表1　欧米におけるNET肝転移に対する肝移植の適応基準

Milanクライテリア2007	ENETSガイドライン2012
1. 症状に関係なくKi67が低い腫瘍が病理学的に確認されている	1. 高分化型NET，Ki67が10%以下
2. 主腫瘍が門脈系をドレナージ静脈とする膵臓か消化管由来	2. 6ヵ月以上前に主腫瘍を切除
3. 肝の50%以下の占拠率	3. 肝の50%以下の占拠率，あるいは治療抵抗性のホルモン症状を持つ場合には75%以下の占拠率
4. 移植前6ヵ月以上の腫瘍状態の安定	4. 移植前6ヵ月以上の腫瘍状態の安定
5. 55歳以下	5. 55歳以下
	6. 瀰漫性の切除不能腫瘍であるが肝に限局

肝移植の成績を報告した。それによると周術期死亡率が10%，3ヵ月以内死亡率の危険因子は早期の再移植，upper abdominal exenteration（UAE，多臓器移植や膵頭十二指腸切除と肝移植の同時施行などの上腹部の大手術），脾摘，長時間手術，付加手術（原発巣切除など）であった。一方，5年生存率は52%，生存期間中央値は67ヵ月，無再発生存期間中央値は24ヵ月で5年無再発生存率は30%であった。この成績は，UNOSのデータベース解析での報告[25]と同程度の成績であり，また，UNOSのHCC 4,693例の5年生存率58%に匹敵する結果である。一般的にNET肝転移症例の5年生存率は著名に改善しており，いくつかの施設では5年生存率は50%を超えている。しかしながら，肝移植は一般的にその他の治療が無効になった後に行われることを考えるとNETに対する肝移植成績は良好といえよう。長期予後不良因子は肝腫大，45歳以上，付加手術（移植術以外の）であり，この因子を持っているか一つのみの集団は5年生存率が79%，5年無再発生存率が57%であった。一方，Mazzaferroら[26]は肝転移に対するミラノ基準として表1に示すように低悪性度，門脈系によってドレナージされる原発腫瘍，50%以下の肝占拠率，6ヵ月以上の病勢コントロール，55歳以下，と移植適応を厳格化し，5年生存率90%，5年無再発生存率77%の成績を報告している。同様の適応基準を先ほどの2000年以後のELTRの登録症例に当てはめると106例中38例の症例に当てはまり，5年生存率が79%，5年無再発生存率が51%となり，適応を厳格化することで良好な成績が期待できる。ENETSガイドラインでも近い基準を推奨している（表1右）。

一方，これらの報告は脳死肝移植が発達している欧米での現状と考え方である。本邦の肝移植の現状は脳死肝移植が年間30～60例と少なく，通常の肝疾患に対して明らかに成績不良のNET肝転移症例に脳死ドナーからの肝臓提供は困難であると考えられる。一方，生体肝移植は健康なドナーにリスクを与えて行う以上，それに見合う高い成功率が求められる。現在京都大学では同様に悪性腫瘍であるHCCに対しては5年生存率80%，再発率10%以下の予測を満たす基準を採用している[27]が，膵NET肝転移に対してもそれに相当する基準を目指す必要がある。加えて明確なエビデンスが確定していないことから保険適応ではなく，治療は自費診療に限定される。以上から現状では本邦においてはNET肝転移に対する肝移植術はきわめて限定された症例にのみ適応となると考えられる。

V．薬物療法

近年，分子標的薬が膵NETに対して保険認可され，肝転移症例においても使用されるようになってきた。ENETSガイドラインでは瀰漫性転移の場合に適応とされ，本邦のガイドラインでもエベロリムス，スニチニブが推奨されている。エベロリムスは細胞の増殖，代謝を制御するPI3キナーゼ/AKTの下流に位置するmTOR酵素[28]の阻害剤であり，内因性にmTOR阻害作用をもつTSC2が膵NETにおいて遺伝子異常を持つことから開発された[29]。第3相試験であるRADIANT-3試験では高，中分化進行膵NET患者410例を対象とし，エベロリムス群とプラセボ群で無増悪生存率を比較した（エベロリムス10 mg/day連日）[30]。それによるとプラセボ群が無増悪生存率中央値が[5]4ヵ月に対し，エベロリムス群では[11]4ヵ月であった（ハザード比0.35，$P<0.001$）。

一方，スニチニブはマルチチロシンキナーゼ阻害剤であり，VEGF受容体（VEFR-1,2,3）[31]および血小板由来増殖因子受容体（PDGFR-A，B），KITチロシンキナーゼ，CSF-1受容体などの阻害を行うことで[32,33]腫瘍そのものの増殖抑制およびに血管新生を抑制し，抗腫瘍効果を発揮する。層別解析をするとエベロリムスでは腫瘍のタイプによって効果に差がみられない傾向があるのに対し，スニチニブでは機能性腫瘍に比して非機能性腫瘍に対して効果が高く，Ki67が5%以下の腫瘍でより強い無再発生存延長効果がみられた。また，本邦ガイドラインでは推奨されていないもののソマトスタチンアナログはCLARINET試験における層

別解析において膵NETに対する抗腫瘍効果が示唆されている。

VI. 膵NECに肝転移に対する治療法

膵NEC肝転移症例に対しては，進展の速さから現在のところ切除等の肝転移に対する局所療法は推奨されていない。一方，薬物治療として，病理学的形態，臨床的病態に類似性を認める小細胞肺癌で得られているエビデンスに準じて本邦では保険未承認ではあるものの，シスプラチンとエトポシド[34]あるいはイリノテカン[35]を併用し高い奏功率が海外から報告されている。しかしながら一旦奏功するもののPDとなった場合の腫瘍進展はきわめて早く，予後が不良であり，二次治療の有効な報告はない。

おわりに

2010年代になり，膵NETに対する治療法はさまざまな選択肢が出現してきた。高分化型NET，とくにKi67の低いものでは腫瘍増大が緩徐なため，肝転移に対してさまざまな治療法が可能である。しかしながら，現在のところ本邦のガイドラインをはじめとしてENETSやNCCNのガイドラインにおいては膵NETの肝転移巣に対してセカンドライン以降の治療アルゴリズムは示されていない。唯一根治的と考えられてきた外科的切除でさえ限りなく根治に近いpalliative therapyであるととらえると，究極的には膵NETに対する治療は肝移植を除いて根治術はほぼ無いことになり，生命予後を規定する肝転移巣に対しては外科的切除，血管内治療，薬物療法など使用可能な手段をすべて使い切ることが結果的に長期生存につながると考える。そういう意味では膵NET肝転移に対する治療は選択肢をなるべく残しておくような順序，治療方法での治療戦略を立てるべきである。

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Changes in Colorectal Cancer Care in Japan before and after Guideline Publication: A Nationwide Survey about D3 Lymph Node Dissection and Adjuvant Chemotherapy

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BACKGROUND: The Japanese Society for Cancer of the Colon and Rectum (JSCCR) published clinical guide lines for the treatment of colorectal cancer (CRC) in 2005. To evaluate the impact of these guidelines on clinical practice nationwide, we examined the change in the proportion of patients receiving the recommended CRC treatments.

STUDY DESIGN: We collected treatment information on patients with stage II and stage III CRC who under went surgery in participating facilities between 2001 and 2010. We focused on the perfor mance of 2 treatments recommended by the JSCCR guidelines: D3 lymph node dissection and postoperative adjuvant chemotherapy.

RESULTS: The data of 46,304 patients treated in 96 institutions were collected. The proportion of patients receiving D3 dissection increased over time from 58.4% in 2001 to 75.0% in 2010. The increase accelerated after the publication of the JSCCR guidelines in 2005 (2.5% from 2001 to 2005 vs 14.1% from 2005 to 2010). Similarly, the percentage of stage III patients receiving adjuvant chemotherapy increased over time from 50.8% in 2001 to 71.0% in 2010, but the increase was smaller after guideline publication (16.3% between 2001 and 2005 vs 3.9% from 2005 to 2010). Although the performance of each of the recommended treatments varied substantially among institutions, the variation decreased over time.

CONCLUSIONS: D3 dissection for stage II to III disease and adjuvant chemotherapy for stage III disease have become more prevalent and the variation in performance among institutions has decreased in the last decade. Importantly, publication of the guidelines has accelerated the spread of surgical standards. (J Am Coll Surg 2014;218:969 977. © 2014 by the American College of Surgeons)

In Japan, the number of colorectal cancer (CRC) patients has markedly risen in the last 30 years. In 2008, CRC was the second most common cancer, with >110,000 new cases per year.[1] Because of the high prevalence and relative simplicity of CRC surgical procedures, many CRC patients in Japan are now treated in nonspecialized general hospitals.

