

以下の①～④に示す治癒切除不能因子のうち、1つ以上3つ以下を認める(①～④に挙げた治癒切除不能因子をひとつも有さない場合、4因子とも有する場合は不適格とする)。造影剤アレルギーがある場合は単純CTで可とする。

①肝切除を行うと仮定した場合に残肝容量が30%未満と予想される肝転移

②以下のいずれかを満たす肺転移

i) 縦隔、心、大血管、気管、食道、椎体、気管分岐部に浸潤が疑われる

ii) 肺切除を行うと仮定した場合に術後予測残存1秒率が40%未満である

iii) 肺切除を行うと仮定した場合に片肺全摘が必要である

iv) 悪性胸水、または胸膜播種を認める

③以下のいずれかを満たす遠隔リンパ節転移

i) 腎静脈下縁レベルより頭側に、CT上短径1cm以上のリンパ節を認める

ii) 肝転移があり、かつ、No. 8、No. 12(胃癌取扱い規約に準ずる)にCT上短径1cm以上のリンパ節を認める

iii) 肺転移があり、かつ、縦隔または肺門にCT上短径1cm以上のリンパ節を認める。

④以下のいずれかを満たす腹膜転移

i) 注腸造影検査またはCT colonographyで腸管の壁不正・狭窄を複数箇所にも有する。

ii) CTで遠隔腹膜領域(横行結腸より頭側)に腫瘤を認める。

6) 腹部造影CTで明らかな他臓器浸潤(SI)がない。

7) 術前画像検査で骨盤腔を越える腹水貯留がない。

8) 骨転移がなく、かつ脳転移がない。

9) PS(ECOG)が0、1のいずれかである。

10) 登録時の年齢が20歳以上74歳以下である。

11) 前治療として他のがん種も含め、一切の化学

療法・放射線療法が行われていない。

12) 臓器機能が保たれている。

13) Grade 2以上の「下痢」、Grade 2以上の「末梢性感覚ニューロパチー」のいずれも認めない(CTCAE v4.0)。

14) 試験参加について患者本人から文書にて同意が得られている。

・治療

A 群：化学療法先行群

mFOLFOX6+BEV 療法による化学療法先行治療群

B 群：原発巣切除+術後化学療法群

原発巣切除術およびmFOLFOX6+BEV 療法による術後化学療法併用群mFOLFOX6+BEV 療法
mFOLFOX6+BEV は2週1コースとして中止規準に該当しない限り継続する。

主要評価項目：全生存期間

副次評価項目：無増悪生存期間、有害事象発生割合、化学療法著効例に対するR0切除割合、化学療法先行群での緩和手術割合

実施期間

登録期間：2012/07/01~2017/06/30

追跡期間：3年(最終症例登録後年)

総試験期間：2012/07/01~2020/06/30

実施予定症例数

770例 当センター 6例

(倫理面への配慮)

研究対象者に対する人権擁護上の配慮、研究方法による研究対象者に対する不利益、危険性の排除や説明と理解(インフォームドコンセント)を登録に先立って十分なインフォームドコンセントを行った。倫理面への配慮の内容及び方法については、患者が原発巣切除、非切除のどちらかの強い希望がなく、ランダム試験への協力が得られる

ことを前提とした。また個人情報、診療情報などのプライバシー保護に努めた。

C. 研究結果

・分担研究としての活動

大阪府立急性期・総合医療センターでは、2012年7月から開始し、25年度末まで登録例は0例である。適格症例に対しては原則すべて本試験のインフォームドコンセントを施行しているが、原発巣切除を強く希望される患者や非切除で早急に化学療法を希望される患者が多かった。他には高度の肝肺多発症例で待機手術するより、早急な化学療法をすべきと倫理的に判断された症例もあった。今後はさらにこの試験の意義を理解していただき、登録に協力していただくよう努力をする方針である。

D. 考察

NCCNのガイドラインでは、切除不能の転移巣を有する症状がない大腸癌には化学療法を先行する治療が勧められているが、その根拠はcategory 2A という低いエビデンスレベルに基づいている。本試験の結果、原発巣切除術+術後化学療法群の優越性が示された場合には、現在の標準治療である化学療法先行治療に延命効果で優る新しい標準治療が確立されることになる。逆に、原発巣切除の有用性が確認されなかった場合には、これまで十分な根拠がないまま広く行われていた治癒切除不能Stage IV 大腸癌に対する化学療法施行前の原発巣切除に対して歯止めをかけ、原発巣は非切除のまま化学療法を先行する治療が推奨されることになる。このように、いずれの結果が得られたとしても、治癒切除不能Stage IV 大腸癌に対する治療について臨床的に重要な情報が得られる。

E. 結論

治癒切除不能の stage4 大腸がん症例に対する原発巣切除の意義を検証するために、JCOG1007 試験を計画実施し、国内医療環境、医療費を考慮した RCT を計画実行することにより、国内において最適な治療レジメンを確立することを目指す。

F. 研究発表

特になし

G. 知的所有権の取得状況

1. 特許取得

特になし

2. 実用新案登録

特になし

3. その他

特になし

治癒切除不能の stage4 大腸がん症例に対する原発巣切除の意義を明らかにする研究

研究分担者 池田 聡 県立広島病院 消化器・乳腺・移植外科 部長

研究要旨：切除不能大腸癌に対する中心的治療は化学療法である。しかし、化学療法導入前の大腸癌原発巣切除の意義は明らかではない。私どもはJCOG1007試験「治癒切除不能進行大腸癌に対する原発巣切除の意義に関するランダム化比較第III相試験」に参加しこれまでに4例の症例登録を行った。

A. 研究目的

切除不能の遠隔転移臓器を有し、かつ原発巣による腸閉塞症状のないStage IV大腸癌に対する標準治療は定まっていない。本研究では、標準治療である化学療法先行治療に対する、化学療法の前に原発巣切除を行う治療（原発巣切除術+術後化学療法）の優越性を、ランダム比較第III相試験にて検証する。

B. 研究方法

「化学療法単独治療」を対照とし「原発巣切除+術後化学療法」を試験治療としたランダム化比較第III相試験（優越性試験）として行う。

（倫理面への配慮）

県立広島病院IRB承認を得ている。

C. 研究結果

現在、4例を登録し治療を開始している。化学療法単独群が3例、原発巣切除+術後化学療法群が1例であった。化学療法群の1例は治療開始後14か月で原発巣が有症状となり大腸ステント挿入が行われた。化学療法群の1例は治療開始後約6か月で切除可能と判断され肝切除と原発巣切除が行

