induced with its use in combination with poly-ICLC and Montanide, but not without poly-ICLC. In this regard, OK-432 could be a feasible immune-modulator for a cancer vaccine with tumor antigens.

Two out of 9 vaccinated patients showed SD in the clinical response. Although strong induction of the NY-ESO-1 antibody against both the peptides used for the vaccine and the NY-ESO-1 protein was observed in these patients, there is no convincing evidence as to whether the strong antibody response is related to the clinical response.

Recently, it was shown that antibodies against immune checkpoint molecules had a significant antitumor effect, and a combination of different antibodies augmented this effect. With the proviso of control of immunosuppression in the tumor microenvironment, the use of immunogenic vaccines will be relevant. Thus, the use of both reagents controlling immunosuppression and immunogenic vaccines will be important in the future. We are planning combination therapies of immune checkpoint modulators with NY-ESO-1 vaccine.

ACKNOWLEDGMENT

The authors thank Junko Mizuuchi for preparation of the manuscript.

CONFLICTS OF INTEREST/ FINANCIAL DISCLOSURES

The study was supported by a Grant-in-Aid for Scientific Research (B) and Project for Development of Innovative Research on Cancer Therapeutics of Ministry of Education, Culture Sports Science and Technology of Japan.

All authors have declared there are no financial conflicts of interest with regard to this work.

REFERENCES

1. Chen YT, Scanlan MJ, Sahin U, et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. *Proc Natl Acad Sci U S A.* 1997;94: 1914–1918.
2. Gnjatic S, Nishikawa H, Jungbluth AA, et al. NY-ESO-1: review of an immunogenic tumor antigen. *Adv Cancer Res.* 2006;95:1–30.
3. Kirkwood JM, Butterfield LH, Tarhini AA, et al. Immunotherapy of cancer in 2012. *CA Cancer J Clin.* 2012;62:309–335.
4. Quakkelaar ED, Melief CJ. Experience with synthetic vaccines for cancer and persistent virus infections in nonhuman primates and patients. *Adv Immunol.* 2012;114:77–106.
5. Thara E, Dorff TB, Pinski JK, et al. Vaccine therapy with sipuleucel-T (Provenge) for prostate cancer. *Maturitas.* 2011;69:296–303.
6. Gajewski TF, Fuertes M, Spaapen R, et al. Molecular profiling to identify relevant immune resistance mechanisms in the tumor microenvironment. *Curr Opin Immunol.* 2011;23:286–292.
7. Lesterhuis WJ, de Vries IJ, Schreibelt G, et al. Route of administration modulates the induction of dendritic cell vaccine-induced antigen-specific T cells in advanced melanoma patients. *Clin Cancer Res.* 2011;17:5725–5735.
8. Trumpfheller C, Longhi MP, Caskey M, et al. Dendritic cell-targeted protein vaccines: a novel approach to induce T-cell immunity. *J Intern Med.* 2012;271:183–192.
9. Kakimi K, Isobe M, Uenaka A, et al. A phase I study of vaccination with NY-ESO-1f peptide mixed with Picibanil OK-432 and Montanide ISA-51 in patients with cancers expressing the NY-ESO-1 antigen. *Int J Cancer.* 2011;129: 2836–2846.
10. Melief CJ. Treatment of established lesions caused by high-risk human papilloma virus using a synthetic vaccine. *J Immunother.* 2012;35:215–216.
11. Zeestraten EC, Speetjens FM, Welters MJ, et al. Addition of interferon-α to the p53-SLP® vaccine results in increased production of interferon-γ in vaccinated colorectal cancer patients: a phase I/II clinical trial. *Int J Cancer.* 2013;132: 1581–1591.
12. Bijker MS, van den Eeden SJ, Franken KL, et al. CD8 + CTL priming by exact peptide epitopes in incomplete Freund's adjuvant induces a vanishing CTL response, whereas long peptides induce sustained CTL reactivity. *J Immunol.* 2007; 179:5033–5040.
13. Melief CJ, van der Burg SH. Immunotherapy of established (pre)malignant disease by synthetic long peptide vaccines. *Nat Rev Cancer.* 2008;8:351–360.
14. Dunne A, Marshall NA, Mills KH. TLR based therapeutics. *Curr Opin Pharmacol.* 2011;11:404–411.
15. Flynn BJ, Kastenmüller K, Wille-Reece U, et al. Immunization with HIV Gag targeted to dendritic cells followed by recombinant New York vaccinia virus induces robust T-cell immunity in nonhuman primates. *Proc Natl Acad Sci U S A.* 2011;108:7131–7136.
16. Morse MA, Chapman R, Powderly J, et al. Phase I study utilizing a novel antigen-presenting cell-targeted vaccine with Toll-like receptor stimulation to induce immunity to self-antigens in cancer patients. *Clin Cancer Res.* 2011;17: 4844–4853.
17. Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity.* 2011;34:637–650.
18. Aoki M, Ueda S, Nishikawa H, et al. Antibody responses against NY-ESO-1 and HER2 antigens in patients vaccinated with combinations of cholesteryl pullulan (CHP)-NY-ESO-1 and CHP-HER2 with OK-432. *Vaccine.* 2009;27: 6854–6861.
19. Okamoto M, Oshikawa T, Tano T, et al. Mechanism of anticancer host response induced by OK-432, a streptococcal preparation, mediated by phagocytosis and toll-like receptor 4 signaling. *J Immunother.* 2006;29:78–86.
20. Hironaka K, Yamaguchi Y, Okita R, et al. Essential requirement of toll-like receptor 4 expression on CD11c + cells for locoregional immunotherapy of malignant ascites using a streptococcal preparation OK-432. *Anticancer Res.* 2006;26: 3701–3707.
21. Hirayama M, Nishikawa H, Nagata Y, et al. Overcoming regulatory T-cell suppression by a lyophilized preparation of *Streptococcus pyogenes*. *Eur J Immunol.* 2013;43:989–1000.
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–247.
23. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res.* 2009;15:7412–7420.
24. Kawabata R, Wada H, Isobe M, et al. Antibody response against NY-ESO-1 in CHP-NY-ESO-1 vaccinated patients. *Int J Cancer.* 2007;120:2178–2184.
25. Uenaka A, Wada H, Isobe M, et al. T cell immunomonitoring and tumor responses in patients immunized with a complex of cholesterol-bearing hydrophobized pullulan (CHP) and NY-ESO-1 protein. *Cancer Immun.* 2007;7:9.
26. Kawada J, Wada H, Isobe M, et al. Heteroclitic serological response in esophageal and prostate cancer patients after NY-ESO-1 protein vaccination. *Int J Cancer.* 2012;130: 584–592.
27. Fujiwara S, Wada H, Kawada J, et al. NY-ESO-1 antibody as a novel tumour marker of gastric cancer. *Br J Cancer.* 2013;108:1119–1125.
28. Tsuji K, Hamada T, Uenaka A, et al. Induction of immune response against NY-ESO-1 by CHP-NY-ESO-1 vaccination and immune regulation in a melanoma patient. *Cancer Immunol Immunother.* 2008;57:1429–1437.

29. Wada H, Sato E, Uenaka A, et al. Analysis of peripheral and local anti-tumor immune response in esophageal cancer patients after NY-ESO-1 protein vaccination. *Int J Cancer*. 2008;123:2362–2369.
30. Gay NJ, Gangloff M. Structure of toll-like receptors. *Handb Exp Pharmacol*. 2008;181–200.
31. Eikawa S, Kakimi K, Isobe M, et al. Induction of CD8 T-cell responses restricted to multiple HLA class I alleles in a cancer patient by immunization with a 20-mer NY-ESO-1f (NY-ESO-1 91-110) peptide. *Int J Cancer*. 2013;132:345–354.
32. Sabbatini P, Tsuji T, Ferran L, et al. Phase I trial of overlapping long peptides from a tumor self-antigen and poly-ICLC shows rapid induction of integrated immune response in ovarian cancer patients. *Clin Cancer Res*. 2012;18:6497–6508.

