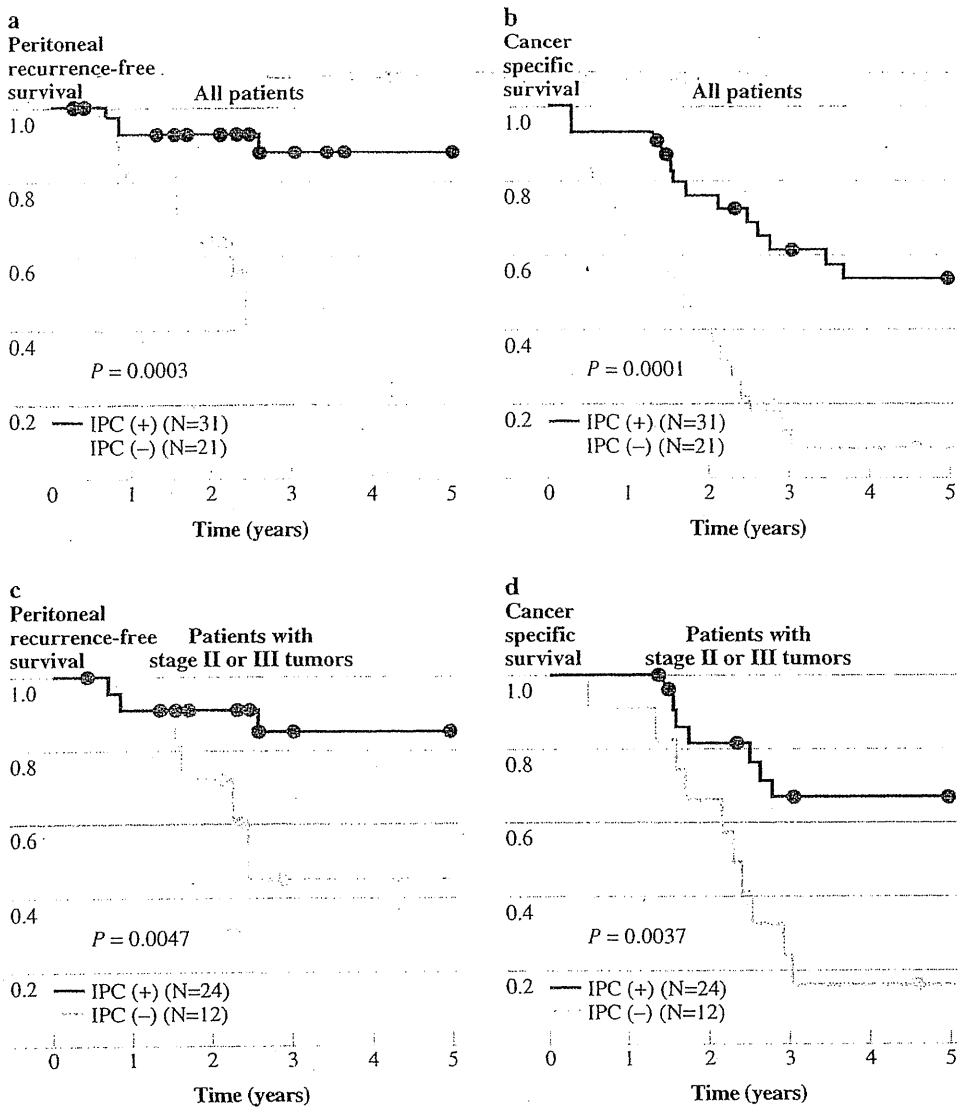

FIG. 1 Peritoneal recurrence-free survival curves (a) and (c) and cancer-specific survival curves (b) and (d) after intraperitoneal chemotherapy (IPC) with mitomycin C in all patients and patients with stage II or III tumors. A significant difference was found in both survival curves

approaches that combine cytoreductive surgery and perioperative IPC have provided good long-term survival in selected patients.[22–27] In a randomized trial of either the standard systemic chemotherapy (5-FU and leucovorin) or cytoreduction and hyperthermic IPC in patients with peritoneal carcinomatosis of CRC, the median disease-specific survival time was 12.6 months in the systemic chemotherapy group and 22.2 months in the group treated with cytoreduction followed by hyperthermic IPC and combined with adjuvant chemotherapy ($P = 0.028$).[24] A study by Elias et al. reported that the median survival time of patients with peritoneal carcinomatosis of CRC was 23.9 months in those who received systemic chemotherapy and 62.7 months in those who were treated by cytoreduction followed by hyperthermic IPC and systemic chemotherapy ($P < 0.05$).[26] The complete cytoreductive surgery was the most important prognostic factor. However, the toxicity of these aggressive therapies was relatively high. Postoperative mortality was 3.3–3.8%.[24,27] Grade 3–4 complications occurred in 31% of the patients, and the expertise of the center had a strong impact on prognosis.[27] Clearly, there is a significant learning curve, and this is not a procedure that can be undertaken occasionally.[28,29]

The major concerns regarding IPC are catheter malfunction or infection, peritonitis, and impaired anastomotic or abdominal wound healing. In a rat model, Hillan et al. demonstrated no difference between intraperitoneal (IP) saline and IP 5-FU administration with respect to anastomotic healing strength.[30] In our study, only 1 patient (1.9%) developed a grade 3 skin ulceration of the drain insertion site for IPC. This patient was treated by conservative therapy. Our IPC was therefore easy and safe.

Studies using conventional cytology to evaluate abdominal washing fluid specimens have found malignant

TABLE 3 Univariate analysis of the clinicopathologic factors for peritoneal recurrence-free and cancer-specific survival in patients with stage II or III tumors ($N = 36$)

	No. of patients ($N = 36$)	Peritoneal recurrence-free 5-year survival	*P* value	Cancer-specific 5-year survival	*P* value
Age (years)					
<60	13	82.5	0.6127	53.8	0.5939
≥60	23	68.1		46.7	
Gender					
Male	21	81.4	0.1309	45.1	0.6552
Female	15	63.6		55.8	
Tumor size (cm)					
<5	13	81.5	0.2584	59.2	0.3185
≥5	23	67.8		43.2	
Tumor site					
Colon	19	75.7	0.8962	47.7	0.8196
Rectum	17	70.0		51.3	
Histologic grade					
Well	10	90.0	0.0258	90.0	0.0045
Others	26	59.5		31.7	
Depth of invasion					
T3	16	80.0	0.7804	73.1	0.0341
T4	20	65.3		31.7	
Regional lymph nodes					
N (−)	6	80.0	0.9614	80.0	0.1137
N (+)	30	72.2		43.1	
Lymphatic invasion					
No	7	80.0	0.2832	83.3	0.0572
Yes	29	65.5		41.0	
Venous invasion					
No	8	87.5	0.3778	80.0	0.0957
Yes	28	69.3		42.9	
Adjuvant chemotherapy					
No	8	70.0	0.5305	68.6	0.2399
Yes	28	74.3		44.6	
Intraperitoneal chemotherapy					
No	12	45.5	0.0047	16.7	0.0037
Yes	24	85.6		67.5	

Well well-differentiated adenocarcinoma, *Others* moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, mucinous adenocarcinoma

cells in 3–28% of patients with CRC.[9,31,32] This wide range may be due to differences in patient populations, lavage cytology methods, or the criteria used for assessment. In the present study, only 52 patients (3.1%) were found to be positive for intraperitoneal cancer cells on cytologic evaluation. This positive rate is low because the strict definition used for identification of cancer cells excluded suspicious or borderline malignant cells. Some authors have used immunohistochemistry or reverse transcriptase-polymerase chain reaction (RT-PCR) to detect disseminated tumor cells in peritoneal lavage fluid.[33–37] In these studies, the detection rates of free cancer cells were comparatively high, ranging from 12% to 47%. Although immunohistochemical and RT-PCR techniques are more sensitive than conventional cytology in detecting cancer cells, their significance for survival is unclear. However, conventional cytology is a practical means of detecting cancer cells because it is a universal and inexpensive method that can be easily performed at any institution worldwide.[38]

Peritoneal recurrence is relatively rare. In this study, one thousand six hundred and twenty-five patients with stage I, II, III, or IV tumors showed negative cytology. In addition, one thousand five hundred and twenty of 1,625 patients had no clinically evident peritoneal dissemination. Overall, peritoneal recurrence was observed in 23 of 1520 patients (1.5%). In our previous study, peritoneal recurrence was observed in only 3.2% of patients (12 of 374 patients with stage II or III tumors). However, peritoneal recurrence was seen in 5 of 15 patients (33.3%) with positive peritoneal cytology and in 7 of 359 patients (1.9%) with negative peritoneal cytology.[12] Similarly, Yamamoto et al. reported the peritoneal recurrence rate to be 4.2% (8 of 189 patients with stage II or III tumors). Peritoneal recurrence was seen in 4 of 11 patients (36.4%) with positive peritoneal cytology and in 4 of 178 patients (2.2%) with negative peritoneal cytology.[9] As a result, 1 of the predictive factors for peritoneal recurrence may be a positive peritoneal lavage cytology finding.

