● しかし欧米とわが国では胃癌手術のコンセプト・qualityが大きく異なるため，術後補助療法の意義も自ずと異なる．わが国ではD2郭清を伴う胃切除術が標準治療として認識されており，JCOG9501試験[10]で予防的D3郭清の効果が否定されたため，手術による局所制御としてはほぼ完成の域に達していると思われる．したがってわが国で要求される術後補助療法としては全身治療を主目的とする化学療法が主体となる．

● 一方，欧米では高度進行胃癌や肥満患者が多いことを背景に，D2郭清はD1郭清に比して合併症発生率は増加し生存率に寄与しないという認識からいまなおD0～1郭清が多く施行されているのが現状である[11,12]．そのため局所再発防止のため術後化学放射線療法による局所制御の検討が多いのが実情である．

1 海外における術後補助化学療法の臨床試験

a．術後補助化学療法

● 過去にさまざまなレジメンの術後補助化学療法と手術単独の比較試験が施行されてきたが，その有用性は示されてこなかった[13～16]．唯一補助化学療法の有用性が示されたのが先述したMAGIC試験である．

b．術後補助化学放射線療法

● **SWOG9008/INT-0116試験**[17]：stageIB～Ⅳの胃癌556症例を対象に術後5-FU/ロイコボリン＋放射線（45Gy）と手術単独群とを比較したRCTである．
・生存期間は手術単独群で27ヵ月に対し，術後化学放射線療法群で36ヵ月，ハザード比は1.35（95% CI, 1.09-1.66；$P=0.005$），再発におけるハザード比も1.52（95% CI, 1.23-1.86；$P<0.001$）と生存期間および無再発生存ともに有意に有用であるという結果であった．
・本試験の結果を受け，NCNN Clinical Practice Guidelines in Oncology™（ver.1，2010）においてもR0手術後のT3～T4もしくはanyT，N＋症例に対する標準治療とされている．しかし本試験の問題点としてリンパ節郭清がD0（54%），D1（36%）でD2郭清は10%に過ぎないこと，またサブグループ解析ではD2郭清症例の術後補助化学療法が有意性を証明できず，わが国の標準治療の現状を考慮すると総合的所見として受容できない．

2 わが国における術後補助化学療法の臨床試験

● わが国における術後補助化学療法に関する試験は古くから行われてきたが，1980年代後半からJCOGによる手術単独群を対象としたRCTが実施されるに至った．

● **JCOG8801試験**[18]：pT1N0を除く漿膜浸潤陰性胃癌579症例を対象とした試験で，術後にMMC/5-FUを投与し，その後にUFTを18ヵ月投与し手術単独群と比較する試験である．5年生存率は手術単独群で82.9%，化学療法群で85.8%と有意差を認めなかった（$P=0.17$）．

● **JCOG9206-1試験**[19]：漿膜浸潤陰性胃癌症例を対象とした術後MFC（マイトマイシン/5-Fu/シタラビン）＋経口5-FUによる化学療法群と手術単独群を比較した試験である．5年生存

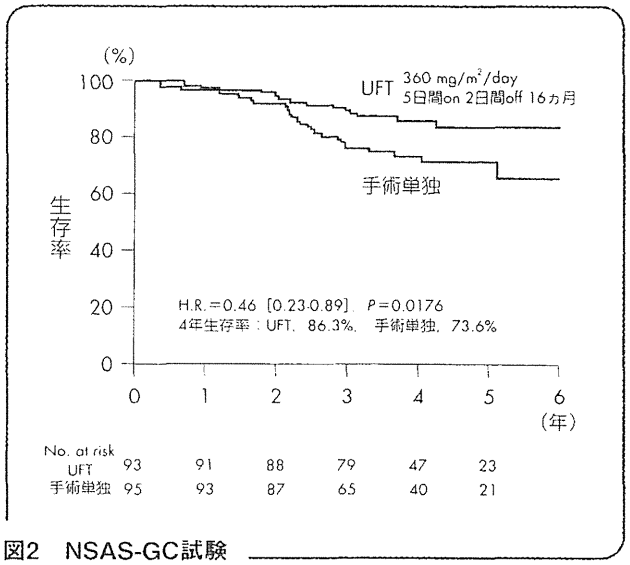

図2 NSAS-GC試験

(文献20) より引用)

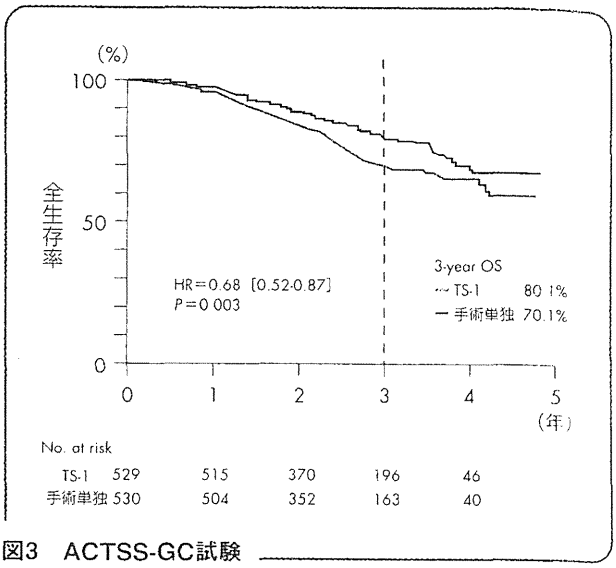

図3 ACTSS-GC試験

(文献21) より引用)

率は手術単独群で86.1%，化学療法群で91.2%と有意差は認められなかった（$P=0.13$）.

● **JCOG9206-2試験**[20]：漿膜浸潤陽性胃癌症例を対象とした術後CDDPip/FP/UFTによる化学療法群と手術単独群を比較した試験である．5年生存率は手術単独群で60.9%，化学療法群で62.0%と有意差を認めなかった（$P=0.482$）.

● **NSAS-GC試験**[21]：T2N1-2症例を対象に術後UFT高用量（360mg/m²）5日間投与，2日間休薬を16ヵ月施行し，手術単独群と比較する試験である.

・本試験は当初予定症例数500例と計画するも，190例の登録に留まったが，中間解析で有意差を認めたため早期公表された.
・5年生存率が手術単独群73%に比して，UFT群86%と有意に良好であった（$P=0.017$）**(図2)**.
・本研究のポイントは従来の試験と比較して高用量のUFT投与によるdose intensityの高さがあげられよう.

● **ACTS-GC試験**[22]
・本試験の詳細は他稿に譲るが，T1症例を除くD2以上の郭清を施行したStageⅡ，Ⅲ胃癌症例を対象にS-1：80mg/m²を原則4週投与2週休薬で1年間投与し，手術単独群と比較した第Ⅲ相試験である.
・中間解析で3年生存率が手術単独群70.1%に比してS-1投与群80.1%と有意差を認めたため（$P=0.003$），試験の中止と早期公表がなされた **(図3)**.

・本試験の5年間の追跡結果がESMO2010で公表されたが，5年生存率は手術単独群で61.1%，S-1群で71.7%（ハザード比：0.669，95% CI：0.540-0.828），5年無再発生存率は手術単独群で53.1%，S-1群で65.4%（ハザード比：0.653，95% CI：0.537-0.793）で，3年時点で報告された結果を強く裏付ける結果であった.
・本試験によりS-1の術後1年間投与がStageⅡ，Ⅲ胃癌の標準治療となり，その後のわが国における胃癌薬物療法のキードラッグとなった.

表1　SAMIT試験の概要

	UFT	S-1
S-1単独	UFT単独群 UFT：267mg/m²連日投与 （4週間）×6コース	S-1単独群（対照） S-1：80mg/m²/day （2週投与1週休薬）×8コース
パクリタキセル逐次併用群	パクリタキセル→UFT逐次併用群 Weekly パクリタキセル 80mg/m² ① Day 1，8（1コース目は3週目に休薬：3週サイクル） ② Day 1，8，15（2，3コース目は4週目に休薬：4週サイクル） 2週間休薬 ③ UFT：267mg/m²連日投与 （4週間）×3コース	パクリタキセル→S-1逐次併用群 Weekly パクリタキセル 80mg/m² ① Day 1，8（1コース目は3週目に休薬：3週サイクル） ② Day 1，8，15（2，3コース目は4週目に休薬：4週サイクル） 2週間休薬 S-1：80mg/m²/day （2週投与1週休薬）×4コース

3 現在進行中の術後補助化学療法の臨床試験

● ACTS-GCの結果で留意すべき点として，N2症例では手術単独群とS-1投与群との生存率が少差である点，StageⅢA，ⅢBの3年生存率も76.2%，64.2%と決して満足のいくものではない点，腹膜再発を十分に抑制しえていない点などがあげられる．これらの改善が，今後の術後補助化学療法の臨床試験に求められる課題と思われる．

● **SAMIT試験**：漿膜浸潤陽性胃癌に対する術後補助化学療法としての，フッ化ピリミジン単独に対するパクリタキセル逐次併用による上乗せ効果の検証と共に，UFTとS-1の比較も同時に行う試験である．予定症例数は1,480例で既に症例登録は終了している．本試験によりUFTのS-1に対する非劣性の証明，パクリタキセルの併用による腹膜再発に対する効果などに関する結果が待たれる（**表1**）．

● **S-1/CDDP療法**[23]：国立がんセンターを中心にS-1/CDDP併用療法の術後補助療法としてのfeasibility試験が行われ2010年のASCO-GIで報告された．その結果，1コース目からS-1/CDDP併用療法を施行せずに，投与1コース目はS-1単独で施行し，2～4コース目はS-1/CDDP併用療法投与することで食欲不振や嘔吐などの有害事象を軽減でき，完遂率は57%から81%に改善可能であった．

● **OGSG0604試験**[24]：StageⅢ胃癌に対する術後S-1/ドセタキセル療法の第Ⅱ相試験で，S-1/ドセタキセルを4コース施行し，その後に術後1年までS-1単剤を投与するレジメンである．S-1/ドセタキセルを4コース投与可能であったのは77.4%で，認容可能なレジメンであると報告している．

● 今後は2011年より切除不能進行・再発胃癌に承認されたカペシタビンや既に大腸癌で承認されているオキサリプラチンなどの新規抗癌剤，同じく本年承認されたトラスツズマブなどの分子標的薬などの出現・導入によりさまざまな臨床試験が展開されることが予想される．

（信岡隆幸／平田公一）

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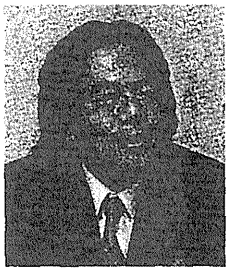

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High-Risk Stage II Colon Cancer After Curative Resection

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Objectives: This study was designed to clarify which attributes of stage II colon cancer are associated with tumor recurrence and survival after curative resection, and the effects of adjuvant chemotherapy (ACT).

Methods: We retrospectively reviewed outcomes and clinicopathological characteristics of 1476 patients with stage II colon cancer who underwent curative resection.

Results: Of 1476 patients, 204 (13.8%) developed recurrence. Macroscopic type, serum CA19-9 levels, venous invasion, emergency operation, and postoperative ileus were independently associated with overall recurrence. Carbohydrate antigen (CA)19-9 levels, the number of dissected lymph nodes (LN), sex, age, ACT, emergency operation, venous invasion, and macroscopic type were independently associated with poor prognosis. Prognosis was significantly better in patients who received ACT than in those who did not. Among patients with extensive venous invasion, those with fewer than 13 dissected LNs, male patients, and patients >50 years old, the prognosis was significantly better in patients who received ACT than in those who did not.

Conclusions: ACT for stage II colon cancer is recommended to improve the prognosis of patients with extensive venous invasion, patients with fewer than 13 dissected LNs, patients >50 years old, and male patients, particularly patients with more than two of these risk factors.
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KEY WORDS: **colon carcinoma; curative resection; prognostic factors; adjuvant chemotherapy**

INTRODUCTION

Colorectal cancer is the second-leading cause of cancer mortality in the United States [1], and the third-leading cause in Japan [2]. Surgical treatment is considered the best approach to cure colorectal cancer, but recurrence still occurs according to the stage of disease after surgery. The most important prognostic indicator for survival in locally advanced colon cancer is tumor stage, which is determined by the depth of invasion, the number of lymph nodes (LNs) involved and the presence of distant metastases, as in the American Joint Committee on Cancer (AJCC)-TNM staging criteria [3]. Thirty to forty percent of colon cancers are diagnosed as AJCC stage II disease at resection [1,4]. These patients have a relatively good prognosis after surgery alone with 5-year survival rates of approximately 80% [5,6].

The goal of adjuvant chemotherapy (ACT) after curative resection of early-stage colon cancer is to eliminate microscopic local or metastatic disease and thus reduce the risk of tumor recurrence and improve survival rate. However, ACT has not been conclusively shown to have a significant benefit on survival because of conflicting results in the literature [7]. Therefore, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines do not recommend the routine use of ACT for stage II colon cancer patients. On the other hand, the ASCO

Conflicts of interest: None

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and NCCN guidelines do state that ACT could be considered for patients with high-risk features, including T4 tumors leading to obstruction, perforation, and for patients with fewer than 12 LNs [8,9]. However, the high-risk features of colon cancer have not yet been determined.

Accordingly, it is important to identify which patients with stage II colon cancer are at high risk of recurrence and have poor prognosis following curative resection to provide an effective and cost-beneficial follow-up program. Therefore, the principle aim of the present study was to identify which attributes of stage II colon cancer are associated with tumor recurrence and survival after curative resection in a large-scale retrospective multicenter study. We also used this opportunity to investigate the effects of adjuvant chemotherapy (ACT) after curative surgery.

PATIENTS AND METHODS

Between January 1991 and December 1996, 1476 patients with stage II colon cancer underwent curative resection at 15 hospitals, which were members of the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer. This included all consecutive patients with stage II colon cancer treated during the study period. The patients were monitored as outpatients at each of the participating hospitals until December 2003, by which time 8.1% (119 patients) of the patients were lost to follow-up. The patients did not receive preoperative radiotherapy or chemotherapy. Cancers associated with ulcerative colitis, Crohn disease, hereditary nonpolyposis colorectal cancer, or familiar adenomatous polyposis were excluded from the analysis. Complete dissection of all regional lymph nodes, including pericolic, intermediate, and major lymph nodes according to the Japanese classification of colorectal carcinoma [10], was performed in all patients. The major lymph nodes were dissected around the root of the feeding artery regardless of any division of the feeding artery. The colon was divided at least 10 cm proximally and distally from the tumor, and at a minimum distance of 10 cm on the proximal side and 6 cm on the distal side for rectosigmoid colon cancer. No evidence of tumor tissue was found at the proximal, distal, and radial margins in any of the patients. Preoperative investigations included barium enema, colonoscopy, chest X-ray, ultrasonography (US), computed tomography (CT) of the liver, and blood levels of carcinoembryonic antigen (CEA) and/or carbohydrate antigen 19-9 (CA19-9). Most institutions established a follow-up examination period exceeding 5 years. The follow-up system consisted of measurement of serum tumor markers every 3 months for the first 3 years and then every 6 months for the next 2 years, hepatic imaging (US and/or CT) and chest X-rays every 6 months, pelvic CT for rectal cancer every year, and colonoscopy every 1–2 years. Data concerning additional treatments, recurrence, and prognosis were retrospectively collected. Preoperative ileus was defined as cases needing the insertion of a long intestinal tube or the creation of a colostomy before tumor resection. Postoperative ileus was defined as cases needing the insert of a long intestinal tube, delays in starting the diet because of abdominal symptoms such as abdominal fullness, nausea, and vomiting, which were thought to be caused by disturbed passage or peristaltic abnormality, or to stop the diet after the initial oral intake. ACT comprised oral 5-FU derivatives such as UFT (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) or 5'DFUR, in all of the patients that received ACT (611 cases). Continuous infusion of 5-FU was performed in 36 patients, and bolus infusion of 5-FU and leucovorin was used in three patients. In these patients, the initial infusion of 5-FU was followed by the administration of oral 5-FU derivatives until at least 12 months after surgery. No significant differences were found in the distribution of ACT among each factor measured. At that time, oral 5-FU derivatives were routinely administrated until at least 12 months after surgery in Japan based on the results of several studies of Japanese patients [11–13]. The mean ± standard deviation duration of ACT administration was 12.0 ± 11.8 months. Based on histological findings, all tumors were classified as either well differentiated, which included well and moderately differentiated adenocarcinoma, and poorly differentiated, which included mucinous carcinoma (32 patients), signet ring cell carcinoma (2 patients), and poorly differentiated adenocarcinoma (39 patients). Tumor location, macroscopic type, venous invasion, and lymphatic invasion were described according to the Japanese classification of colorectal carcinoma [10]. The rectosigmoid was defined as the portion of the large intestine that is located between the promontory and the inferior border of the second sacral vertebra [10], corresponding to about 12 cm from the anal verge [14], and was included in this analysis. Based on macroscopic findings, all tumors were classified as either a macroscopic pushing type, which corresponds to tumors with a clear margin, and the macroscopic infiltrating type, which corresponds to tumors with an infiltrating margin. Based on microscopic findings (magnification, ×4), vessel invasion was histologically classified according to the severity of venous or lymphatic invasion as either slight (0–3 affected vessels) or extensive (>3 affected vessels) [10]. Emergency operation was indicated for perforation or obstructive ileus caused by the tumor. Resection was considered for recurrence in the absence of any medical contraindications to surgery when the recurrence was technically resectable and no metastases in other organs were present. We retrospectively determined which factors were associated with recurrence and prognosis in stage II colon cancer.

Statistical Analysis

Statistical analysis was performed using Statview version 5.0 software (Abacus Concepts, Inc, Berkeley, CA). All data are expressed as the mean ± standard deviation. The χ^2 test or Fisher's exact probability test was used to compare recurrence rates. Logistic regression analysis was performed to further evaluate the factors associated with the recurrence found to be significant in χ^2 tests or Fisher's exact probability test at a level of $P < 0.05$ to identify which factors were independently associated with recurrence. Survival rates were calculated by the Kaplan–Meier method and compared by the log-rank test and the generalized Wilcoxon test. Survival analysis was done using the stepwise forward Cox regression model for factors that were found to be significant by the log-rank test or the generalized Wilcoxon test at a level of $P < 0.05$ to determine which factors were independently associated with survival. Values of $P < 0.05$ were considered significant for all analyses.

RESULTS

Cancer Recurrence

Recurrence was discovered in 204 patients (13.8%). The median time to recurrence after the initial resection for colon cancer was 17.5 ± 24.3 months. The median duration of follow-up of patients with recurrence and those without recurrence was 52.5 ± 41.7 and 101.5 ± 43.4 months, respectively. The recurrence rates according to the clinicopathological categories are shown in Table I. Tumor location in the rectosigmoid colon, macroscopic infiltration type [10], ≤12 dissected LNs, well-differentiated type, extensive venous invasion, >2-fold elevations in serum CEA levels, high serum CA19-9 levels relative to the normal limit, emergency operation, postoperative ileus, and postoperative chemotherapy were significantly associated with an increased recurrence rate. On the other hand, age, sex, circumference, and diameter of the tumor, depth of invasion, lymphatic invasion, perforation during surgery, leakage and preoperative ileus were not significantly associated with recurrence. Logistic regression analysis of factors that were

TABLE I. Recurrence Rates According to Clinicopathological Factors

Variable	Category	Patients with recurrence (%)	Patients without recurrence (%)	Total	*P* value
Age	≤50	33(18.4)	145(81.0)	179	0.06
	>50	171(13.2)	1105(85.3)	1296	
Sex	Men	125(14.2)	747(84.8)	881	0.62
	Women	79(13.3)	504(84.7)	595	
Location	Rs	46(19.3)	188 (79.0)	238	0.007
	Colon	158(12.8)	1062(85.9)	1237	
Macroscopic type	Pushing type	173(13.0)	1141(85.6)	1333	0.003
	Infiltrating type	30(23.4)	96(75.0)	128	
Circumference	≥80%	100(14.6)	570(83.2)	685	0.42
	<80%	58(13.1)	378(85.5)	442	
Diameter (cm)	≤5	87(13.6)	543(85.1)	638	0.68
	>5	114(14.2)	678(84.2)	805	
Number of dissected LN	≤12	74(17.8)	338(81.4)	415	0.005
	>12	120(12.5)	825(85.7)	963	
Histology[a]	Well	199(14.2)	1181(84.5)	1398	0.03
	Poorly	5(6.8)	65(89.0)	73	
Depth of invasion	<T3	182(13.3)	1164(85.3)	1364	0.06
	T4	22(19.6)	87(77.7)	112	
Lymphatic invasion	Slight	166(13.4)	1059(85.3)	1242	0.24
	Extensive	38(16.8)	184(81.4)	226	
Venous invasion	Slight	156(12.7)	1063(86.4)	1230	0.005
	Extensive	47(19.8)	190(75.95)	237	
Serum levels of CEA	≤NL × 2	130(12.3)	906(86.0)	1053	0.003
	>NL × 2	48(19.8)	191(78.6)	243	
Serum levels of CA19-9	≤NL × 1	143(12.95)	950(85.8)	1107	0.001
	>NL × 1	32(25.8)	89(71.8)	124	
Emergency operation	+	12(38.7)	19(61.3)	31	0.0001
	−	191(13.2)	1231(85.3)	1443	
Perforation during surgery[a]	+	2(28.6)	5(71.4)	7	0.26
	−	200(13.7)	1244(84.9)	1465	
Leakage[a]		7(26.9)	19(73.1)	26	0.06
	−	194(13.4)	1229(85.1)	1444	
Preoperative ileus	+	14(21.5)	51(78.5)	65	0.07
	−	188(13.4)	1198(85.1)	1407	
Postoperative ileus	+	15(24.2)	47(75.8)	62	0.02
	−	187(13.3)	1201(85.2)	1409	
Postoperative ChT	+	101(16.5)	505(82.7)	611	0.01
	−	103(11.9)	745(86.2)	864	

LN, lymph node; ChT, chemotherapy; Well, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Rs, rectosigmoid colon; NL, normal limit.

[a]Fisher's exact probability test; other analyses were performed by χ test. Macroscopic type, venous invasion, and lymphatic invasion are defined according to the Japanese classification of colorectal carcinoma.

significantly associated with recurrence in χ^2 tests and Fisher's exact probability test revealed that macroscopic type, venous invasion, serum CA19-9 levels, emergency operation, and postoperative ileus were independently associated with overall recurrence (Table II).

Prognosis after Surgery

The 5-year survival rate of all patients with stage II colon cancer was 83.7%. The overall 5-year survival rate according to clinicopathological categories is shown in Table III. Patients within the

TABLE II. Multivariate Regression Analysis for Overall Recurrence of Stage II Colon Cancer

		HR	95% CI	*P* value
1. Macroscopic type	Pushing vs. infiltrating	0.382	0.226–0.645	0.0003
2. Serum levels of CAI9–9	≤1× vs. >1×	2.313	1.438–3.721	0.0005
3. Venous invasion	Slight vs. extensive	1.847	1.204–2.834	0.005
4. Emergency operation	+ vs. −	2.856	1.206–6.764	0.017
5. Postoperative ileus	+ vs. −	2.354	1.143–4.848	0.020
6. Location	Colon:Rs	0.685	0.465–1.010	0.056
7. Serum levels of CEA	≤2× vs. >2×	1.404	0.927–2.127	0.11
8. Number of dissected LN	≤12 vs. >12	0.742	0.507–1.084	0.12
9. Histology	Well vs. poorly	1.679	0.572–4.931	0.35
10. Postoperative ChT	+ vs. −	1.046	0.733–1.493	0.80

HR, hazard ratio; CI, confidence interval; LN, lymph node; ChT, chemotherapy; Well, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Rs, rectosigmoid colon.

following groups had significantly worse prognosis based on the log rank test and/or generalized Wilcoxon test: >50 years old, males, tumor located in the rectosigmoid colon, macroscopic infiltration-type tumors, tumor circumference >80% of the intestinal circumference, T4 tumor, extensive lymphatic/venous invasion, ≤12 dissected LNs, 2-fold higher than normal serum CEA levels or high serum CA19-9 levels, emergency operation, and leakage. On the other hand, postoperative chemotherapy improved prognosis. Diameter, histology, perforation during surgery, preoperative ileus, and postoperative ileus were not significantly associated with overall survival. Multivariate Cox regression analysis of factors associated with prognosis on log rank tests and generalized Wilcoxon tests revealed that the serum CA19-9 levels, the number of dissected LNs, sex, age, emergency operation, venous invasion, and macroscopic type were independently associated with overall prognosis (Table IV). Postoperative chemotherapy was independently associated with improved prognosis.

Effects of ACT on Recurrence and Prognosis

The recurrence rate was significantly higher in patients who received ACT (16.5%) than in those who did not (11.9%) (Table I). Conversely, the 5-year survival rate was significantly better in patients who received with ACT (86.0%) than in those who did not (82.3%) (Table III). Furthermore, multivariate Cox regression analysis revealed that ACT was independently associated with overall prognosis in stage II colon cancer (Table IV).

There was no significant difference in the duration of ACT between patients with (12.0 ± 8.9 months) and without (12.0 ± 12.2 months) recurrent diseases. The disease-free time after surgery was 21.5 ± 24.0 months among patients who received ACT versus 16.1 ± 20.1 months in patients who did not. However, there was no significant difference in disease-free time between the two groups. The clinicopathological characteristics of patients with or without ACT are summarized in Table V. The frequencies of young patients, larger number of dissected LNs, preoperative ileus, and high serum levels of CEA and CA19-9 were significantly greater in patients who received ACT than in those who did not. Recurrence sites included the liver (49 patients), lung (21 patients), and local sites (15 patients) in 101 cases who received ACT, and in the liver (53 patients), lung (19 patients), and in local sites (14 patients) of 103 patients who did not receive ACT. There were no significant differences in the numbers of patients for each recurrent site between patients who did or did not receive ACT. Surgery for recurrent disease was performed in

TABLE III. Clinicopathologic Variables and Overall Survival of Stage II Colon Cancel

Variable	Category	*n*	5-year survival (%)	*P* value log rank/Wilcoxon
Age	<50	179	87.1	0.02/0.07
	>50	1296	83.3	
Sex	Men	881	81.5	0.004/0.002
	Women	595	87.1	
Location	Rs	1237	85.0	0.03/0.08
	Colon	238	79.0	
Macroscopic type	Pushing type	1333	85.7	0.07/0.01
	Infiltrating type	128	72.6	
Circumference	≥80%	685	81.1	0.03/0.03
	<80%	442	87.3	
Diameter (cm)	≤5	638	85.1	0.10/0.13
	>5	805	82.0	
Number of dissected LN	≤12	415	78.8	0.0001/0.001
	>12	963	85.6	
Histology	Well	1398	82.6	0.89/0.89
	Poorly	73	84.2	
Depth of invasion	<T3	1364	85.4	0.02/0.006
	T4	112	74.4	
Lymphatic invasion	Slight	1242	85.1	0.05/0.04
	Extensive	226	81.1	
Venous invasion	Slight	1230	85.4	0.01/0.01
	Extensive	237	80.7	
Serum levels of CEA	≤NL × 2	1053	85.3	0.005/0.002
	>NL × 2	243	76.0	
Serum levels of CAI 9-9	≤NL × 1	1107	85.3	0.0001/0.0001
	>NL × 1	124	69.5	
Emergency operation	+	31	59.0	0.002/0.0001
	−	1443	85.1	
Perforation during surgery	+	7	71.4	0.66/0.53
	−	1465	84.9	
Leakage	+	26	66.9	0.05/0.02
	−	1444	84.9	
Preoperative ileus	+	65	70.4	0.10/0.02
	−	1407	85.2	
Postoperative ileus	+	62	87.9	0.40/0.42
	−	1409	85.2	
Postoperative ChT	+	611	86.0	0.006/0.006
	−	864	82.3	

LN, lymph node; ChT, chemotherapy; Well, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Rs, rectosigmoid colon; NL, normal limit.
Macroscopic type, venous invasion, and lymphatic invasion are defined according to the Japanese classification of colorectal carcinoma.

TABLE IV. Multivariate Regression Analysis for Overall Survival of Stage II Colon Cancer

		HR	95% CI	*P* value
1. Serum CA19-9 levels	≤1× vs. >1×	2.029	1.437–2.864	0.0001
2. Number of dissected LNs	≤12 vs. >12	0.604	0.459–0.795	0.0003
3. Sex	Male vs. female	1.504	1.148–1.970	0.003
4 Age	≤50 vs. >50	2.173	1.281–3.687	0.004
5. Postoperative ChT	+ vs.−	0.682	0.523–0.891	0.005
6. Emergency operation	+ vs. −	2.626	1.296–5.323	0.007
7. Venous invasion	Slight vs. massive	1.444	1.068–1.953	0.017
8. Macroscopic type	Pushing vs. infiltrating	0.624	0.412–0.944	0.026
9. Serum levels of CEA	≤2× vs. >2×	1.342	0.995–1.809	0.054
10. Leakage	+ vs. −	1.878	0.918–3.845	0.08
11. Circumference	+ vs. −	1.234	0.856–1.779	0.24
12. Lymphatic invasion	Slight vs. Massive	1.216	0.862–1.715	0.27
13. Depth of invasion	−T3 vs. T4	0.822	0.536–1.261	0.37
14. Preoperative ileus	+ vs. −	1.297	0.668–2.518	0.44
15. Location	Colon vs. Rs	1.052	0.807–1.370	0.71

HR, hazard ratio; CI, confidence interval; LN, lymph node; ChT, chemotherapy; Rs, rectosigmoid colon.

TABLE V. Background of Patients With or Without Postoperative Chemotherapy

Variable	Category	With chemotherapy	Without chemotherapy	*P*
Age		63.0 ± 10.4	66.0 ± 11.8	0.0001
Location	Colon/Rs	511/100	726/138	0.84
Sex	Male/female	368/243	513/351	0.74
Histology	Well/poorly	582/29(0)	814/45 (5)	0.23
Macroscopic type	Pushing/infiltrating	549/56 (6)	783/72 (9)	0.34
Depth of invasion	<T3 T4	562/49	801/63	0.60
Lymphatic invasion	Slight/massive	518/87(6)	724/138(2)	0.61
Venous invasion	Slight/massive	229/423(5)	290/570(4)	0.12
Number of dissected LN		23.5 ± 18.3	20.9 ± 14.3	0.002
Serum levels of CEA	≤2/>2	414/108(89)	645/129(90)	0.004
Serum levels of CA19-9	≤1/>1	369/53(189)	636/71(157)	0.00001
Postoperative ileus	+/−	33/574(4)	29/834(1)	0.054
Emergency operation	+/−	14/586(1)	17/846 (1)	0.64
Diameter		15.5 ± 2.4	40.0 ± 2.4	0.57
Circumference	≥80%/<80%	200/297(114)	242/387(235)	0.051
Preoperative ileus	+/−	39/569(3)	25/838(1)	0.001
Leakage	+/−	9/597(5)	17/846(1)	0.48
Perforation during surgery	+/−	3/605(3)	4/859(1)	0.94

LN, lymph node; ChT, chemotherapy; Well, well-differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Rs, rectosigmoid colon. Numbers in parentheses represents the number of patients with unknown data.

56/101 patients (48.7%) who received ACT, and in 56/103 patients (44.4%) who did not receive ACT, which was not significantly different. Similarly, there were no significant differences in the frequency of surgery for recurrent disease for each recurrent site between patients who did or did not receive ACT. The 5-year survival rate of patients with recurrent diseases was 52.0% in patients who received ACT versus 42.9% in patients who did not receive ACT. There was no significant difference in the prognosis of patients with recurrent diseases between those who received ACT and those who did not. However, the 5-year survival rate of patients without recurrent diseases was 92.4% for those who received ACT versus 89.4% for patients who did not (log rank: $P = 0.003$; Wilcoxon $P = 0.005$). Regarding patients who were deemed to be at high risk of recurrence based on the predictive factors identified in Table II, there was no significant difference in the overall frequency of recurrence between patients who did or did not receive ACT. Comparisons of the prognosis between patients who did or did not receive ACT according to each independent prognostic factor (Table IV) are shown in Table VI. The prognosis was significantly better for patients who received ACT than for those who did not if they had extensive venous invasion, had ≤12 dissected LNs, were male patients or were >50 years old (Table VI). Survival curves according to the number of independent factors are shown in Figure 1. When the proximal colon was defined as sites between the cecum and transverse colon, the proximal colon was significantly more frequently involved in patients with one independent factor (45.5%) than in patients with more than one independent factor (34.1%; $P = 0.0001$). There were no significant differences in patient characteristics, except for the independent factors among the groups of patients. None of the patients had more than five independent prognostic factors. All of the patients without any of these independent prognostic factors survived for longer than 5 years. The 5-year survival rate was 88.6% in patients with one independent factor. Survival was significantly better in patients with no independent prognostic factors than in patients with one independent prognostic factor ($P = 0.036$). Prognosis worsened with increasing number of independent prognostic factors ($P = 0.008$ for 2 and 3 factors; $P = 0.007$ for 3 and 4 factors). The survival curves for patients who did or did not receive ACT

TABLE VI. Five-Year Survival Rate of Patients With or Without Postoperative Chemotherapy Among Patients the Poor Prognosis

	With ChT		Without ChT		
	N	5SR	N	5SR	*P*
Macroscopic type (infiltrating type)	56	76.2%	72	68.5%	0.42
Venous invasion (massive invasion)	90	83.5%	147	78.7%	0.038
Serum CA19-9 levels (<1)	53	72.9%	71	67.8%	0.57
Number of dissected LNs (≤12)	178	83.4%	237	75.2%	0.005
Emergency operation	14	72.2%	17	43.1%	0.21
Male	368	86.2%	513	77.5%	0.0001
Age >50 years	513	86.3%	783	81.4%	0.001

ChT, chemotherapy; 5SR, 5-yeasr survival rate; LN, lymph node.

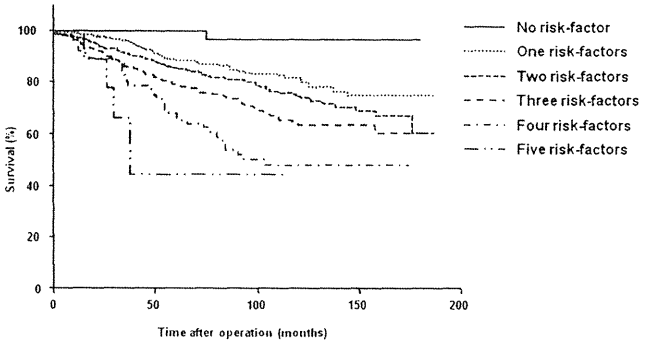

Fig. 1. The prognosis of stage II colon cancer worsened with increasing number of independent prognostic factors ($P = 0.036$ for 0 or 1 factors; $P = 0.008$ for 2 or 3 factors; $P = 0.007$ for 3 and 4 factors).

according to the number of independent prognostic factors are shown in Figure 2. Among patients with more than one independent prognostic factor, the 5-year survival rate was significantly better in patients who received ACT (86.1%) than in those who did not (78.0%) (Fig. 2). However, among patients with only one factor, the 5-year survival rate was significantly worse in those who received ACT (83.3%) than in those who did not (93.0%) (Fig. 2). Among patients with one prognostic factor, significantly more patients with high serum levels of CA19-9 received ACT than did not, although there were no significant differences in the characteristics between patients who received ACT and those who did not.

DISCUSSION

The recurrence rate of stage II colon cancer was reported to range from 7.9 to 22%, while the 5-year survival rate was reported to range from 75 to 92% [5,6,15]. In the present study, the corresponding rates were 13.8 and 83.7%, respectively. Clearly, patients with stage II colon cancer generally show a relatively low recurrence rate and good prognosis after surgery. However, some patients with stage II colon cancer do develop recurrence and a poor prognosis as frequently as that of stage III colon cancer, representing high-risk for recurrence and poor prognosis. The recurrence rate of Dukes C colon cancer was reported to be 24.3% [16], while the 5-year survival rate of Dukes C colon cancer in patients with fewer than four positive nodes was reported to be about 80% [17,18]. In the present study, macroscopic infiltrating-type tumors, high serum CA19-9 levels, extensive venous invasion, emergency operation, and postoperative ileus were independently associated with high risk of recurrence for stage II colon cancer. Meanwhile, high serum CA19-9 levels, ≤12 dissected LNs, males, >50 years old, emergency operation, extensive venous invasion, and macroscopic infiltrating-type tumors were independently associated with poor overall prognosis. The recurrence and 5-year survival rates of patients with these factors seemed to be

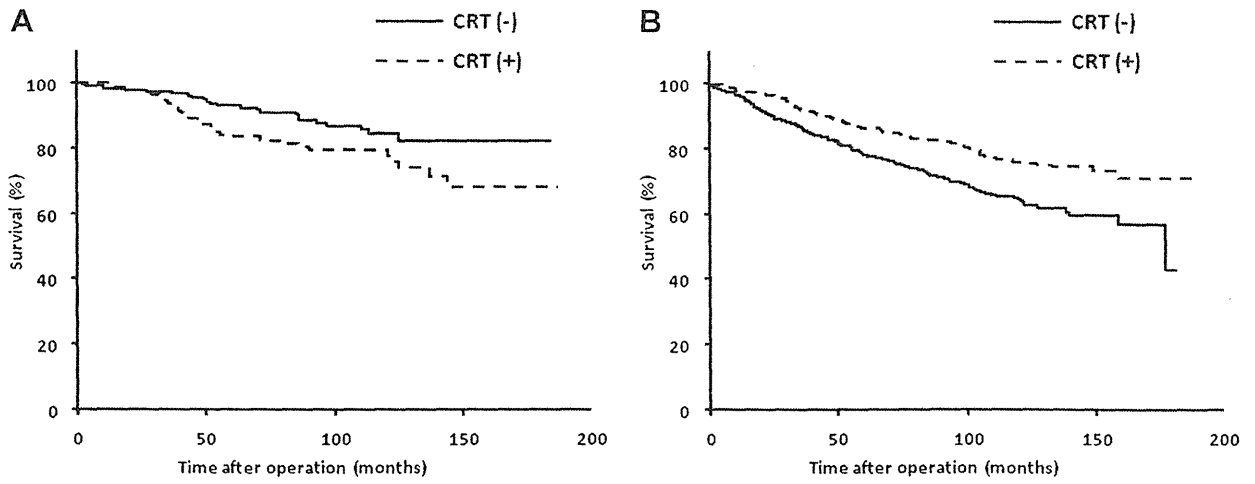

Fig. 2. (**A**) Among patients with only one independent prognostic factor, the 5-year survival rate was significantly worse in patients who received ACT (83.3%) than in those who did not receive ACT (93.0%). (**B**) Among patients with more than one independent prognostic factor, the 5-year survival was significantly better in patients who received ACT (86.1%) than in those who did not receive ACT (78.0%).

similar to or worse than those for stage III colon cancer. Therefore, patients with these factors were considered to have a high risk of recurrence and poor prognosis. On the other hand, all of the patients without any of these prognostic factors survived for longer than 5 years. Consequently, ACT is recommended for use in stage III colon cancer [7]. The results of our study also suggest that patients with stage II colon cancer at high of recurrence or poor prognosis can also be considered as candidates for ACT.

Postoperative ACT was independently and favorable associated with overall prognosis, suggesting that 5-FU-based postoperative ACT is an important approach that can improve the prognosis of stage II colon cancer. A survival benefit of FU-based ACT in stage II colon cancer was also reported by the Adjuvant Colon Cancer Endpoints (ACCENT) group with a similar follow-up duration to that in the present study [19]. However, ACT is not recommended for routine use in stage II colon cancer patients because the overall survival benefit of ACT has not been clearly demonstrated in stage II colon cancer [6,20]. The QUASAR Collaborative Group reported that chemotherapy with fluorouracil acid and folinic acid reduced the relative risk of recurrence for 2 years after surgery in patients with stage II colon cancer, although it did not improve prognosis [21]. ACT may be administered to patients with high-risk stage II colon cancer as well as stage III colon cancer. The ASCO and the NCCN guidelines recommend considering ACT for patients with stage II colon cancer patients and the presence of high-risk features, including T4 tumors leading to obstruction, perforation, and fewer than 12 LNs [8]. The National Surgical Adjuvant Breast and Bowel Project group revealed a survival benefit of ACT in stage II colon cancer in patients with poor prognosis, namely those with T4 tumor and those with obstruction or perforation [22]. However, T4 tumors were not independently associated with recurrence or prognosis in our study, although emergency operation for perforation or obstruction was a significant independent prognostic factor. The present study also revealed that ACT should be considered for stage II colon cancer in patients with macroscopic infiltrating-type tumors, high serum CA19-9 levels, extensive venous invasion, and postoperative ileus because of a high risk of recurrence. Furthermore, male patients, patients $\leq$50 years old, and those with $\leq$12 dissected LNs will also benefit from ACT because of the poor prognosis associated with these factors. Several other predictive factors have been proposed recently, including microsatellite instability (MSI), 18q deletions, k-ras mutations, TP53, and TS gene expression, of which MSI seems to be a particularly promising factor. Tumors with high MSI are associated with more favorable outcome while fluoropyrimidine-based chemotherapy seems to have limited efficacy and is sometimes detrimental in patients with such tumors [9].

The present study showed that the prognosis was significantly better in patients who received ACT than in those who did not. This was particularly true in patients without recurrent diseases, despite the high recurrence rate in patients who received ACT. The disease-free time was longer, the rate of surgery for recurrent disease was higher, and the survival of the patients with recurrence was better among those who received ACT than among those who did not, although these differences did not reach statistical significance. These results in patients with recurrent diseases, as well as the significantly better prognosis in patients who received ACT than in patients who did not receive ACT among those without recurrent diseases, could explain why the prognosis was significantly better in patients who received ACT, despite the higher recurrence rate in these patients. ACT was also independently associated with overall prognosis. ACT was more frequently administered to younger patients, patients with high serum levels of CEA and CA19-9, and patients with preoperative ileus, a group of patients representing high risk of recurrence and poor prognosis. This implies that ACT was administered in accordance with the correct criteria at each institute, and may also explain why recurrence was more common in patients who received ACT than in those who did not. On the other hand, there was no significant difference between patients who did or did not receive ACT in terms of the frequency of overall recurrence among patients considered to be at high risk of recurrence. Meanwhile, among patients considered to have a poor prognosis group, namely those with extensive venous invasion, $\leq$12 dissected LNs, males, and $>$ 50 years old, survival was significantly better in those who received ACT than in those who did not. Thus, ACT seemed to improve the prognosis of these patients with poor prognosis, particularly those with more than one of these prognostic factors. ACT also significantly improved the prognosis of patients with more than one of these independent prognostic factors. The reason why the prognosis was significantly worse in patients who received ACT than in those who did not for patients with only one of these independent prognostic factors is currently unclear. However, the proximal colon, in which high MSI is more common than in the distal colon, was significantly more frequently involved in patients with one independent prognostic factor than in patients with more than one factor. Furthermore, among patients with one factor, significantly more patients who received ACT than those who did not had high serum CA19-9 levels, another independent factor associated with poor prognosis. This may explain why the prognosis was significantly worse among patients with only one prognostic factor who received ACT than those who did not receive ACT. Based on these findings, it does not seem to be appropriate to administer ACT in patients with only one of these prognostic factors.

Oral 5-FU derivatives used in ACT, such as 5-FU, UFT, or 5'DFUR, were the most commonly used treatments for stage II colon cancer in Japan during the period studied. 5-FU- and leucovorin-based infusional regimens, such as FOLFOX4, mFOLFOX6, and FLOX, and other oral 5-FU derivatives such as capecitabine and UFT +Uzel, have been used in several studies that demonstrated the effectiveness of ACT in stage III colon cancer after curative resection [23–30]. The present study does not downplay the efficacy of all 5-FU-based regimens as ACT for treat stage II colon cancer. Rather, the results suggest that fluoropyrimidine-based ACT might be appropriate for patients with extensive venous invasion, patients with $\leq$12 dissected LNs, males, and patients $>$50 years old.

Overall, the results presented here suggest that factors concerned with recurrence and poor prognosis should be taken into account in the management of patients with stage II colon cancer after curative surgery. Large-scale randomized clinical trials are now required to provide definitive conclusions regarding the indications for ACT in stage II colon cancer.

REFERENCES

1. Jemal A, Tiwari RC, Murray T, Ghafoor A, et al.: Cancer statistics. CA Cancer J Clin 2004;54:8–29.
2. Kotake K, Honjo S, Sugihara K, et al.: Changes in colorectal cancer during a 20-year period: an extended report from the multi-institutional registry of large bowel cancer, Japan. Dis Colon Rectum 2003;46:32–43.
3. American Joint Committee on Cancer: AJCC cancer stageing manual, 6th edition. New York, USA: Springer; 2002. pp. 113–124.
4. Jessup JM, McGinnis LS, Steele GD Jr, et al.: The National Cancer Data Base. Report on colon cancer. Cancer 1996;78: 918–926.
5. Schrag D, Rifas-Shiman S, Saltz L, et al.: Adjuvant chemotherapy use for medicare beneficiaries with stage II colon cancer. J Clin Oncol 2002;19:3999–4005.
6. IMPACT B2: Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer trials investigators. J Clin Oncol 1999;17: 1356–1363.

7. Gill S, Loprinzi CL, Sargent DJ, et al.: Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer. J Clin Oncol 2004;22:1797–1806.
8. Benson AB 3rd, Schrag D, Somerfield MR, et al.: American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22: 3408–3419.
9. National Comprehensive Cancer Network. Engstrom PF, Arnoletti JP, Benson AB 3rd, et al.: NCCN clinical practice guidelines in oncology: colon cancer. V.3.2010. http://www.nccn.org/, 2010.
10. Japanese Society for Cancer of the Colon and Rectum: Japanese classification of colorectal carcinoma. Tokyo, Japan: Kanehara & Co., Ltd.; 1997.
11. Kodaira S, Kikuchi K, Yasutomi M, et al.: Postoperative adjuvant chemotherapy with mitomycin C and UFT for curatively resected rectal cancer. Results from the Cooperative Project No. 7 Group of the Japanese Foundation for Multidisciplinary Treatment of cancer. Int J Clin Oncol 1998;3:357–364.
12. Kato T, Ohashi Y, Nakazato H, et al.: Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial. Langenbeck's Arch Surg 2002;386:575–581.
13. Akasu T, Moriya Y, Yasuo O, et al.: Adjuvant chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicenter randomaized controlled trial. Jpn J Clin Oncol 2006;36:237–244.
14. Park IJ, Choi G, Lim KH, et al.: Different patterns of lymphatic spread of sigmoid, rectosigmoid, and rectal cancers. Ann Surg Oncol 2008;15:3478–3483.
15. Gertler R, Rosenberg R, Schuster T, et al.: Defining a high-risk subgroup with colon cancer stages I and II for possible adjuvant therapy. Eur J Cancer 2009;45:2992–2999.
16. Kobayashi H, Mochizuki H, Sugihara K, et al.: Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer: a multicenter study. Surgery 2007;141:67–75.
17. Wolmark N, Rockette H, Fisher B, et al.: The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from national surgical adjuvant breast and bowel project protocol C-03. J Clin Oncol 1993;11: 1879–1887.
18. Yano H, Saito Y, Kirihara Y, Takashima J: Tumor invasion of lymph node capsules in patients with Dukes C colorectal adenocarcinoma. Dis Colon Rectum 2006;49:1867–1877.
19. Sargent D, Sobrero A, Grothey A, et al.: Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2009;27:872–877.
20. Marsoni S: International Multicenter Pooled Analysis of Colon Cancer Trials Investigators. efficacy of adjuvant fluorouracil and leucovorin in stage B2 and C colon cancer. Semin Oncol 2001;28:14–19.
21. QUASAR Collaborative Group: Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomized study. Lancet 2007;370:2020–2029.
22. Mamounas E, Wieand S, Wolmark N, et al.: Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04). J Clin Oncol 1999;17:1349–1355.
23. Haller DG, Catalapo PJ, Macdonald JS, Mayer RJ: Phase III study of fluorouracil, leucovorin and levamisole in high risk stage II and III colon cancer: final report of intergroup 0089. J Clin Oncol 2005;23:8671–8678.
24. International multicentre pooled analysis of colon cancer trials (IMPACT): Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 1995;345:939–944.
25. Twelves C, Wong A, Nowacki MP, et al.: Capecitabine as adjuvant treatment for stage III colon cancer. N Eng J Med 2005;352:2696–2704.
26. Kuebler JP, Wieand HS, O'Connell MJ, et al.: Oxaliplatin combined with weekly bolus fliorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSAB P C-07. J Clin Oncol 2007;25:2198–2204.
27. Andre T, Boni C, Mounedji-Boudiaf L, et al.: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Eng J Med 2004;350:2343–2351.
28. de Gramont A, Boni C, Navarro M, et al.: Oxaliplatin/5-FU/LV in adjuvant colon cancer: updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of 6 years. J Clin Oncol 2007;25:18S, (suppl; abstr 4007).
29. Cheeseman SL, Joel SP, Chester JD, et al.: A "modified de Gramont" regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Brit J Cancer 2002;87:393–399.
30. Welles L, Hochster H, Ramanathan R, et al.: Preliminary results of a randomized study of safety and tolerability of three oxaliplatin-based regimens as first-line treatment for advanced colorectal cancer ("Tree" study). J Clin Oncol 2004;22:14S, (suppl; abstr 3537).

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SURGERY TODAY

Review Article

Laparoscopic Hepatectomy: A Systematic Review, Meta-Analysis, and Power Analysis

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Abstract

Purpose. A previous meta-analysis study demonstrated that bleeding and the duration of the hospital stay following laparoscopic hepatectomy (Lap) were significantly smaller and shorter, respectively, than for patients undergoing an open approach (Op). The aim of the present study was to re-evaluate perioperative variables and adverse outcomes in patients undergoing Lap versus (vs) Op after 2000.

Methods. A PubMed and Ovid Medline search identified clinical studies that compared the outcomes of Lap vs Op patients after 2000. A meta-analysis and power analysis were performed.

Results. Operative time was not significantly different between the two approaches (95% confidence interval [CI]: −0.063 to 0.992). Patient bleeding in the Lap group was significantly lower than in the Op group (95% CI: −1.027 to −0.390). Complications with Lap patients were significantly less frequent (95% CI: 0.231–0.642), and the duration of the hospital stay for Lap patients was significantly shorter (95% CI: −0.950 to −0.530) than for Op patients. Only one paper presented 80% power with 0.05 α-errors in all four outcomes, whereas four studies did not have sufficient statistical power.

Conclusions. The clinical benefits of Lap include a smaller incidence of complications and a shorter duration of hospital stay at the current time. Several studies had too few cases to sufficiently evaluate these factors, although other studies were appropriately analyzed.

Key words Laparoscopy · Liver resection · Operative time · Bleeding · Complication · Hospital stay

Introduction

Laparoscopic hepatectomy (Lap) was first reported in 1991 for the treatment of patients who have benign liver tumors in gynecologic laparoscopic surgery.[1] Since then, a pure laparoscopic approach[2–4] and hand-assisted approach[5–7] for liver resection have been developed.[8,9] Lap is ideal for patients who elect for hepatectomy because of a lower degree of invasiveness when oncological curability and perioperative safety are obtained.[9–11] However, it is difficult to guarantee both oncological safety and perioperative safety in cases with tumors located near the inferior vena cava, regardless of tumor size. Therefore, the indication for Lap is generally limited to patients in whom the tumor lies on the peripheral surface of the liver at segment (S) 3, S4, S5, or S6.[10] Conversely, recent reports have shown that even major hepatectomy can be performed using Lap.[3,12,13] Although it cannot be employed for all liver tumors, assisted-approach Lap has been widely conducted to reduce surgical stress compared to the open approach (Op).[8]

A previous meta-analysis demonstrated that operative blood loss and the duration of the hospital stay for Lap patients were significantly lower and shorter, respectively, than for Op patients.[11] Recent reports have also demonstrated that new surgical devices for liver resection might help to reduce blood loss, the duration of the hospital stay, and the total hospital fees incurred.[14] Even in our institution, the surgical devices used for liver resection in recent years are completely different from those used 10 years ago.[15] Therefore, it may be difficult to compare recent reports and older reports published more than a decade ago. The aim of the present study was to reevaluate the perioperative variables and adverse outcomes in patients undergoing Lap vs Op since 2000.

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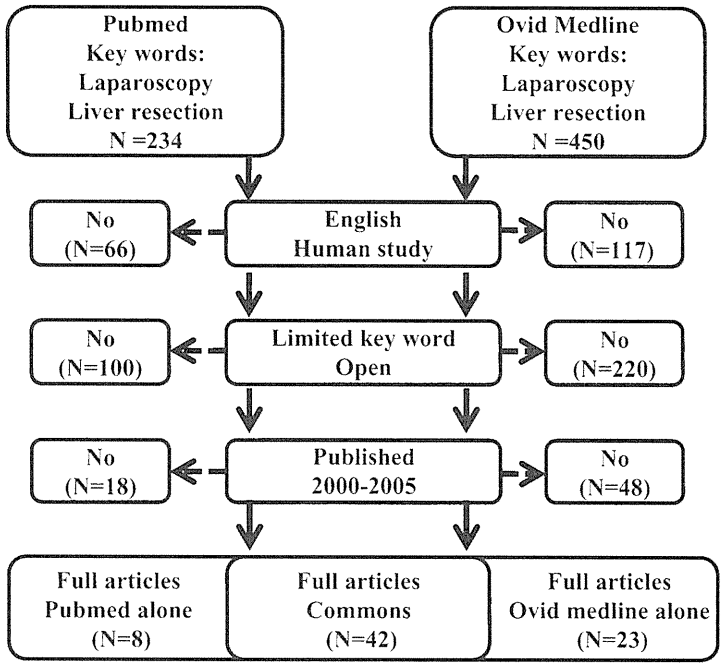

Excluded as:			
Review	2	4	
Case report	1	1	2
Video		1	1
Other disease	2	4	7
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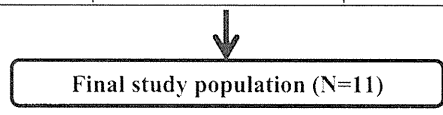


Fig. 1. Flow chart of search history. PubMed and Ovid Medline searches were conducted. A total of 11 studies were extracted according to our inclusion and exclusion criteria

Patients and Methods

Study Selection

A search of all the published comparative studies on Lap, including assisted techniques, vs Op for the resection of malignant tumors, was carried out with PubMed and Ovid Medline. Publications from 1965 to March 2009 were reviewed, and the following "MeSH" search headings were used: "laparoscopy" and "liver resection." No English studies or human studies were excluded. The further search heading "open" was used, and all publications from 2000 and later were included. The study selection is shown in Fig. 1. A total of 11 studies was analyzed based on our selection criteria. Among these 11 studies, 6[16–21] duplicated the previously published study of Simillis et al.[11] Four studies were published after 2005.[14,22–24]

Data Extraction

Two reviewers (T.M. and M.K.) independently extracted the following parameters from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, matching criteria, and the number of subjects operated on with each technique. There was 100% agreement between the two reviewers.

Inclusion Criteria

To be included in the analyses, each study had to: (1) compare Lap and Op for malignant tumors; (2) be a clinical study; (3) clearly report the indications for surgery; (4) be written in English; (5) be published in 2000 or later.

Table 1. Studies included in this review

No.	First author[Ref.]	Journal	Study design	Year
1	Shimada[28]	Surg Endosc	Retrospective cohort	2001
2	Farges[17]	J HPB Surg	Prospective cohort	2002
3	Mala[16]	Surg Endosc	Retrospective cohort	2002
4	Lesurtel[20]	J Am Coll Surg	Prospective case control	2003
5	Laurent[19]	Arch Surg	Prospective case control	2003
6	Morino[18]	Surg Endosc	Retrospective case control	2003
7	Kaneko[21]	Am J Surg	Retrospective case control	2005
8	Belli[22]	Surg Endosc	Retrospective case control	2007
9	Aldrighetti[24]	J Gastrointest Surg	Prospective case control	2008
10	Troisi[25]	Surg Endosc	Retrospective case control	2008
11	Polignano[14]	Surg Endosc	Prospective case control	2008

Exclusion Criteria

Studies were excluded from the analysis if: (1) the outcomes of interest were not clearly reported; (2) it was impossible to extract or calculate the appropriate data from the published results; (3) there was considerable overlap between authors, centers, or patient cohorts evaluated in the published literature, including review articles; (4) resections were carried out only for the purpose of cyst excision, biopsy, or benign tumors.

Outcomes of Interest and Definitions

The following outcomes were used to compare patients undergoing Lap with those undergoing Op: operative time, operative blood loss, postoperative complications, and duration of hospital stay.

Statistical Analysis

The meta-analysis was carried out using the MedCalc software package (version 8.0.1.0; MedCalc, Mariakerke, Belgium), and a comprehensive meta-analysis software package (Biostat, Englewood, NJ, USA). The power analysis was carried out using the Power and precision V3 software package (Biostat).

The statistical analyses of dichotomous variables were carried out using the odds ratio (OR) as the summary statistic, and continuous variables were analyzed using the standardized mean difference (SMD); both were reported with 95% confidence intervals (CIs). The odds ratios represent the odds of an adverse event occurring in the Lap group compared with the Op group, whereas the SMDs summarize the differences between the two groups with respect to continuous variables, accounting for sample size. For studies that presented continuous data as means and range values, the standard deviations (SDs) were calculated. The Mantel–Haenszel method was used to combine the OR for the outcomes of interest by using the "random effect" meta-analytical technique. Heterogeneity was assessed by graphic exploration, and funnel plots were used to evaluate any publication bias. A power analysis for a test of the null hypothesis was performed using the Power and Precision statistical software package (Biostat). For each study, the null hypothesis that the proportion positive was identical in the two populations was tested. The criterion for significance (α) was set to 0.05. The test was two-tailed, which meant that an effect in either direction was interpreted. The power of each study was calculated by the number of proposed study groups.

Results

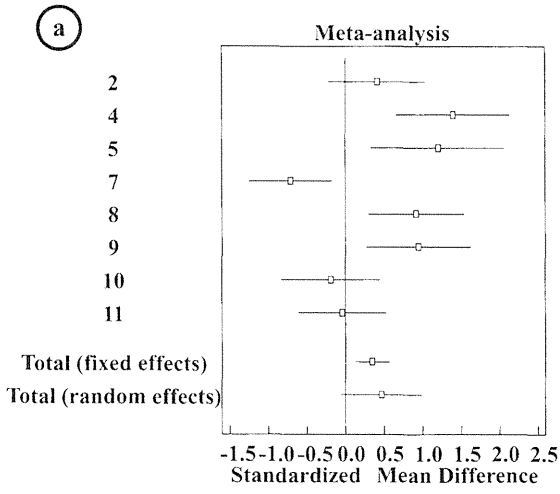
We reviewed Lap studies published since 2000 as described in Patients and Methods (Fig. 1). A total of 11 studies were analyzed (Table 1), all of which described the differences between Lap and Op patients and provided data with means and standard deviations.

Meta-Analysis of Operative Variables

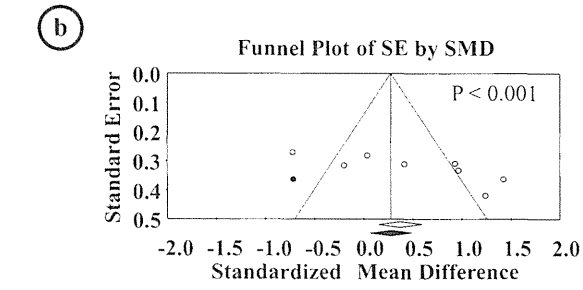
Eight studies reported on the operative time, which was not found to be significantly different (SMD: 0.464; 95% CI: –0.063 to 0.992) between the two groups (Fig. 2a: $P = 0.072$). The funnel plot of the test for heterogeneity was significantly different ($P < 0.001$) for this result (Fig. 2b). Nine studies reported on bleeding during surgery, which was found to be significantly lower (SMD: –0.709; 95% CI: –1.027 to –0.390) in the Lap group than in the Op group (Fig. 3a: $P < 0.001$). However, the funnel plot of the test for heterogeneity was significantly different for this result (Fig. 3b: $P = 0.019$).

Meta-Analysis of Postoperative Variables

All 11 studies reported on postoperative complications, which were found to be significantly less frequent (odds ratio: 0.385; 95% CI: 0.231–0.642) in the Lap group than in the Op group (Fig. 4a: $P < 0.001$). The funnel plot of



Study	Lap	Op	Total	SMD	95% CI	P-value
2	21	21	42	0.412	-0.219 to 1.043	0.179
4	18	20	38	1.397	0.654 to 2.140	< 0.001
5	13	14	27	1.204	0.331 to 2.077	0.003
7	30	28	58	-0.709	-1.253 to -0.165	0.007
8	23	23	46	0.919	0.291 to 1.546	0.001
9	20	20	40	0.951	0.272 to 1.630	0.002
10	20	20	40	-0.191	-0.833 to 0.451	0.539
11	25	25	50	-0.0414	-0.610 to 0.527	0.882
Total (fixed effects)	170	171	341	0.347	0.125 to 0.569	0.001
Total (random effects)	170	171	341	0.464	-0.063 to 0.992	0.072



Study	Lap (mean ± SD: m.)	Op (mean ± SD: m.)
2	177 ± 57	156 ± 42
4	202 ± 48	145 ± 31
5	267 ± 79	182 ± 57
7	182 ± 38	210 ± 40
8	148 ± 29.73	125.21 ± 17.48
9	260 ± 50	220 ± 30
10	220.25 ± 122.28	241.8 ± 97.7
11	362 ± 113	366 ± 73

Fig. 2. **a** Annotated forest plot for the meta-analysis of operative time for laparoscopic hepatectomy (*Lap*) versus open approach (*Op*). **b** Annotated funnel plot of standard error (*SE*) by standardized mean difference (*SMD*) for the meta-analysis of operative time for Lap vs Op. *Open circles*, original data; *closed circles*, imputed values. The *diamonds* at the bottom show the overall means with a 95% confidence interval (CI) of SMDs. The *open diamond* represents original data points and the *closed diamond* represents imputed values. *P* values were calculated by test for heterogeneity. *m*, minutes

the test for heterogeneity did not show a significant difference ($P = 0.923$) for this result (Fig. 4b). Nine studies reported on the duration of the hospital stay, which was found to be significantly shorter (SMD: –0.740; 95% CI: –0.950 to –0.530) in the Lap group than in the Op group (Fig. 5a: $P < 0.001$). Furthermore, the funnel plot of the test for heterogeneity was not significantly different ($P = 0.439$) for this finding (Fig. 5b).

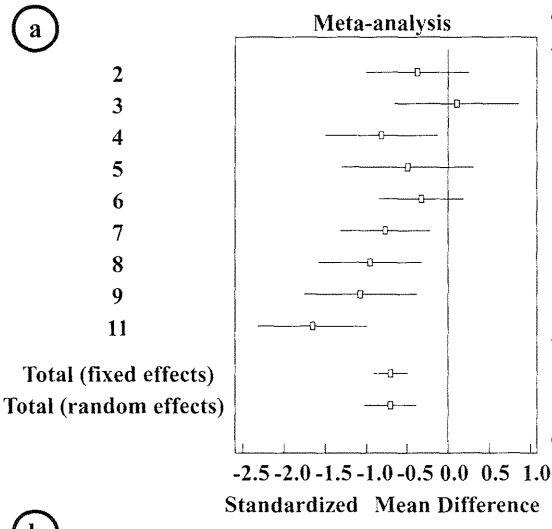
Power Analysis for 0.05 α Error

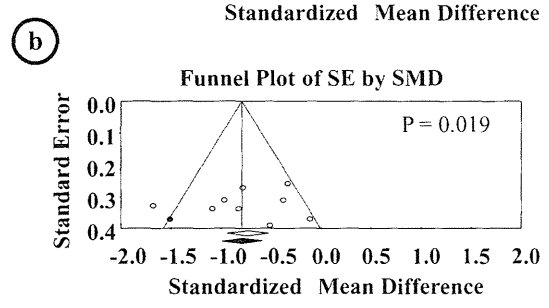
Data were re-evaluated by a power analysis in conditions with a 0.05 α error (Table 2). The power of each study was calculated and the number required for each study to satisfy an 80% power was estimated. Four studies demonstrated a power of 80% or less for all of their results (Nos. 1, 3, 6, and 10). Three studies satisfied 80% power in one of their findings (Nos. 2, 4, and 11). Three studies satisfied 80% power in two of their results (Nos. 5 and 7). Only one study showed more than 80% power for all of its results (No. 8).

Discussion

We reviewed the Lap studies published since 2000 and evaluated them using both a meta-analysis and a power analysis. Although the analyses of operative time and intraoperative bleeding did not indicate agreement concerning the superiority of either technique, there were fewer postoperative complications in the Lap patients than in the Op patients, and the duration of the hospital stay in the Lap group was shorter than in the Op group. The power analyses indicated that several studies might have had an insufficient number of patients to reach their conclusions.

In general, the clinical merits of the Lap approach compared to the Op approach include less intraoperative bleeding, a lower requirement for postoperative pain control, faster recovery, and shorter hospital stay.[9] However, the clinical outcomes of Lap studies varied greatly, depending on the institution and the time they were published. Because the Lap technique is now rapidly progressing and the outcome may also be





Study	Lap	Op	Total	SMD	95% CI	P-value
2	21	21	42	-0.375	-1.004 to 0.255	0.220
3	15	14	29	0.108	-0.655 to 0.871	0.765
4	18	20	38	-0.809	-1.498 to -0.121	0.015
5	13	14	27	-0.497	-1.304 to 0.310	0.190
6	30	30	60	-0.330	-0.851 to 0.191	0.198
7	30	28	58	-0.771	-1.318 to -0.224	0.004
8	23	23	46	-0.951	-1.581 to -0.321	0.002
9	20	20	40	-1.066	-1.755 to -0.377	0.001
11	25	25	50	-1.652	-2.318 to -0.986	< 0.001
Total (fixed effects)	195	195	390	-0.704	-0.912 to -0.495	< 0.001
Total (random effects)	195	195	390	-0.709	-1.027 to -0.390	< 0.001

Study	Lap (mean ± SD: ml)	Op (mean ± SD: ml)
2	218 ± 173	285 ± 178
3	600 ± 850	500 ± 950
4	236 ± 155	429 ± 286
5	620 ± 130	182 ± 57
6	320 ± 387	479 ± 550
7	350 ± 505	505 ± 185
8	260 ± 127	376.95 ± 114.32
9	165 ± 43	214 ± 47
11	135 ± 84	420 ± 225

Fig. 3. **a** Annotated forest plot for the meta-analysis of intraoperative bleeding for Lap vs Op. **b** Annotated funnel plot of SE by SMD for the meta-analysis of intraoperative bleeding in Lap vs Op. *Open circles*, original data; *closed circles*, imputed values. The *diamonds* at the bottom show the overall mean with a 95% CI of the SMDs. The *open diamond* represents original data and the *closed diamond* represents imputed values. *P* values were calculated by test for heterogeneity

improving daily, we evaluated those Lap studies that compared the Op techniques for malignant tumors that were published since 2000.

Operative Time

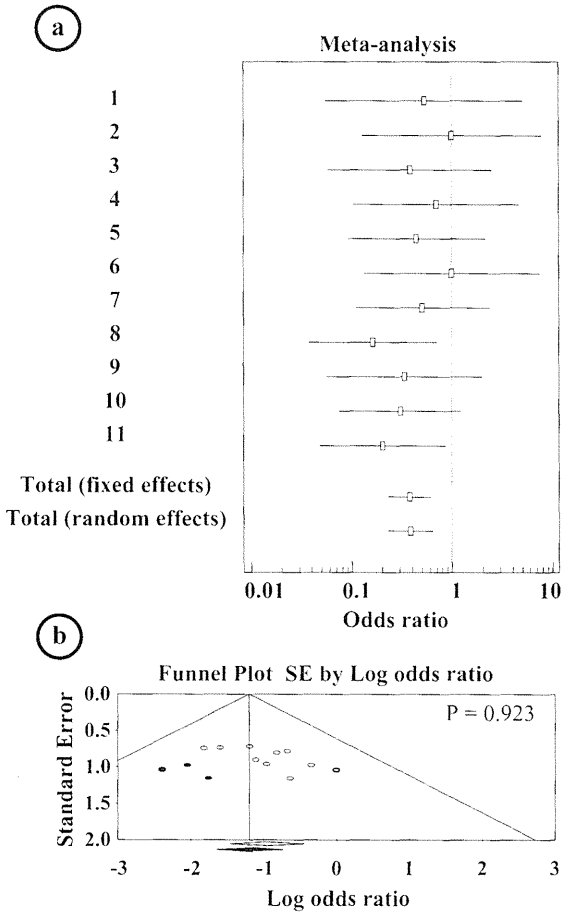
The operative time for the Lap technique appeared to be longer than for the Op technique.[19,20,22,24] The tight surgical field and small surgical instruments in the Lap group caused a longer operative time. The lack of a standard technique in the Lap group led surgeons to devote more of their efforts to each operative step than for the Op group. In addition, a history of previous surgery may have caused surgeons to divide adhesion for a longer time in the Lap approach compared to the Op approach.[25] The overall operative time in the Lap group could be shortened in proportion to which the Lap technique becomes the predominant procedure in the future. Further prospective studies should be conducted to determine whether the operative time for Lap could be shorter than for Op in the coming years.

Bleeding

Bleeding in patients who have undergone the Lap technique can be lower than for the Op technique. All recent studies after 2004 reported less bleeding in the patients who underwent Lap.[14,21–24] Therefore, bleeding control in the Lap group could be established as a result of recent technical progress. The high magnification of the image on the monitor can reveal fine ductal structures during parenchymal dissection. In addition, magnified bleeding motivates surgeons to control bleeding, even when present as a small amount compared to patients who have undergone Op. Furthermore, various surgical devices used to obtain hemostasis and vessel sealing could help control bleeding.[26,27] Although the test for heterogeneity is significantly different for bleeding at this time, additional studies may prove whether Lap or Op is superior for controlling bleeding in the future.

Postoperative Complications

There were significantly fewer postoperative complications in the Lap group than in the Op group without



Study	Lap	Op	Odds	95% CI	P-value
1	1/17	4/38	0.531	0.054 to 5.145	0.585
2	2/21	2/21	1.000	0.127 to 7.851	1
3	2/15	4/14	0.385	0.058 to 2.538	0.321
4	2/18	3/20	0.524	0.131 to 2.096	0.361
5	4/13	7/14	0.034	0.003 to 0.359	0.005
6	2/30	2/30	1.000	0.131 to 7.605	1
7	3/30	5/28	0.511	0.110 to 2.374	0.392
8	3/23	11/23	0.098	0.025 to 0.382	0.001
9	2/20	5/20	0.333	0.056 to 1.971	0.226
10	4/20	9/20	0.306	0.074 to 1.246	0.098
11	3/25	10/25	0.205	0.048 to 0.870	0.032
Total (fixed effects)	28/232	62/253	0.381	0.230 to 0.629	< 0.001
Total (random effects)	28/232	62/253	0.385	0.231 to 0.642	< 0.001

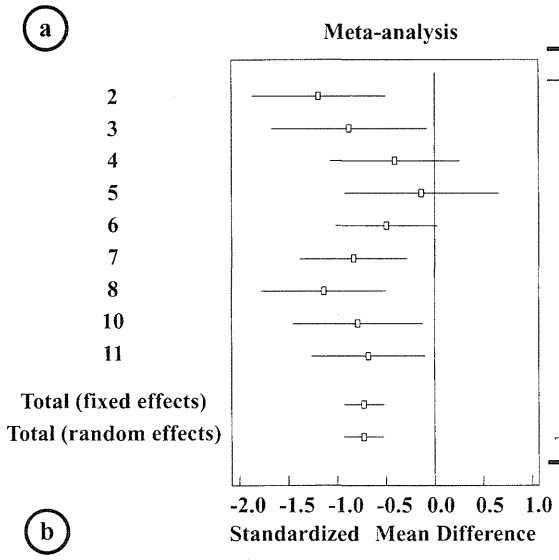
Fig. 4. **a** Annotated forest plot for the meta-analysis of postoperative complications for Lap vs Op. **b** Annotated funnel plot of SE by SMD for the meta-analysis of postoperative complication for Lap vs Op (b). *Open circles*, original data; *closed circles*, imputed values. The *diamonds* at the bottom show the overall mean with a 95% CI of the SMDs. The *open diamond* represents original data and the *closed diamond* represents imputed values. *P* values were calculated by test for heterogeneity

Table 2. Power analysis of the studies

No.	First author[Ref.]	Numbers		Power of the study (%)				Required *n* for 80% power			
		Lap *n*	Op *n*	Ope T	Bleeding	Comp	Hosp S	Ope T	Bleeding	Comp	Hosp S
1	Shimada[28]	17	38	—	—	9.3	—	—	—	488	—
2	Farges[17]	21	21	26.4	22.7	5	96.8	91	109	X	OK
3	Mala[16]	15	14	—	6	18	64.5	—	1277	101	22
4	Lesurtel[20]	18	20	99	69.7	14.9	23.7	OK	24	174	90
5	Laurent[19]	13	14	87.2	24.9	96.1	6.3	OK	60	OK	848
6	Morino[18]	30	30	—	24.7	5	47.8	—	142	X	66
7	Kaneko[21]	30	28	76.6	83.2	14	88.2	32	OK	295	OK
8	Belli[22]	23	23	87.3	89.5	96.7	96.7	OK	OK	OK	OK
9	Aldrighetti[24]	20	20	84.8	91.8	23.4	—	OK	OK	100	—
10	Troisi[23]	20	20	9.2	—	38.9	71.2	418	—	54	25
11	Polignano[14]	25	25	5.2	99.9	62.3	66.8	8880	OK	38	34

α error = 0.05

Lap, laparoscopic hepatectomy; Op, open hepatectomy; Ope T, operation time; Comp, complication; Hosp S, hospital stay; X, the required number cannot be obtained due to infinity; OK, there was a sufficient number to analyze each endpoint



Study	Lap	Op	SMD	95% CI	P-value
2	5.1 ± 1.3	6.5 ± 1.0	-1.207	-1.865 to -0.550	< 0.001
3	4.0 ± 1.8	8.5 ± 7.0	-0.897	-1.661 to -0.133	0.021
4	8.0 ± 3.0	10.0 ± 6.0	-0.415	-1.058 to 0.229	0.207
5	15.3 ± 8.6	17.3 ± 18.9	-0.134	-0.890 to 0.621	0.727
6	6.4 ± 4.5	8.7 ± 4.8	-0.497	-1.011 to 0.017	0.058
7	14.9 ± 7.1	21.6 ± 8.8	-0.841	-1.378 to -0.304	0.002
8	8.2 ± 2.6	12.0 ± 3.9	-1.152	-1.777 to -0.528	<0.001
10	7.1 ± 4.4	10.5 ± 3.9	-0.804	-1.448 to -0.160	0.014
11	6.2 ± 3.0	9.7 ± 6.5	-0.691	-1.262 to -0.121	0.018
Total (fixed effects)			-0.740	-0.946 to -0.534	< 0.001
Total (random effects)			-0.740	-0.950 to -0.530	< 0.001

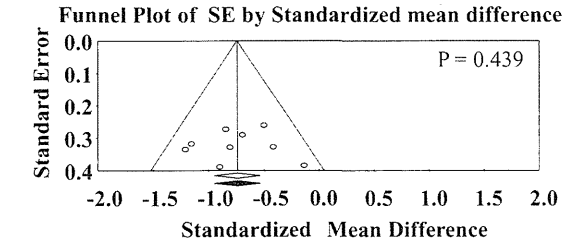


Fig. 5. **a** Annotated forest plot for the meta-analysis of duration of hospital stay for Lap vs Op. **b** Annotated funnel plot of SE by SMD for the meta-analysis of the duration of hospital stay for Lap vs Op. *Open circles*, original data; *closed circles*, imputed values. The *diamonds* at the bottom show the overall mean with a 95% CI of the SMDs. The *open diamond* represents original data and the *closed diamond* represents imputed values. *P* values were calculated by test for heterogeneity

heterogeneity, although only 3 of the 11 studies supported these results. The range of morbidity was between 6.7%[18] and 47.8%[22] for Op, and was between 5.9%[28] and 34.2%[19] for Lap. Although the different morbidities may represent institutional superiority in technical and empirical considerations, these rates may represent various inclusion criteria for complications in each institution. Most reports did not provide a clear definition of these complications. Another reason could be the heterogeneity of the patients, even though hepatectomy was conducted for patients with malignant tumors. The pathological background may differ regardless of etiology, even in hepatocellular carcinoma patients who have cirrhosis or simple chronic hepatitis. This would give varying morbidities among the patients. We conclude that complications with Lap appear to be fewer in number than Op. However, common criteria for postoperative complications should be selected,[29,30] and homogeneous patients should therefore be recruited in future studies.

Hospital Stay

The postoperative hospital stay after Lap appeared to be shorter than after Op in the present meta-analyses. This may reflect the lower morbidity of the Lap procedure. Although surgical stress was not evaluated in any of the studies, it appears that a lower level of surgical stress helped the Lap patients to recover faster than the Op patients. For example, the postoperative wound pain in Lap patients may be lower than in the Op patients, and may be associated with wound length. In addition, bowel movements in patients following Lap appeared to be recovered faster than in Op patients, due to a shorter exposure time of the intestine and colon to open air. Several reports have noted that oral intake after Lap occurred faster than after Op.[21,23] A clinical interpretation of the these results is difficult at the current time because the studies were based on a retrospective or case–control analysis. However, the postoperative hospital stay for the patients who successfully underwent Lap surgery was significantly shorter than for those who underwent Op surgery within the last decade.

Bias Affecting the Results and Conclusion

Although the present study focused on papers published since 2000, techniques for liver parenchymal tran-

section could affect the results and conclusions. In the Cochrane review,[27] the clamp-crush technique is considered to be the best technique because it avoids the need for special equipment. However, the newer methods do not appear to offer any additional benefits in decreasing the morbidity or transfusion requirement. In Op patients, intraoperative bleeding can be controlled by vascular exclusion,[31,32] including the Pringle maneuver or manual compression of the parenchyma. However, it is more difficult to control bleeding in Lap patients because a hand cannot be used to assist hemostasis. Therefore, several hemostatic surgical devices should be used for Lap.[33] The endoscopic clamp method was used in the initial Lap reports, but hemostatic devices such as a bipolar electrocoagulator, LigaSure (Valleylab Tyco Healthcare, Boulder, CO, USA), Harmonic Scalpel (Ethicon, Cincinnati, OH, USA), SonoSurg (Olympus, Tokyo, Japan), Floating ball (Salient Surgical Tech, Portsmouth, NH, USA), Sealing hook (Salient Surgical Tech), and an argon beam coagulator have also been used.[26] Coaptive coagulation uses a low temperature (50–100°C) to denature proteins in the tissues, forming a hemostatic protein coagulum that seals vessels and bile ducts.[34] Therefore, various surgical devices and techniques were used in the studies according to the historical background. Even though the superiority between these particular devices has not yet been proven, a surgical device bias could not be eliminated in the present meta-analysis. A learning bias may have also played a role. It takes a certain amount of time and a sufficient number of cases to learn all of the new surgical techniques, including the use of surgical devices.[21,35] Learning bias is inevitable in a retrospective study; therefore, a prospective study is required in the future.

Oncological Aspects

Care should be taken to decide the indications for Lap in the case of malignant tumors. The oncological outcome should be confirmed before employing Lap for all patients with malignant tumors. The surgical margin is considered to be one of the prognostic factors for patients with metastatic liver tumors arising from primary colorectal cancers,[36,37] and it can be significantly more difficult to secure the surgical margin using Lap than using Op.[17] However, most studies using the Lap approach showed no significant differences of surgical margin or postoperative survival between the two procedures.[8,17–19] Furthermore, no port metastases after Lap hepatectomy have been reported,[16,21,35] and the incidence of recurrence after Lap should be the same as for Op.[38] R0 resection is the ideal surgery for malignant tumors, but the use of R1 resection of metastatic liver tumors in a study using Op for the treatment of patients with colorectal metastatic tumors revealed no survival differences or disease-free differences.[39] Furthermore, the surgical margin of hepatocellular carcinomas remains controversial. Although anatomical resection showed prognostic merit,[40] a minimal surgical margin had no different prognostic impact compared to a wide surgical margin.[41,42] One possible reason for the lack of a survival difference between R0 resection and R1 resection for metastatic tumors could be the improvement of postoperative adjuvant therapies.[39] Another reason may be the enhanced in situ surgical margin, or the so-called heat-zone effect, after using thermoablation devices.[43] In the present case, the pathological surgical margin did not represent the actual in situ surgical margin. Recent surgical devices for hemostasis may help to secure the in situ surgical margin in Lap patients. Long-term prospective comparative studies of the oncological aspects of Lap should be conducted in the future.

Study Design

Clinical studies should be assessed for the methodological quality.[44] Retrospective case–control studies should not report the favorable experiences alone. An appropriate number of patients should be recruited to obtain a sufficient statistical power. However, the outcomes of several studies were on the borderline of reaching sufficient power. Most of the studies were short by 10 cases or fewer. A power analysis should therefore be considered to confirm any conclusions before publishing or presenting results. If no result reaches 80% power in a study, it must be concluded that it is an insufficient study. Even in retrospective studies, the power of the results should be ensured.

In conclusion, we reviewed recent studies since 2000 that compared the Lap approach to the Op approach. Although the meta-analysis contains many biases, the Lap approach appears to have less patient morbidity and a shorter hospital stay compared to the Op approach. Because of rapid technological progression, firm conclusions regarding the operating time and bleeding could not be reached in the current analyses. Further prospective studies are needed to clarify the superiority of each approach in the future. Even in retrospective and case control studies, the power of the results must be considered before reaching any conclusions.

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References

1. Reich H, McGlynn F, DeCaprio J, Budin R. Laparoscopic excision of benign liver lesions. Obstet Gynecol 1991;78:956–8.