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

Megumi Ishiguro, MD, PhD, Takahiro Higashi, MD, PhD, Toshiaki Watanabe, MD, PhD, Kenichi Sugihara, MD, PhD, on behalf of the Japanese Society for Cancer of the Colon and Rectum Guideline Committee

BACKGROUND: The Japanese Society for Cancer of the Colon and Rectum (JSCCR) published clinical guidelines 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 underwent surgery in participating facilities between 2001 and 2010. We focused on the performance 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

Disclosure Information: Dr Ishiguro receives pay as a consultant from and honoraria from Taiho Pharmaceutical Co., Ltd and Chugai Pharmaceutical Co., Ltd. Dr Watanabe receives grants and honoraria from Taiho, Chugai, Takeda, Daiichi Sankyo, Yakult Honsha, Bristol-Myers, and Merck Serono. Dr Sugihara receives pay as a consultant, grants, and honoraria from Taiho, Chugai, Bayer Yakuhin, Bristol-Myers, and Merck Serono; grants from Otsuka, Takeda, Yakult Honsha, and Daiichi Sankyo; and honoraria from Takeda, Yakult Honsha, and Kyowa Hakko Krirn. All these financial activities are outside of this study. Dr Higashi has nothing to disclose.

This work was conducted by the Japanese Society for Cancer of the Colon and Rectum Guideline Committee with their budget.

Abstract presented at the 77th Meeting of the Japanese Society for Cancer of the Colon and Rectum, Tokyo, Japan, July 2012.

Received October 9, 2013; Revised December 25, 2013; Accepted December 30, 2013.

From the Departments of Translational Oncology (Ishiguro) and Surgical Oncology (Sugihara), Graduate School, Tokyo Medical and Dental University, Division of Cancer Health Services Research, Center for Cancer Control and Information Services, National Cancer Center of Japan (Higashi), and Department of Surgical Oncology, Graduate School of Medicine, the University of Tokyo (Watanabe) Tokyo, Japan.

Correspondence address: Megumi Ishiguro, MD, PhD, Department of Translational Oncology, Graduate School, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. email: ishiguro.srg2@tmd.ac.jp

ISSN 1072-7515/14/$36.00
http://dx.doi.org/10.1016/j.jamcollsurg.2013.12.046

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.

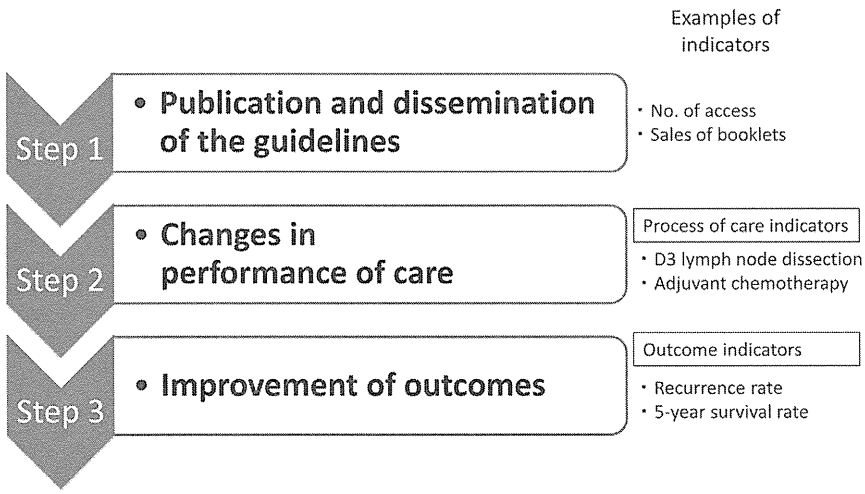


Figure 1. Three important steps for improving the quality of cancer care.

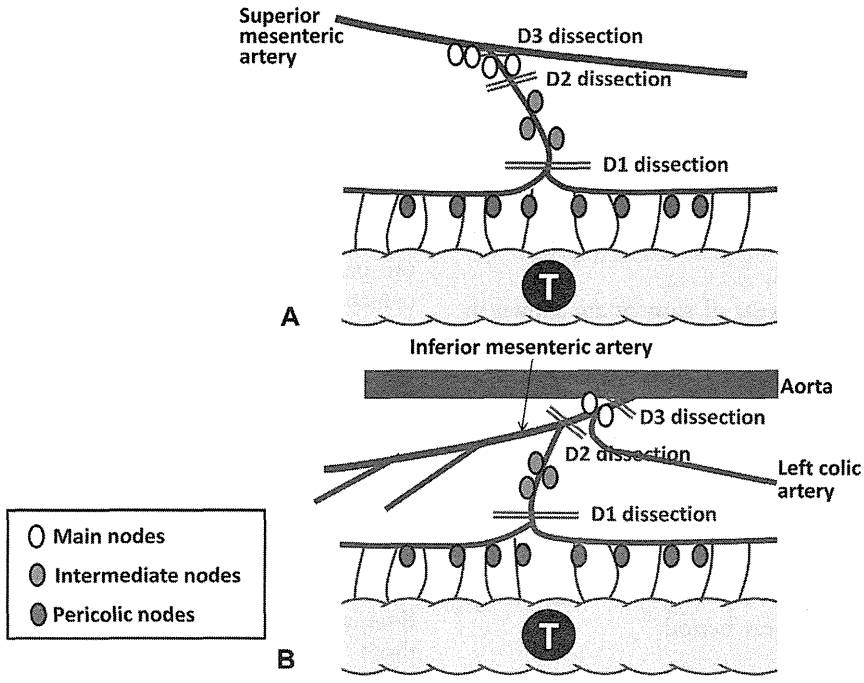


Figure 2. Scope of lymph node dissection in Japan. (A) Right-sided colon. (B) Left-sided and rectosigmoid colon. The double, parallel blue lines indicate transection points for the vessels.

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

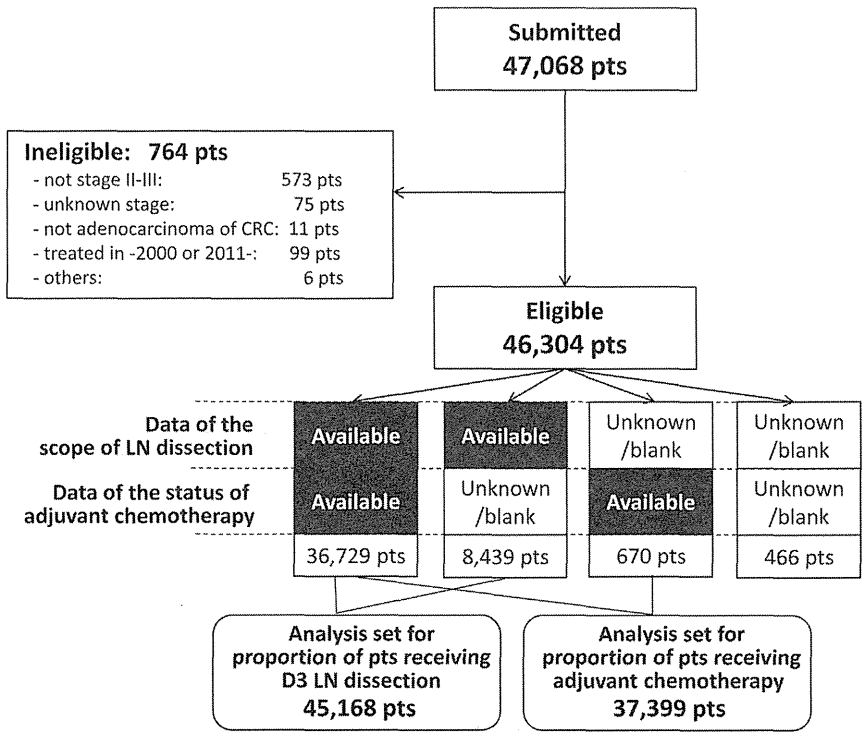


Figure 3. Subject flow diagram. CRC, colorectal cancer; LN, lymph node; pts, patients.

