermore, they reported that the presence of ECI in the N1 metastatic lymph nodes may be a marker of metastasis in more distant regional lymph node groups (N2) in patients with colorectal cancer, because it possibly represents the ability of the colorectal tumor cells to disseminate to distant lymph nodes,[13] but no relationship was noted with the presence/absence of metastasis in the N3 lymph nodes. However, there have been no studies on the significance of the presence/absence of ECI in relation to the lymph node group involved. This study is the first to determine the prognostic significance of the presence/absence of ECI in the main/lateral lymph nodes in pN3 patients. We demonstrated that pN3-ECI positivity was the only factor that was statistically significantly associated with the disease-free survival rate. Yano et al[6] also reported that the presence of ECI in the metastatic lymph nodes was the only factor that was statistically significantly associated with the disease-free survival; however, their report did not refer to the location of the metastatic lymph nodes showing ECI. Heide et al[7] reported that the presence of ECI in the metastatic lymph nodes had a strong negative impact on the local control rate, independent of other prognostic factors, and that it was also associated with a high frequency of distant metastasis.

Two critically important implications of this study need to be emphasized here. First, stratification of pN3 cases based on the ECI status is useful. Patients without ECI in the main metastatic lymph nodes, ie, pN3-ECI-negative cases were analogous, in terms of the prognosis, to pN2 cases, whereas the prognosis was significantly poorer in the pN3-ECI-positive cases. Second, while determining the lymph node metastasis status for staging, de-

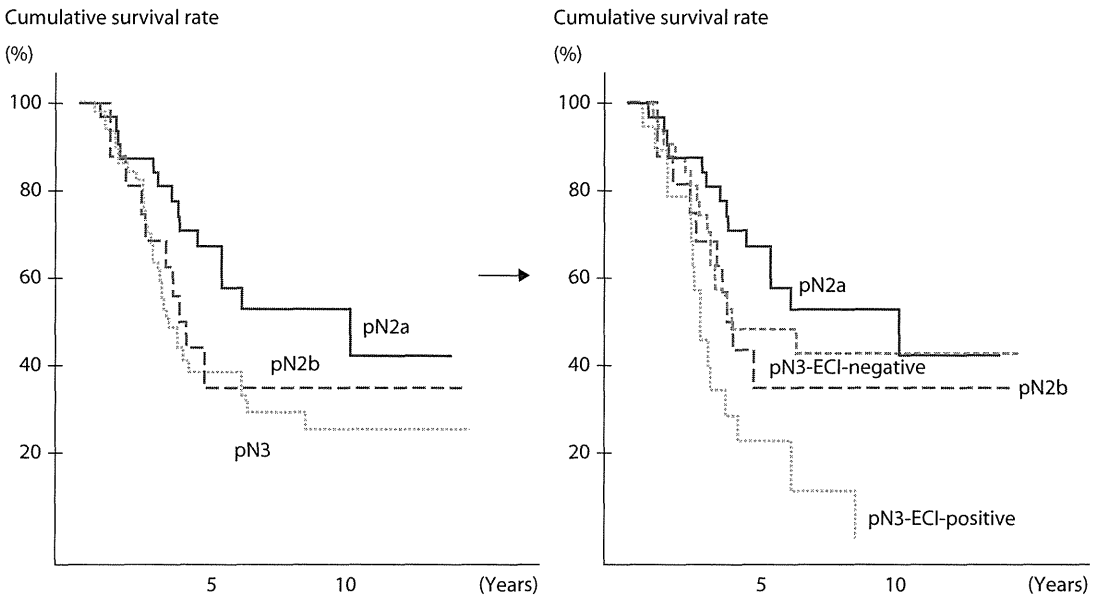

FIGURE 3. Overall survival rates in the enrolled patients. Left, pN2a, pN2b, and pN3 cases. Right, pN2a, pN2b, pN3-ECI-positive, and pN3-ECI-negative cases. ECI = extracapsular invasion.

termination of not only the number of metastatic lymph nodes, but also that of the lymph node groups involved has a crucial role in predicting the prognosis. Kanemitsu et al[14] reported that high ligation of the inferior mesenteric artery allows curative resection and long-term survival in patients with sigmoid colon or rectal cancer and emphasized that complete resection of the main lymph nodes was important. Especially, although pN3-ECI-positive was dominated in the systemic recurrence, the presence of ECI in the metastatic lymph nodes was a predictor of potential systemic involvement.