We retrospectively investigated the significance of IPC with MMC in this study. In all patients, univariate analyses showed the 5-year peritoneal recurrence-free and cancer-specific survival rates to be significantly higher in patients with IPC than in patients without IPC ($P < 0.0005$). In multivariate analyses, IPC remained an independent prognostic factor for peritoneal recurrence-free survival ($P = 0.0274$). In 36 patients with stage II or III tumors, univariate analyses showed that the 5-year peritoneal recurrence-free and cancer-specific survival rates were significantly higher in patients with IPC than in patients without IPC ($P < 0.005$). In stage II or III patients with positive peritoneal lavage cytology, the overall peritoneal recurrence rate was 12.5% (3 of 24 patients) in the IPC (+) group and 50.0% (6 of 12) in the IPC (−) group. The incidence of peritoneal recurrence in the IPC (+) group was significantly lower than that of IPC (−) group ($P = 0.0362$). The histological grade is significantly associated with peritoneal recurrence-free and cancer-specific survival in all patients and in patients with stage II or III tumors. The reason may be that the histological grade has a strong correlation with IPC. Generally, lymph node metastasis is a powerful marker for a poor prognosis.

TABLE 4 Multivariate Cox regression analysis of the peritoneal recurrence-free and cancer-specific survival in all patients ($N = 52$)

Factors	Peritoneal recurrence-free survival			Cancer-specific survival		
	RR	95% CI	*P* value	RR	95% CI	*P* value
Histologic grade (Others:Well)	2.710	0.279–26.316	0.3903	2.062	0.644–6.579	0.2234
Depth of invasion (T4:T3)	–	–	–	1.290	0.556–2.992	0.5528
Regional lymph nodes (N(+):N(−))	–	–	–	1.842	0.518–6.579	0.3542
Lymphatic invasion (Yes:No)	–	–	–	5.435	0.399-71.429	0.2041
Venous invasion (Yes:No)	1.873	2.295–15.385	0.5576	1.570	0.220–11.236	0.6531
Distant metastasis (Yes:No)	–	–	–	5.236	2.320–11.905	<0.0001
Intraperitoneal chemotherapy (No:Yes)	5.319	1.205–23.256	0.0274	2.160	0.877–5.319	0.0938

Well well-differentiated adenocarcinoma, *Others* moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, mucinous adenocarcinoma, *RR* relative risk, *95% CI* 95% confidence interval

TABLE 5 Comparison of patterns of recurrent site in patients with stage II or III tumors ($N = 36$)

	Intraperitoneal chemotherapy (+) ($N = 24$)	Intraperitoneal chemotherapy (−) ($N = 12$)	*P* value
Lung	3	3	0.3781
Liver	1	1	0.9999
Lymph node	1	2	0.2527
Local	1	0	0.9999
Peritoneum	3	6	0.0362

However, in this study, lymph node metastasis was not a prognostic factor for peritoneal recurrence-free and cancer-specific survival in all patients or patients with stage II or III tumors. This is because this study investigated selected patients with positive peritoneal cytology whose prognosis was poor.

The timing of IPC is important. Postoperative adhesion formation is the major concern. In order to allow optimal contact between tumor cells and IP drug, treatment is preferred in the early postoperative period. Sugarbaker et al. performed a prospective randomized trial of intravenous versus IP 5-FU in patients with advanced primary CRC.[18] Although there was no difference in the disease-free or overall survival between the 2 groups, IP 5-FU decreased the incidence of peritoneal carcinomatosis significantly. In our study, IPC prolonged the prognosis; however, adjuvant chemotherapy did not improve the prognosis. One of the reasons may be the chemotherapeutic agents. With respect to adjuvant chemotherapy, further investigation is therefore necessary.

Although the effectiveness of cytoreductive surgery and hyperthermic IPC is clear, the optimum chemotherapeutic agents for IP treatment have not yet been defined. While several drugs have been used for IPC, the most common drugs used in hyperthermic IPC protocols worldwide for patients with colorectal peritoneal carcinomatosis are MMC or oxaliplatin.[22–24,26,27] In a mouse model, IPC with MMC or irinotecan provided a survival benefit compared with intravenous FOLFIRI therapy. Furthermore, combination IP therapy with MMC, panitumumab, and irinotecan was superior to all other agents tested alone or in combination.[39] However, with regard to the combination IPC, further phase I clinical trials will be necessary to integrate into clinical practice.

In conclusion, it appears that IPC with MMC is therefore an effective treatment for the prevention of peritoneal recurrence in CRC patients who had no clinical evidence of peritoneal dissemination and whose status of peritoneal lavage cytology was positive. However, adjuvant chemotherapy was not found to be effective. IPC with MMC is an easy, safe, and feasible treatment. However, the number of cases studied so far evaluated is relatively limited, and they were also investigated at a single institution. Therefore, a prospective trial where patients with positive cytology could be randomized to IPC plus the best systemic therapy versus the best systemic therapy alone is necessary to justify our results.

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腹腔鏡補助下低位前方切除術

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はじめに

直腸低位前方切除術は，直腸切離部位が腹膜翻転部より肛門側となる手術であり，1939年Dixonが前方切除による肛門温存手術を報告した後[1]，より低位での手術が可能となり確立された。その後，器械吻合器の開発によって安全性が増したが，それでも難易度の高い手術であることには変わりがなかった。1991年に世界で初めて，本邦でも1993年に腹腔鏡下大腸切除術が報告され[2,3]，低侵襲で整容性にすぐれた点から，その適応は進行大腸癌や直腸癌まで拡大され，2002年4月からは保険適応となった。腹腔鏡手術では，スコープが骨盤底まで挿入可能なうえ，その拡大視効果により微細な構造の視認を可能とするなど，直腸癌手術におけるアドバンテージがあるが，技術的安全性を高めるためには，術者と助手の協調作業による良好な術野展開にが必要で，剝離層や切離線を明示するための手順の定型化が重要である。

Ⅰ．適　応

進行癌に対しても，原発巣についてはT4症例や腫瘍の最大径が8 cm以上の症例をのぞいて適応としている。また，直腸Rb癌では，側方リンパ節郭清を要する症例をのぞいて，中枢側の系統的D3リンパ節郭清は腹腔鏡下手術で同等の手術が可能と考えている。

Ⅱ．術前処置

必要があれば，前日に大腸内視鏡で病変部近傍の直腸前壁に点墨，またはクリッピングを行う。クリッピングの場合には，切離前に腸鉗子がクリップよりも肛門側を把持していることを直腸診で確認し，その肛門側でステイプラーを用いて切離して，咬み込まないようにする。

Ⅲ．使用する手術器具

カメラは10 mmのフレキシブルスコープを使用している。鉗子類は助手用に有窓把持鉗子を2本準備する。1本は把持部が長くラチェット付き，もう1本は把持部が短くラチェットなしで，前者は大きな組織の把持，牽引用で，後者は膜などの脆弱な部位を繊細に把持するために使用している。術者は，左手用にバイポーラー把持鉗子（HiQ＋バイポーラー，特無傷性，有窓型，WA63120Cオリンパス），右手用にへら型（カーブスパチュラ）の電気メス，メリーランド型剝離鉗子（モノポーラー），超音波凝固切開装置

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key words
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（ハーモニックACEエルゴノミックハンドル，エチコンエンドサージェリー）を使用している。

Ⅳ．手術準備と体位

体位は低砕石位とし，鉗子操作の妨げとならないよう股関節はなるべく伸展した状態に保つ。体位の固定はマジックベッドとパッドで行い，ローテーションテストによる確認（体の固定性，バイタルサイン，輸液ライン，周囲の医療機器と干渉の有無）を必ず行っている（図1）。

Ⅴ．手術のポイント

1．Total Mesorectal Excision（TME）または Tumor Specific Mesorectal Excision（TSME）による直腸周囲の剝離

直腸癌の予後不良の原因である局所再発を抑える目的で1982年Healdによって提唱されたTMEは直腸固有間膜に包まれた直腸間膜を全周性に，肛門管直上まで完全に切除する方法であり[4]，複数の論文によって局所再発率を抑えることが確認され，現在，欧米での標準術式となっている。本邦では直腸固有筋膜で包まれた剝離面で直腸後面を授動するが，肛門側断端における切離線は腫瘍の位置によって決めるTumor Specific Mesorectal Excision（TSME）が一般に行われている[5]。

2．血管処理とリンパ節郭清

欧米ではGuidelines 2000によって進行癌に対しても，上直腸動脈（SRA）を左結腸動脈（LCA）の分枝部の末梢側で切離するlow ligationが推奨されている（Guidelines 2000ではLCA分枝部から末梢をSRAと定義）[6]。本邦での標準術式は，下腸間膜動脈（IMA）根部の結紮切離（highligation）を伴うD3郭清である。No.253にリンパ節転移が疑われない場合には，残存腸管の血流保持のためLCAを温存している[7]。

3．自律神経系の温存

腹腔鏡による拡大視効果によって自律神経系（頭側から腰内臓神経，上下腹神経叢，下腹神経，骨盤神経叢）の神経線維を視認し温存すると同時に，剝離面と近接する直腸周囲の剝離の際は，直腸固有筋膜やDenonnvillier筋膜を同定し，神経の走行する層に進入しないように剝離を進め温存する。