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

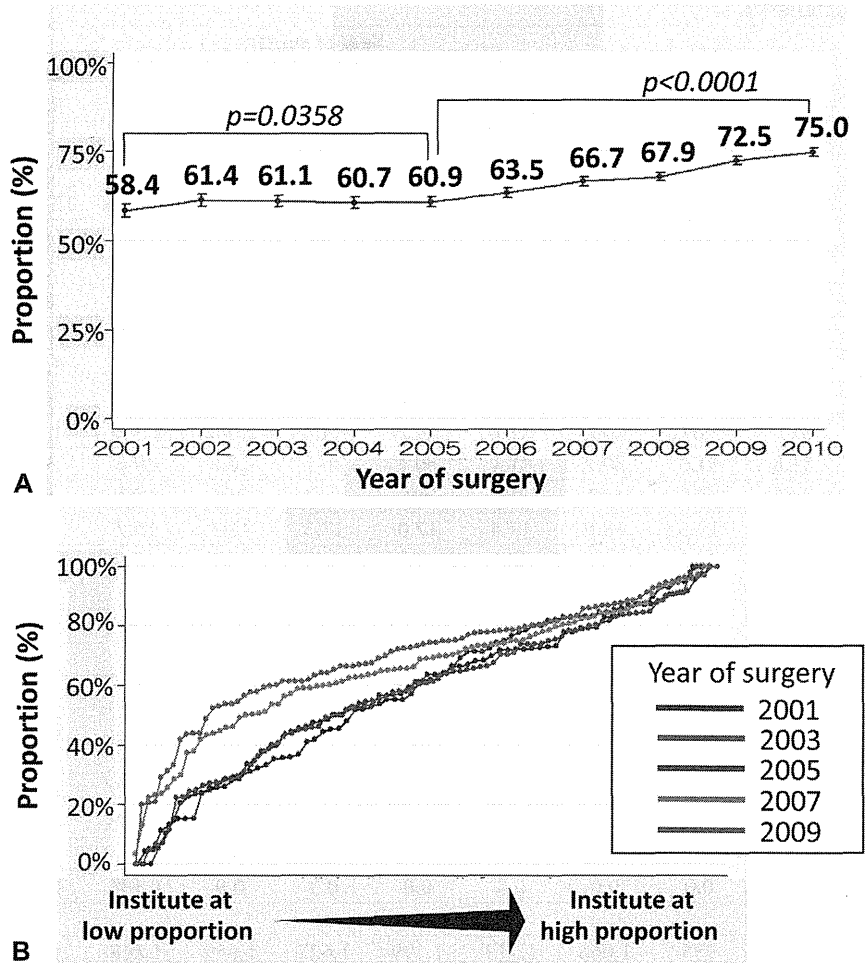


Figure 4. Proportion of patients receiving D3 lymph node dissection by year of surgery. (A) Proportion by year of surgery (n = 45,168). (B) Variation in the proportion among institutions.

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

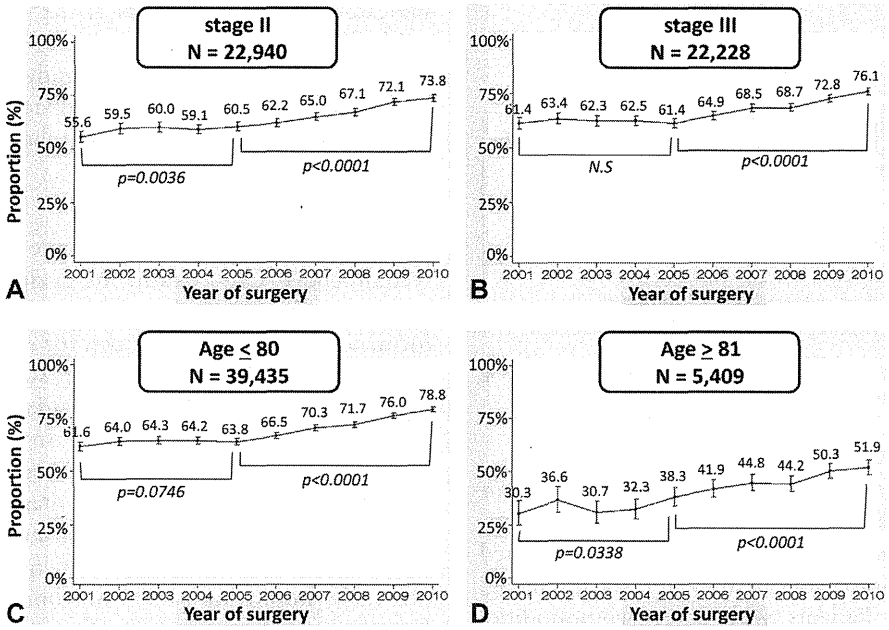


Figure 5. Proportion of patients receiving D3 lymph node dissection in different subgroups. (A) Proportion in stage II patients. (B) Proportion in stage III patients. (C) Proportion in patients aged 80 years and younger. (D) Proportion of patients aged 81 years and older.

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

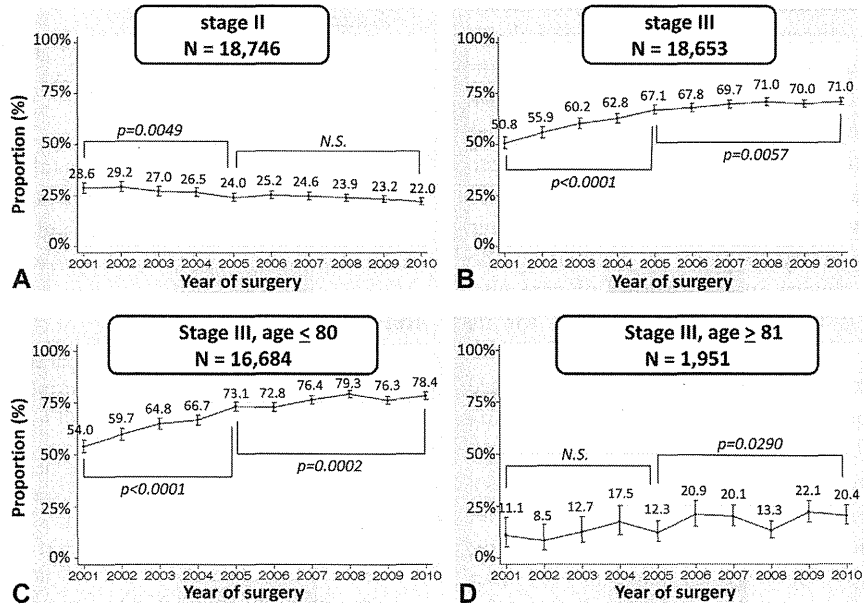


Figure 6. Proportion of patients receiving adjuvant chemotherapy in different subgroups. (A) Proportion in stage II patients. (B) Proportion in stage III patients. (C) Proportion in patients aged 80 years and younger with stage III disease. (D) Proportion of patients aged 81 years and older with stage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

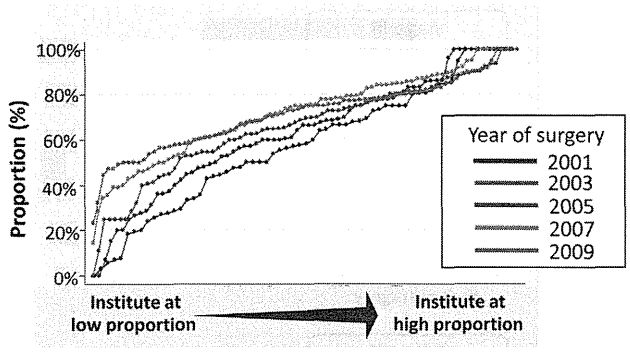


Figure 7. Variation in the proportion of stage III patients receiving adjuvant chemotherapy among institutions.

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

Acknowledgment: The authors thank all of the patients and the co-investigators for their cooperation in this study. The names of participating institutions are provided in the Appendix (online only; available at: http://www.journalacs.org).

REFERENCES

1. Foundation for Promotion of Cancer Research. Cancer statistics in Japan 2012. Available at: http://ganjoho.jp/professional/statistics/backnumber/2012_jp.html. Accessed September 17, 2013.
2. The Japanese Society for Cancer of the Colon and Rectum. JSCCR Guidelines 2005 for the Treatment of Colorectal Cancer. Tokyo: Kanehara & Co., Ltd.; 2005.
3. The Japanese Society for Cancer of the Colon and Rectum. JSCCR Guidelines 2010 for the Treatment of Colorectal Cancer. Tokyo: Kanehara & Co., Ltd.; 2010.
4. Watanabe T, Itabashi M, Shimada Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 2012;17:1–29.

5. Kotake K, Honjo S, Sugihara K, et al. Number of lymph nodes retrieved is an important determinant of survival of patients with stage II and stage III colorectal cancer. Jpn J Clin Oncol 2012;42:29–35.
6. The National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; Colon Cancer Version 3. 2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed September 17, 2013.
7. Schmoll HJ, Van Custem E, Stein A, et al. ESMO Consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 2012;23:2479–2516.
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. The Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal Carcinoma, Second English Edition. Tokyo: Kanehara & Co., Ltd.; 2009.
10. West NP, Hohenberger W, Weber K, et al. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol 2010;28:272–278.
11. West NP, Kobayashi H, Takahashi K, et al. Understanding optimal colonic cancer surgery. Comparison of Japanese D3 resection and European complete excision with central vascular ligation. J Clin Oncol 2012;30:1763–1769.
12. American College of Surgeons. Rapid Quality Reporting System (RQRS). Available at: http://www.facs.org/cancer/ncdb/rqrs.html. Accessed September 17, 2013.
13. American Society of Clinical Oncology. The Quality Oncology Practice Initiative (QOPI). Available at: http://qopi.asco.org/. Accessed September 17, 2013.