Assessment of the ECI status in the metastatic lymph nodes can be easily performed by routine staining, ie, H & E staining of tissue sections, without any need for the use of immunostaining techniques. Yano et al[6] also reported that the presence of ECI in the metastatic lymph nodes determined by routine H & E staining is a potent prognostic factor in patients with stage III colorectal cancer. In this study, ECI was defined as invasion of the perinodal fat or extranodal location of the tumor cells continuously, hence, not discontinuously. In Japan, most surgeons commonly separate the lymph nodes from the resected specimens before presenting them to the pathologists. Consequently, it is difficult to retrieve discontinuous tumor cells. If the resected specimens were submitted intact to the pathologists, discontinuous tumor cells could also be examined, as in the case of the extranodal cancer deposits reported by Ueno et al.[9] However, this is not easy and not very common in practical clinical use.

CONCLUSION

Detailed stratification of pN3 cases based on the presence/absence of ECI has the potential to contribute significantly to more available prediction of the prognosis of patients with stage III colorectal cancer.

REFERENCES

1. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol.* 2007;25:2198–2204.
2. Kanemitsu Y, Komori K, Ishiguro S, Watanabe T, Sugihara K. The relationship of lymph node evaluation and colorectal cancer survival after curative resection: a multi-institutional study. *Ann Surg Oncol.* 2012;19:2169–2177.
3. Japanese Research Society for Cancer of the Colon and Rectum. *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus.* 7th ed, revised version. Tokyo, Japan: Kanahara Shuppan; 2006.
4. Komuta K, Okudaira S, Haraguchi M, Furui J, Kanematsu T. Identification of extracapsular invasion of the metastatic lymph nodes as a useful prognostic sign in patients with resectable colorectal cancer. *Dis Colon Rectum.* 2001;44:1838–1844.
5. Stitzenberg KB, Meyer AA, Stern SL, et al. Extracapsular extension of the sentinel lymph node metastasis: a predictor of nonsentinel node tumor burden. *Ann Surg.* 2003;237:607–612.
6. Yano H, Saito Y, Kirihara Y, Takashima J. Tumor invasion of lymph node capsules in patients with Dukes C colorectal adenocarcinoma. *Dis Colon Rectum.* 2006;49:1867–1877.

7. Heide J, Krüll A, Berger J. Extracapsular spread of nodal metastasis as a prognostic factor in rectal cancer. *Int J Radiat Oncol Biol Phys.* 2004;58:773–778.
8. Komori K, Kanemitsu Y, Ishiguro S, Shimizu Y, Sano T, Kato T. Analysis of lymph node metastatic pattern according to the depth of in-growth in the muscularis propria in T2 rectal cancer for lateral lymph node dissection. *Dig Surg.* 2011;28:352–359.
9. Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. *Am J Clin Pathol.* 2007;127:287–294.
10. André T, Boni C, Mounedji-Boudiaf L, et al; Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med.* 2004;350:2343–2351.
11. Monga DK, O'Connell MJ. Surgical adjuvant therapy for colorectal cancer: current approaches and future directions. *Ann Surg Oncol.* 2006;13:1021–1034.
12. Fujii T, Tabe Y, Yajima R, et al. Extracapsular invasion as a risk factor for disease recurrence in colorectal cancer. *World J Gastroenterol.* 2011;17:2003–2006.
13. Fujii T, Tabe Y, Yajima R, et al. Process of distant lymph node metastasis in colorectal carcinoma: implication of extracapsular invasion of lymph node metastasis. *BMC Cancer.* 2011;11:216.
14. Kanemitsu Y, Hirai T, Komori K, Kato T. Survival benefit of high ligation of the inferior mesenteric artery in sigmoid colon or rectal cancer surgery. *Br J Surg.* 2006;93:609–615.