われた。

D. 考察

試験開始から間がなく評価をするに至らないが今後の治療経過を慎重に見守る必要があると考えた。

E. 結論

JCOG1007試験「治癒切除不能進行大腸癌に対する原発巣切除の意義に関するランダム化比較第III相試験」に4例の登録を行い、現在治療経過観察中である。

F. 研究発表

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G. 知的所有権の取得状況

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

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
<u>Kanemitsu Y, Komori K, Kimura K, Kato T</u>	D3 Lymph Node Dissection in Right Hemicolectomy with a No-touch Isolation Technique in Patients With Colon Cancer.	Dis Colon Rectum	56(7)	815-24	2013
<u>Komori K, Kanemitsu Y, Kimura K, Sano T, Ito S, Abe T, Senda Y, Shimizu Y.</u>	Detailed stratification of TNM stage III rectal cancer based on the presence/absence of extracapsular invasion of the metastatic lymph nodes.	Dis Colon Rectum	56(6)	726-32	2013
<u>Komori K, Kanemitsu Y, Kimura K, Hattori N, Sano T, Ito S, Abe T, Senda Y, Misawa K, Ito Y, Uemura N, Shimizu Y.</u>	Tumor necrosis in patients with TNM stage IV colorectal cancer without residual disease (R0 Status) is associated with a poor prognosis.	Anticancer Res	33(3)	1099-105	2013
<u>Komori K, Kanemitsu Y, Kimura K, Yawata K, Shimizu Y, Sano T, Ito S, Abe T, Senda Y, Misawa K, Ito Y, Uemura N, Kato T.</u>	Efforts to advance surgical treatments for patients with familial adenomatous polyposis for 40 years in a cancer hospital.	Hepatogastroenterology.	60	741-746	2013
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Akagi Y, Shirouzu K, Fujita S, Ueno H, <u>Takii Y</u> , <u>Komori K</u> , Ito M, Sugihara K.	Benefit of the measurement of mesorectal extension in patients with pT3N1-2 rectal cancer without pre-operative chemoradiotherapy: Post-operative treatment strategy.	Experimental and Therapeutic medicine	3	661-666	2013
Mori T, Ohue M, <u>Takii Y</u> , Hashizume T, Kato T, Kotake K, Sato T, Tango T.	Factors predicting the response to oral fluoropyrimidine drugs: a phase II trial on the individualization of postoperative adjuvant chemotherapy using oral fluorinated pyrimidines in stage III colorectal cancer treated by curative resection (ACT-01 Study).	Oncol Rep.	29(2)	437-44	2013
<u>Takii Y</u> , Maruyama S.	Safety and Efficacy of Modified FOLFOX6 plus High-Dose Bevacizumab in Second-Line or Later Treatment of Patients with Metastatic Colorectal Cancer.	Chemotherapy	59(2)	79-84	2013
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滝口伸造, 早田浩明, 山本宏, 永田松夫, 鍋谷圭宏, 池田篤	巨大会陰骨盤腫瘍に対する広範会陰膣後壁切除および大臀筋切除を伴う腹会陰式直腸切断と薄筋皮弁による再建術	手術	67(13)	1897-1900	2013
早田浩明, 山本宏, 永田松夫, 滝口伸造, 貝沼修, 池田篤, 鍋谷圭宏, 趙明浩, 武藤頼彦, 外岡亨	同時多発遠隔臓器転移のある大腸癌治療への取り組みと予後因子	癌の臨床	59 (6)	623-627	2013
池田篤, 滝口伸造, 早田浩明, 永田松夫, 山本宏, 杉山孝弘	態変化のみられた lymphoid stroma を伴う横行結腸癌の1例	日本臨床外科学会雑誌	74(6)	1627-1631	2013

IV. 研究成果の刊行物・印刷

D3 Lymph Node Dissection in Right Hemicolectomy with a No-touch Isolation Technique in Patients With Colon Cancer

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BACKGROUND: The role of lymph node dissection in the management of right-sided colon cancer remains controversial.

OBJECTIVE: The aim of this study was to investigate the surgical treatment of curable right-sided colon cancer by using D3 lymphadenectomy with a no-touch isolation technique and to determine the extent of lymph node dissection optimal for the prognosis of right-sided colon cancer.

DESIGN: This research is a retrospective cohort study from a prospectively collected database.

SETTING: The investigation took place in a specialized colorectal surgery department.

PATIENTS: Data on 370 consecutive patients who underwent D3 lymph node dissection for right-sided colon cancer with a no-touch isolation technique were identified.

MAIN OUTCOME MEASURES: The survival of patients with involvement of main nodes at the roots of colonic arterial trunks along superior mesenteric vessels through intermediate nodes in the right mesocolon was determined.

RESULTS: The 5-year overall survival of patients with stage I (n = 73, 19.7%), II (n = 155, 41.9%), and III

(n = 142, 38.4%) cancer were 94.5%, 87.6%, and 79.2%. The 5-year disease-specific survival of patients with stages I, II, and III cancer were 100.0%, 94.5%, and 85.0%. Eleven patients (3.0%) had metastatic involvement of main lymph nodes, whereas 49 (13.2%) had metastases to intermediate lymph nodes. The 5-year overall survival and disease-specific survival of patients with metastases to main lymph nodes were 36.4% for both, and 5-year overall survival and disease-specific survival of patients with metastases to intermediate lymph nodes were 77.6% and 83.5%.

LIMITATIONS: This study was limited by its nonrandomized retrospective design.

CONCLUSIONS: D3 lymphadenectomy with a no-touch isolation technique allows curative resection and long-term survival in a cohort of patients with cancer of the right colon.

KEY WORDS: Colon cancer; Right hemicolectomy; Lymphadenectomy; No-touch isolation technique; D3; Prognosis.