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.

Annals of Oncology 25: 1743–1749, 2014
doi:10.1093/annonc/mdu232
Published online 18 June 2014

S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial)

M. Yoshida[1], M. Ishiguro[2], K. Ikejiri[3], I. Mochizuki[4], Y. Nakamoto[5], Y. Kinugasa[6], A. Takagane[7], T. Endo[8], H. Shinozaki[9], Y. Takii[10], H. Mochizuki[11], K. Kotake[12], S. Kameoka[13], K. Takahashi[14], T. Watanabe[15], M. Watanabe[16], N. Boku[17], N. Tomita[18], E. Nakatani[19] & K. Sugihara[20]* on behalf of the ACTS-CC study group

[1]Cancer Chemotherapy Center, Osaka Medical College Hospital, Osaka; [2]Department of Translational Oncology, Tokyo Medical and Dental University, Graduate School, Tokyo; [3]Department of Surgery, Center of Gastroenterology, National Hospital Organization Kyushu Medical Center, Fukuoka; [4]Department of Gastroenterological Surgery, Iwate Prefectural Central Hospital, Iwate; [5]Department of Surgery, Kobe City Medical Center West Hospital, Hyogo; [6]Division of Colon and Rectal Surgery, Shizuoka Cancer Center Hospital, Shizuoka; [7]Department of Surgery, Hakodate Goryoukaku Hospital, Hokkaido; [8]Department of Colorectal Surgery, Japanese Red Cross Medical Center, Tokyo; [9]Department of Surgery, Saiseikai Utsunomiya Hospital, Tochigi; [10]Department of Surgery, Niigata Cancer Center Hospital, Niigata; [11]Department of Surgery, National Defense Medical College, Saitama; [12]Department of Surgery, Tochigi Cancer Center, Tochigi; [13]Department of Surgery II, Tokyo Women's Medical University, Tokyo; [14]Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo; [15]Department of Surgical Oncology and Vascular Surgery, The University of Tokyo, Graduate School of Medicine, Tokyo; [16]Department of Surgery, Kitasato University School of Medicine, Kanagawa; [17]Department of Clinical Oncology, St Marianna University, Kanagawa; [18]Department of Surgery, Hyogo College of Medicine, Hyogo; [19]Department of Statistical Analysis, Translational Research Informatics Center, Hyogo; [20]Department of Surgical Oncology, Tokyo Medical and Dental University, Graduate School, Tokyo, Japan

Received 19 May 2014; revised 9 June 2014; accepted 11 June 2014

Background: S-1 is an oral fluoropyrimidine whose antitumor effects have been demonstrated in treating various gastrointestinal cancers, including metastatic colon cancer, when administered as monotherapy or in combination chemotherapy. We conducted a randomized phase III study investigating the efficacy of S-1 as adjuvant chemotherapy for colon cancer by evaluating its noninferiority to tegafur–uracil plus leucovorin (UFT/LV).

Patients and methods: Patients aged 20–80 years with curatively resected stage III colon cancer were randomly assigned to receive S-1 (80–120 mg/day on days 1–28 every 42 days; four courses) or UFT/LV (UFT: 300–600 mg/day and LV: 75 mg/day on days 1–28 every 35 days; five courses). The primary end point was disease-free survival (DFS) at 3 years.

Results: A total of 1518 patients (758 and 760 in the S-1 and UFT/LV group, respectively) were included in the full analysis set. The 3-year DFS rate was 75.5% and 72.5% in the S-1 and UFT/LV group, respectively. The stratified hazard ratio for DFS in the S-1 group compared with the UFT/LV group was 0.85 (95% confidence interval: 0.70–1.03), demonstrating the noninferiority of S-1 (noninferiority stratified log-rank test, $P < 0.001$). In the subgroup analysis, no significant interactions were identified between the major baseline characteristics and the treatment groups.

Conclusion: Adjuvant chemotherapy using S-1 for stage III colon cancer was confirmed to be noninferior in DFS compared with UFT/LV. S-1 could be a new treatment option as adjuvant chemotherapy for colon cancer.

ClinicalTrials.gov: NCT00660894.

Key words: adjuvant chemotherapy, colon cancer, S-1, UFT/LV

introduction

Postoperative adjuvant chemotherapy for patients with stage III colon cancer is internationally regarded as a standard care for improving survivals. While Western guidelines recommend i.v. 5-fluorouracil (5-FU) and folic acid (leucovorin, LV) or capecitabine combined with oxaliplatin (FOLFOX or CapeOX) as the first choice for adjuvant chemotherapy in stage III colon cancer [1–4], fluoropyrimidine alone remains one of the options [3, 4].

In Japan, oral fluoropyrimidine derivatives have been preferred because of their convenience, leading to the development of several oral fluoropyrimidine derivatives with different properties. Tegafur–uracil (UFT, Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is a combination drug comprising tegafur, a prodrug of 5-FU, and uracil, an inhibitor of the 5-FU-degrading

*Correspondence to: Prof. Kenichi Sugihara, Department of Surgical Oncology, Tokyo Medical and Dental University Graduate School, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. Tel: +81-3-5803-5257; Fax: +81-3-5803-0138; E-mail: k-sugi.srg2@tmd.ac.jp

enzyme, dihydropyrimidine dehydrogenase (DPD), in a molar ratio of 1 : 4. Both the NSABP C-06 trial conducted in the United States [5] and the JCOG0205 study conducted in Japan [6] demonstrated the noninferiority of UFT/LV to i.v. 5-FU/LV as adjuvant chemotherapy for stage III disease. UFT/LV is one of the commonly used regimens in adjuvant chemotherapy for stage III patients in Japan.

S-1 (Taiho Pharmaceutical Co., Ltd) is another oral fluoropyrimidine approved in Japan for various cancers including colorectal cancer, and for gastric cancers in a total of 38 countries (Asia and Europe). It combines tegafur, gimeracil, and oteracil in a molar ratio of 1 : 0.4 : 1. Gimeracil, a DPD inhibitor, is ~180-fold more potent than uracil. Oteracil inhibits the conversion of 5-FU to active metabolites in the gastrointestinal tract, resulting in reduction of the gastrointestinal toxicity [7]. Phase III studies have demonstrated that combination with S-1 and other cytotoxic agents, such as cisplatin in advanced gastric cancer and irinotecan and oxaliplatin in advanced colorectal cancer, is noninferior to conventional 5-FU-based regimens [7, 8]. Regarding adjuvant chemotherapy, postoperative S-1 treatment significantly improved survival in patients with gastric cancer and pancreatic cancer [7, 9]. Additionally, S-1 has some potential advantages including lower drug cost compared with UFT/LV, and reported lower frequency of hand–foot syndrome (HFS) compared with capecitabine [7]. However, the efficacy of S-1 as adjuvant chemotherapy for colon cancer has not been established.

We therefore conducted an open-label, multicenter, randomized, controlled noninferiority study, ACTS-CC, to evaluate the noninferiority of S-1 to UFT/LV and thereby confirm the usefulness of S-1 in the adjuvant setting for stage III colon cancer. The results of safety analysis have been previously reported [10]. This paper focuses on disease-free survival (DFS) as the primary end point.

patients and methods

patients

This study was conducted in accordance with the Declaration of Helsinki and Japanese Ethical Guidelines for Clinical Research, and was approved by the Institutional Review Boards of each participating institute. Written informed consent was obtained from all patients before enrollment.

The main inclusion criteria were as follows: age 20–80 years, histologically confirmed stage III colon adenocarcinoma after curative surgery, performance status of 0–1, no prior chemotherapy or radiotherapy for colon cancer, no other active malignancy, adequate oral intake, and preserved major organ function.

randomization and masking

Random assignment was carried out centrally; a minimization algorithm was used to maintain a 1 : 1 (S-1 : UFT/LV) treatment balance within each institute and within lymph node (LN) metastasis strata (N1 or N2 in UICC-TNM 7th classification). Treatment assignment was not masked from investigators or patients.

protocol treatment

In the S-1 group, S-1 was orally administered at a dose corresponding to the body surface area (BSA) (40 mg with BSA <1.25 m^2; 50 mg with BSA 1.25–1.50 m^2; 60 mg with BSA >1.50 m^2) twice daily after meals for 28 consecutive days, followed by a 14-day rest. A total of four courses (24 weeks) were administered.