Ⅳ．実際の手順

われわれが行っている手順を紹介する。

1．トロカール挿入，体位の変換と術野展開

臍上部からカメラ用の12 mmトロカールを直視下で挿入し腹腔内を十分に観察後，右下に12 mm（術者右手），右上（術者左手）と左上下（助手用）に5 mmを3本の合計4本のトロカールを順次挿入する（図1）。トロカールの位置は，骨盤内操作が容易なように，やや尾側よりに置くが，左結腸曲部の授動が必要となりそうな場合，両方の操作が可能な位置決めを行う。体位を頭低位，右下位として大網と横行結腸を頭側に，小腸を右頭側に排除を行い，骨盤内の術野を確保する。

2．直腸固有間膜の同定と直腸背側の剝離

（助手）右手でIMA，左手で上部直腸間膜右側を把持して，腹側に挙上し，直腸間膜に緊張をかける（図2）。

（術者）左手で岬角右側の腹膜を把持して腹膜を少し挙上する。背側に大血管のない岬角付近から腹膜の切開を開始する。直腸を腹側に持ち上げながら，線維性の組織を鈍的に背側におろすように剝離し，直腸固有筋膜を同定する。剝離層がはっきりしない場合には，腹膜の切開を頭側に進めて，IMA/SRAの全体像を確認するとともに，大動脈前面からの内側アプローチを先行し，後腹膜下筋膜前面に入り，その剝離層を肛門側に延長しTME/TMSEの層で直腸を授動すると，下腹神経から骨盤神経叢が背側に温存される。直腸固

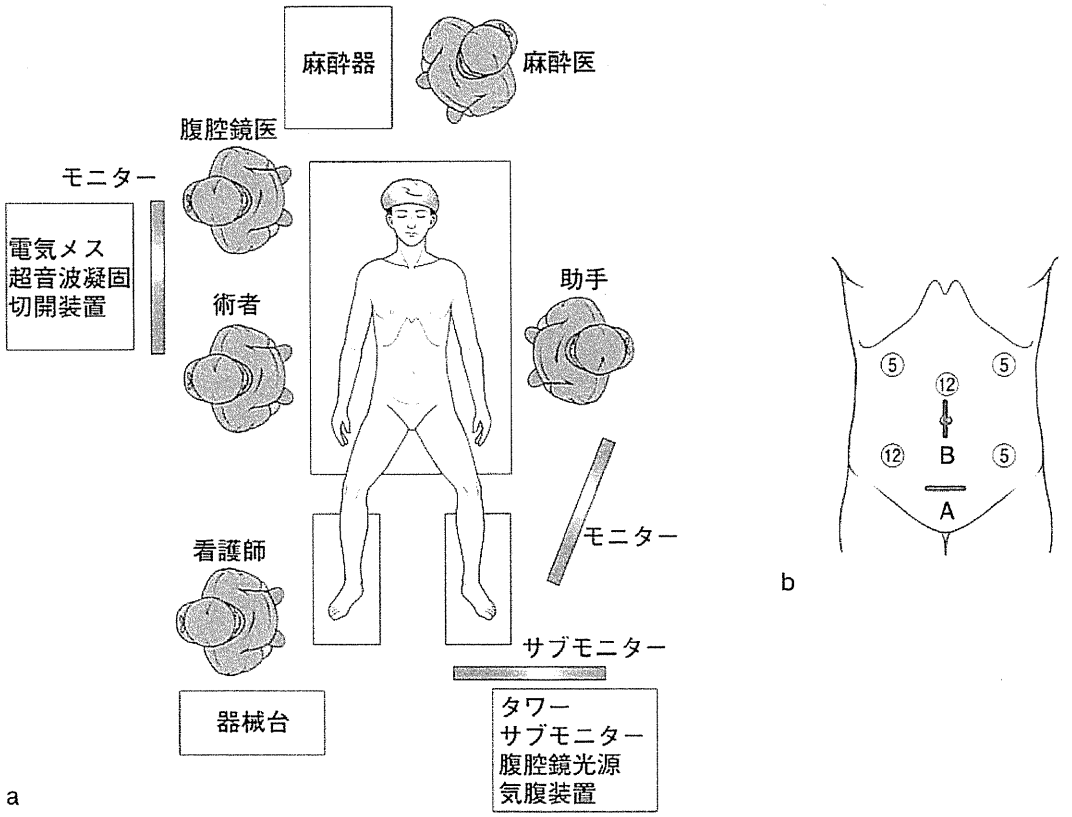


図1　手術室配置とポート位置

a）機器の配置と手術チームの位置
b）ポートと小切開の位置
⑤，⑫：5mm，12mm のポート
A：Pfannenstiel 切開
B：臍部縦切開

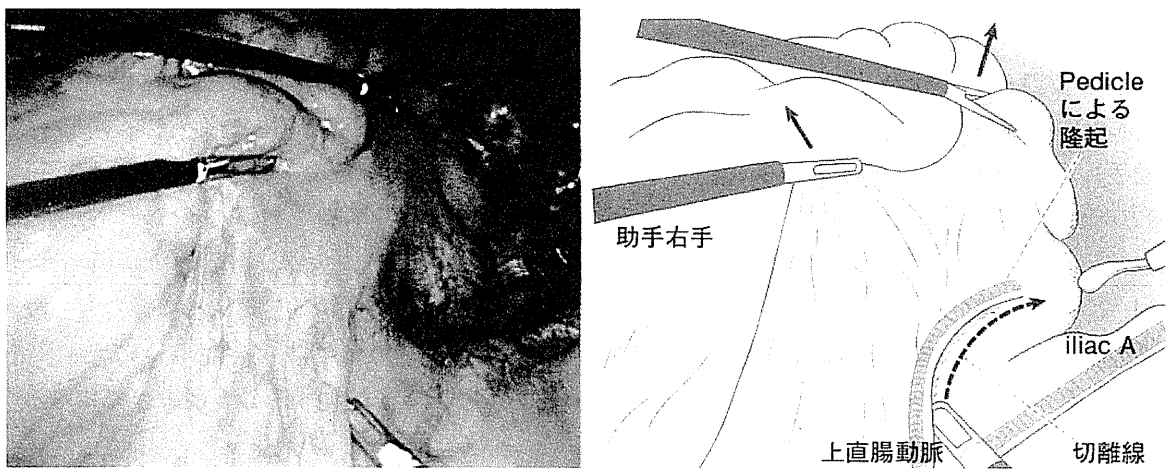
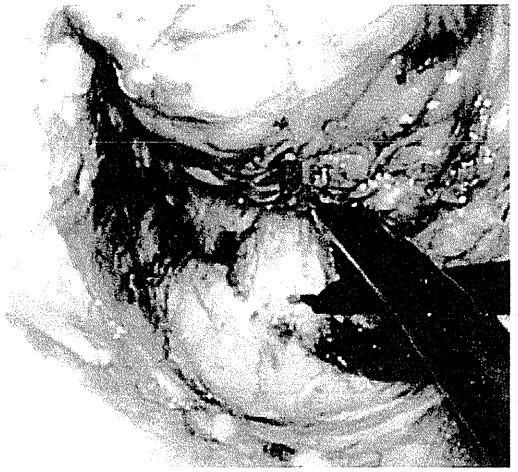


図2

有筋膜面を意識して切開，剝離をU字状に左右に延長し下腹神経の直腸枝を切離しながら骨盤底に進める。仙骨直腸靱帯を鋭的に切開したのち，直腸固有筋膜を仙骨前面から腹側に持ち上げるように進めると，肛門尾骨靱帯と肛門挙筋が確認できる（図3）。



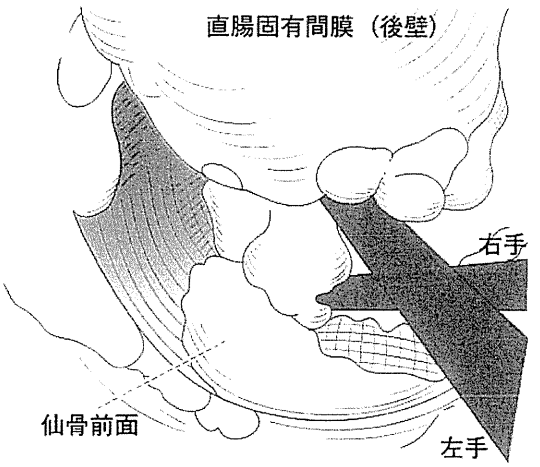
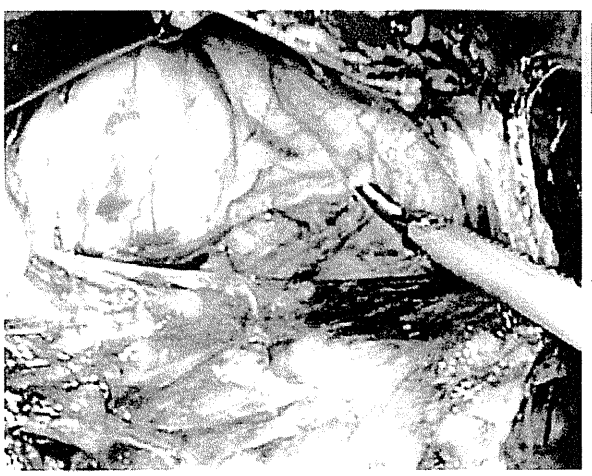