Colorectal cancer is the third most common cancer and the second leading cause of cancer-related mortality in the United States.¹ In Japan, colorectal cancer is the third most common cancer and the third leading cause of cancer death² and is anticipated to become the leading cause of cancer death by 2015. Patients with localized colorectal cancer are deemed potentially curable and can undergo curative resection.³

The most important prognostic factor in colorectal cancer is nodal status, where the presence of lymph node metastasis is a determinant for adjuvant chemotherapy and a predictor of disease-free and overall survival.⁴⁻⁶ Retrieval of small numbers of lymph nodes may cause the extent of cancer to be underestimated, and recent reports

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815

suggest that survival improves when more lymph nodes are harvested, regardless of node status.^{3,7-10} Adequate lymphadenectomy, including pericolic, intermediate, and main node dissection (D3 lymphadenectomy), is important for accurate staging and therapy.¹¹ This approach is "standard" protocol for Japanese colorectal surgeons.¹¹

Lesions of the cecum, ascending colon, and right segment of the transverse colon are usually treated with a right hemicolectomy. Performing both a D3 lymphadenectomy and right hemicolectomy is challenging because of the complicated vasculature. We present a safe procedure for right hemicolectomy with a medial approach to dissection of regional lymph nodes along the superior mesenteric vein and artery. This method has the advantages of early vessel division and "no-touch" dissection¹² and is convenient and safe. This procedure does not remove the root of the vessel, although ligation of the vascular pedicles and division of the bowel before handling the cancer-bearing segment are advocated.¹³

The aim of this study was to determine whether radical D3 lymphadenectomy and our standardized medial to lateral no-touch right hemicolectomy approach improved survival probability in patients with surgically curable right-sided colon cancer.

MATERIALS AND METHODS

Patients

Between April 1990 and December 2003, 381 consecutive patients with stages I to III right-sided colon cancer underwent right or extended right hemicolectomies with D3 lymphadenectomy via the no-touch isolation technique. Inclusion criteria for right-sided colon cancer included cancers located at the cecum, ascending colon, hepatic flexure, or transverse colon. Eleven patients with cancer of the appendix, previous malignancies, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, metachronous cancer, or histology other than adenocarcinoma, or those receiving preoperative chemotherapy or undergoing partial colectomy were excluded. Laparoscopic resection was not used in any patients. The Aichi Cancer Center Hospital Institutional Review Board approved the study protocol.

D3 lymphadenectomy involves complete dissection of regional lymph nodes, including pericolic nodes (*N1* region, stations 201, 211, and 221), intermediate nodes (*N2* region, stations 202, 212, and 222), and main nodes along superior mesenteric vessels (*N3* region, stations 203, 213, and 223) as defined by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) (Fig. 1).¹⁴ The radicality of the lymph node dissection is determined by the clinical preoperative staging. Although the JSCCR advocates that stage II and III tumors will undergo D3 resection clinically,

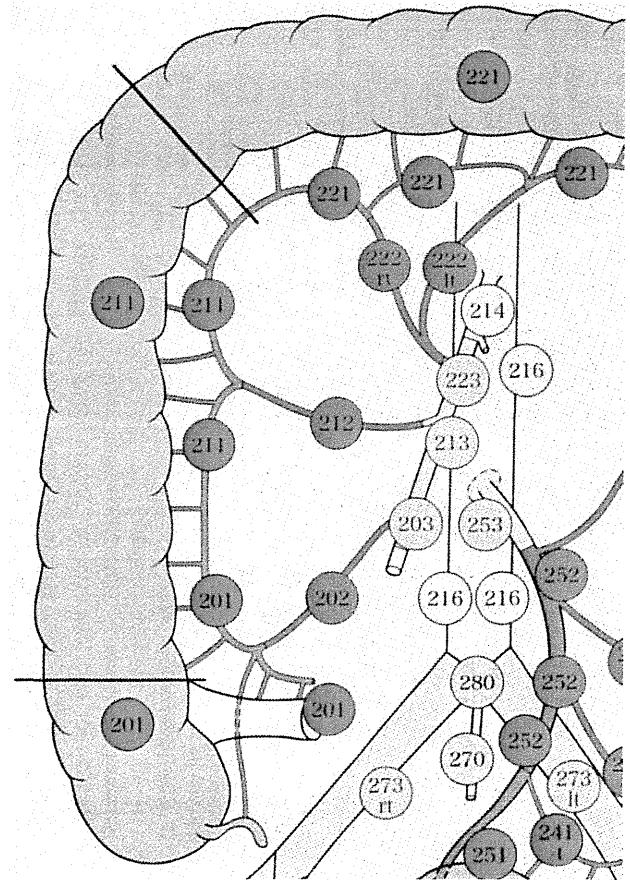


FIGURE 1. Definition of lymph node mapping for right-sided colon cancer by the Japanese Society for Cancer of the Colon and Rectum. Figure shows lymph node groups and station numbers in a right colon classified as illustrated in the schematic drawing just for the lymph node mapping system. Lymph nodes are grouped according to independent lymphatic spread: pericolic nodes (red circles, stations 201, 211, and 221) are classified as *N1*, intermediate nodes (blue circles, stations 202, 212, and 222) are classified as *N2*, and main nodes along superior mesenteric vessels (yellow circles, stations 203, 213, and 223) are classified as *N3*. White circles denote lymph nodes proximal to the main lymph nodes. D3 dissection was defined as excision of *N1*, *N2*, and *N3* lymph nodes.

high ligation of the feeding artery for D3 resection in all patients with any stages who will undergo a curative-intent surgery has been adopted as a standard procedure in the Aichi Cancer Center Hospital, because there is no method of accurately assessing pathological stage preoperatively. Surgical time, estimated blood loss, and intraoperative adverse events were recorded along with tumor size, tumor location, tumor extent (T stage), lymph node involvement (N stage), and number of harvested lymph nodes. Patient demographics, surgical factors, and postoperative complications were also analyzed.

Postoperative follow-up consisted of serum tumor marker measurements every 3 months for the first 2 years, then every 6 months for 3 years; hepatic imaging (ultrasonography or CT) and chest x-rays every 3 to 6 months;

and a colonoscopy every 2 to 3 years. Adjuvant chemotherapy with the use of fluorouracil/leucovorin or oral compounds was administered to patients with stage III disease. Follow-up data were documented prospectively until an event or the study cutoff date of March 2011. The entire cohort of 370 patients was followed-up completely, with a median follow-up time for live patients of 123.6 months (range, 60.2–193.1).

Hemicolectomy with D3 Lymphadenectomy by Using the No-touch Isolation Technique Based on an Original Medial to Lateral Approach

Tumor presence was confirmed by visual and tactile examination. First, the small intestine was moved to the right, out of an abdominal incision. The root of the mesentery was exposed, and an incision was made in the peritoneum (arrow, Fig. 2A). The horizontal portion of the duodenum was exposed, and the fusion fascia was separated from the prepancreatic arcade. The right ureter and gonadal vessels were protected by a thin membrane, near the back.