To eliminate the disparities in care nationwide and to improve the quality of cancer care, it is essential to effectively disseminate information on the current standards of

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care. For this purpose, the Japanese Society for Cancer of the Colon and Rectum (JSCCR) published the *JSCCR Guidelines 2005 for the Treatment of Colorectal Cancer* in July 2005.[2] The guidelines were updated in July 2009 and July 2010[3,4] and a total of 88,000 booklets have been circulated.

Although the publication of the guidelines is the first step to improvement in the quality of cancer care, the next important step is to assess how frequently the recommended treatment is performed in clinical practice (Fig. 1). However, trends in CRC care in Japan have not been systematically evaluated.

The JSCCR Guideline Committee, therefore, conducted a multicenter study to investigate the change in CRC care during the past 10 years and to evaluate the impact of guideline publication on the change in CRC care (step 2 in Fig. 1).

METHODS

Patients

We invited member institutions of the JSCCR to submit information on all stage II to III CRC patients surgically treated in their institutions from 2001 to 2010. The survey period was selected to investigate changes in care during a sufficiently long period before and after publication of the JSCCR guidelines in 2005.

Evaluation of guideline recommendations for colorectal cancer treatment

Two CRC treatments recommended in the JSCCR guidelines[4] were selected to evaluate the impact of guideline publication on the change in CRC treatment. These were selected because they contribute to improvement in prognosis[5-8] and because data could be collected easily from the available clinical database and/or medical records.

Recommendation 1: D3 lymph node dissection for stage II to III colorectal cancer

In the *Japanese Classification of Colorectal Carcinoma*,[9] regional lymph nodes (LNs) are classified into 3 groups (ie, pericolic/perirectal, intermediate, and main), and the scope of LN dissection is graded as D1, D2, or D3[9-11] (Fig. 2). In the JSCCR guidelines,[4] the recommended scope of LN dissection depends on the preoperative clinical findings or intraoperative gross evaluation of LN metastasis and depth of tumor invasion. For cT3 and cT4 diseases, D3 dissection is recommended. For cT1 and cT2 diseases, D3 dissection is indicated in the case of clinically apparent LN metastasis.

Analysis of data from the Japanese Cancer Registry demonstrated that LN metastasis around the origin of the feeding artery occurred in 0.7% and 2.7% to 7.6% of patients with pT2 and pT3 or pT4 tumors, respectively.[4] The analysis of data from 16,865 patients with pathological stage II to III CRC in the JSCCR database disclosed that the number of LNs examined was significantly associated with survival in both stage II and III patients, and was most prominently determined by the scope of LN dissection (D3 or not).[5] From these observations, and to decrease recurrence and improve survival, the JSCCR guidelines recommended D3 dissection of LNs from around the origin of the feeding artery in cases of clinical stage II and stage III CRC. We therefore selected "D3 dissection" as a target of this study.

Recommendation 2: postoperative adjuvant chemotherapy for stage III colorectal cancer

Postoperative adjuvant chemotherapy for patients with stage III CRC is an established standard of care intervention that improves survival.[6-8] We therefore selected this treatment as another target of this study.

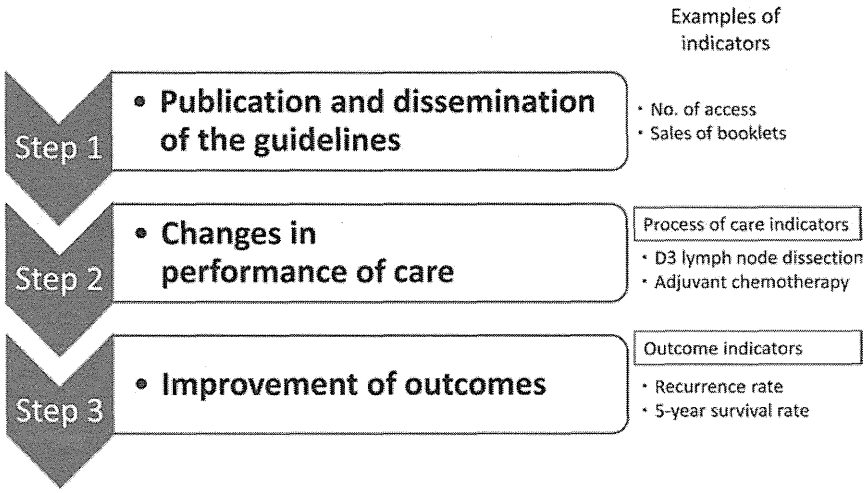

Figure 1. Three important steps for improving the quality of cancer care.

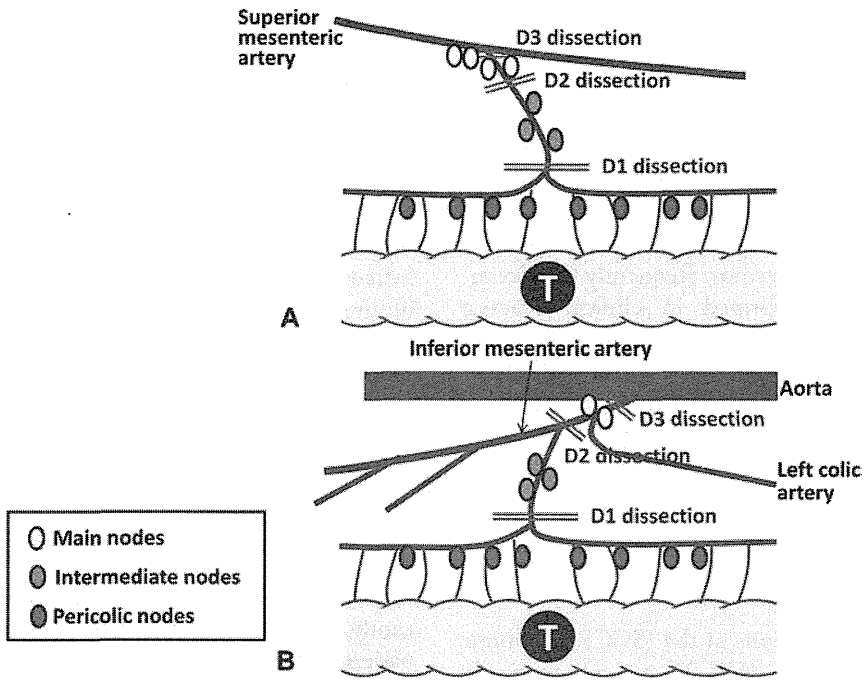

Figure 2. Scope of lymph node dissection in Japan. (A) Right sided colon. (B) Left sided and rectosigmoid colon. The double, parallel blue lines indicate transection points for the vessels.

For stage II disease, on the other hand, major Western guidelines recommend adjuvant chemotherapy when patients have risk factors, including T4 lesions, <12 LNs examined, perforation, poorly differentiated histopathology, and lymphovascular involvement, even though the efficacy of adjuvant chemotherapy for stage II CRC has not been well established and remains controversial.[6,8] In the JSCCR guidelines also,[4] adjuvant chemotherapy is recommended for patients with stage III CRC, but not for all patients with stage II CRC. The supplementary comments by the JSCCR Guideline Committee stated that adjuvant chemotherapy might be acceptable only for "high-risk" stage II patients. In this study, no information on the risk factors for stage II disease was collected. Therefore, our analysis focused on stage III patients, and the results of stage III patients were contrasted with those of stage II patients.

Data collection and statistical analyses

Patient information was collected retrospectively from the clinical database and/or by review of medical records at each participating institution. The collected data included year of surgery, sex, age at surgery, tumor location, stage, scope of LN dissection (D0/D1/D2/D3), and postoperative adjuvant chemotherapy (with or without), and the name of the institution.

From the data, we calculated the proportion of patients who received each of the 2 recommended treatments and change in treatment performance over time. The proportions of patients stratified by tumor location, age, and disease stage, and the variation in performance rate among institutions, were examined. To graphically show the variation, the rate of performance of the recommended treatment was calculated for each institution and plotted from the lowest to the highest value. To simplify the presentation of the trend over time, only the odd-year data were plotted.