Int Surg 2013;**98**:200–204
DOI: 10.9738/INTSURG-D-13-00027.1

Sex Differences Between cT4b and pT4b Rectal Cancers

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We retrospectively evaluated rectal cancer surgery cases in which resection had been performed for invasion of other organs in terms of pathologic findings from the viewpoint of sex differences. We enrolled 61 consecutive patients with rectal cancer who had undergone curative surgery with resection of invaded adjacent organs. We investigated invasion of adjacent organs in terms of pathologic findings according to sex differences. Among males, 4 cases (13.8%) had received combined radical resections of more than 2 organs, while the number of such female cases was 15 (46.9%). The difference between males and females was statistically significant ($P = 0.006$). Among male cases, histopathologic invasion was present in 4 (13.8%), while 9 female cases (28.1%) showed this feature. Nevertheless, there was not a statistically significant difference between males and females ($P = 0.08$); the rate in females was roughly twice that in males. No significant difference was recognized in the overall survival rates between males and females, but more females than males experienced local recurrence. In cases with rectal cancer invading neighboring organs, the effect of the invasion must be carefully determined, and the most appropriate operative approach selected accordingly.

Key words: Rectal cancer – Invasion of other organs – Sex differences

It is important to prevent local recurrences of rectal cancer. Obtaining a sufficient circumferential resection margin (CRM) is thus a critical surgical procedure.[1,2] This is especially true for local advanced rectal cancer with distant invasion of adjacent organs (pT4b). Total pelvic exenteration remains the first-line surgical treatment for pT4b cases,[3] but recently organ-sparing therapy has also frequently been chosen.[4] However, the mode of invasion in highly aggressive rectal cancer has been less well studied. We retrospectively evaluated rectal cancer surgery cases in which resection had

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Table 1 Clinicopathological findings

	Male cases (%), N = 29	Female cases (%), N = 32
Age	60 ± 9	63 ± 12
Size (cm)	3.5 ± 2.0	5.9 ± 1.9
Figure		
Polypoid type	1 (3.4)	1 (3.1)
Ulcerated with clear margin type	24 (82.8)	22 (68.8)
Ulcerated with infiltration type	4 (13.8)	8 (25.0)
Diffuse infiltrating type	0 (0.0)	1 (3.1)
Unclassified type	0 (0.0)	0 (0.0)
Histology		
Well-differentiated and moderately differentiated	27 (93.1)	30 (93.8)
Others (poorly differentiated, mucinous, and Signet-ring cells)	2 (6.9)	2 (6.3)
Surgical procedure		
Low anterior resection	14 (48.4)	14 (43.8)
Hartmann's procedure	1 (3.4)	5 (15.6)
Abdominoperineal resection	11 (37.9)	10 (31.3)
Total pelvic exenteration	3 (10.3)	3 (9.3)
TNM		
IIA	0 (0.0)	0 (0.0)
IIB	11 (37.9)	8 (25.0)
IIC	0 (0.0)	2 (6.2)
IIIA	0 (0.0)	0 (0.0)
IIIB	7 (24.2)	6 (18.8)
IIIC	11 (37.9)	16 (50.0)

been performed for invasion of other organs in terms of pathologic findings from the viewpoint of sex differences.

Materials and Methods

We enrolled 61 consecutive patients with rectal cancer who had undergone curative surgery with resection of invaded adjacent organs at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan, between January 1990 and December 2001. Intraoperatively, if we recognized the primary rectal cancer as having invaded adjacent organs, combined radical resection was performed. None of our patients had received either chemotherapy or radiation therapy prior to surgery. Complete dissection of all regional lymph nodes with mesorectal excision was carried out in all cases. In Japan, lateral lymph node dissection is generally indicated if the lower margin of the primary cancer is located below the peritoneal reflection or anal canal with invasion into the muscularis propria or beyond. There were no cancer cells in the CRM in any of our cases. The resected specimens were fixed in 10% formalin for several days, and sections were prepared across the maximum diameter of the tumor and stained with hematoxylin and eosin (HE), without specific immunostaining. The slides were then evaluated by simple light microscopy.