The length of bowel to be resected included a 10-cm tumor margin. The ileum was temporarily transected, and the mesentery was then transected in the direction of the ileal veins peripheral to the superior mesenteric vein (SMV). Upon reaching the ileal veins, the ventral, dorsal, and right sides of the mesentery were separated, continuing up to the left side of the superior mesenteric artery (SMA) and toward the central sides while simultaneously removing fat. The SMV was also separated, and the ileocolic artery and vein were cut at their respective roots (Fig. 2B). The greater omentum was separated from the transverse colon, and the omental bursa was opened. The inferior border of the pancreas was exposed, and the transverse colon, duodenum, and fusion fascia of the pancreatic head were separated. Toward the descending limb of the duodenum, fascia layers were continuously separated from the peripheral vessels, and the transverse colon was temporarily transected to cut between the right colic and middle colic arteries (Fig. 2C).

The mesocolon was opened toward the lower border of the pancreas on the central side, which exposed the anterior surface of the SMV. The mesocolon was transected while exposing the preserved middle colic arteries and veins. If the right colic artery branch of the middle colic artery was present, it was transected (Fig. 2D). The right colic artery can also include an artery referred to either as the right branch of the right colic flexure artery or the right branch of the middle colic artery. If neither artery was present, transection continued along the middle colic artery to the ventral side of the SMV and SMA (Fig. 2E). With the gastrocolic trunk exposed, all vascular divisions were complete when the right colic vein, which drains from the resected side, was cut at the inflow area. Therefore, it is actually routine to dissect nodes situated anterior

to the surgical trunk in D3, ie, the SMV between the Henle gastrocolic trunk and the ileocolic vein running along the ventral side of the SMA. D3 resection was classified as high tie in which the primary feeding artery is ligated at its origin, and the surgical resection encompassed the pericolic, middle, and apical groups of mesenteric lymph nodes. In contrast, the border clearly defined for D2 as running on the right-hand side of the SMV. This involves division of the right colic vessels at their origin from the SMV instead of the artery. D2 resections were those cases in which only the pericolic and middle groups of lymph nodes were removed with the primary cancer (Fig. 2D, E). After the right colon was resected and removed from the surgical field along with the layers of fusion fascia, anastomosis was performed with either a linear stapler or interrupted sutures; interrupted sutures were preferred by the surgeons.

Pathological Examination

Regional lymph nodes were dissected from the adipose connective tissue by the surgeons immediately following resection. The fat-clearing method was not used to collect lymph nodes. Node numbers and locations were recorded by using a lymph node map and assigned to the appropriate station according to the Japanese General Rules criteria.¹⁴ As many nodes as possible were collected from the resected tissue. Specimens were fixed in 10% formalin and embedded in paraffin, sectioned 4 μ m wide, and stained with hematoxylin and eosin for histological analysis. A single section of each lymph node was examined.

Statistical Analysis

Statistical analyses were performed using S-plus software (Version 2000, Seattle, WA). Descriptive statistics were reported for relevant variables. Disease-specific survival (DSS) was defined as the time from the date of surgery to the date of death from primary colorectal cancer. Overall survival (OS) was defined as the time from primary surgery to death from any cause. Censoring with the Kaplan-Meier method¹⁵ was performed for patients who did not experience the defined outcome. Special attention was paid to intermediate or main lymph node metastasis in relation to the tumor site, depth of invasion, and patient survival data. To provide a more relevant comparison, survival by American Joint Committee on Cancer (AJCC) staging¹⁶ and the JSCCR nodal staging¹⁴ was compared. All *p* values were 2-sided, with $\alpha = 0.05$.

To evaluate the therapeutic value of lymph node dissection, we used the same method to determine the actual benefit of node dissection as described previously.^{17–19} In brief, the frequency of metastasis to each region (N2 or N3) was determined in this series by dividing the number of patients with metastasis at the lymph node region by the number of patients whom the region was dissected. The cumulative 5-year survival rate of patients with metastasis