When the scope of the LN dissection and the status of postoperative adjuvant chemotherapy were "unknown" or "blank," the patient was excluded from the respective analyses. Preoperative chemotherapy or chemoradiotherapy, intraoperative radiotherapy, and intraoperative lavage with chemotherapeutic agents were not considered postoperative adjuvant chemotherapies.

Proportions were compared using the chi-square test. A difference at a p value of ≤ 0.05 was considered statistically significant. Data were analyzed using Stata software, version 11.2 (Stata Corp).

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Epidemiological Study published by the Japanese government. The study protocol was approved by the ethical review boards of the JSCCR.

RESULTS

Patient characteristics

The data of 47,068 patients were collected from 96 institutions between March 6, 2012 and May 16, 2012. The 96 institutions consisted of 8 cancer center hospitals, 44 university hospitals, and 44 general hospitals. We excluded 764 patients with disease classified as unknown stage, not stage II to III, or not adenocarcinoma, and 46,304 were eligible (Fig. 3).

Patient characteristics by year of surgery are shown in Table 1. Overall, median age at surgery was 68 years (range 16 to 101 years) and 57.3% were male. The proportion of elderly patients (ie, aged 70 years or older) increased over time (40.4% in 2001 to 47.1% in 2010; $p < 0.0001$). During the 10-year period, the median age at surgery increased by 2 years. The proportion of patients with right-sided colon cancer increased by 3% (30.5% in 2001 to 33.5% in 2010; $p = 0.0055$). The distribution of patients by sex and stage did not change significantly during the 10-year period.

Proportion of patients receiving D3 dissection

After excluding 1,136 patients with "unknown" or "blank" LN dissection status, the proportion of patients who underwent D3 dissection was analyzed in 45,168 patients. The proportion continuously increased from 58.4% in 2001 to 60.9% in 2005 and 75.0% in 2010. The increase was accelerated after the publication of the JSCCR guidelines in 2005 (2.5% between 2001 and 2005 and 14.1% between 2005 and 2010) (Fig. 4A).

The analysis stratified by tumor location showed similar trends in performance of D3 dissection in both colon and rectal cancer patients (56.5% to 61.3% and 76.2% in colon cancer and 61.4% to 60.4% and 72.9% in rectal cancer in 2001, 2005, and 2010, respectively). Although the proportion of patients receiving D3 dissection was consistently lower in the stage II disease group than in the stage III disease group, the proportion in both groups increased over time (Fig. 5A, B). Patients aged 81 years or older were less likely to receive D3 dissection than patients aged 80 years and younger ($p < 0.0001$). However, the proportion in both age groups increased over time. More than half of patients aged 81 years and older received D3 dissection in 2010 (Fig. 5C, D).

Performance of D3 dissection varied substantially among institutions, but the variation decreased over time, and the increase in performance was greater among those institutions where the proportion of patients receiving D3 dissection was low initially (Fig. 4B).

Proportion of patients receiving postoperative adjuvant chemotherapy

After excluding 8,905 patients with "unknown" and "blank" adjuvant chemotherapy status, 37,399 patients

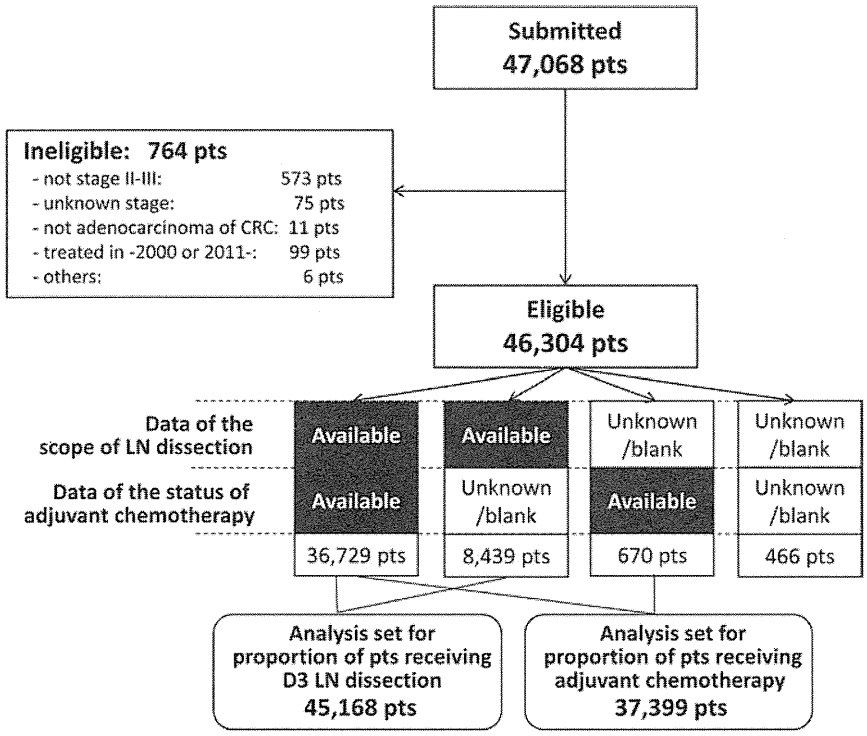

Figure 3. Subject flow diagram. CRC, colorectal cancer; LN, lymph node; pts, patients.

Table 1. Patient Characteristics

	Year of surgery										
Patient characteristics	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**Total**
Patient, n	2,850	3,111	3,468	4,069	4,695	4,956	5,596	5,761	5,872	5,926	46,304
No. of institutions	74	77	80	85	87	89	92	92	93	94	96
Age, y, median	67	67	68	68	68	68	69	69	69	69	68
Age range, y	22 98	18 97	18 96	20 99	19 98	21 99	16 96	23 98	17 101	23 98	16 101
Older than 89 y, n	26	16	30	43	56	5	83	72	60	77	517
Older than 89 y, %	0.9	0.5	0.9	1.1	1.2	1.1	1.5	1.2	1.0	1.3	1.1
80 89 y, n	301	309	370	457	574	661	778	837	873	868	6,028
80 89 y, %	10.6	9.9	10.7	11.2	12.2	13.3	13.9	14.5	14.9	14.6	13.0
70 79 y, n	824	949	1,110	1,274	1,500	1,568	1,749	1,834	1,839	1,847	14,494
70 79 y, %	28.9	30.5	32.0	31.1	31.9	31.6	31.3	31.8	31.3	31.2	31.3
60 69 y, n	907	964	1,048	1,267	1,429	1,490	1,602	1,705	1,765	1,805	13,982
60 69 y, %	31.8	31.0	30.2	31.1	30.4	30.1	28.6	29.6	30.1	30.5	30.2
50 59 y, n	543	611	643	706	796	857	969	902	856	869	7752
50 59 y, %	19.1	19.6	18.5	17.4	17.0	17.3	17.3	15.7	14.6	14.7	16.7
Younger than 50 y, n	214	236	242	288	300	293	329	376	407	396	3081
Younger than 50 y, %	7.5	7.6	7.0	7.1	6.4	5.9	5.9	6.5	6.9	6.7	6.7
Unknown, n	35	26	25	34	40	33	86	35	72	64	450
Unknown, %	1.2	0.8	0.7	0.8	0.9	0.7	1.5	0.6	1.2	1.1	1.0
Sex											
Male, n	1,625	1,814	1,991	2,328	2,720	2,880	3,208	3,237	3,366	3,355	26,524
Male, %	57.0	58.3	57.4	57.2	57.9	58.1	57.3	56.2	57.3	56.6	57.3
Female, n	1,224	1,296	1,476	1,740	1,974	2,063	2,338	2,519	2,502	2,569	19,701
Female, %	42.9	41.7	42.6	42.8	42.0	41.6	41.8	43.7	42.6	43.4	42.5
Unknown, n	1	1	1	1	1	13	50	5	4	2	79
Unknown, %	0.0	0.0	0.0	0.0	0.0	0.3	0.9	0.1%	0.1%	0.0	0.2
Location of tumor											
Right sided colon, n	870	955	1,066	1,319	1,499	1,627	1,859	1,848	1,955	1,985	14,983
Right sided colon, %	30.5	30.7	30.7	32.4	31.9	32.8	33.2	32.1	33.3	33.5	32.4
Left sided colon, n	857	956	1,096	1,166	1,416	1,492	1,681	1,694	1,702	1,730	13,790
Left sided colon, %	30.1	30.7	31.6	28.7	30.2	30.1	30.0	29.4	29.0	29.2	29.8
Rectum, n	1,123	1,192	1,301	1,583	1,776	1,824	2,049	2,214	2,207	2,206	17,475
Rectum, %	39.4	38.3	37.5	38.9	37.8	36.8	36.6	38.4	37.6	37.2	37.8
Unknown, n	0	8	5	1	4	13	7	5	8	5	56
Unknown, %	0.0	0.3	0.1	0.0	0.1	0.3	0.1	0.1	0.1	0.1	0.1
Stage											
II, n	1,482	1,618	1,746	2,099	2,416	2,547	2,827	2,830	2,968	2,931	23,464
II, %	52.0	52.0	50.3	51.6	51.5	51.4	50.5	49.1	50.5	49.5	50.7
III, n	1,368	1,493	1,722	1,970	2,279	2,409	2,769	2,931	2,904	2,995	22,840
III, %	48.0	48.0	49.7	48.4	48.5	48.6	49.5	50.9	49.5	50.5	49.3