In the UFT/LV group, UFT (300 mg with BSA <1.17 m^2, 400 mg with BSA 1.17–1.49 m^2, 500 mg with BSA 1.50–1.83 m^2, 600 mg with BSA >1.83 m^2) and LV (75 mg/body) were administered orally in three divided doses (every 8 h) more than 1 h before or after meals for 28 consecutive days, followed by a 7-day rest. A total of five courses (25 weeks) were administered.

Assigned treatment was started within 8 weeks after surgery. Additional details, i.e. dose modifications, were provided previously [10].

follow-up

After completion of the protocol treatment, patients were followed-up according to a predefined surveillance schedule until recurrence, other malignancies, or death was confirmed. The surveillance schedule included serum tumor marker test every 3 months for 3 years and then every 6 months for up to 5 years; chest and abdominal computed tomography every 6 months for 5 years; and colonoscopy at 1, 3, and 5 years after surgery. Recurrence was confirmed on the basis of imaging studies.

DFS was defined as the time from randomization to recurrence, other malignancies, or death, whichever occurred first. Overall survival (OS) was calculated from randomization to death from any cause.

statistical design and analysis

The primary objective of the study was to demonstrate the noninferiority of S-1 to UFT/LV in terms of DFS. Based on the results reported by the Japanese clinical trial and cancer registry [11, 12], the 3-year DFS rate was assumed to be 75.0% in both groups. The steering committee deemed that a 6% lower 3-year DFS rate for S-1 than for UFT/LV would be clinically acceptable as the lower limit for noninferiority; this corresponded to a hazard ratio (HR) noninferiority margin of 1.29. With a type 1 error of ≤5% in the one-sided test and a power of ≥80%, considering an accrual period of 15 months, the required number of DFS events and patients was estimated to be 381 and 1436 per study, respectively [13]. A target sample size of 1480 was determined in consideration of a 3% drop-out rate.

Primary analysis was carried out using a data cutoff at 3 years after enrollment of the last patient (data cutoff date: 5 October 2012). Primary comparisons were based on the intention-to-treat principle, with data of the full analysis set. DFS curves were estimated using the Kaplan–Meier method, and the noninferiority log-rank test with stratification by LN metastasis (N1/N2) was carried out with a one-sided significance level of 0.05 [14]. The HR for DFS and its confidence interval (CI) were calculated using a stratified Cox proportional hazard model with LN metastasis (N1/N2) as stratification factor. In addition, the HR adjusted with key baseline factors using a multivariate Cox regression model was also estimated. Subgroup analysis was carried out using a Cox proportional hazard model with baseline patient characteristics, treatment groups, and these corresponding interaction terms. Secondarily, OS was analyzed in the same manner as DFS. With a median follow-up of 3 years, it was too early to compare OS, and only descriptive analysis of OS is presented in this paper. Updated survival data will be open in 2015. Data were analyzed using the SAS version 9.3 software (SAS Institute, Inc., Cary, NC) and R version 2.13.0 software (R Foundation for Statistical Computing).

results

patient characteristics

From April 2008 to June 2009, 1535 patients were enrolled from 358 hospitals in Japan. After excluding 17 patients who were found to be ineligible, 1518 were included in the full analysis set

(758 and 760 in the S-1 and UFT/LV group, respectively) (Figure 1).

The median age at enrollment was 66 years, and 35.3% patients were ≥70 years. Wide LN dissection (D3 in the Japanese Classification [15]) was carried out in 79.8% patients, and the median number of LNs examined was 17. Regarding the number of metastatic LNs, 78.6% patients had one to three positive nodes, and the median was 2. The TNM-stage distribution was similar in the two groups (Table 1).

disease-free survival

At the time of the analysis [median follow-up, 41.3 months; interquartile range (IQR), 37.9–45.0], 197 (26.0%) patients in the S-1 group and 227 (30.0%) in the UFT/LV group had DFS events; The DFS rate at 3 years was 75.5% (95% CI 72.2–78.4) in the S-1 group and 72.5% (95% CI 69.1–75.5) in the UFT/LV group (supplementary Table S1, available at *Annals of Oncology* online). The DFS curves for both groups are shown in Figure 2A. The *P* value for a noninferiority log-rank test with stratification was <0.001, demonstrating the noninferiority of the S-1 group to the UFT/LV group. The stratified HR for DFS was 0.85 (95% CI 0.70–1.03), which was similar even after excluding patients without the allocated treatment ($N = 1504$). And the HR adjusted by key baseline factors shown in Figure 3 was 0.87 (95% CI 0.71–1.06). DFS curves were clearly separated by TNM-stage subgroup (Figure 2B). In the subgroup analysis, no significant interactions were identified between the major baseline characteristics and the therapeutic effects of S-1 and UFT/LV; noninferiority of S-1 was not excluded in any subgroup defined on the basis of prognostic factors at baseline (Figure 3).

overall survival

At the time of the cutoff date for the primary analysis, 67 (8.8%) patients in the S-1 group and 77 (10.1%) in the UFT/LV group had died; the OS rate at 3 years was 93.6% (95% CI 91.5–95.1) in the S-1 group and 92.7% (95% CI 90.6–94.4) in the UFT/LV group.

safety

Details of the safety analysis have been previously reported [10]. In brief, stomatitis, anorexia, hyperpigmentation, and hematologic toxicities were common in S-1, while increased ALT and AST were common in UFT/LV. Except for diarrhea in the UFT/LV group (incidence, 5.5%), grade 3 or 4 toxicities occurred in <5% of both groups (supplementary Figure S1, available at Annals of Oncology online). The protocol treatment completion rate in the S-1 and UFT/LV group was 76.5% and 73.4%, respectively, with no significant difference ($P = 0.171$). The mean

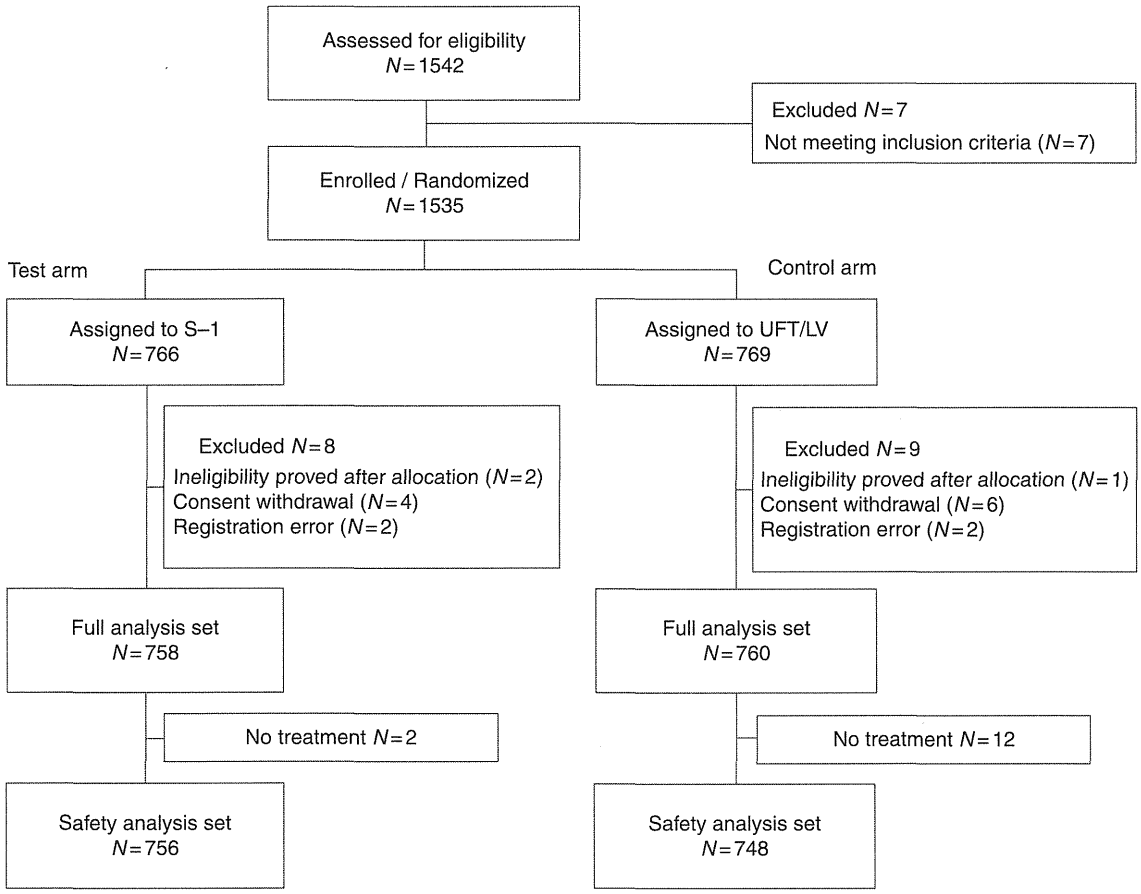


Figure 1. CONSORT diagram.