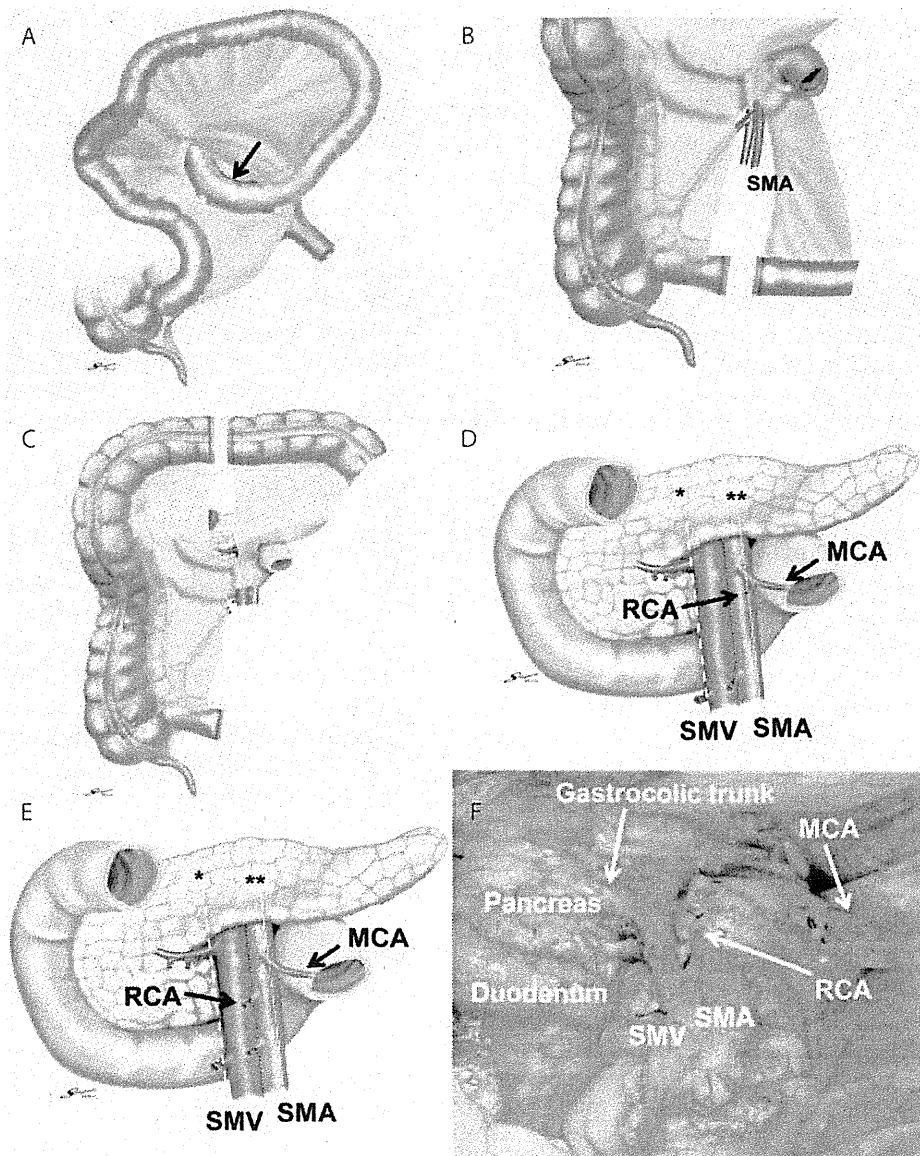


FIGURE 2. Right hemicolectomy with D3 lymphadenectomy using the no-touch isolation technique. A, The root of the mesentery is exposed and an incision is made in the peritoneum (arrow). B, Separation is continued up to the left side of the SMA toward the central sides while removing fat. C, The transverse colon is temporarily transected to cut between the vessels. D, The right colic artery that bifurcates from the middle colic artery is present. E, Right colic artery as it originates directly from the SMA. F, Situs after lymph node dissection for right-sided colon cancer. SMA = superior mesenteric artery; SMV = superior mesenteric vein; MCA = middle colic artery; RCA = right colic artery. Dashed line (*) shows the level at which the vessels are tied in D2 dissection; while dotted line (**) shows the level at which the vessels are tied in D3 dissection.

at each nodal region was calculated irrespective of the presence/absence of metastasis at other nodal regions. Theoretically, the ideal lymph node dissection includes stations with a higher predicted incidence of metastasis. Moreover, lymph node dissection of positive nodes should improve the patient's long-term survival. Therefore, a therapeutic index of the benefit gained by dissection of each region can be calculated by multiplication of the frequency of metastasis at the nodal region and the 5-year survival rate of patients with metastasis at the nodal region.

RESULTS

Characteristics of the 370 patients who underwent potentially curative resection with D3 lymphadenectomy with the use of a no-touch isolation technique are shown in Table 1. There were 192 women (51.9%) and 178 (48.1%) men (mean age, 62.7 years; range, 27–88). The tumor was located in the cecum in 89 (24.1%), ascending colon in 173 (46.7%), and the right segment of the transverse colon in 108 patients (29.2%). Thirty-four patients (9.2%) had

TABLE 1. Characteristic of 370 patients who underwent right hemicolectomy with curative intent

Characteristics	No. of patients
Age, y ^a	62.7 (63.0) (27–88)
Sex ratio (F:M)	192:178
Primary site	
Cecum	89 (24.1)
Ascending	173 (46.7)
Transverse	108 (29.2)
Operative time, min ^a	164.8 (154.5) (88–650)
Blood loss, mL ^a	84.2 (50.0) (0–1210)
Multivisceral resection	29 (7.8)
No. of lymph nodes examined per patient ^a	31.0 (29.0) (3–115)
No. of metastatic lymph nodes per patient ^a	1.2 (0.0) (0–12)
T-stage	
1	34 (9.2)
2	52 (14.1)
3	199 (53.8)
4	85 (22.9)
N-stage (TNM staging) ^b	
0	228 (61.6)
1	106 (28.6)
2	36 (9.8)
n-stage (Japanese staging) ^c	
0	228 (61.6)
1	82 (22.2)
2	49 (13.2)
3	11 (3.0)
TNM stage	
I	73 (19.7)
II	155 (41.9)
III	142 (38.4)
Postoperative mortality	0 (0.0)
Postoperative morbidity	104 (28.1)
Ileus	29 (7.8)
Wound infection	21 (5.7)
Intra-abdominal infection or abscess	6 (1.6)
Anastomotic leakage	6 (1.6)
Urinary tract infection	3 (0.8)
Urinary dysfunction	1 (0.3)
Bleeding	1 (0.3)
Nonsurgical (cardiac, respiratory, renal, cerebral)	17 (4.6)
Others	15 (4.1)
Postoperative chemotherapy	
Yes	113 (30.5)
No	257 (69.5)

Values in parentheses are percentages unless otherwise indicated.

^aValues are mean (median) (range).

^bAccording to the sixth edition of the American Joint Committee on Cancer TNM staging system: N1, metastasis in 1 to 3 regional lymph nodes; N2, metastasis in ≥4 or more regional lymph nodes.

^cAccording to the second English edition of the Japanese Classification of Colorectal Carcinoma: n1, metastasis to pericolic nodes; n2, metastasis to intermediate nodes; n3, metastasis to main nodes.

T1 tumors, 52 (14.1%) had T2 tumors, 199 (53.8%) had T3 tumors, and 85 (22.9%) had T4 tumors. Seventy-three patients (19.7%) had stage I tumors, 155 (41.9%) had stage II tumors, and 142 (38.4%) had stage III tumors. Twenty-nine patients underwent multivisceral resections (7.8%), and specimens for 15 (51.7%) demonstrated tumor invasion. No patients died immediately

postoperatively, although 104 (28.1%) had one or more surgical complications: ileus (29 patients, 7.8%), wound infection (21 patients, 5.7%), intra-abdominal infection or abscess (6 patients, 1.6%), and anastomotic leakage (6 patients, 1.6%). One hundred thirteen patients (30.5%) received adjuvant chemotherapy after surgery. Twenty-nine elderly patients with stage III disease did not receive adjuvant chemotherapy. Patients with stage III disease were recommended to undergo adjuvant chemotherapy, with approximately 80% receiving it, and adjuvant chemotherapy was not offered for stage II disease in this cohort.