図3



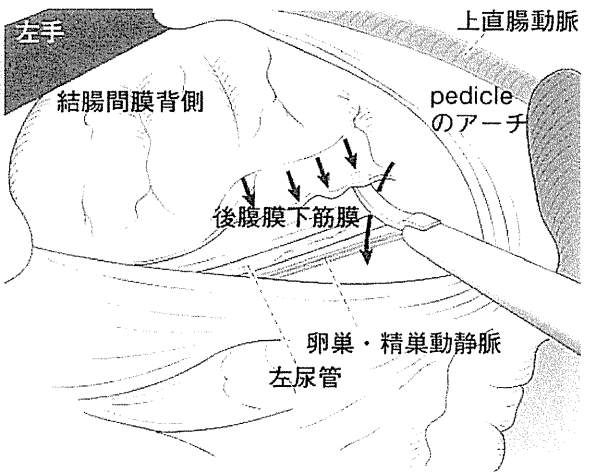


図4

3. 内側アプローチ，尿管，卵巣／精巣動・静脈の同定（図3）

（助手）左手でIMAの尾側を大きく把持して尾側方向に軽く牽引するとともに，右手で術者が内側アプローチを行う部位のIMA周囲の組織を把持して軽く腹側に持ち上げる。

（術者）腹膜の切離線を大動脈分岐部付近のS状結腸間膜起始部（大動脈の右側）にそって，IMA根部に向かって伸ばす。大動脈前面，またはIMAの背側に上下腹神経叢を確認，これを温存しつつ剝離を左外側に進める。

結腸間膜の背側面の光沢のある膜が見えるまでIMAを含む間膜から組織を背側に落とすと，後腹膜下筋膜前面で剝離され，左尿管，精巣，卵巣動・静脈が温存される（図4）。内側アプローチの最深部にガーゼを挿入しておき，外側からの切離時の指標とする。D3郭清を行う場合には，IMAの根部の背側を剝離後，内側アプローチの剝離層（後腹膜下筋膜前面の剝離層）を頭側に拡げ，No.253のリンパ節郭清の背側面の剝離を行っておく。この際，左腰内臓神経の上下腹神経叢へのの本幹もIMAに近接しているため，IMAへの分枝のみを処理することが重要である。

4，血管処理とリンパ節の郭清（D3の場合のNo.253リンパ節郭清）

（助手）左手の鉗子で直腸上部把持し正中よりやや右側に牽引する。右手の鉗子でIMA（LCA分岐部付近）の間膜を把持し正中に置く。これにより術者の右手の鉗子やエナージーソースと

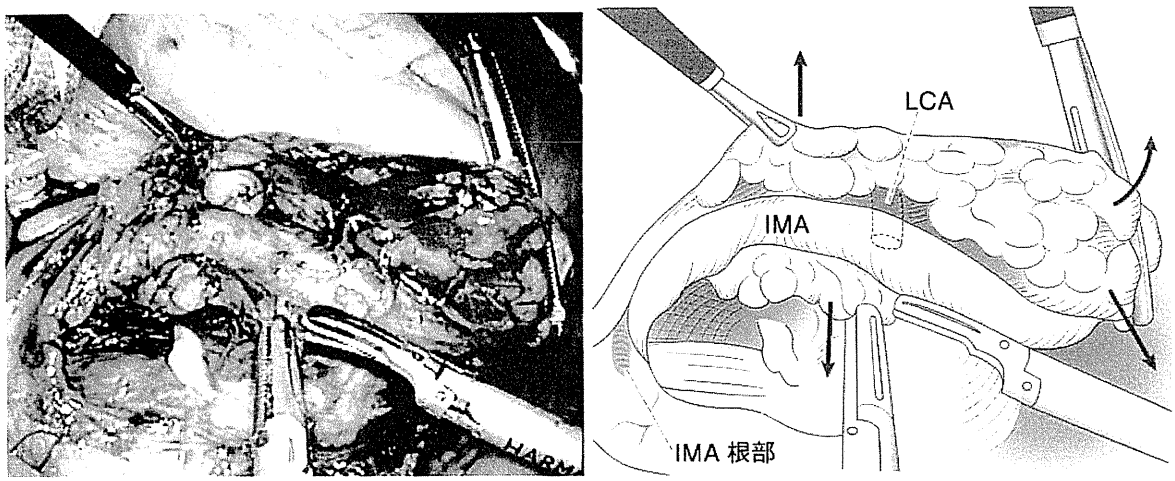


図5

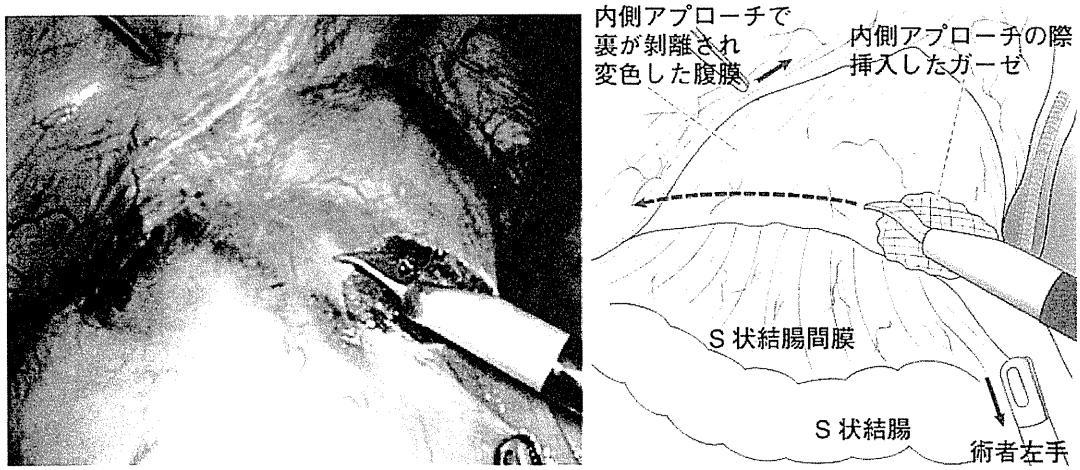


図6

IMAとの角度が鋭角となり，血管周囲の剝離層に入りやすくなる（図5）。

（術者）D2郭清の場合：IMAの右側で血管周囲の結合織を切開し，LCA分岐部を確認後，IMAをLCA分枝部より末梢で切離し，そこから外側に向かって腸間膜を切離後，IMVを同定し，切離する。腸間膜を2～3 cm程度，外側に切離しておくと小切開からの腸間膜の処理が容易となる。

D3郭清（LCA温存）の場合：IMAの背面に入る左腰内臓神経および上下腹神経叢からの分枝を処理してIMA根部への剝離を進める。前述したように，この剝離面を腸間膜背側で外側に拡大し，No.253のリンパ節郭清の背側切離面とする。リンパ節を含む脂肪織を郭清するため，IMA根部まで血管周囲の結合織を切開し，LCAを同定する。LCAを左側にむかって剝離し，IMVを同定する。リンパ節郭の左側剝離面としてIMVの右縁を剝離し，頭側では，IMA根部のレベルでIMVの右側まで外側方向に切離してNo.253のリンパ節を*en block*に郭清する。SRAとIMVの血管処理はD2と同様に行いLCAを温存する。

5，下行結腸（脾彎部）の授動と直腸左側の切離

（助手）SD junctionの結腸間膜付着部を把持し，内側に牽引。

（術者）SD junctionからMonkのwhite lineで腹膜を切開し，内側アプローチの際に留置したガーゼを指標に左外側腹膜の切離を行い，下行結腸を授動する（図6，7）。

肥満症例やS状結腸が短い症例では，脾彎部

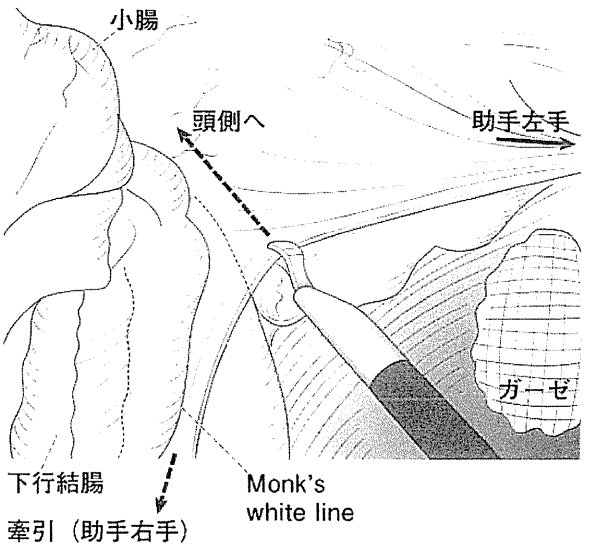
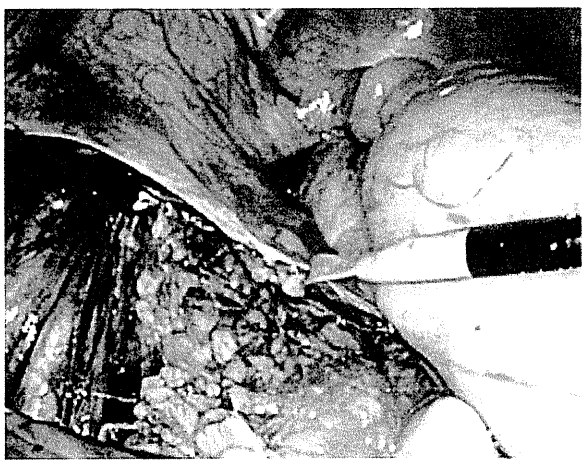