Table 1. Patient characteristics ($N = 1518$)

	S-1		UFT/LV	
	$N = 758$	%	$N = 760$	%
Age				
Median [range]	66.0 [23–80]		65.5 [32–80]	
≥70 years	279	36.8	257	33.8
Gender				
Male	411	54.2	403	53.0
Female	347	45.8	357	47.0
PS (ECOG)				
0	722	95.3	727	95.7
1	36	4.7	33	4.3
BMI				
Median [range]	21.9 [13.2–32.4]		22.1 [14.1–33.9]	
Tumor location				
Right-sided colon	324	42.7	268	35.3
Left-sided colon	278	36.7	314	41.3
Rectosigmoid colon	156	20.6	178	23.4
Preoperative CEA level				
≤5 ng/ml	470	62.0	499	65.7
>5 ng/ml	261	34.4	242	31.8
Unknown	27	3.6	19	2.5
Scope of LN dissection[a]				
D1	5	0.7	6	0.8
D2	143	18.9	153	20.1
D3	610	80.5	601	79.1
No. of LN examined				
Median [range]	18.0 [1–78]		16.0 [1–78]	
≥12	576	76.0	548	72.1
Depth of tumor invasion (TNM 7th)				
T1	41	5.4	47	6.2
T2	76	10.0	77	10.1
T3	429	56.6	433	57.0
T4a	184	24.3	169	22.2
T4b	28	3.7	34	4.5
Histology[a]				
Papillary	14	1.8	22	2.9
Tubular	693	91.4	685	90.1
Poorly, mucinous, signet	51	6.7	53	7.0
Lymphatic invasion				
Negative	131	17.3	146	19.2
Positive	627	82.7	613	80.7
Unknown	–	–	1	0.1
Venous invasion				
Negative	254	33.5	241	31.7
Positive	504	66.5	518	68.2
Unknown	–	–	1	0.1
No. of LN metastasis				
Median [range]	2.0 [1–26]		2.0 [1–25]	
LN metastasis (TNM 7th)				
N1a	331	43.7	331	43.6
N1b	266	35.1	265	34.9
N2a	116	15.3	115	15.1
N2b	45	5.9	49	6.4
Stage (TNM 7th)				
IIIA	106	14.0	119	15.7
IIIB	551	72.7	525	69.1
IIIC	101	13.3	116	15.3

Right-sided colon includes cecum, ascending, and transverse colon. Left-sided colon includes descending and sigmoid colon.

[a]Japanese Classification of Colorectal Carcinoma, Second English Edition [15].

PS, performance status; ECOG, Eastern Cooperative Oncology Group; BMI, Body mass index; CEA, carcinoembrionic antigen; LN, lymph node.

of the relative dose intensity, including discontinuation cases, was 76.5% and 76.0% in the S-1 and UFT/LV group, respectively; the median was 95% in both groups.

discussion

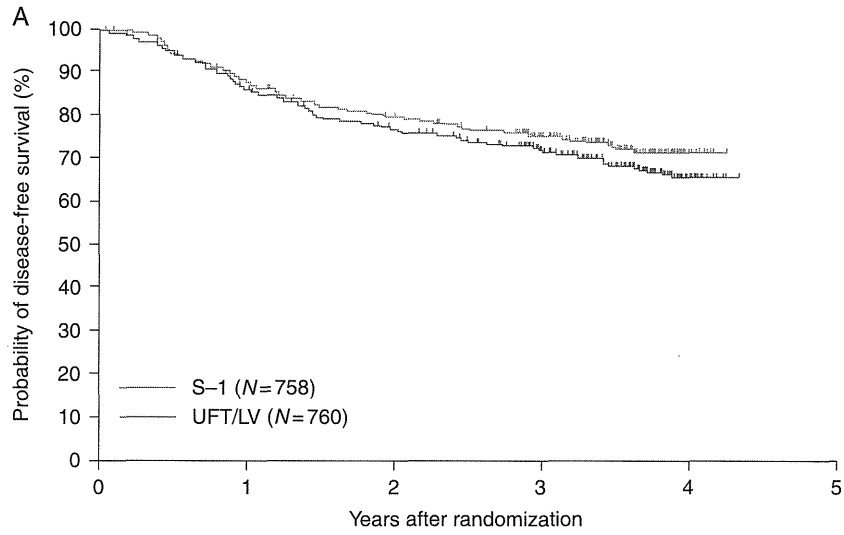
This study, for the first time, demonstrated the efficacy of S-1 as adjuvant chemotherapy for stage III colon cancer by confirming its noninferiority to UFT/LV in terms of DFS. As we previously reported [10], though the profile of toxicities differed, no significant difference was observed in terms of safety and feasibility between S-1 and UFT/LV.

Additionally, S-1 has several potential advantages over UFT/LV. First, the drug cost in Japan for 6 months of S-1 treatment is half that of UFT/LV treatment. Given its noninferiority in DFS, S-1 could be a welcome development from the both patients' and payers' perspective. An associated cost-effectiveness analysis is being conducted.

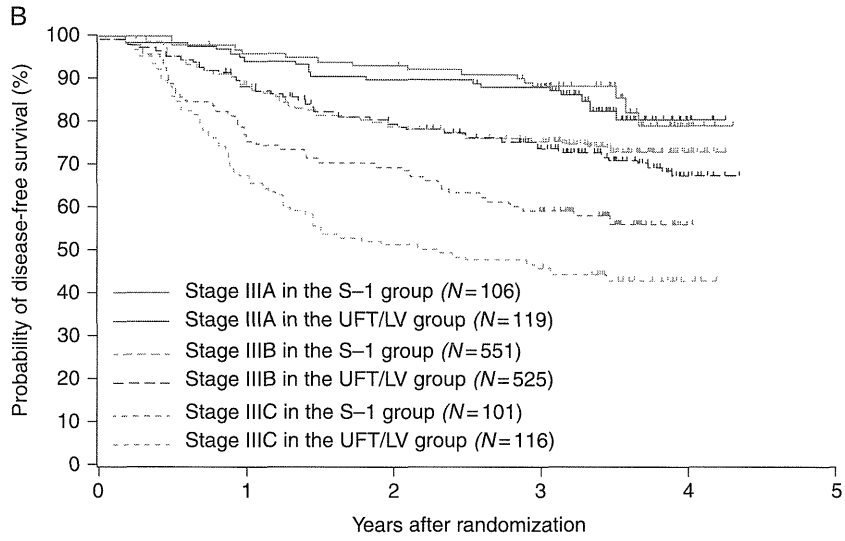
Second, S-1 may be more convenient to administer than UFT/LV. Although no definite difference in treatment compliance between the groups was observed over the relatively short treatment period (~6 months) [10], many physicians think that patients regard the complex UFT/LV treatment schedule (every 8 h, avoiding 1 h before or after meals) as an obstacle, and the simpler S-1 treatment schedule (twice daily after meals) to be preferable.

Furthermore, when comparing S-1 with another oral fluoropyrimidine, capecitabine, the incidence of HFS must be taken into consideration. HFS is a common AE in capecitabine treatment, which often interferes with the patients' daily living; the X-ACT study showed that 60% patients treated with capecitabine experienced HFS, and 17% experienced ≥grade 3 [16]. In our study, S-1 rarely caused HFS (incidence, 1.3%) [10]; this can be a notable advantage of S-1 over capecitabine. A phase III study comparing S-1 and capecitabine as adjuvant chemotherapy for stage III colon cancer is currently in progress in Japan (UMIN-CTR: UMIN000003272).