The mean number of nodes examined per patient was 31.0. Mean node yields of 13.6 from the pericolic node level, 8.4 from the intermediate node level, and 6.1 from the main node level were obtained per patient. The incidence of metastasis to intermediate nodes was 13.2% (49/370), more frequent in patients with pT3 and pT4 cancer (Table 2). The incidence of metastasis to main nodes was 3.0% (11/370). This value also represented the frequency of residual nodes typically left behind in D2 dissection. Of these 11 patients, 6 had no cancer deposits in the intermediate nodes (skipped metastases). There was also a steady increase in the proportion of positivity in the main nodes with increasing depth of invasion, regardless of the tumor location; however, no metastases occurred in patients with pT1 or pT2 cancer (Table 3). Mean positive node yields were 1.3 to 1.7 from the intermediate nodes and 1.3 to 1.5 from the main nodes.

Cancer staging correlated strongly with survival rates. The 5-year actuarial OS of patients with stages I, II, and III cancer were 94.5% (95% CI, 89.3%–99.7%), 87.6% (95% CI, 82.4%–92.8%), and 79.2% (95% CI, 72.5%–85.8%) ($p < 0.0001$). The 5-year actuarial DSS of patients with stages I, II, and III cancer were 100.0% (95% CI, 100.0%), 94.5% (95% CI, 90.8%–98.2%), and 85.0% (95% CI, 79.0%–90.9%) ($p < 0.0001$). The 5-year OS of patients with metastases to the intermediate nodes (N2+, $n = 49$) was 77.6% (95% CI, 65.9%–89.2%) and 36.4% (95% CI, 7.9%–64.8%) for patients with metastases to the main nodes (N3+, $n = 11$) (Fig. 3A). Overall survival by Japanese N-stage was stratified according to AJCC staging, ie, the 5-year OS rates for N2+ were 84.9% in stage IIIB ($n = 33$) and 62.5% in stage IIIC ($n = 16$), whereas those for N3+ were 60.0% in stage IIIB ($n = 5$) and 16.7% in stage IIIC ($n = 6$) (Fig. 3B). The 5-year DSS of patients with N2+ was 83.5% (95% CI, 73.0%–93.9%) and 36.4% (95% CI, 7.9%–64.8%) for patients with N3+ (Fig. 3C). Disease-specific survival by Japanese N-stage was also stratified according to AJCC staging, ie, the 5-year DSS rates for N2+ were 87.7% in stage IIIB and 75.0% in stage IIIC, whereas those for N3+ were 60.0% in stage IIIB and 16.7% in stage IIIC (Fig. 3d). Although the index of estimated benefit from intermediate nodal dissection was 11 (incidence rate of metastasis 13.2%, times survival

TABLE 2. Nodal metastases to the intermediate nodes (stations 202, 212, and 222)

Site	Metastatic incidence (# of metastatic patients/total # of patients)				
	pT1	pT2	pT3	pT4	Total
Cecum	0.0 (0/6)	0.0 (0/19)	11.9 (5/42)	13.6 (3/22)	9.0 (8/89)
Ascending colon	0.0 (0/22)	4.3 (1/23)	20.0 (17/85)	14.0 (6/43)	13.9 (24/173)
Transverse colon	0.0 (0/6)	10.0 (1/10)	15.8 (9/57)	20.0 (7/35)	15.7 (17/108)
Total	0.0 (0/34)	3.8 (2/52)	16.8 (31/184)	16.0 (16/100)	13.2 (49/370)

rate 83.5%), the index of estimated benefit from main nodal dissection was 1.1 (incidence rate of metastasis 3%, times survival rate 36.4%). The index was high for the intermediate nodes by D3 lymphadenectomy. By contrast, modest value was gained by dissection of the main nodes.

There were no changes in preoperative staging throughout the study nor were there temporal changes with main node involvement. Preoperative investigations included barium enema, colonoscopy, chest x-ray, CT, and CEA blood testing. Among the 11 patients with main nodal disease, 6 patients had palpable main nodes intraoperatively. Of all 370 patients who underwent D3 lymph node dissection, 56 patients had a recurrence: liver (18 patients), lung (15), peritoneum (11), para-aortic lymph nodes (8), locoregional sites (2), ovary (1), and bone (1). It is worthy of note that 10 patients (22.7%) had hematogenous recurrence (6 liver, 3 lung, 1 bone), none had para-aortic nodal recurrence, and one had peritoneal recurrence as the initial site of recurrence in 44 patients with intermediate nodal metastases and no main nodal metastases. In contrast, 9 of 11 patients (81.8%) with main nodal metastases had a recurrence of cancer. Five of these patients had para-aortic nodal recurrence, 2 had recurrent disease confined to the lung, 1 had disease in both the para-aortic nodes and lung, 1 had disease in both the liver and lung, and none had peritoneal recurrence as the initial site of recurrence.

DISCUSSION

The no-touch isolation technique for cancer surgery was first proposed in 1967.¹² No-touch isolation involves closure of the mesocolic main vessels and bowel lumen before mobilization of the tumor to reduce the risk of metastatic induction. Conventional D3 dissection involves dividing

the vessels after mobilizing the tumor. The benefits of the no-touch procedure are controversial. The only reported clinical trial claimed no significant benefits.²⁰ However, the reported data reflected both the right and left colon. Moreover, the no-touch group was consistently superior to the control group with respect to the disease-free curve for liver metastasis, suggesting that significant differences were not found because the number of patients was insufficient.

An advantage of a radical hemicolectomy is its inclusion of the entire regional arterial supply regardless of variations in the branching seen in colic vessels. This branching necessitates rational radical resection.^{21,22} The ventral side of the SMV and SMA is a difficult area to dissect, not only because the fat is thick, but also because the greatest vessel variation occurs here. If separation of the right mesocolon is completed proximal and distal to this area by the use of our medial to lateral approach with no-touch isolation, transections can be performed safely. The no-touch approach fits smoothly with laparoscopic procedures and has attracted more interest than laparotomy procedures.^{23,24} The no-touch procedure also gives priority to vascular treatment, does not increase surgical invasiveness, and can be performed quickly; these advantages make the method worth considering. Although no hard research evidence is currently available, a Japanese randomized trial (JCOG1006 trial, UMIN000004957) comparing no-touch isolation with the conventional lateral approach is underway.