were examined as to whether they received postoperative adjuvant chemotherapy. In 18,653 patients with stage III disease, the proportion of patients receiving adjuvant chemotherapy increased continuously from 50.8% in 2001 to 67.1% in 2005 and 71.0% in 2010, the increase was smaller after guideline publication (16.3% between 2001 and 2005 vs 3.9% between 2005 and 2010) (Fig. 6B). The performance of adjuvant chemotherapy in stage III patients varied substantially among institutions in the early years. However, the variation decreased over time, with greater increases occurring in institutions that started with a low proportion of patients receiving adjuvant chemotherapy (Fig. 7).

In the 80 years and younger age group of patients with stage III CRC, the longitudinal increase in the proportion of adjuvant chemotherapy recipients was remarkable, and

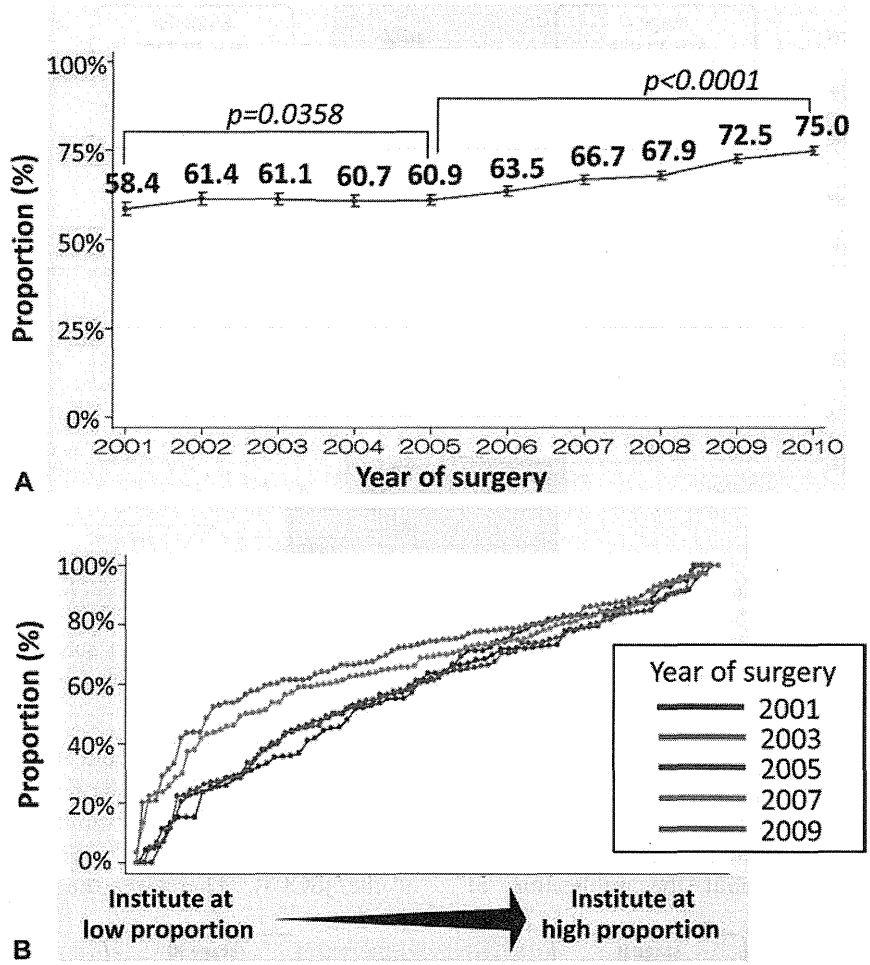

Figure 4. Proportion of patients receiving D3 lymph node dissection by year of surgery. (A) Proportion by year of surgery (n 45,168). (B) Variation in the proportion among institutions.

the proportion in 2010 was 78.4%. The increase between 2001 and 2005 (19.1%) was greater than the increase between 2005 and 2010 (5.3%) (Fig. 6C). The proportion each year and during the survey period was lower in patients aged 81 years and older than in patients aged 80 years and younger (Fig. 6D).

In contrast to the proportion of stage III patients, that of stage II patients receiving adjuvant chemotherapy was lower each year and decreased over time (Fig. 6A).

DISCUSSION

This study revealed a nationwide increase over time in the performance of 2 important treatments recommended in the clinical practice guidelines for CRC, that is, D3 LN dissection for stage II to III patients and postoperative chemotherapy for stage III patients. Importantly, the rate of D3 dissection performance accelerated after the publication of the guidelines in 2005 and appeared to be larger in initially low-performing institutions, indicating that publication of the guidelines might have played a role in promoting the acceptance of surgical care practice standards nationwide.

On the other hand, the performance rate of postoperative chemotherapy tended to differ from that of D3 dissection. In stage III patients, the rate of increase in the proportion of patients receiving postoperative chemotherapy decelerated after 2005, and the rate of increase in the proportion of patients receiving D3 dissection accelerated after 2005. Since intravenous L-leucovorin was approved for CRC in Japan in 1999, the knowledge that 5-FU plus L-leucovorin regimen had efficacy as adjuvant chemotherapy for stage III disease appeared to spread rapidly to the point of saturation. At the time of the publication of the guidelines in 2005, this standard of care might have already been well accepted. In

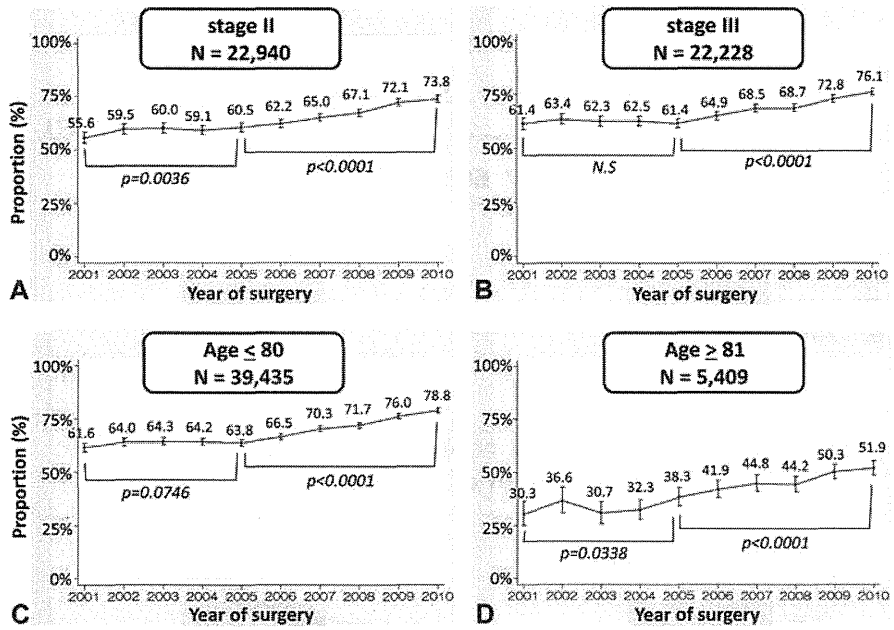

Figure 5. Proportion of patients receiving D3 lymph node dissection in different subgroups. (A) Proportion in stage II patients. (B) Proportion in stage III patients. (C) Proportion in patients aged 80 years and younger. (D) Proportion of patients aged 81 years and older.

contrast, the controversy about the efficacy of adjuvant chemotherapy for stage II patients was concomitantly disseminated, leading to the decrease in the proportion of patients treated. This finding might indicate that such knowledge spreads without the publication of clinical practice guidelines, but the guidelines can play a role in treatment decisions by revealing the controversy.