図7



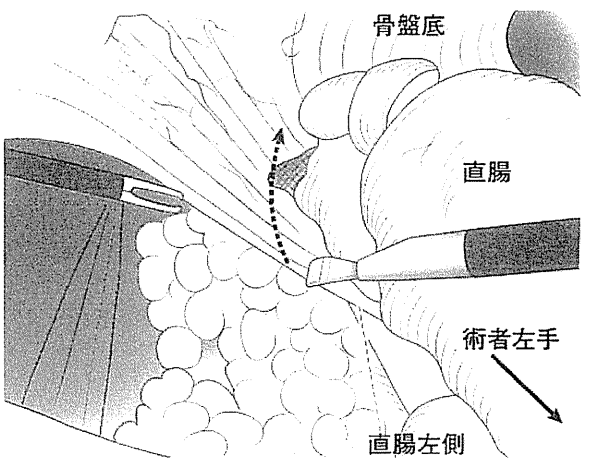


図8

の授動が必要となる場合がある。脾結腸間膜の切離には，下行結腸外側から口側に剝離するとともに，大網を切開して，網嚢腔に入ったうえで横行結腸側から脱転を完了させる。

下行結腸の授動につづけて直腸左側の腹膜も切開しておく（図8）。

6. 直腸右側と前方の切離

（助手）右手で上部直腸間膜の右側を把持して直腸を骨盤内から頭側に引き出して直線化し，左手で術者の切離方向の臓器（子宮や卵巣，壁側腹膜など）を持ち上げ術野を確保する。

（術者）左手で腹膜切離断端を右側に牽引しながら，直腸の右側の腹膜を切離し，直腸前壁の腹膜翻転部で腹膜を切開する（図9）。

女性では腟壁，男性では精嚢を確認してDenonvilliers筋膜を切除側に残して肛門側に剝離をつづける（図10）。男性の場合，前立腺の背側では，Denonvilliers筋膜を切開し，直腸壁前面に入って肛門側に剝離する。

7. 直腸固有間膜の処理と直腸肛門側の切離

小切開から行う場合：Pfannenstiel切開（恥骨上横切開）を行い，綿テープで直腸を緊縛して頭側に牽引し，切離部を小切開から到達可能とする。

必要な場合には直腸間膜の処理を行ったのち，肛門側の直腸を切離する。

腹腔内で行う場合：

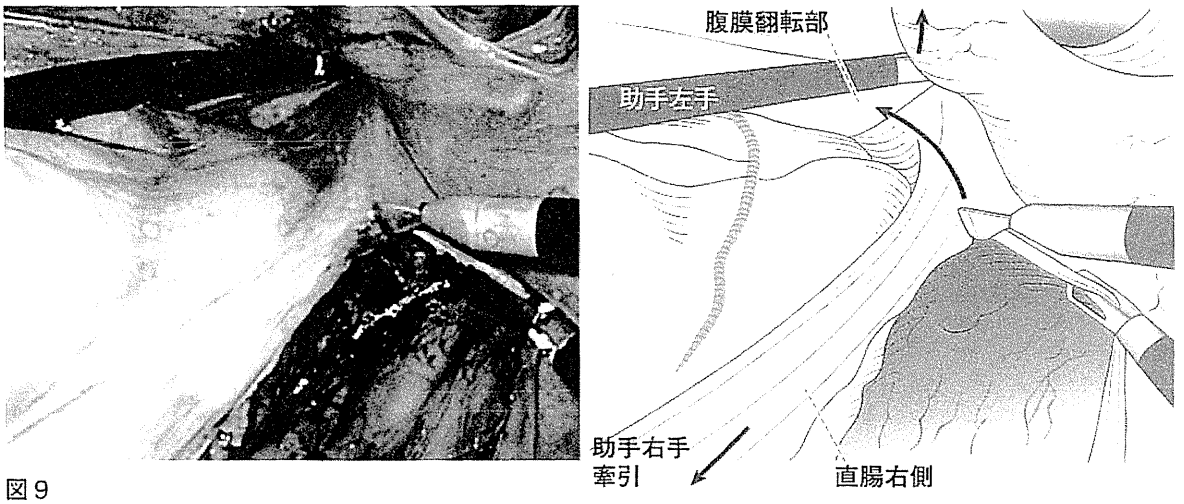


図9

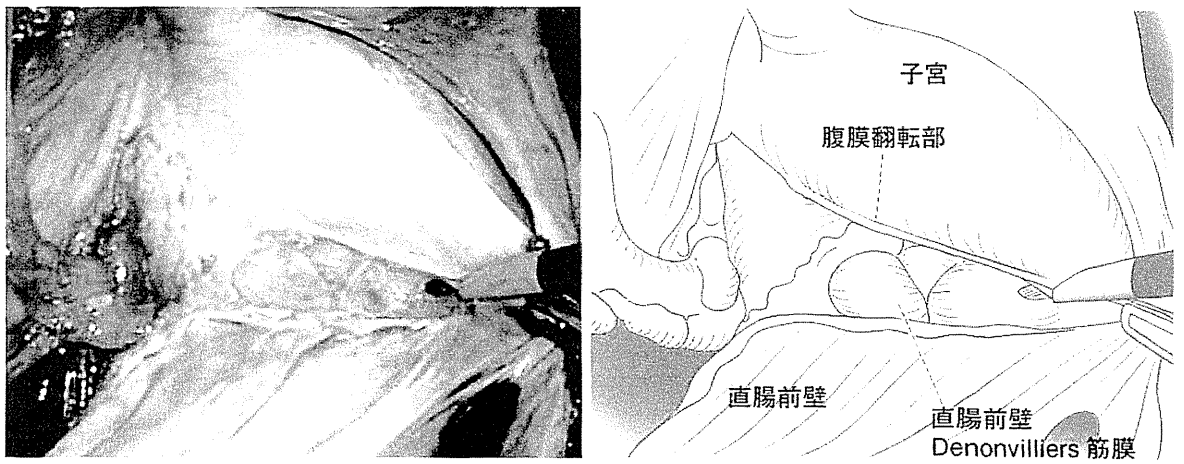


図10

（**助手**）両手で直腸を把持，牽引し，切離または間膜の処理する部位を術野に入れる

（**術者**）直腸間膜の処理が必要な場合には，エナジーソースを使って腸間膜を処理する。直腸をクランプ後，肛門より内腔を洗浄し，肛門側を自動縫合器で切離する。

8，小切開からの操作と閉腹

腹腔内で肛門側を切離した場合には，臍部を縦切開し，直腸を引き出す。

口側の切離線を決定後，腸間膜の血管を処理し，口側を切離する。切離断端に巾着縫合で自動吻合器のアンビルを装着し，腹腔内に戻す。再気腹後，double staple technique で吻合を行い，leak test で確認する。左下腹部よりドレーンを仙骨前面に留置し，12 mm のポート創はヘルニア防止のため腹膜筋膜を縫縮し，他のポート創は皮下縫合を行い，小切開部を閉創し手術を終了する。

おわりに

直腸癌に対する腹腔鏡下低位前方切除術は，縫合不全などの合併症発生率が高いことから，難易度の高い手術であり，各施設における手順書を作成し，効率よく安全に手術を行う必要がある。現在，大腸癌研究会（腹腔鏡下大腸切除研究会）において c-stage 0-Ⅰで腫瘍占居部位が Ra，Rb の直腸癌患者を対象として第Ⅱ相の臨床試験が行われており，腹腔鏡下手術の技術的安全性と腫瘍学

的予後が評価されつつある。患者にとってメリットの大きい低侵襲で整容性の高い腹腔鏡下直腸癌手術のエビデンスの確立によって，さらなる普及が望まれる。

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会　告

第19回日本消化器関連学会週間
Japan Digestive Disease Week 2011（JDDW2011）

会　期：2011年10月20日（木）～23日（日）

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SURGERY TODAY

Original Article

Adequate Lymph Node Examination Is Essential to Ensure the Prognostic Value of the Lymph Node Ratio in Patients with Stage III Colorectal Cancer

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Abstract

Purpose. This study aimed to assess the prognostic value of the lymph node ratio (LNR), estimated by dividing the number of positive lymph nodes (LNs) by the number of LNs examined, for stage III colorectal cancer in comparison to the new tumor, nodes, and metastasis (TNM) system, and to evaluate the relationship between the number of LNs examined and the prognostic value of the LNR.