The principal objective of colon cancer resection is to remove the primary tumor and its lymphovascular supply. Because the lymphatics of the colon accompany its main arterial supply, the regional arterial vasculature should be removed at its origin to ensure adequate resection. Patients demonstrating an invasion depth of T3 or more should

TABLE 3. Nodal metastases to the main nodes (stations 203, 213, and 223)

Site	Metastatic incidence (# of metastatic patients/total # of patients)					Skip metastasis ^a
	pT1	pT2	pT3	pT4	Total	
Cecum	0.0 (0/6)	0.0 (0/19)	2.4 (1/42)	9.1 (2/22)	3.4 (3/89)	2.2 (2/89)
Ascending colon	0.0 (0/22)	0.0 (0/23)	5.9 (5/85)	4.7 (2/43)	4.0 (7/173)	2.3 (4/173)
Transverse colon	0.0 (0/6)	0.0 (0/10)	0.0 (0/57)	2.9 (1/35)	0.9 (1/108)	0.0 (0/108)
Total	0.0 (0/34)	0.0 (0/52)	3.3 (6/184)	5.0 (5/100)	3.0 (11/370)	1.6 (6/370)

^aNode-positive in the main nodes without nodal involvement in the intermediate nodes.

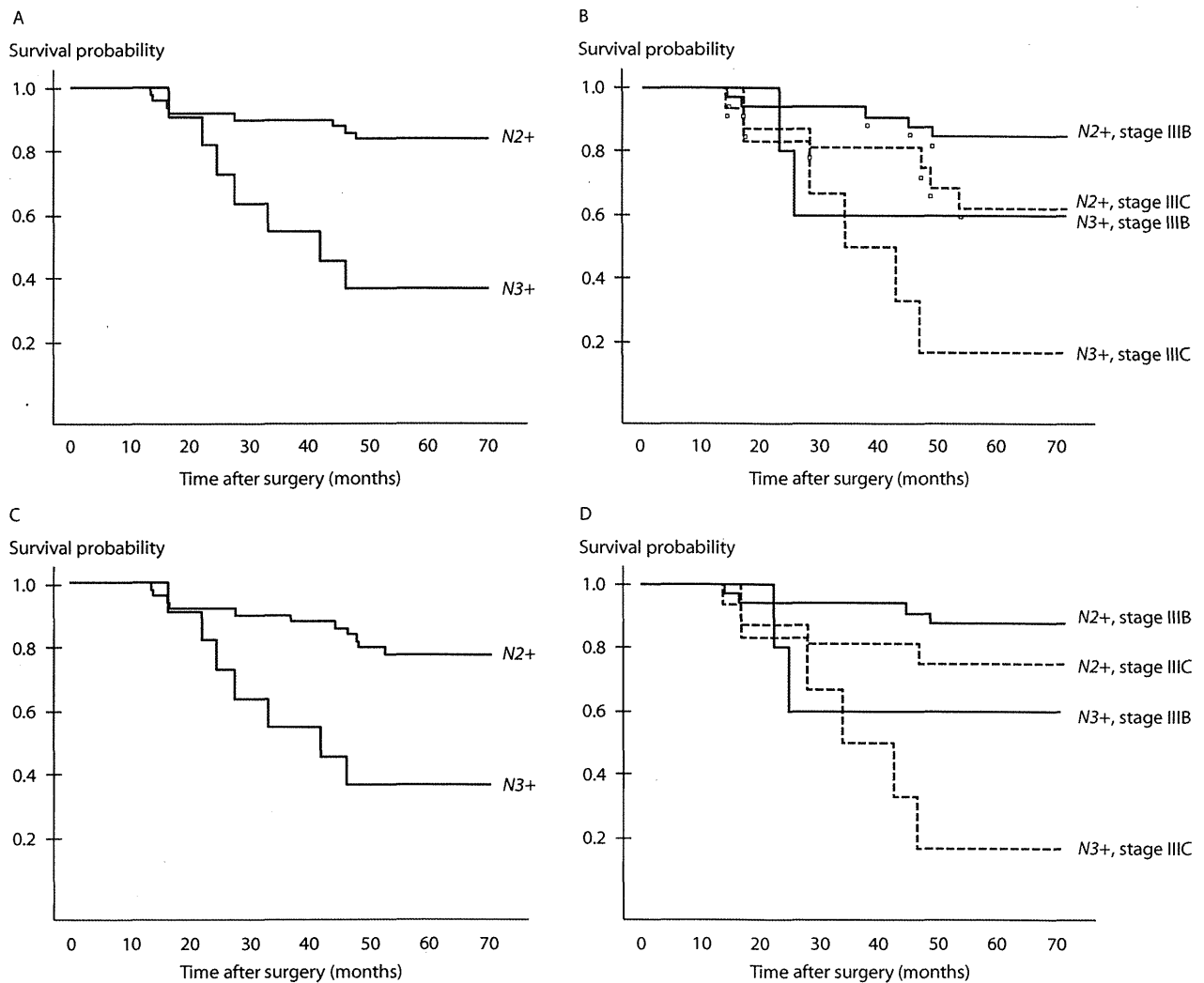


FIGURE 3. A, Overall survival curves for patients with right-sided colon cancer who underwent D3 lymphadenectomy, by mesenteric lymph node status. B, Overall survival stratified by mesenteric lymph node status and AJCC staging. C, Disease-specific survival curves for patients with right-sided colon cancer who underwent D3 lymphadenectomy, by mesenteric lymph node status. D, Disease-specific survival stratified by mesenteric lymph node status and AJCC staging. AJCC = American Joint Committee on Cancer; N2+ = metastatic intermediate nodal disease present; N3+ = metastatic main nodal disease present.

undergo a D3 lymphadenectomy and an adequate colonic resection.²⁵ In this study, positivity rates for the intermediate and main lymph nodes increased steadily as the depth of invasion increased, regardless of the tumor location. For stage T3 or greater, our results support D3 resection to avoid residual metastatic main nodes that are typically left behind after D2 dissection (only pericolic and intermediate nodes removed). Curative resection by D3 dissection was performed in 60 patients with intermediate and/or main nodal involvement. Because some of these nodes would not have been removed with D2 or D1 (pericolic lymph nodes only) dissection, the curative rate increased by 16.2% (60/370) at worst (assuming D2 would include ligation of the feeding arteries distal to the right side of the SMV).

The effectiveness of lymphadenectomy remains controversial. Previous studies have reported that increasing the number of retrieved nodes corresponds to increased survival.³⁻⁶ This relationship may be due to stage migration²⁶ or a decrease in local recurrence and distant metastasis from resection of affected lymph nodes. To evaluate survival benefit without any concept of staging of lymph node metastasis, we modified a previously published method.¹⁷⁻¹⁹ Our hypothesis was that D3 dissection results in a curative resection in some patients in whom D1 or D2 dissection is insufficient and is associated with remaining disease in regional lymph nodes. The frequency of metastasis was evaluated in lymph node stations typically left behind after D1 or D2 dissection, and the therapeutic effect of dissection was determined by examining the

incidence of metastases and survival rates of patients with nodal deposits at the overlooked stations, regardless of nodal metastases to any other station, to prevent selection bias. Therefore, an index of the benefit gained by dissection of each region is calculated by multiplying the frequency of metastasis at the nodal region by the 5-year survival rate of patients with metastasis in that region. Results show the therapeutic benefit of D3 dissection, because D1 or D2 dissection would have likely produced no long-term survivors.²⁷ However, the benefit of routine D3 dissection for patients undergoing resection was modest (3.0%, 11/370), and only 1.1% of patients with right-sided colon cancer are likely to be cured by D3 dissection (incidence rate of metastasis 3% times survival rate 36%). That is not to say that this low incidence of metastasis in the lymph nodes at the base of the feeding arteries undermines the rationale behind D3 dissection. Patients with stage I, II, or III disease had high survival rates, suggesting indirectly a positive effect of the D3 resection on survival. D3 dissection will remove the highest draining nodes that may harbor occult metastases, because colonic lymph nodes tend to follow the arterial supply. Indeed, the survival of patients was stratified by Japanese N-stage and AJCC staging in which patients with fewer metastatic lymph nodes had more favorable prognosis according to the regional lymph node spread level. It is compatible with the notion of regional lymph node spread burden. Therefore, by improved clearance of micrometastatic disease, D3 dissection may improve survival in patients with node-negative disease (N0) or early node metastases (metastases to pericolic or intermediate lymph nodes) in routine histological examination where frequent occurrence of microinvolvement is found²⁸; however, these data are inconclusive.

The need to secure and retain local and regional control of solid tumors will assume increasing importance as systemic therapy improves and reduces death from distant metastases. In some cancers, such as breast cancer or Lynch syndrome, patients' low-volume distant tumor has been controlled by systemic therapy. However, indolent local and regional disease represents a threat to those patients, because prevention of locoregional recurrence remains an important goal in cancer treatment. Whether a survival advantage is best pursued through lymphadenectomy or through a combination of resection with systemic therapy is as yet unknown, but the effect of regional metastases on survival cannot be ignored. Still, demonstrating the influence of surgical expertise on long-term survival after colon cancer operations has been more difficult. Randomized clinical trials comparing D2 and D3 dissection are needed to confirm our results.

Despite the relatively small benefit of D3 lymphadenectomy during colectomy to prevent SMA lymph node recurrence and reduce mortality, the absence of accurate SMA node status predictors may justify this

procedure, because there is no reliable intraoperative assessment of node metastases.²⁹ Nearly half of the patients with positive main nodal metastases in this study had no intermediate nodal metastases. Involvement of the main lymph nodes along the SMA indicates that further proximal spread may have already taken place, because the para-aortic nodes were the predominant site of recurrence in patients with main nodal metastases in this study. However, we found a survival rate of approximately 40% in patients with metastases to the central lymph nodes showing that metastatic nodes along the SMA are still locoregional, and we believe that the removal of those nodes could be curative. D3 dissection may have the greatest effect on patients with involved intermediate nodes rather than main nodes. Dissection of lymph node-bearing tissue along the main trunk artery to the main nodes situated anterior to the trunk has been accepted as the standard for right-sided colon cancer since 1946 in Japan³⁰ and was defined as D3 dissection in 1977 by the JSCCR.³¹ Complete mesocolic excision (CME) or mesocolic plane surgery also involves central ligation of vessels at their roots, as with D3 lymphadenectomy. Hohenberger et al³² obtained a surgical mortality of 2.9% by using CME and central ligation in a study of Western patients, whereas mortality in our study was 0%. This may be related to a lower BMI in Japanese patients, given that studies have shown that obesity may be associated with unfavorable surgical outcomes including increased operative mortality.³³ Complete mesocolic excision and D3 dissection both remove the entire local tumor drainage system, and there is indirect but significant evidence of excellent outcomes despite a lack of randomized trials.^{30,32,34,35} The negligible mortality and morbidity rates in our study prove that D3 dissection can be safely executed. At this stage of surgery, the bowel to be resected is completely detached from its central connection. As the bowel is mobilized medially, the gonadal vessels, ureter, vena cava, duodenum, and head of the pancreas are identified and protected by sweeping them posteriorly until the already isolated segment of intestine is completely removed. As Lavery et al³⁶ stated before, this method, modified based on the principles of the preliminary lymphovascular isolation technique first described by Turnbull et al,¹² seems to be convenient and safe for performing a right colon resection for the treatment of cancer. Note that the original procedure does not mobilize the pancreas, expose the SMV, or remove the root of the vessel. Because this measure has no increase in morbidity or mortality and can be performed quickly, there is an option to still support the no-touch isolation technique in the West.³⁷ Another study shows that a D3 lymphadenectomy using a medial to lateral approach is a feasible and safe procedure for the treatment of curable right-sided colon cancer in both the open and laparoscopic surgery.³⁸ A move toward CME with central vascular ligation has been proposed by other European centers,

resulting in a marked improvement in the oncologic quality of the specimen produced³⁹ that does not increase the postoperative complication or mortality rates.⁴⁰

There are limitations to our study. First, this study did not contain a control group. A randomized, controlled trial is essential to evaluate the benefits of this technique. However, D3 dissection is not technically demanding, is less time-consuming than presumed, and is not associated with a higher operative risk or morbidity. We also acknowledge that definitive conclusions about a survival benefit with D3 dissection cannot be drawn from this study and remain to be proven. Second, the possibility of a reporting bias exists regarding the safety of this technique.

Results show that radical resection with D3 lymphadenectomy provided satisfactory 5-year survival for patients with colon cancer in stages I to III, that D3 dissection can be safely performed with a no-touch isolation technique, and that D3 dissection is therapeutic for patients with right-sided colon cancer and node metastases in the right mesocolon.

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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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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.

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726

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,

DISEASES OF THE COLON & RECTUM VOLUME 56: 6 (2013)

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



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).

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.

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 al⁹ 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