Our study has some limitations. First, all of the institutions included in the study were member institutions of the JSCCR. Therefore, the proportion of patients

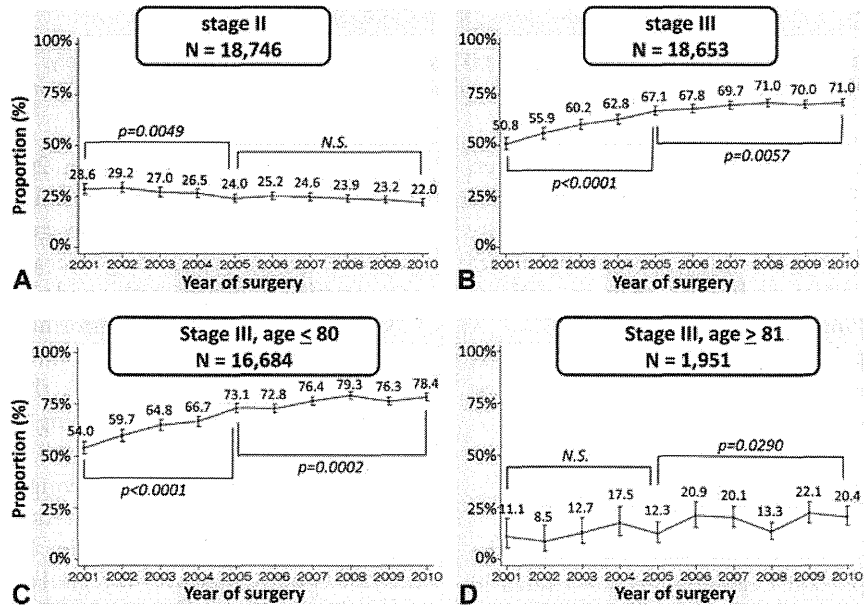

Figure 6. Proportion of patients receiving adjuvant chemotherapy in different subgroups. (A) Proportion in stage II patients. (B) Proportion in stage III patients. (C) Proportion in patients aged 80 years and younger with stage III disease. (D) Proportion of patients aged 81 years and older with stage III disease.

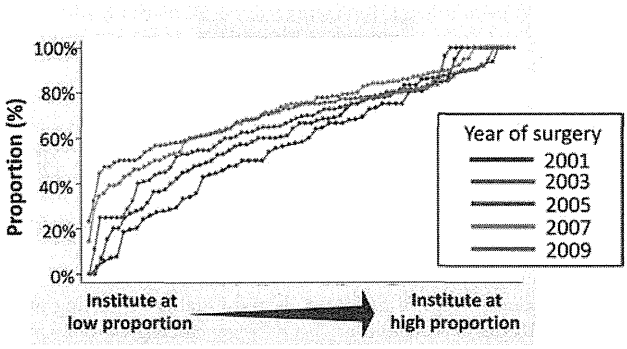

Figure 7. Variation in the proportion of stage III patients receiving adjuvant chemotherapy among institutions.

receiving the recommended care might be higher in our study population than in the general clinical practice population in Japan. Second, information on patient-related factors, such as comorbidities or activities of daily living, was not collected. Patients with severe comorbidities might be appropriately excluded from D3 dissection or adjuvant chemotherapy. The proportion of elderly patients undergoing these procedures was lower than that of younger patients and, therefore, the performance rate tended to be low in institutions with many elderly patients. If we are to interpret the performance of these treatments as indicators of quality of cancer care, this information would be necessary. Third, details related to the quality of the surgical technique and chemotherapy (eg, regimens, doses, and durations) were not considered. Our focus was on the dissemination of knowledge about the standards of care and change in performance, not on the details of the quality of care. Fourth, in this study, we did not examine outcomes. Although we believe, based on earlier evidence, that these increases in performance of recommended care would have led to improved outcomes, a longer follow-up period (eg, at least 5 years after surgery) would be necessary to prove it. Evaluating the relationship between change in the process of care and oncologic outcomes is the next important task for us (step 3 in Fig. 1).

Periodic assessment (with feedback) of standards of care implementation has been commonly done in many countries, especially in the United States. The American College of Surgeons continuously assesses (with feedback) quality of care standards for approved cancer programs using the National Cancer Database and 6 indicators, including adjuvant chemotherapy for stage III patients.[12] A data collection and feedback system via the web has been established. The American Society of Clinical Oncology operates a similar quality assurance system, the Quality Oncology Practice Initiative, with a larger number of indicators.[13] For Japan, this is the first study to assess (with feedback) the performance of 2 standards of care for CRC at each institution. This study is expected to evolve into a periodic assessment and feedback system of "process of care" indicator evaluation using the cancer registry.

CONCLUSIONS

This is the first study to demonstrate trends in guideline-recommended CRC treatments during a 10-year period in a large clinical practice population in Japan. The performance of both D3 dissection for stage II to III disease and adjuvant chemotherapy for stage III disease has become more prevalent, and the variation in performance among institutions has decreased. In particular, the publication of the guidelines is considered to have accelerated the spread of surgical standards. Periodic assessment of performance of cancer care will promote the standardization of cancer care and improve the quality of cancer care, eventually improving patient outcomes. Additional study focusing on other standards of care is now in progress, and we plan to evaluate the relationship between the change in the rate of performance of the recommended treatments and oncologic outcomes in the future.

Author Contributions

Study conception and design: Ishiguro, Higashi, Watanabe, Sugihara
Acquisition of data: Ishiguro, Higashi
Analysis and interpretation of data: Ishiguro, Higashi, Watanabe, Sugihara
Drafting of manuscript: Ishiguro, Higashi
Critical revision: Ishiguro, Higashi, Watanabe, Sugihara

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APPENDIX 1. PARTICIPATING 96 INSTITUTIONS

The authors thank all of the participating institutions for their cooperation in this study:

Kyoto University, Kawasaki Medical School, Kyushu University, Akita Kumiai General Hospital, Kanagawa Cancer Center, Japanese Red Cross Gifu Hospital, Jichi Medical University Saitama Medical Center, Hiroshima Prefectural Hospital, NTT West Osaka Hospital, Sapporo Social Insurance General Hospital, Tokyo Medical and Dental University, Japanese Red Cross Akita Hospital, Higashiosaka City General Hospital, Kurashiki Central Hospital, Kurume University, National Hospital Organization Kobe Medical Center, Tochigi Cancer Center, Niigata City General Hospital, Teikyo University, Kagawa University, Omori Red Cross Hospital, Ehime University, Tokyo Medical University Ibaraki Medical Center, Tokyo Kosei Nenkin Hospital, Kyushu Cancer Center, National Center for Global Health and Medicine, Teikyo University Chiba Medical Center, Kyoto Prefectural University of Medicine, Kurume University Medical Center, Aichi Cancer Center Aichi Hospital, Shikoku Cancer Center, Shizuoka Cancer Center Hospital, Misawa City Hospital, Tottori Red Cross Hospital, FukuiKen Saiseikai Hospital, National Hospital Organization Okayama Medical Center, National Hospital Organization Kyushu Medical Center, National Hospital Organization Higashi-hiroshima Medical Center, Oita University, Hyogo College of Medicine, Suita Municipal Hospital, Sakai City Hospital, Hokkaido PWFAC Engaru-Kosei General Hospital, Kyoto Katsura Hospital, Osaka University, Wakayama Medical University, National Cancer Center Hospital East, Tenri Hospital, Fujikoshi Hospital, Osaka General Medical Center, Takano Hospital, Fukui University, Mie University, Hitachi General Hospital, Fukushima Medical University, Dokkyo Medical University, Ibaraki Prefectural Central Hospital, Tokai University, Fujita Health University Banbuntane Hotokukai Hospital, Hiratsuka Ichou Hospital, Kyushu University, Kitasato University, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Tokyo Metropolitan Tama Medical Center, Iwate Medical University, Nagasaki University, Kawakita General Hospital, Fukushima Prefectural Aizu General Hospital, Sapporo Medical University, Keiyukai Sapporo Hospital, Kobe University, Iwata City Hospital, Toho University Ohashi Medical Center, Saitama Medical University International Medical Center, Nagaoka Chuo General Hospital, Kyoto Second Red Cross Hospital, St. Luke's International Hospital, Chiba University, Kagoshima University, National Defense Medical College, Tokyo Women's Medical University, Cancer Institute Hospital, Social Insurance Chuo General Hospital, Hakodate Goryoukaku Hospital, Nagoya University, Kurume Coloproctology Center, Osaka City University, Saitama Medical University Saitama Medical Center, Shiga University of Medical Science, Matsushita Memorial Hospital, Yamagata University, Gunma University, Okayama University, Kinki Central Hospital of Mutual Aid Association for Public School Teachers, Kinki University, Hokkaido University.