Methods. We retrospectively reviewed the clinicopathological data of a cohort of 266 patients with stage III colorectal cancer. We assessed the impact of LNR on the prediction of cancer recurrence in comparison to the TNM system, as well as the prognostic value of LNR in patients with a low LN count.

Results. In multivariate analysis, the LNR was found to be an independent risk factor of cancer recurrence. The application of the LNR, in addition to the new TNM system, was more predictive of survival than the TNM system alone. A prognostic separation by LNR was observed in patients who had an adequate number of LNs examined, but not in patients with a low LN count.

Conclusions. A stronger prognostic separation can be obtained by using the LNR together with the new TNM system. Adequate lymph node examination is important to ensure the prognostic value of LNR in patients with stage III colorectal cancer.

Key words Colorectal cancer · Lymph node ratio · Lymph node examination · TNM 7th edition

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Introduction

The presence of lymph node (LN) metastasis is one of the most important prognostic factors in patients who undergo surgery for colorectal cancer with curative intent. According to the TNM staging system proposed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), cancer with nodal disease is defined as stage III, and N categories are determined by the number of positive LNs (N1, 1–3; N2, 4 or more).[1] However, recent evidence indicates that the total number of LNs examined is also an important prognostic factor for colorectal cancer outcome, with potential for stage migration depending on the degree to which specimens are examined and the total number of LNs removed.[2] Hence, the N category of the current TNM system, which disregards the number of LNs examined, has been suggested to be a potential limitation to predicting cancer survival.[3,4] The lymph node ratio (LNR), estimated by dividing the number of positive LNs by the number of LNs examined, has recently been proposed as a potentially more accurate prognostic indicator for solid tumors including gastric,[5] breast,[6,7] and pancreatic cancers.[8] Berger et al. first described the LNR as a prognostic factor for colon cancer in a large retrospective study of the Intergroup trial 0089, a study investigating adjuvant chemotherapeutic regimens.[9] To date, several other studies have reported the prognostic significance of the LNR in colorectal cancer.[3,4,9–27] It has also been suggested that the LNR can predict survival more accurately than the number of positive LNs.[3,4,11,13,16,19] Furthermore, the application of the LNR, together with the TNM system, may be more predictive of cancer recurrence and survival.[18,23]

In December 2009, a new TNM grading system (7th edition) revised by the AJCC and UICC was released in which the nodal stage was further divided into

subgroups according to the number of positive LNs in stage III colorectal cancer.[1] Although the current guidelines and new TNM system recommend the excision and evaluation of a minimum of 12 LNs in the tumor specimen to adequately assess the tumor stage, the N category of the new TNM system does not reflect the number of LNs examined or the LNR. The LNR can be easily influenced by the completeness of LN evaluation and the adequacy of surgical resection, and therefore, the real prognostic value of the LNR remains unclear. Two conflicting studies of large populations have been published. Berger et al. found that the LNR was not predictive of disease-free survival (DFS) or overall survival (OS) in patients with 10 or fewer LNs examined,[9] whereas Wang et al. found the LNR to be a significant predictor of outcome even for patients in whom 11 or fewer LNs were examined.[18] Therefore, the prognostic value of the LNR in patients with a low LN count remains controversial.

The aim of this study was to assess the prognostic impact of the LNR for stage III colorectal cancer according to the new TNM staging system (7th edition), and to evaluate the influence of the number of LNs examined on the prognostic value of the LNR in patients with stage III colorectal cancer in a single institution.

Patients and Methods

We retrospectively reviewed 266 patients with stage III colorectal cancer who underwent curative resection from January 1991 to December 2008 in the Department of Surgery of Hiroshima University. Curative resection was defined by pathologically clear margins on the resected specimen, with no evidence of metastatic spread on preoperative computed tomography scans of the chest, abdomen, and pelvis. Patients were identified from a prospective database of all patients undergoing therapy for colorectal cancer. Patients with metastatic disease and inflammatory bowel disease were excluded. The tumor location was categorized as right colon (from the cecum to the distal transverse colon), left colon (splenic flexure colon to rectosigmoid colon), or rectum. All patients underwent standard resection of the colon and rectum with regional lymphadenectomy according to the Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, 7th Edition (JGR),[28] and all procedures were performed by colorectal surgeons. Individual demographic and clinicopathological data were collected, including age, sex, tumor location, tumor stage (depth of invasion), nodal stage, tumor histology, tumor size, presence of lymphovascular invasion, preoperative serum carcinoembryonic antigen (CEA) level, administration of adjuvant chemotherapy, disease recurrence, and the survival rate. In addition, the number of LNs examined, number of metastatic LNs, and the LNR were determined for each patient. Receiver operating characteristic (ROC) curve analysis for cancer recurrence was performed to obtain the area under the ROC curve (AUC) and optimal cutoff point of the LNR for predicting cancer recurrence. The optimal cutoff point was defined as the point on the ROC curve nearest to the point where the both sensitivity and specificity were 1.

All specimens were examined as follows. After tumor removal, the excised specimen was opened along the antimesenteric border by the surgeon. The surgeon identified the lymph nodes, isolated them, and recorded both their number and distribution according to the JGR. After formalin fixation, a pathologist examined the specimens and lymph nodes, and histological diagnosis was determined according to JGR. Each tumor stage was coded according to the new TNM system, as described in the UICC (7th edition) revised in 2009. Although we did not analyze tumor deposits (satellites without regional nodes) defined by the new TNM system (new N category, N1c), the N1c status does not influence the N category classification (N1 and N2) or stage grouping of node-positive colorectal cancer patients.

The differences between the two groups were analyzed by the chi-square test and the Mann–Whitney *U*-test. Survival curves were plotted by the Kaplan–Meier method, and univariate analyses of DFS were estimated using the log-rank test. The Cox proportional hazard model was used for multivariate analyses. In all analyses, statistical significance was set at $P < 0.05$. All statistical analyses were performed using the JMP 8 software package (version 8.02; SAS Institute, Cary, NC, USA).

Results

Clinicopathological Features

The clinicopathological features of the 266 patients are summarized in Table 1. One hundred and fifty-one male (56.8%) and 115 female (43.2%) patients were included in this study, with a median age of 64.0 years (range, 24–92 years). The median follow-up time of the population was 42.4 months (range, 0.59–183.7 months). The distribution of tumor locations included 164 colon (61.2%; right colon: 61, left colon: 103) and 102 rectal cancers (38.7%). Of the 266 patients, 56 had stage IIIA disease (21.0%), 176 had stage IIIB disease (66.2%), and 34 had stage IIIC disease (12.8%). The tumor stage (depth of invasion) was classified as T1 in 28 patients (10.5%), T2 in 36 (13.5%), T3 in 171 (64.3%), T4a in 26 (9.8%), and T4b in 25 (9.4%). The median size of tumors

Table 1. Clinicopathological features of the 266 patients

	Total: 266 patients
Sex	
Male/female	151/121
Age (median) years	64.0 (range, 24–92)
Tumor location	
Right/left/rectum	61/103/102
UICC stage 7th edition	
IIIA/IIIB/IIIC	56/176/34
Tumor stage	
T1	28
T2	36
T3	171
T4a	26
T4b	5
Nodal stage	
N1a	110
N1b	89
N2a	42
N2b	25
Size (median) mm	40 (range, 9.9–108)
Histological type	
Well differentiated adenocarcinoma	81
Moderately differentiated adenocarcinoma	155
Poorly differentiated adenocarcinoma	10
Mucinous adenocarcinoma	19
Undifferentiated adenocarcinoma	1
Lymphatic invasion	
Negative/positive	54/212
Venous invasion	
Negative/positive	123/143
Serum CEA level (median) ng/ml	4.0 (range, 0.5–84.9)
Adjuvant chemotherapy	
No/yes/unknown	61/199/6
LNs examined (median)	14 (range, 1–76)
LNs involved (median)	2 (range, 1–27)
Proportion of patients with 12 or more LNs examined	175 (65.8%)
LNR (median)	0.16 (range, 0.01–1)
Low (0.01–0.20)	164
High (0.21–1)	102

UICC, Union Internationale Contre le Cancer; CEA, carcinoembryonic antigen; LN, lymph node; LNR, lymph node ratio

was 40 mm (range, 9.9–108 mm). The tumor was classified as well-differentiated adenocarcinoma in 81 patients (30.5%), moderately differentiated adenocarcinoma in 155 (58.3%), poorly differentiated adenocarcinoma in 10 (3.8%), mucinous adenocarcinoma in 19 (7.1%), and undifferentiated adenocarcinoma in 1 (0.4%). Lymphatic invasion was observed in 212 patients (79.7%), and venous invasion was observed in 143 patients (53.8%). The median preoperative serum CEA level was 4.0 ng/ml (range, 0.5–84.9 ng/ml).