Personalization of adjuvant chemotherapy is an important issue to be resolved. We have focused on the differences in the mechanism of action between S-1 and UFT/LV or capecitabine,



No. at risk						
S–1		758	656	593	495	20
UFT/LV		760	647	572	466	21



No. at risk						
Stage IIIA	S–1	106	99	95	83	4
	UFT/LV	119	111	105	93	2
Stage IIIB	S–1	551	481	428	356	16
	UFT/LV	525	459	409	328	15
Stage IIIC	S–1	101	76	70	56	0
	UFT/LV	116	77	58	45	4

Figure 2. Disease-free survival. (A) Disease-free survival by treatment arm. Noninferiority stratified log-rank test, $P < 0.001$. The hazard ratio in the S-1 group compared with the UFT/LV group was 0.85 [95% confidence interval (CI) 0.70–1.03]. The disease-free survival rate at 3 years was 75.5% (95% CI 72.2–78.4) in the S-1 group and 72.5% (95% CI 69.1–75.5) in the UFT/LV group. (B) Disease-free survival by UICC-TNM 7th stage. Disease-free survival rates at 3 years in stage IIIA, IIIB, and IIIC patients were 88.3%, 75.9%, and 60.1%, respectively, in the S-1 group, and 87.9%, 74.2%, and 46.4%, respectively, in the UFT/LV group.

and associated translational researches investigating the tumor mRNA expressions and DNA copy numbers of 5-FU-related enzymes are being conducted.

On the basis of their reported superiority in DFS with a constant HR of 0.8 compared with 5-FU/LV [3, 4], oxaliplatin-containing regimens have been adopted as standard adjuvant chemotherapy in the United States and Europe since the mid-2000s. While oxaliplatin is an efficacious agent, its expected benefit may not be the same in all patients. de Gramont et al. indicated that stage III consists of subgroups of patients with

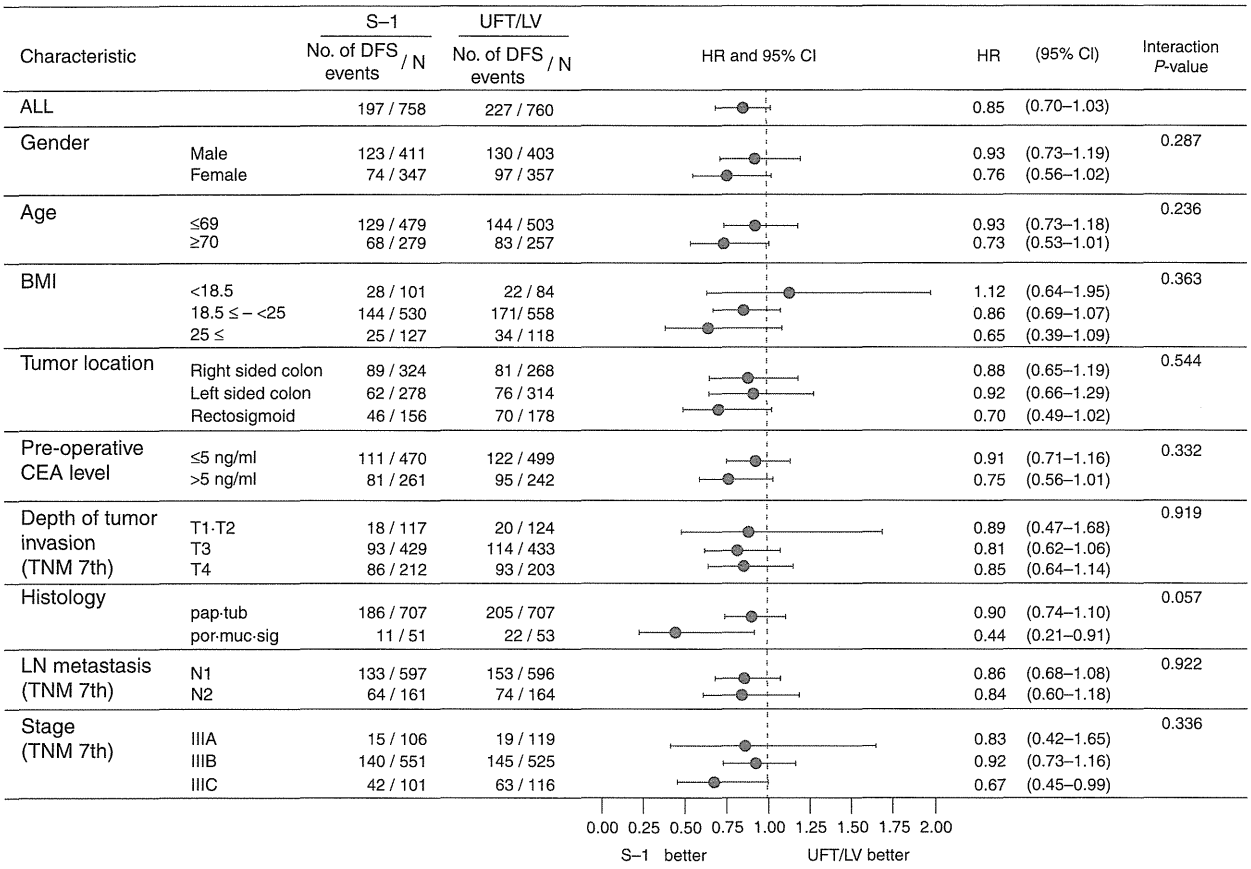


Figure 3. Subgroup analysis of disease-free survival in the S-1 group compared with the UFT/LV group. DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CEA, carcinoembryonic antigen; pap, papillary adenocarcinoma; tub, tubular adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; sig, signet-ring cell carcinoma.

various prognoses, and the expected benefits of oxaliplatin could vary according to stage subgroups [17].

The prognosis of stage IIIA patients in this study was favorable; their 3-year DFS rate was 88%, and it was similar to that (84.3%) of the stage II subgroup of the 5-FU/LV group in the MOSAIC study which did not recommend FOLFOX for stage II patients [18]. Similarly, when the HR for DFS with adding oxaliplatin is estimated to be 0.8 as reported [3, 4], the expected gain in 3-year DFS rate by adding oxaliplatin in these patients would be as small as 2%–3%. On the other hand, in the MOSAIC study, 15% patients received FOLFOX experienced some form of peripheral sensory neuropathy even at 4 years later [3]. Considering the expected benefits and the possible risks of increased toxicity and medical costs, oral fluoropyrimidine alone can be a considerable option for stage IIIA patients. In contrast, the prognosis of stage IIIC patients is poor. Oxaliplatin can be required for these 'high-risk stage III' patients.

Increasing numbers of elderly cancer patients is a common tendency among the developed nations. Patients aged ≥70 occupy 35% of our study population and 60% of colon cancer patients in the Japanese nationwide cancer registry [19]. Recent subgroup analysis showed marginal survival benefit from oxaliplatin as adjuvant treatment of patients aged ≥70, whereas oral fluoropyrimidines retained their efficacy [18, 20]. Therefore, oral fluoropyrimidines may play an important role in adjuvant chemotherapy for elderly patients. Age subgroup analyses are currently in progress.

In conclusion, adjuvant chemotherapy using S-1 for stage III colon cancer was demonstrated to be noninferior in DFS compared with UFT/LV. This study has presented S-1 as a new adjuvant treatment option that offers a lower drug cost and more convenient administration than UFT/LV and a lower incidence of HFS than capecitabine.

acknowledgements

We are grateful to all patients and co-investigators for their cooperation for the ACTS-CC trial (Adjuvant Chemotherapy Trial of TS-1® for Colon Cancer). A list of participating institutions is given in the supplementary Appendix, available at *Annals of Oncology* online. The authors also thank the following additional investigators for their contributions to this trial: Yasuyo Kusunoki, Fumie Kinoshita, Hideki Kono, and Naoko Kashiwagi for data management; Akinori Ogasawara and Yuri Ueda as the project office staff; Hiroyuki Uetake, Toshiaki Ishikawa, Yoko Takagi, Aiko Saito, Sachiko Kishiro, and Yasuyo Okamoto as the translational study office staff; and Masanori Fukushima as a director of the Translational Research Informatics Center. The authors dedicate this article to the memory of Prof. Hiroya Takiuchi, who contributed to the conception and design of this study.

funding

This work was supported by the Foundation for Biomedical Research and Innovation, Translational Research Informatics Center, under the funding contract with Taiho Pharmaceutical Co. Ltd., Japan.

disclosure

MY has received honoraria from Taiho Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co. Ltd, Chugai Pharmaceutical Co. Ltd, Bristol-Myers Squibb, Merck Serono Co. Ltd, Bayer Yakuhin, Ltd; research funding from Taiho, Takeda, Chugai, Bristol-Myers, Daiichi Sankyo Co. Ltd, Sanofi K.K., Kyowa Hakko Kirin Co. Ltd, Nippon Kayaku Co. Ltd, Ono Pharmaceutical Co. Ltd, and Jansen Pharmaceutical K.K. MI has received consulting fees from Taiho; honoraria from Taiho, Chugai, and Yakult Honsha Co. Ltd. KI has received research funding from Taiho. AT has received honoraria from Taiho. HM has received consulting fees from Otsuka Pharmaceutical Factory, Inc., and Sysmex Co.; honoraria from Taiho, Otsuka, Chugai, Yakult Honsha, Daiichi Sankyo, and Astellas Pharma, Inc.; research funding from Taiho, Otsuka, Takeda, and Pfizer Co. Ltd. KK has received consulting fees from Taiho and Chugai; honoraria from Taiho, Otsuka, Chugai, Takeda, Bristol-Myers, and Merck Serono. SK has received honoraria from Taiho, and Takeda; research funding from Taiho, Takeda, and Pfizer. KT has received honoraria from Taiho, Takeda, and Chugai. TW has received honoraria and research funding from Taiho, Takeda, Chugai, Daiichi Sankyo, Yakult Honsha, Bristol-Myers, and Merck Serono. MW has received consulting fees from Taiho, Chugai, Yakult Honsha, Johnson and Johnson KK and Covidien Japan Co. Ltd. NB has received honoraria from Taiho, Takeda, Daiichi Sankyo, Yakult Honsha, and Ono; research funding from Taiho. NT has received honoraria from Taiho, Takeda, Chugai, and Merck Serono; research funding from Taiho, Chugai, and Yakult Honsha. KS has received consulting fees from Taiho, Chugai, Bayer Yakuhin, Bristol-Myers, and Merck Serono; honoraria from Taiho, Takeda, Chugai, Yakult Honsha, Bristol-Myers, Merck Serono, and Kyowa Hakko Kirin; research funding from Taiho, Otsuka, Takeda, Chugai, Yakult Honsha, Daiichi Sankyo, Bristol-Myers, Merck Serono, Kyowa Hakko Kirin, Ono, Tsumura & Co., Eisai Co. Ltd, Torii Pharmaceutical Co. Ltd, and Kaken Pharmaceutical Co. Ltd. All remaining authors have declared no conflicts of interest.

references

1. Labianca R, Nordlinger B, Beretta GD et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 (suppl 6): vi64–vi72.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; Colon cancer version 3. 2014; http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (9 June 2014, date last accessed).
3. André T, Boni C, Navarro M et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009; 27: 3109–3116.
4. Haller DG, Tabernero J, Maroun J et al. Capecitabine plus oxaliplatin compared with fluorouracil and folnic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011; 29: 1465–1471.
5. Lembersky BC, Wieand HS, Petrelli NJ et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. J Clin Oncol 2006; 24: 2059–2064.
6. Shimada Y, Hamaguchi T, Mizusawa J et al. Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. Eur J Cancer 2014 June 20 [epub ahead of print], doi: 10.1016/j.ejca.2014.05.025.
7. Satoh T, Sakata Y. S-1 for the treatment of gastrointestinal cancer. Expert Opin Pharmacother 2012; 13: 1943–1959.
8. Yamada Y, Takahari D, Matsumoto H et al. Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizmab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomized phase 3 trial. Lancet Oncol 2013; 14: 1278–1286.
9. Uesaka K, Fukutomi A, Boku N et al. Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 for patients with resected pancreatic cancer (JASPAC-01 study). J Clin Oncol 2013; 31: 4s (abstr 145).
10. Mochizuki I, Takiuchi H, Ikejiri K et al. Safety of UFT/LV and S-1 as adjuvant therapy for stage III colon cancer in phase III trial: ACTS-CC trial. Br J Cancer 2012; 106: 1268–1273.
11. Hamaguchi T, Shirao K, Moriya Y et al. Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). Cancer Chemother Pharmacol 2011; 67: 587–596.
12. Watanabe T, Itabashi M, Shimada Y et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 2012; 17: 1–29.
13. Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics 1982; 38: 163–170.
14. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons, 1980.
15. Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal Carcinoma-Second English Edition. Tokyo: Kanehara & Co., Ltd., 2009.
16. 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.
17. de Gramont A, Chibaudel B, Bachet JB et al. From chemotherapy to targeted therapy in adjuvant treatment for stage III colon cancer. Semin Oncol 2011; 38: 521–532.
18. Tournigand C, André T, Bonnetain F et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer Trial. J Clin Oncol 2012; 30: 3353–3360.
19. Foundation for Promotion of Cancer Research. Cancer statistics in Japan 2013; http://ganjoho.jp/pro/statistics/en/backnumber/2013_en.html (9 June 2014, date last accessed).
20. McCleary NJ, Meyerhardt JA, Green E et al. Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: findings from the ACCENT database. J Clin Oncol 2013; 31: 2600–2606.

J Gastroenterol (2014) 49:1047–1055
DOI 10.1007/s00535-013-0860-8

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—ALIMENTARY TRACT

Risk model for right hemicolectomy based on 19,070 Japanese patients in the National Clinical Database

Hirotoshi Kobayashi · Hiroaki Miyata · Mitsukazu Gotoh · Hideo Baba · Wataru Kimura · Yuko Kitagawa · Tohru Nakagoe · Mitsuo Shimada · Naohiro Tomita · Kenichi Sugihara · Masaki Mori

Received: 10 March 2013 / Accepted: 17 July 2013 / Published online: 27 July 2013

Abstract
Background Right hemicolectomy is a very common procedure throughout the world, although this procedure is known to carry substantial surgical risks. The present study aimed to develop a risk model for right hemicolectomy outcomes based on a nationwide internet-based database.
Methods The National Clinical Database (NCD) collected records on over 1,200,000 surgical cases from 3,500 Japanese hospitals in 2011. After data cleanup, we analyzed 19,070 records regarding right hemicolectomy performed between January 2011 and December 2011.
Results The 30-day and operative mortality rates were 1.1 and 2.3 %, respectively. The 30-day mortality rates of patients after elective and emergency surgery were 0.7 and 6.0 %, respectively ($P < 0.001$). The odds ratios of preoperative risk factors for 30-day mortality were: platelet <50,000/μl, 5.6; ASA grade 4 or 5, 4.0; acute renal failure, 3.2; total bilirubin over 3 mg/dl, 3.1; and AST over 35 U/l, 3.1. The odds ratios for operative mortality were: previous peripheral vascular disease, 3.1; cancer with multiple metastases, 3.1; and ASA grade 4 or 5, 2.9. Sixteen and 26 factors were selected for risk models of 30-day and operative mortality, respectively. The c-index of both models was 0.903 [95 % confidence interval (CI) 0.877–0.928; $P < 0.001$] and 0.891 (95 % CI 0.873–0.908; $P < 0.001$), respectively.
Conclusion We performed the first reported risk stratification study for right hemicolectomy based on a nationwide internet-based database. The outcomes of right hemicolectomy in the nationwide population were satisfactory. The risk models developed in this study will help to improve the quality of surgical practice.

Keywords Right hemicolectomy · Colorectal cancer · Mortality · Risk model · National Clinical Database

H. Kobayashi
The Japanese Society of Gastroenterological Surgery, Database Committee Working Group, Tokyo, Japan

H. Kobayashi (✉)
Center for Minimally Invasive Surgery, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
e-mail: h-kobayashi.srg2@tmd.ac.jp

H. Miyata · M. Gotoh
National Clinical Database, Tokyo, Japan

H. Miyata · M. Gotoh · H. Baba · W. Kimura · Y. Kitagawa · T. Nakagoe · M. Shimada · N. Tomita
The Japanese Society of Gastroenterological Surgery, Database Committee, Tokyo, Japan

K. Sugihara · M. Mori
The Japanese Society of Gastroenterological Surgery, Tokyo, Japan

Introduction

The rate of colorectal cancer in Japan is rapidly increasing [1, 2]. Although the extent of lymphadenectomy for colorectal cancer differs according to institutions, operative procedures such as bowel resection and anastomosis have been established. Right hemicolectomy is one of the standard approaches to treating colorectal diseases. Although an established procedure, some risks of postoperative mortality and morbidity are associated with hemicolectomy. The risk of intraoperative bleeding is higher after more aggressive lymphadenectomy such as D3 lymph node