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ORIGINAL ARTICLE

Factors associated with technical difficulties and adverse events of colorectal endoscopic submucosal dissection: retrospective exploratory factor analysis of a multicenter prospective cohort

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Abstract
Background Colorectal endoscopic submucosal dissection (C-ESD) is a promising but challenging procedure. We aimed to evaluate the factors associated with technical difficulties (failure of *en bloc* resection and procedure time, ≥2 h) and adverse events (perforation and bleeding) of C-ESD.

Methods We conducted a retrospective exploratory factor analysis of a prospectively collected cohort in 15 institutions. Eight-hundred sixteen colorectal neoplasms larger than 20 mm from patients who underwent C-ESD were included. We assessed the outcomes of C-ESD and risk factors for technical difficulties and adverse events.

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Results Of the 816 lesions, 767 (94 %) were resected *en bloc*, with a median procedure time of 78 min. Perforation occurred in 2.1 % and bleeding in 2.2 %. Independent factors associated with failure of *en bloc* resection were low-volume center (<30 neoplasms), snare use, and poor lifting after submucosal injection. Factors significantly associated with long procedure time (≥2 h) were large tumor size (≥4 cm), low-volume center, less-experienced endoscopist, CO_2 insufflation, and use of two or more endoknives. Poor lifting was the only factor significantly associated with perforation, whereas rectal lesion and lack of a thin-type endoscope were factors significantly associated with bleeding. Poor lifting after submucosal injection occurred more frequently for nongranular-type laterally spreading tumors (LST) and for protruding and recurrent lesions than for granular-type LST (LST-G).
Conclusions Poor lifting after submucosal injection was the risk factor most frequently associated with technical difficulties and adverse events on C-ESD. Less experienced endoscopists should start by performing C-ESDs on LST-G lesions.

Keywords Colonoscopy · Colorectal neoplasm · Endoscopic gastrointestinal surgery · Endoscopic submucosal dissection

Introduction

Endoscopic resection is a noninvasive, standard treatment for patients with superficial colorectal neoplasms (adenoma/early cancer) without risk of lymph node metastasis [1–3]. Small colorectal neoplasms can be removed easily with conventional polypectomy or endoscopic mucosal resection (EMR). However, conventional EMR may result in piecemeal resection (i.e., tumor resection in multiple fragments) of large-sized tumors [4–6]. Limitations of piecemeal resection include incomplete histological assessment of the specimen and a greater risk of tumor recurrence [7]. Indeed *en bloc* resection (i.e., resecting the entire tumor in one piece) is preferred for precise histological assessment of the resected specimen and to ensure elimination of any residual tumor [4].

Endoscopic submucosal dissection (ESD), of superficial gastrointestinal neoplasms results in high *en bloc* resection rates, regardless of tumor size, location, or fibrosis in the submucosa (SM) [1]. However, colorectal ESD is associated with technical difficulties resulting in poor outcomes, such as failure of *en bloc* resection and long procedure time [8]. Additionally, the adverse events of colorectal ESD (e.g., perforation and bleeding) may be quite severe [9]. These technical difficulties and adverse events may be associated with lesion characteristics, type of endoscopic device, and operator experience. Limitations in attempting to perform colorectal ESD may be due to a lack of information on these technical difficulties and adverse events. Assessing factors associated with such technical difficulties and adverse events may help in formulating training programs for colorectal ESD and treatment strategies for large colorectal tumors. Although several large case-series have assessed the feasibility and efficacy of colorectal ESD, these were retrospective analyses in well-experienced single centers [10, 11]. Outcomes of colorectal ESD were also assessed in a prospective multicenter study, but those centers were all advanced institutions [12]. Therefore, the outcomes of colorectal ESD performed at institutions with various levels of experience have not yet been evaluated.

Considering that the rates of adverse events and tumor recurrence following EMR and ESD had never been directly compared, we performed a prospective cohort study comparing EMR and ESD for large (≥20 mm) colorectal neoplasms [13, 14]. In the prospectively collected cohort, there was a large number of ESD procedures (816 ESDs vs. 1,029 EMRs). Therefore, we retrospectively explored the factors associated with technical difficulty and adverse events on colorectal ESD in the cohort.

Patients and methods

This retrospective analysis involved the patients undergoing colorectal ESD in the prospectively selected patients undergoing colorectal endoscopic resection at 18 tertiary institutions with various levels of experience. The study was performed by the Japanese Society for Cancer of the Colon and Rectum to compare recurrence rates after EMR and ESD for colorectal neoplasms ≥20 mm [13, 14]. The study protocol was approved by the institutional review board of each center and registered in the University Hospital Medical Information Network Clinical Trials Registry as number UMIN 000001642. This manuscript followed the STROBE

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guidelines [15]. All the authors had reviewed and approved the final manuscript.

Study participants

Consecutive patients >20 years old with superficial colorectal neoplasms ≥20 mm in diameter undergoing endoscopic resection between October 2007 and December 2010 were eligible for inclusion in the original cohort trial. Lesions predicted to be noninvasive neoplasms and carcinomas with minute (<1,000 μm) SM invasion, thought to have no risk of lymph node metastasis, were removed by endoscopic resection. The subjects in that trial who underwent ESD were included in this retrospective exploratory factor analysis (Fig. 1). The choice between EMR and ESD was made by each participating colonoscopist, based on the proposed guidelines of the Colorectal ESD Standardization Implementation Working Group [16, 17]. Lesions with contraindications to endoscopic resection, as determined by the colonoscopist, including lesions involving the orifice of the appendix, those encompassing the entire circumference of the colonic wall, those showing massive invasion of the ileum, and lesions inaccessible by colonoscopy, were excluded and treated by surgical colectomy. Written informed consent was obtained from each patient.

Procedures

All procedures were performed by colonoscopists who had been physicians for at least 5 years and were either board-certified by the Japanese Gastroenterological Endoscopy Society (JGES) or had knowledge and endoscopic techniques equal to that of board-certificated colonoscopists. Therefore, no trainees were involved in any of these cases. Endoscopic devices (endoknives), endoscopes, endoscopic systems, and medications were not regulated by the study protocol, and all procedures were performed according to each institution's standard procedure. Patients were considered admitted to hospital when they underwent ESD. Although the fasting and hospitalization periods and examination after colonic ESD were determined according to each institution's protocol, in Japan the usual fasting period is 2 days, including the day on which ESD is performed, and the hospitalization period is 7 days with blood tests performed the day after ESD. The histopathology of each resected specimen was assessed at each institution, following the Japanese classification of colorectal carcinoma [2]. Lesions histopathologically diagnosed as low/high-grade adenoma, intramucosal carcinoma, or carcinoma with minute SM invasion (<1,000 μm), without high pathologic risk features (lymph-vascular involvement and/or poorly differentiated adenocarcinoma), were regarded as curable because they had no risk of lymph node metastasis. By contrast, lesions histopathologically diagnosed as carcinoma with deep SM invasion (≥1,000 μm) or with high-risk pathologic features were regarded as incurable, and these patients were referred for additional surgery, including lymph node dissection.