The median number of LNs examined was 14 (range, 1–76). Eleven or fewer LNs were examined in 91 patients (34.2%). The median number of tumor-positive LNs was 2 (range, 1–27). One to three positive LNs (N1 disease) were observed in 199 patients (74.8%), and four or more positive LNs (N2 disease) were observed in the remaining 67 patients (25.2%). The LNR ranged from 0.1 to 1, with a median of 0.16. The best LNR cutoff value was selected as 0.20 based on ROC analysis. Therefore, patients were divided into two groups: LNR-low (0–0.2) and LNR-high (0.21–1). One hundred and sixty-four patients (61.7%) were classified as LNR-low, and 102 patients (38.3%) were classified as LNR-high. The median number of LNs examined in cases of colon and rectal cancer was 16 (range, 1–76) and 13 (range, 2–73), respectively ($P = 0.0699$). The median LNR values for cases of colon and rectal cancer were 0.13 (range, 0.01–1) and 0.17 (range, 0.04–1), respectively ($P = 0.0102$).

Adjuvant chemotherapy, administered according to pathological stage and the physical condition of the patient, was performed in 199 patients (76.5%). The

most common regimen before 2000 was oral tegafur/uracil therapy (100 patients, 50.2%). The standard regimens recommended by the current guidelines of the National Comprehensive Cancer Network such as 5-fluorouracil/leucovorin therapy, oral tegafur-uracil/folinate therapy, and capecitabine therapy, were performed after 2001 (99 cases, 49.8%). Oxaliplatin-based regimens, such as FOLFOX, were not administered to any of the patients in this study. In the LNR-low group, 43 patients received no chemotherapy (26.2%), and 118 patients (73.3%) received chemotherapy. In the LNR-high group, 17 patients received no chemotherapy (21.0%), and 81 patients (82.7%) received chemotherapy. No statistically significant difference in the frequency of the application of adjuvant chemotherapy was observed between the LNR groups ($P = 0.0833$). No patient received chemotherapy or radiation therapy before surgery.

Cancer recurrence was observed in 90 patients (33.8%). The sites of first recurrence (including overlapped cases) were the liver ($n = 36$), lung ($n = 30$), local recurrence ($n = 20$), lymph node ($n = 18$), peritoneal dissemination ($n = 7$), brain ($n = 3$), and bone ($n = 3$).

Risk Factors for Disease-Free Survival: Univariate and Multivariate Analyses

To estimate the risk factors for DFS, univariate analysis was performed for the following variables: sex (male vs female), tumor location (colon vs rectum), tumor stage (T1–T2 vs T3–T4), nodal stage (N1 vs N2), size of the tumor (≤30 mm vs >30 mm), histological type (well-differentiated adenocarcinoma vs other types), lymphatic invasion (negative vs positive), venous invasion (negative vs positive), serum CEA level (≤5.0 ng/ml vs >5.0 ng/ml), the administration of adjuvant chemotherapy (no vs yes), number of LNs examined (≤11 vs. ≥12), and LNR (low vs high). Tumor location (rectum, $P = 0.0002$), tumor stage (T3–T4, $P = 0.0118$), nodal stage (N2, $P = 0.0031$), lymphatic invasion (positive, $P = 0.0117$), the serum CEA level (>5.0 ng/ml, $P = 0.0199$), and the LNR (high, $P < 0.0001$) were identified as significant risk factors of reduced DFS (Table 2).

In a multivariate analysis of the selected variables found to be significant in the univariate analysis, only the tumor location (rectum, $P = 0.0047$) and the LNR (high, $P = 0.0003$) were identified as independent predictive factors for DFS (Table 3).

Five-Year Survival

The 5-year DFS for patients with stage IIIA, IIIB, and IIIC disease was 88.2%, 56.5%, and 38.4%, respectively ($P < 0.0001$). The 5-year OS for patients with stage IIIA, IIIB, and IIIC disease was 92.4%, 71.5%, and 41.7%, respectively ($P = 0.0001$). According to the LNR grading, the 5-year DFS in the LNR-low and LNR-high groups was 70.1% and 46.4%, respectively ($P < 0.0001$), and the 5-year OS in the LNR-low and LNR-high groups was 81.3% and 59.7%, respectively ($P = 0.0032$) (Fig. 1).

For patients with colon cancer, the 5-year DFS and the 5-year OS were 69.9% and 78.1%, respectively. According to the LNR grading, the 5-year DFS in the LNR-low and LNR-high groups was 79.8% and 53.8%, respectively ($P = 0.0009$), and the 5-year OS in these groups was 84.5% and 67.1%, respectively ($P = 0.121$) (Table 4A). For patients with rectal cancer, the 5-year DFS and OS was 45.9% and 63.7%, respectively. According to the LNR grading, the 5-year DFS in the LNR-low and LNR-high groups was 51.8% and 35.6%, respectively ($P = 0.0165$), and the 5-year OS in these groups was 75.3% and 49.7%, respectively ($P = 0.0179$) (Table 4B). Although there was no statistically significant difference in the 5-year OS in cases of colon cancer, a substantial prognostic separation was observed when we considered the LNR for both colon and rectal cancers.

For patients with stage IIIA disease, the 5-year DFS in the LNR-low and LNR-high groups was 91.2% and 82.4%, respectively ($P = 0.1861$). The 5-year OS in the LNR-low and LNR-high groups was 95.7% and 85.6%, respectively ($P = 0.4934$). For patients with stage IIIB disease, the 5-year DFS in the LNR-low and LNR-high groups was 64.6% and 41.7%, respectively ($P = 0.0019$). The 5-year OS in the LNR-low and LNR-high groups was 79.2% and 59.3%, respectively ($P = 0.0394$). For patients with stage IIIC disease, the 5-year DFS in the LNR-low and LNR-high groups was 54.7% and 33.4%, respectively ($P = 0.0166$), and the 5-year OS in the LNR-low and LNR-high groups was 72.9% and 35.4%, respectively ($P = 0.2244$) (Table 5). A stronger prognostic separation was observed in the DFS and OS of patients with stage IIIB disease by the application of LNR in addition to the new TNM system, than by the new TNM staging system alone. Conversely, no prognostic separation was seen in the DFS and OS of patients with stage IIIA and stage IIIC disease.

Relationship Between the Clinical Impact of the LNR and the Number of LNs Examined

To clarify the prognostic value of the LNR in patients with a low LN count (11 or fewer LNs examined), we separately analyzed patients with 11 or fewer LNs examined and patients with 12 or more LNs examined. For patients with a low LN count, the 5-year DFS in the LNR-low and LNR-high groups was 65.9% and 60.7%, respectively ($P = 0.3910$) (Fig. 2A), and the 5-year OS in the LNR-low and LNR-high groups was 76.2% and

Table 2. Risk factor of DFS: univariate analysis

Factor		5-year DFS (%)	*P* value
Sex	Male	65.4	0.1804
	Female	57.4	
Location	Colon	69.9	0.0002
	Rectum	45.9	
TNM tumor stage	T1, T2	79.0	0.0118
	T3, T4	55.3	
TNM nodal stage	N1	66.2	0.0031
	N2	43.9	
Size (mm)	≤30	68.5	0.0857
	>30	56.7	
Histological grade	Well	65.6	0.1543
	Others	58.8	
Lymphatic invasion	Negative	82.0	0.0117
	Positive	57.0	
Venous invasion	Negative	66.0	0.402
	Positive	57.4	
Serum CEA level (ng/ml)	≤5.0	68.6	0.0199
	>5.0	48.2	
Adjuvant chemotherapy	No	60.2	0.3847
	Yes	64.4	
No. of LNs examined	≤11	63.0	0.6319
	≥12	60.0	
LNR	Low	70.2	<0.0001
	High	46.4	

DFS, disease-free survival

Table 3. Risk factor of DFS: multivariate analysis

Selected risk factor	*P* value	Hazard ratio	95% confidence interval
Location (rectum)	0.0047	1.8933	1.2195–2.9412
TNM tumor stage (T3, T4)	0.0779	1.7342	0.9158–3.2787
TNM nodal stage (N2)	0.9296	1.0231	0.6161–1.7007
Lymphatic invasion (positive)	0.1080	1.7670	0.8396–0.3717
Serum CEA level (>5.0ng/ml)	0.1048	1.4503	0.9259–2.2727
LNR (high)	0.0003	2.4247	1.4970–3.9216

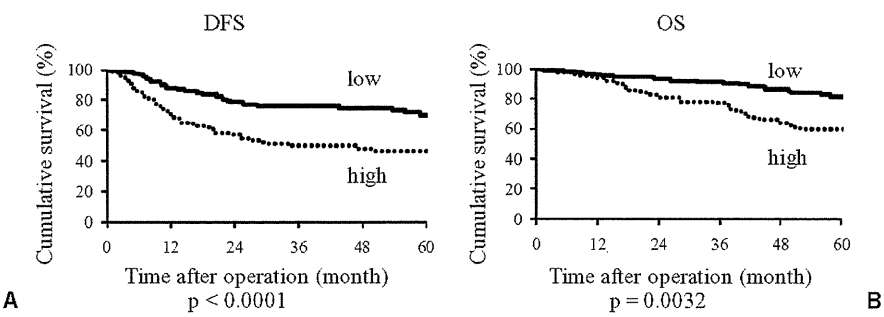

Fig. 1. Disease-free survival (*DFS*) (**A**) and overall survival (*OS*) (**B**) in the low lymph node ratio (LNR-low) and LNR-high patient subgroups

65.5%, respectively ($P = 0.9835$) (Fig. 3A). For patients with 12 or more LNs examined, the 5-year DFS in the LNR-low and LNR-high groups was 72.4% and 29.5%, respectively ($P < 0.0001$) (Fig. 2B), and the 5-year OS in the LNR-low and LNR-high groups was 82.7% and 52.2%, respectively ($P < 0.0001$) (Fig. 3B). Prognostic separation was not observed in the patients with a low LN count. The LNR was predictive of DFS and OS in patients with stage III colorectal cancer, especially when 12 or more LNs were examined.