We conducted a review of the relevant hospital records to obtain clinicopathologic information about the patients, including sex and age, macroscopic configuration of the tumor, maximum tumor size, and histologic type of the tumor. Adenocarcinomas of the rectum are graded predominantly on the basis of their glandular appearance and are classified as well/moderately differentiated (W/M) or others (poorly differentiated, mucinous, and Signet-ring cells), according to the World Health Organization (WHO) histopathologic classification of tumors of the colon and rectum,[5] and the Japanese Classification of Colorectal Carcinoma.[6]

This study included cases with rectal cancer defined as a tumor whose lowest border is located between the anal verge and the sacral promontory and the rectosigmoid colon. Tumors are classified into 5 types on the basis of their macroscopic appearance: (1) polypoid, (2) ulcerated with clear margin, (3) ulcerated with infiltration, (4) diffuse infiltrating, and (5) unclassified. Surgical procedures are classified into 4 approaches: (1) low anterior resection, (2) Hartmann's procedure, (3) abdominoperineal resection, and (4) total pelvic exenteration. In terms of the TNM staging system, all cases were classified as having stage II or stage III tumors. Most notably, we investigated invasion of adjacent organs

Table 2 The resected organs in males and females

Male: Resection 29 cases	Resection cases			Histopathological invasion (+)
Seminal vesicles	14 (48.3%)	25 (86.2%)	a	0 (0.0%)
Prostate	2 (6.9%)			0 (0.0%)
Urinary Bladder	9 (31.0%)			1 (3.4%): Urinary Bladder
Seminal vesicles + Prostate	1 (3.4%)	4 (13.8%)		1 (3.4%): Seminal vesicles
Seminal vesicles + Urinary bladder + Ureter	1 (3.4%)			1 (3.4%): Ureter
Seminal vesicles + Prostate + Ureter	1 (6.9%)			0 (0.0%)
Prostate+ Urinary bladder + Ileum	1 (6.9%)			1 (3.4%): Ileum
Total				4 (13.8%)[c]

Female: Resection 32 cases	Resection cases			Histopathological invasion (+)
Uterus	5 (15.6%)	17 (53.19%)	b	0 (0.0%)
Ovary	5 (15.6%)			0 (0.0%)
Vagina	6 (18.8%)			2 (6.3%): Vagina
Ureter	1 (3.1%)	15 (46.9%)		0 (0.0%)
Uterus + Ovary	4 (12.5%)			1 (3.4%): Uterus
Uterus + Vagina	7 (21.9%)			2 (6.3%): Vagina
Uterus + Urinary bladder + Sigmoid colon	1 (3.1%)			1 (3.1%): Sigmoid colon
Vagina + Urinary bladder	2 (6.3%)			2 (6.3%): Vagina + Urinary bladder
Uterus + Ovary+ Urinary bladder	1 (3.1%)			1 (3.1%): Uterus + Urinary bladder
Total				9 (28.1%)[d]

[a]Significantly different, $P = 0.006$.

[b]Significantly different, $P = 0.006$.

[c]Significantly different, $P = 0.08$.

[d]Significantly different, $P = 0.08$.

in terms of pathologic findings, according to sex differences (Table 1). After the operation, TNM stage III cases were administered oral chemotherapy, with oral 5-fluorouracil, 5′-doxifluridine, carmofur, or uracil-tegafur with leucovorin being the most commonly used drugs, for approximately 6 to 12 months.[7–9] None of the patients received radiation therapy.

All data are expressed as mean ± SD. The χ^2 test was subsequently performed to identify factors possibly influencing pathologic invasion and recurrence. The log-rank test was used to evaluate the difference in local disease-free survival rates between groups. Statistical significance was set at $P < 0.05$.

Results

Table 2 shows the resected organs and whether histopathologic invasion was present (pT4b). In male cases, combined radical resections involved the seminal vesicles, prostate, urinary bladder, and/or ileum. The seminal vesicles were the most commonly resected adjacent organs (14 of 29 cases; 48.3%). Four cases (13.8% of males) underwent combined radical resection of more than 2 organs. In female cases, combined radical resection involved the uterus, ovaries, vagina, urinary bladder, ureters, and sigmoid colon. The vagina was the most commonly resected adjacent organ (6 of 32 cases; 18.8%). Fifteen cases (46.9% of females) underwent combined radical resection of more than 2 organs. There was a statistically significant difference between males and females in the number of patients undergoing combined radical resection ($P = 0.006$). The results (Table 2) for histopathologic invasion are shown. Histopathologic invasion was present in only 4 males (13.8%). Yet, among females, histopathologic invasion was observed in 9 cases (28.1%). The difference between males and females was not statistically significant ($P = 0.08$), but the rate in females was roughly twice that in males. Figure 1 shows the partially resected posterior wall of the vagina. The cancer had spread showing discontinuity, and the shortest distance between the deepest part of the cancer and the incised surface was only 500 μm.

Figure 2 shows the overall survival rates of the patients enrolled in this study. No significant differences in the overall survival rate were observed between T4a cases in males with and in females ($P = 0.561$), or T4b cases in males with and in females ($P = 0.728$). But there was a statistically significant difference between T4a cases and T4b cases in males ($P = 0.005$), and in T4a cases and T4b cases in females ($P < 0.001$) in the overall survival rate.

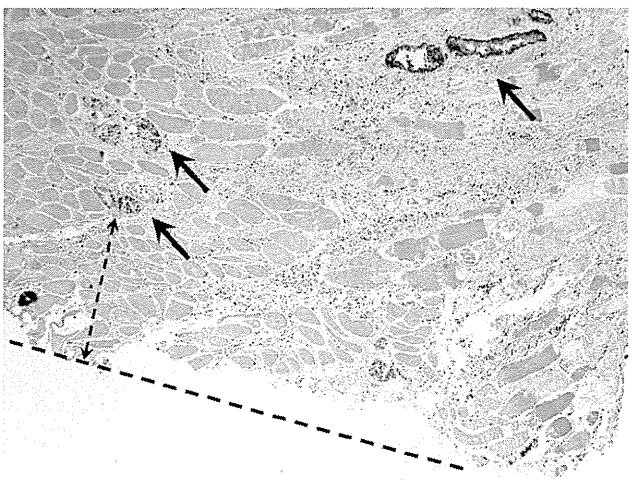

Fig. 1 This figure shows the partially resected posterior wall of the vagina. The cancer shows discontinuous spread (black arrow), and the shortest distance between the deepest part of the cancer and the incised surface (dotted line) was only 500 μm (dotted black arrow). H&E (×100).

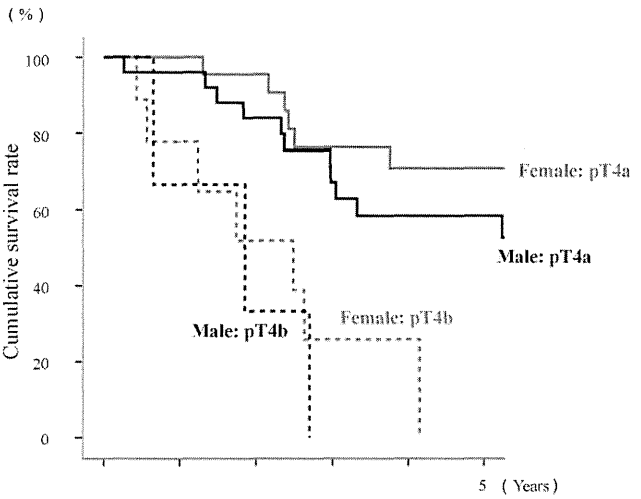

Fig. 2 This figure shows the overall survival rates of the study patients. Male: pT4a vs. Female pT4a : p=0.561; Male: pT4b vs. Female pT4b : p=0.728; Male: pT4a vs. Male pT4b : p=0.005; Female: pT4a vs. Female pT4b : p<0.561.

Table 3 shows the organs affected by recurrence in males and females. While no significant difference was recognized in local recurrence rates between males and females undergoing resection ($P = 0.220$), the number of local recurrences in females receiving resection exceeded that in males.

Discussion

Previously, we reported pathologic studies of combined radical resection of seminal vesicles in the treatment of rectal cancer, and we emphasized that it is possible to ensure a sufficiently large CRM and to thereby attenuate local recurrence.[10] However, most previously published reports do not make reference to sex differences. This study is the first, to our knowledge, to demonstrate sex differences in response to combined radical resection for the treatment of rectal cancer. Our data therefore have prognostic significance. Bonfanti *et al* report extensively on the organs resected for invasive colorectal cancer, providing considerable detail, but do not mention sex differences.[11]

Recently, many studies have examined neoadjuvant treatment with chemotherapy and pelvic radiotherapy for locally advanced rectal cancer. Neoadjuvant treatment, employing chemotherapy and pelvic radiotherapy, contributes to better outcomes, with the former inhibiting distant metastases and the latter inhibiting local recurrences.[12] However, because of the lack of pathologic findings without neoadjuvant treatment (*i.e.*, the spread of rectal cancer in the absence of other factors), this study provides data critical for determining the optimal treatment of pT4b cases.

It is of major interest that the rate of histopathologic invasion in females exceeded that in males. The reason is unclear, but in 15 female cases (46.9%) multiple organs were resected based on an intraoperative diagnosis of cT4b, making it reasonable to speculate that female anatomic structures are more susceptible to tumor invasion. This study showed tumors to be in proximity to the incised surface.

The local recurrence rate in females was approximately twofold that in males, such that the surgical margins in females were apparently insufficient. The many recurrences in our female patients prompted us to speculate that the operative method employed might be less than optimal in women. When rectal cancer invaded the posterior wall of the vagina, partial resection of the vagina was often deemed necessary, but this procedure was found to be insufficient to prevent recurrence. If intraoperative cT4b is recognized, it is essential that adequate combined resection be performed. Harris *et al* report that an aggressive surgical strategy with complete resection is predictive of long-term survival.[13] And, the high-potency adjuvant treatment with chemo-

Table 3 The organs affected by recurrence in males and females

	Male cases (%), N = 29	Female cases (%), N = 32
All recurrence cases	9 (31.0)	10 (31.3)
Local	1 (3.4)	4 (12.5)
Anastomosis line	1 (3.4)	1 (3.4)
Distant (lung, liver, bone)	5 (17.2)	4 (12.5)
Distant peritoneum	1 (3.4)	1 (3.4)
Lymph nodes	1 (3.4)	0 (0.0)

[a]Significantly different, $P = 0.220$.

[b]Significantly different, $P = 0.220$.

therapy is essential for pT4b cases in males and females.[13]

Our data showed that no pathologic invasion cases account for about 80% of resected adjacent organs in males and females. So, it is essential to rule out the cases except pT4b, but it is very difficult intraoperatively. The reasonably accurate diagnostic imaging is essential before operation.

In rectal cancer cases with invasion of neighboring organs, the effect of the invasion must be carefully determined, and the most appropriate operative approach selected accordingly.

Acknowledgments

References

1. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986;**2**(8514):996–999
2. Bernstein TE, Endreseth BH, Romundstad P, Wibe A. Circumferential resection margin as a prognostic factor in rectal cancer. *Br J Surg* 2009;**96**(11):1348–1357
3. Yamada K, Ishizawa T, Niwa K, Chuman Y, Aikou T. Pelvic exenteration and sacral resection for locally advanced primary and recurrent rectal cancer. *Dis Colon Rectum* 2002;**45**(8):1078–1084
4. Saito N, Suzuki T, Tanaka T, Sugito M, Ito M, Kobayashi A *et al.* Preliminary experience with bladder preservation for lower rectal cancers involving the lower urinary tract. *J Surg Oncol* 2010;**102**(7):778–783
5. Bosman FT, Carneiro F, Hruban RH, Theise ND. *WHO Classification of Tumours of the Digestive System*. Vol 3. 4th ed. Lyon, France: WHO, 2010
6. Japanese Society for Cancer of the Colon and Rectum. *The Japanese Classification of Colorectal Carcinoma*. Tokyo, Japan: Kanehara & Co, Ltd, 2009
7. Kuebler JP, Colangelo L, O'Connell MJ, Smith RE, Yothers G, Begovic M *et al.* Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol* 2007;**25**(16):2198–2204
8. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T *et al.* Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;**350**(23):2343–2351
9. Monga DK, O'Connell MJ. Surgical adjuvant therapy for colorectal cancer: current approaches and future directions. *Ann Surg Oncol* 2006;**13**(8):1021–1034
10. Komori K, Hirai T, Kanemitsu Y, Shimizu Y, Sano T, Ito S *et al.* Pathology studies of combined radical resection of seminal vesicle in the treatment of rectal cancer. *Int Surg* 2011;**96**(1):51–55
11. Bonfanti G, Bozzetti F, Doci R, Baticci F, Marolda R, Bignami P. *et al.* Results of extended surgery for cancer of the rectum and sigmoid. *Br J Surg* 1982;**69**(6):305–307
12. Sadahiro S, Suzuki T, Ishikawa K, Fukasawa M, Saguchi T, Yasuda S *et al.* Preoperative radio/chemo-radiotherapy in combination with intraoperative radiotherapy for T3-4Nx rectal cancer. *Eur J Surg Oncol* 2004;**30**(7):750–758
13. Harris DA, Davies M, Lucas MG, Drew P, Carr ND, Beynon J. Multivisceral resection for primary locally advanced rectal carcinoma. *Br J Surg* 2011;**98**(4):582–588

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(3)321–323
doi:10.1093/jjco/hys219
Advance Access Publication 28 December 2012

Clinical Trial Notes

Prospective Feasibility Study to Evaluate Neoadjuvant-synchronous S-1 + RT for Locally Advanced Rectal Cancer: A Multicenter Phase II Trial (UMIN ID: 03396)

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Received July 23, 2012; accepted December 1, 2012

In Western countries, the standard treatment for locally advanced rectal cancer is preoperative chemoradiotherapy followed by total mesorectal excision. However, in Japan, the treatment results without preoperative chemoradiotherapy are by no means inferior; therefore, extrapolation of the results of preoperative treatment in Western countries to Japan is controversial. We consider that survival may be improved by preoperative chemoradiotherapy with new anticancer agents as they are expected not only to decrease the local recurrence rate but also to prevent distant metastases. We are conducting a multicentre Phase II study to evaluate the safety and efficacy of neoadjuvant chemoradiotherapy using S-1 in patients with locally advanced rectal cancer. The primary endpoint is the rate of complete treatment of neoadjuvant chemoradiotherapy. Secondary endpoints are the response rate of neoadjuvant chemoradiotherapy, short-term clinical outcomes, rate of curative resection and pathological evaluation. The short-term clinical outcomes are adverse events of neoadjuvant chemoradiotherapy and surgery-related complications. Thirty-five patients are required for this study.

Key words: rectal cancer – neoadjuvant chemoradiotherapy – S-1

INTRODUCTION

The standard treatment for locally advanced rectal cancer is well known to differ between Japan and Western countries. In Western countries, multimodal therapies such as preoperative short-term intensive radiotherapy or conventional long-term radiotherapy in combination with 5-fluorouracil (5-FU)-based chemotherapy have gained widespread acceptance for the treatment of locally advanced rectal adenocarcinoma (1). These treatments provide improved local control when compared with surgery alone, although only one study has shown a survival benefit (2). The local control benefit of preoperative radiotherapy remains relevant even in the era of total mesorectal excision (TME) (3). The addition of chemotherapy to preoperative conventional long-term radiotherapy (RT) has been demonstrated to be feasible, with enhanced tumoricidal effects (4). In Japan, TME or tumor-specific mesorectal excision followed by adjuvant chemotherapy without preoperative treatment is a standard strategy, and lateral lymph node (LN) dissection is added in patients with lower rectal cancer (5). The results of the surgical treatment without RT in Japan are by no means inferior to those in Western countries that do use RT with surgery. Therefore, extrapolation of the results of preoperative treatment in Western countries to Japan is controversial.

Recently, new anticancer agents have markedly improved the response rate and prognosis of unresectable and recurrent colorectal cancer. Locally advanced rectal cancer may be controlled by the addition of new anticancer agents. In Western countries, new treatment strategies have been tested, including the addition of new cytotoxic drugs and/or