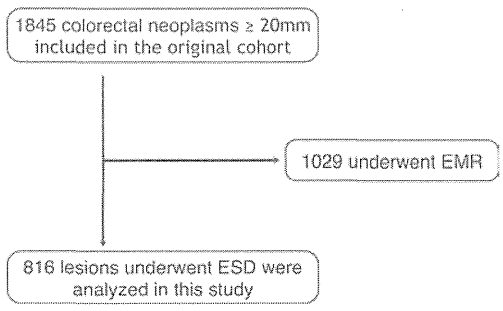

Fig. 1 Study design, showing a flow diagram of enrolled subjects

Data collection and measured outcomes

Detailed data sheets on each participating patient were completed by the investigators and faxed to the independent data center. Information about endoscopic resection (e.g., endoscopic devices, endoscopes, and medications) was collected after the procedure. Data included patient characteristics (age and sex), diagnostic modality prior to endoscopic resection (with or without magnifying endoscopy), tumor characteristics (location, estimated size, type, and history of biopsy), institution, the experience of each colonoscopist (<11 or ≥11 years), fluid injected to form a SM cushion (sodium hyaluronate or others), type of power source used for electrical cutting and its setting, type of electrosurgical endoknife, type of insufflation gas (CO_2 or air), lifting condition after SM injection (good or poor), completeness of the endoscopic resection (*en bloc*, piecemeal, or unresected), diagnostic modality for assessment of residual tumor after endoscopic resection (with or without magnifying endoscopy), procedure time (from the beginning of SM injection until lesion removal), adverse events (perforation, bleeding, and others), treatments administered for adverse events and their outcomes, histopathological diagnosis of the resected specimen (histological type, lymph-vascular involvement, and tumor involvement on the lateral and proximal margins) according to the Japanese classification of colorectal carcinoma [2], and additional therapy for incurable lesions.

Outcomes indicating technical difficulties included failure of *en bloc* resection and procedure time and adverse events included perforation and bleeding. The factors associated with each were also evaluated.

Definitions

ESD was defined as endoscopic dissection of a colorectal tumor using an electrosurgical endoknife, consisting of circumferential mucosal cutting and SM dissection or

circumferential SM incision prior to EMR (CSI-EMR) [18], as it was difficult to distinguish whether CSI-EMR was initially planned prior to the procedure or was used to rescue a procedure which was difficult to complete. As ESD is intended for *en bloc* resection, a failed procedure was defined as failure of *en bloc* resection (i.e., piecemeal resection or incomplete procedure). Tumors were classified as being located on the colon (cecum, ascending, transverse colon, descending or sigmoid colon) or the rectum. Endoknives were classified into three categories (needle knife, IT knife, and scissors types), as well as with or without water-jet function. Tumors were classified into five categories, based on the Paris classification and models of tumor growth during the development of colorectal neoplasia [3, 19]. The five types were: (1) granular-type laterally spreading tumor (LST-G), (2) nongranular-type laterally spreading tumor (LST-NG), (3) protruding tumor, (4) recurrent tumor after endoscopic resection, and (5) unclassified. Lifting conditions after SM injection were assessed as good or poor [20]. Histopathological diagnoses were based on the Japanese classification and were re-classified according to the Vienna classification [21]. Low-grade adenomas according to the Japanese classification were equivalent to noninvasive low-grade neoplasias according to the Vienna classification, whereas high-grade adenomas and intramucosal carcinomas according to the Japanese classification were equivalent to noninvasive high-grade neoplasias according to the Vienna classification. Based on the median number of ESDs performed at each institution during the study period (30 cases/3 years; i.e., 10 cases/year), institutions were classified as low (<30 lesions) and high (≥30 lesions) volume centers. Colonoscopists were classified as those who were less (<11 years) and more (≥11 years) experienced, because it takes at least 5 years to be a board-certified member of JGES and it is thought that it takes more 5 years to experience enough ESD cases. Procedure time >2 h was defined as long, because 30 % of the ESDs needs procedure time >2 h, and it can be said they are relatively difficult cases than average. Lesion size was classified as <40 and ≥40 mm. A bleeding episode was defined as bleeding resulting in (1) apparent hematochezia or melena after the procedure, (2) a ≥2-g/dL decrease in hemoglobin concentration, or (3) a blood transfusion (the decision for transfusion was left each institution's criterion and 7.0 g/dL in hemoglobin concentration is generally accepted as a criterion for transfusion). Perforation was defined as a full-thickness defect of the colonic wall with visible peritoneal fat or the presence of extra-gastrointestinal air on X-ray or abdominal computed tomography. Although observation period for delayed adverse events was not defined, the patients were generally followed up for at least one year because the follow-up period of the original cohort study was one year. Therefore, we could collect the information about late adverse events for two to four weeks [22].

Sample size estimation and statistical analysis

This study was a retrospective exploratory factor analysis of a prospective cohort study. The cohort involved 1,845 colorectal neoplasms ≥20 mm in diameter. The lesions from patients who underwent ESD were included to this exploratory analysis. Multiple lesions in the same patient were counted as independent lesions.

All data were collected and analyzed at an independent data center. Continuous, parametric variables are reported as means (standard deviation (SD)) and nonparametric data as medians (interquartile range (IQR) or range). Categorical variables were reported as incidence or rates (%) and compared using the χ^2 test or Fisher's exact test, as appropriate. Univariate and multivariate logistic regression analyses were performed to examine the factors associated with technical difficulty (failure of *en bloc* resection and procedure time, >2 h), whereas the number of adverse events (perforation and bleeding) was too small for multivariate analysis and only univariate analysis was done to examine the factors associated with adverse events. Variables with p values for association ≤0.2 on univariate analysis were considered potential risk factors in multivariate logistic regression analysis. All statistical analyses were performed using JMP version 10 (SAS Institute Inc, Cary, NC). All analysis were exploratory and P values were two-tailed, with $p<0.05$ defined as statistically significant.

Results

Study design and baseline patient characteristics

The participants' flow is shown in Fig. 1. Between October 2007 and December 2010, 1,845 colorectal neoplasms ≥20 mm in diameter were enrolled in the prospective cohort study. Of these, 816 lesions underwent colorectal ESD and were included in this analysis, and the remainder underwent conventional EMR.

Baseline patient characteristics are shown in Table 1. ESD procedures were performed at 15 of the 18 participating institutions, with a median of 30 lesions (IQR, 11–94 lesions) treated per center. The median lesion size was 35 mm (IQR, 28–47 mm). Almost two thirds of the lesions (64 %) were located in the colon. LST-G was the most frequent type (56 %), with 55 % of the lesions biopsied prior to ESD. Approximately 90 % of the lesions were removed by colorectal ESD at a high-volume center, with 65 % of these procedures performed by more experienced colonoscopists. One fourth of the lesions (25 %) showed poor lifting after SM injection.

Table 1 Baseline demographic and clinical characteristics of the study subjects

		Number		Percent	
Number of lesions		816			
Sex (male/female)		468:348			
Mean age (year (±SD))		67 (±10)			
Median tumor size, mm (IQR)		35 (28 47)			
Tumor location					
Colon	Cecum	520	71	64 %	9 %
	Ascending colon		152		19 %
	Transverse colon		144		18 %
	Descending colon		32		4 %
	Sigmoid colon		121		15 %
Rectum		296		36 %	
Type					
LST G		459		56 %	
LST NG		281		34 %	
Protruding		59		7 %	
Recurrent tumor after ER		5		1 %	
Unclassified		12		2 %	
Institution					
High volume (≥30 patients), 8 institutions		715		88 %	
Low volume (<30 patients), 7 institutions		101		12 %	
Experience of endoscopist					
More experienced (≥11 years)		531		65 %	
Less experienced (<11 years)		285		35 %	
Lifting after submucosal injection					
Good		608		75 %	
Poor		208		25 %	

Abbreviations: *IQR* interquartile range, *LST G* granular type laterally spreading tumor, *LST NG* nongranular type laterally spreading tumor, *ER* endoscopic resection

Procedures for colorectal ESD

Almost all procedures used CO_2 gas and sodium hyaluronate (Table 2). Various types of electrosurgical endoknives were used. Of the colorectal ESDs, 68 % required one electrosurgical endoknife, with the remaining 32 % requiring two or more. Endoknives with water-jet function were used to remove 29 % of the colorectal ESDs, with only 5 % requiring an endoscopic snare. Most of the colonoscopists (86 %) preferred to use a thin endoscope (thin caliber colonoscope or gastroscope). A gastroscope was used in 25 % of the procedures, whereas endoscopes equipped with a water-jet function were utilized in 70 %.

Therapeutic outcomes

Therapeutic outcomes are shown in Table 3. The median procedure time was 78 min (IQR, 50–120 min). Procedure times were longer than 2 h for 30 % of the lesions and longer than 3 h for about 10 %. We found that 57 % of the lesions were noninvasive high-grade neoplasms, 24 % were noninvasive low-grade neoplasms, and 18 % were invasive adenocarcinomas, including 7 % that were unexpectedly deep (≥1,000 μm) invasive SM cancers. These latter tumors were regarded as incurable by endoscopic local resection and were referred for additional surgery. Almost all the tumors (94 %) were resected *en bloc*, with 6 % requiring piecemeal resection or surgical colectomy.