Table 4. Five-year DFS and OS for colon cancer (A) and rectal cancer (B) according to LNR

LNR	5-year DFS (%)	*P* value	5-year OS (%)	*P* value
A. Colon cancer ($n = 164$)				
Total	69.9		78.1	
Low	79.8	0.0009	84.5	0.1207
High	53.8		67.1	
B. Rectal cancer ($n = 102$)				
Total	45.9		63.7	
Low	51.8	0.0165	73.5	0.0179
High	35.6		49.7	

OS, overall survival

Table 5. 5-year DFS and OS in the LNR-low and LNR-high groups according to TNM classification (7th edition)

Stage	LNR	5-year DFS (%)	*P* value	5-year OS (%)	*P* value
Stage IIIA ($n = 56$)	Total	88.2		92.4	
	Low	91.2	0.1861	95.7	0.4934
	High	82.4		85.6	
Stage IIIB ($n = 176$)	Total	56.5		71.5	
	Low	64.6	0.0019	79.2	0.0394
	High	41.7		59.3	
Stage IIIC ($n = 34$)	Total	38.4		41.7	
	Low	54.7	0.1661	72.9	0.2244
	High	33.4		35.4	

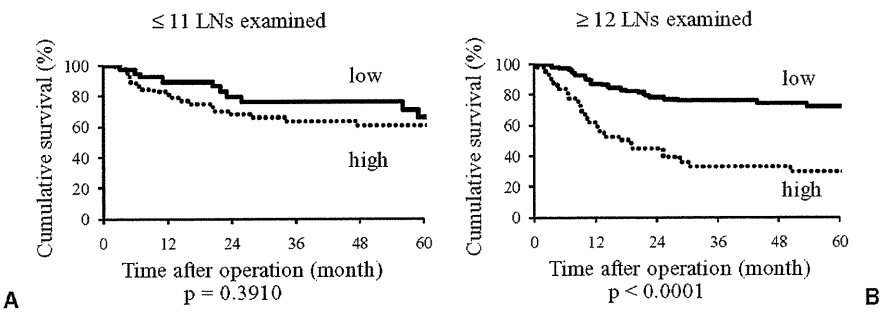

Fig. 2. Disease free survival (*DFS*) in the LNR-low and LNR-high subgroups analyzed separately for patients with 11 or fewer lymph nodes (*LNs*) examined (**A**) and 12 or more LNs examined (**B**)

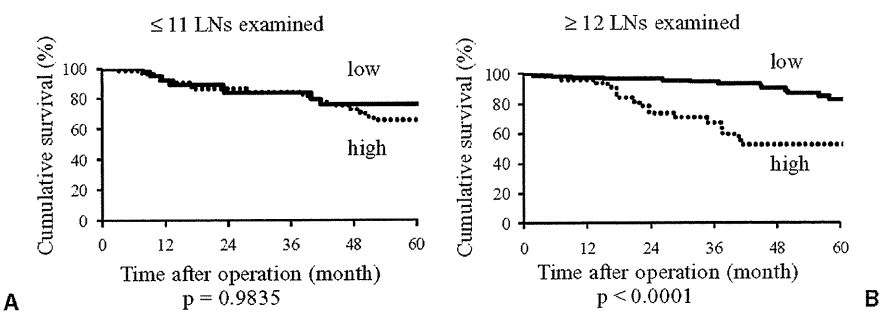

Fig. 3. Overall survival (*OS*) in the LNR-low and LNR-high subgroups analyzed separately for patients with 11 or fewer LNs examined (**A**) and 12 or more LNs examined (**B**)

Discussion

Because recent evidence has indicated that the number of positive LNs is an important factor in patients with colorectal cancer, N categories are determined by the number of positive LNs in the TNM staging system.[1] In addition, the current literature indicates that the accuracy of staging and OS in colorectal cancer patients

increases proportionally to the number of LNs examined in both node-negative and node-positive colorectal cancer,[2,29] because there is a potential for stage migration depending on the degree to which specimens are examined and the total number of LNs examined.[2] Although what constitutes adequate LN evaluation is still under debate,[2,30,31] the current guidelines issued by the AJCC and UICC recommend the excision and evaluation of a minimum of 12 LNs in the tumor specimen to adequately assess the tumor stage.[1] Therefore, the N category of the current TNM system, which disregards the number of LNs examined, has been suggested to be a potential limitation to the prediction of cancer survival, and the LNR has been proposed as a more accurate prognostic indicator in colorectal cancer. The LNR reflects the number of LNs examined, and may diminish stage migration and consequently predict survival more accurately than using only the number of positive LNs.[9] The presence of nodal disease influences the decision to recommend adjuvant chemotherapy, which is well known to improve survival in colorectal cancer patients with positive nodes. For many years, 5-fluorouracil/leucovorin therapy has been accepted as the standard adjuvant chemotherapy for stage III colorectal cancer.[32] Recently, oxaliplatin-based adjuvant chemotherapies, such as FOLFOX, have been shown to improve the outcome of colon cancer patients with positive nodes.[33,34] If patients with a high or low risk of recurrent disease could be accurately identified by the LNR, individual chemotherapeutic strategies might be utilized according to their risk of recurrence.

A new TNM grading system (7th edition) revised by the AJCC and UICC was released in December 2009.[1] In the new TNM system, stage III colorectal cancer was classified into stage IIIA (T1/2 and N1, T1 and N2a), IIIB (T3/T4a and N1, T2/3 and N2a, T1/2 and N2b), and IIIC (T4a and N2a, T3/4a and N2b, T4b and N1/2). N1a defines a tumor with only 1 metastatic LN, N1b defines a tumor with 2–3 metastatic LNs, N1c defines disease with satellites in the subserosa, without regional nodes, N2a defines tumors with 4–6 metastatic LNs, and N2b defines those with 7 or more metastatic LNs. In light of evidence that the number of LNs examined is an important prognostic factor for colorectal cancer, node-negative cases with a low LN count (11 or fewer) are now defined as pN0 by the new TNM system. However, for node-positive cases, neither the number of LNs examined nor the LNR are reflected as prognostic factors. In the present study, we demonstrated a stronger prognostic separation by the application of the LNR in addition to the new TNM system in patients with stage IIIB disease, although prognostic separation was not observed in patients with stage IIIA or IIIC disease. As shown in Table 1, our cohort consisted of 56 patients with stage IIIA disease, 176 patients with stage IIIB disease, and 34 patients with stage IIIC disease. According to the new TNM system, the proportion of patients with stage IIIB disease was relatively high, and that of patients with IIIA and IIIC disease was low. We speculated that this may be one of the reasons why no prognostic separation was observed in our patients with stage IIIA and IIIC disease. Further investigation is required to evaluate the possibility that prognostic separation can also be observed in patients with stage IIIA and IIIC disease by using the LNR.

The extent of LN dissection, surgical technique, the thoroughness of the pathologist, and the technique of LN isolation can all influence the assessment of the LNR.[27] Therefore, the prognostic impact of the LNR must be assessed cautiously. In particular, the prognostic value of the LNR in patients with a low LN count (11 or fewer examined) is still controversial. The present study supports the report of Berger et al.[9] that the LNR is not a predictive factor if there is a low LN count. Several studies have excluded patients with a low LN count, on the basis of insufficient LN examination according to the current guidelines.[12,13,19,25] Despite the existence of guidelines recommending that at least 12 LNs be examined, several published studies present median examined LN numbers of 11 or fewer.[9,13,27] Regardless of sufficient surgical resection and LN examination, other factors, such as tumor location, tumor stage, older age, and obesity may influence the number of LNs examined. In addition, the number of LNs examined may also be related to the immune response of the patient.[27] For this reason, we sometimes encounter cases of a low LN count even when adequate surgical resection and LN examination are performed. We therefore believe that clarification of the real prognostic value of the LNR in patients with a low LN count was meaningful.

To clarify this issue, we reviewed 21 articles concerning the prognostic impact of the LNR on colorectal cancer published to date in English.[3,4,9–27] A MEDLINE search was conducted to provide an overview of the literature concerning the prognostic impact of the LNR using the keywords "colorectal cancer" and "lymph node ratio." Of these 21 articles, 7 reports, including the present study, addressed the relationship between the prognostic impact of the LNR and the number of LNs examined.[3,4,9,16,18,24] Table 6 summarizes these seven reports, with an emphasis on the number of LNs examined and the proportion of patients with a low LN count. Four reports concluded that the prognostic value of the LNR was independent of the number of LNs examined[3,4,16,18] and three reports, including the present study, concluded that the prognostic value of the LNR was not significant in patients with a low LN count.[9,24] As shown in Table 6, the proportion of each TNM stage, the mean or median number of LNs examined, and the