Perforation occurred in 17 patients (2.1 %). Although most perforations were treated endoscopically using endoclips without surgical intervention, one required emergency surgery. Bleeding occurred in 20 patients (2.2 %), with most (19 patients) being postoperative. One patient with severe uncontrolled intraoperative bleeding required emergency surgery. There were no fatal adverse events.

Factors associated with difficulty and adverse events of colorectal ESD

Tables 4, 5, 6, and 7 show the results of univariate and multivariate analyses of factors associated with technical

Table 2 Devices used for colorectal endoscopic submucosal dissection

	Number	Percent
CO_2	693	85 %
Sodium hyaluronate	788	97 %
Electrosurgical endoknife (multiple choice answers)		
Needle type[a]	806	98 %
IT type[b]	169	21 %
Scissors type[c]	32	4 %
Endoknife with water jet function	238	29 %
Number of electrosurgical endoknives used		
1	558	68 %
≥2	258	32 %
Snare used	42	5 %
Thin caliber endoscope (Gastroscope)	703 (205)	86 % (25 %)
Water jet endoscope	568	70 %

[a] Includes Flushknife (DK2618JN, Fujifilm Medical, Tokyo, Japan), Flushknife BT (DK2618JB, Fujifilm Medical), Dual knife (KD 650Q, Olympus Co, Tokyo, Japan), Hook knife (KD 620QR, Olympus), Flex knife (KD 630 L, Olympus), needle type bipolar needle knife (BSBK21S45, Xeon Medical Co, Tokyo, Japan), and ball tipped bipolar needle knife (BSBK21B35, Xeon Medical)

[b] Includes IT knife (KD 610 L, Olympus), IT knife 2 (KD 611 L, Olympus), and IT knife nano (KD 612Q, Olympus)

[c] Includes SB knife (MD 47706, Sumitomo Bakelite, Tokyo, Japan) and SB knife Jr. (MD 47703, Sumitomo Bakelite)

difficulties (failure of *en bloc* resection and long procedure time) and adverse events (perforation and bleeding). Univariate analysis showed that protruding type tumor, low-volume center (<30 neoplasms), lack of sodium hyaluronate use, snare use, poor lifting after SM injection, noninvasive high-grade dysplasia and deeply invasive carcinoma (≥1,000SMμm) were possible risk factors associated with failure of *en bloc* resection. Multivariate analysis showed that low-volume center, snare use, and poor lifting after SM injection were independent risk factors associated with failure of *en bloc* resection (Table 4). Factors associated with long procedure time (≥2 h) on univariate analysis included large tumor size (≥4 cm), colonic lesion, LST-NG, protruding-type tumor, low-volume center (<30 lesions), less-experienced endoscopist, CO_2 use, use of two or more electrosurgical endoknives, snare use, noninvasive high-grade neoplasm and deeply invasive carcinoma (≥1,000 μm). On multivariate analysis, large tumor size, low-volume center, less-experienced endoscopist, CO_2 use, and use of two or more electrosurgical endoknives were independent risk factors for long procedure time (Table 5).Univariate analysis showed that poor lifting after SM injection was the only risk factor associated with perforation (Table 6). Factors associated with bleeding on univariate analysis included rectal lesions and lack of thin-type endoscope (Table 7).

Poor lifting after SM injection occurred more frequently in LST-NG and in protruding and recurrent lesions than in LST-G, with the incidence of poor lifting after SM injection being extremely high (80 %) for recurrent lesions, although the incidence of poor lifting was not related to history of biopsy (Table 8).

Table 3 Clinical outcomes of colorectal endoscopic submucosal dissection

	Number	Percent
Median procedure time (min (range))	78 (50 120)	
Procedure time ≥2 h	240	30 %
Histology		
Noninvasive low grade neoplasm	195	24 %
Noninvasive high grade neoplasm	466	57 %
SM <1,000 μm	88	11 %
SM ≥1,000 μm	62	7 %
Unknown	5	1 %
Completeness of the procedure		
En bloc resection	771	94 %
Piecemeal resection	44	5 %
Unresected	1	1 %
R0 resection	638	78 %

Abbreviation: *SM* submucosa

Discussion

We found that colorectal ESD yielded satisfactory outcomes in this prospective cohort treated at several participating institutions with various levels of experience. Acceptable outcomes of colorectal ESD have also been reported in western countries, but improvements are needed because of its technical difficulties [23]. Adverse events such as perforation and bleeding [13] have been reported, as have failure of *en bloc* resection and long procedure time. We therefore assessed factors independently associated with these technical difficulties and adverse events.

We found that poor lifting after SM injection was independently associated with failure of *en bloc* resection and with increased perforation. Poor lifting after SM injection is thought to be associated with fibrosis in the SM layer. In single center trials, fibrosis was reported related to failure of *en bloc* resection and perforation [20]; and tumor size and the presence of fibrosis were found to be independent risk factors for perforation [24, 25]. Although a multicenter trial showed that only large tumor size and performance of the procedure at a low-volume institution were risk factors for perforation and postoperative bleeding, that trial did not assess lifting condition or fibrosis [13]. Our finding, that poor lifting was a significant risk factor for failure of *en bloc* resection and

Table 4 Univariate ($p \leq 0.2$) and multivariate logistic analyses of factors associated with failure of *en bloc* resection during colorectal endoscopic submucosal dissection

	Univariate analysis			Multivariate analysis		
Variable	*En bloc* resection	Failure of *en bloc* resection	*p* value	Adjusted OR	95 % CI	*p* value
Institution (*n*; %)						
High volume (≥30 patients)	682/715 (95)	33/715 (5)				
Low volume (<30 patients)	89/101 (88)	12/101 (12)	0.0008	5.52	2.25 13.37	0.0003
Snare						
	744 /774 (95)	30/774 (4)				
+	27/42 (64)	15/42 (36)	<0.001	25.32	10.37 63.94	<0.0001
Lifting condition after SM injection						
Good	590/608 (97)	18/608 (3)				
Poor	181/208 (87)	27/208 (13)	<0.001	10.74	4.49 25.18	<0.0001

Abbreviations: *OR* odds ratio, *LST G* granular type laterally spreading tumor, *LST NG* nongranular type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

adverse events, was similar to the results of these earlier trials. The causes of fibrosis are not completely known, but we frequently observed the lesions with poor lifting in LST-NG and in protruding and recurrent lesions. These findings suggest that endoscopists in low-volume centers should start by performing colorectal ESDs on LST-G lesions.

We also found that performance of ESD at a low-volume institution was an important risk factor for failure of *en bloc* resection and long procedure time. Similarly, another study reported that the total number of ESDs performed per institution was inversely associated with the incidence of adverse events [13]. In this study, institutions performing fewer than ten colorectal ESDs per year were regarded as low-volume centers and these institutions should be selective in performing colorectal ESD. Unfortunately, we could not collect the colorectal ESD volume of each colonoscopist and we had to assess the experience of ESD by each institution, not by each colonoscopist. However, since colorectal ESD is a technically challenging and relatively rare procedure, we expect that within each institution such cases are performed by

Table 5 Univariate ($p \leq 0.2$) and multiple regression analyses of factors associated with longer procedure time (≥2 h) during colorectal endoscopic submucosal dissection

	Univariate analysis			Multivariate analysis		
Variable	<2 h	≥2 h	*p* value	OR	95 % CI	*p* value
Tumor size (%)						
<4 cm	396/477 (83)	81/477 (17)				
≥4 cm	180/339 (53)	159/339 (47)	<0.0001	4.97	3.35 7.47	<0.0001
Institution (*n* (%))						
High volume (≥30 patients)	516/715 (72)	199/715 (28)				
Low volume (<30 patients)	60/101 (59)	41/101 (41)	0.01	2.75	1.59 4.78	0.0003
Endoscopist						
Experienced	400/531 (75)	131/531 (25)				
Less experienced	176/285 (62)	109/285 (38)	<0.0001	2.31	1.61 3.34	<0.0001
CO_2						
	98/123 (80)	25/123 (20)				
+	478/693 (69)	215/693 (31)	0.02	2.02	1.17 3.61	0.012
Number of electrosurgical endoknives used						
1	425/558 (76)	133/558 (24)				
≥2	151/258 (58)	107/258 (42)	<0.0001	2.48	1.70 3.62	<0.0001

Abbreviations: *OR* odds ratio, *LST G* granular type laterally spreading tumor, *LST NG* nongranular type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa