Table 1 The characteristics of identified claims (per person-month)

	Moderate risk	Percent	High risk	Percent	Total	Percent
Number of claims	7,369	60.7	4,764	39.3	12,133	100.0
Number of patients	1,375	50.0	1,374	50.0	2,749	100.0
Age (range)		(18–89)		(18–75)		(18–89)
Mean (SD)	53.1	(10.4)	51.2	(10.8)	52.4	(10.6)
Under 29 years old	166	2.3	157	3.3	323	2.7
30–49 years old	2,282	31.0	1,864	39.1	4,146	34.2
50–69 years old	4,582	62.2	2,579	54.1	7,161	59.0
Above 70 years old	339	4.6	164	3.4	503	4.1
Under 50 years old	2,448	33.2	2,021	42.4	4,469	36.8
Gender						
Female	3,528	47.9	2,984	62.6	6,512	53.7
Male	3,841	52.1	1,780	37.4	5,621	46.3
Primary cancer site						
Colorectal	3,330	40.0	35	0.7	3,365	24.7
Breast	508	6.1	1,831	34.5	2,339	17.2
Lung	1,094	13.1	415	7.8	1,509	11.1
Stomach	245	2.9	588	11.1	833	6.1
Uterus	496	6.0	216	4.1	712	5.2
Prostate	5	0.1	8	0.2	13	0.1
Others	1,691	20.3	1,671	31.5	3,362	24.7
More than one site	3,651	43.9	1,478	27.8	5,129	37.6
Chemotherapeutic drug[a]						
High emetic risk agent						
Cisplatin (iv)			2,134	44.8		
Epirubicin and cyclophosphamide (iv)			1,444	30.3		
Anthracycline and cyclophosphamide (iv)			1,033	21.7		
Cyclophosphamide (iv) >1,500 mg			505	10.6		
Moderate emetic risk agent[a]						
Carboplatin (iv)	2,042	27.7				
Irinotecan (iv)	1,952	26.5				
Oxaliplatin (iv)	1,949	26.4				
Methotrexate (iv)	409	5.6				
Cyclophosphamide (iv)<=1,500 mg	406	5.5				
Pirarubicin (iv)	233	3.2				
Epirubicin single use (iv)	230	3.1				
Nedaplatin (iv)	222	3.0				
Amrubicin (iv)	121	1.6				
Idarubicin (iv)	46	0.6				
Daunorubicin (iv)	34	0.5				
Actinomycin D (iv)	7	0.1				
CMF	110	1.5				

iv intravenous injection, *CMF* combination of cyclophosphamide (oral medication), methotrexate, and 5-fluorouracil

[a] Some drugs were prescribed more than once

available before 2009, we also analyzed the trend of prescribing antiemetic drugs after excluding DPC/PDPS admissions, as a sensitivity analysis. This sensitivity analysis was intended to examine the effects of systematic changes in information starting in 2009. All analyses were performed using Stata 12.1 (Stata Corporation, College Station, TX, USA).

Ethical consideration

This study was approved by the ethical committee at the School of Medicine, University of Tokyo.

Results

We extracted 12,133 claims for chemotherapy with high or moderate emetic risk for 2,749 patients (high emetic risk—4,764 claims for 1,374 patients; moderate emetic risk—7,369 claims for 1,375 patients). Table 1 shows the characteristics of the samples. The mean age at treatment was 52.4 years. In the high emetic risk group, 62.6 % of the patients (N=2,984) were female, and 34.5 % of the patients in this group (N=1,831) had breast cancer. In the moderate emetic risk group, 40.0 % of the patients (N=3,330) had colorectal cancer. Multiple cancer diagnoses were found in 37.6 %. Cisplatin (44.8 %) was the most frequently used chemotherapy agent for the high emetic risk group. Carboplatin (27.7 %), irinotecan (26.5 %), oxaliplatin (26.4 %), and methotrexate (5.6 %) were the most frequently used chemotherapy agents for the moderate emetic risk group.

Figures 1 and 2 show the prescription trends for antiemetic drugs. Overall, two-drug antiemetic prescriptions for the high emetic risk group increased from 81.1 % in 2005 to 95.5 % in 2011 (p<0.001), and prescriptions for the moderate emetic risk group increased from 78.5 % in 2005 to 89.9 % in 2011 (p<0.001). After approval of an NK_1 antagonist, the rate of prescribing the three-drug combination was 37.0 % in 2010 (95 % confidence interval, 32.6–41.5 %) and 60.1 % in 2011 (95 % CI, 55.3–64.7 %) for the high emetic risk group. The rate of prescribing the three-drug combination for patients who received irinotecan, carboplatin, and/or methotrexate, for which the guidelines specifically recommend three-drug combination, also rose from 9.0 % in 2010 (95 % CI, 5.8–13.7 %) to 25.8 % in 2011 (95 % CI, 18.9–34.2 %).

After excluding claims for DPC/PDPS programs, 9,245 claims remained: 3,360 for the high emetic risk group and 5,885 for the moderate emetic risk group (please see Online Resource 1). Patient characteristics (e.g., age, primary cancer site, gender) were similar to our previous data. The percentage of prescribing antiemetic drugs increased from 81.1 % in 2005 to 94.8 % in 2011 in the high emetic risk group (p=0.059) and from 78.4 % in 2005 to 91.0 % in 2011 in the moderate emetic risk group (p<0.001).

Discussion

A gradual increasing trend was identified in the rate of prescribing antiemetic drugs for both high and moderate emetic risk groups from 2005 to 2011. The same trend was also found for the data that excluded the claims of DPC/PDPS programs. Prescriptions for the three-drug combination with an NK_1 antagonist, as well as the traditional two-drug combination of a $5\text{-}HT_3$ antagonist and a corticosteroid, dramatically increased after the approval of an NK_1 antagonist in the high emetic risk group. Prescriptions for the three-drug combination for patients in the moderate emetic risk group also increased between 2010 and 2011. Japan's guidelines recommend the preventive use of aprepitant in addition to the $5\text{-}HT_3$ antagonist and corticosteroid for patients with moderate emetic risk who are prescribed irinotecan, carboplatin, and/or

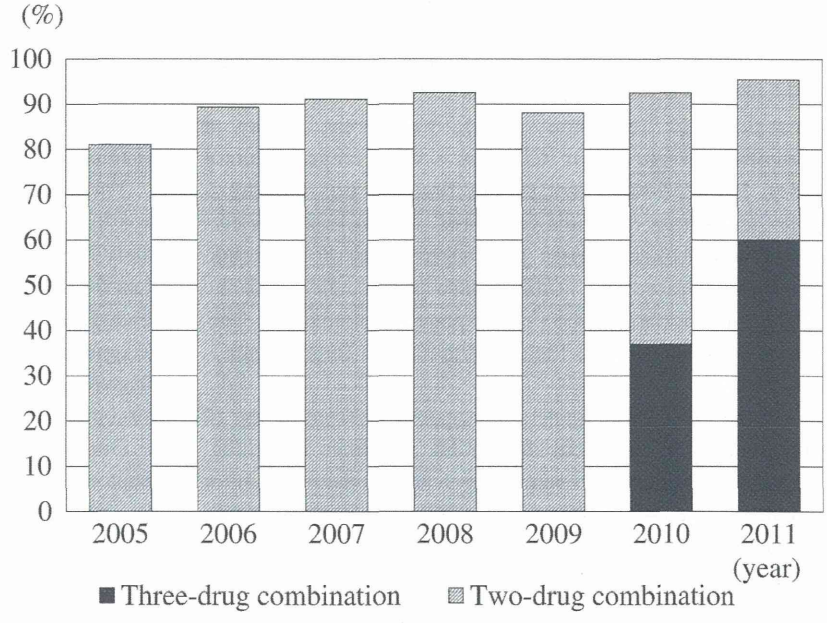

Fig. 1 Antiemetic therapy trends for high emetic risk patients. Three-drug combination: aprepitant, a $5\text{-}HT_3$ antagonist, and a corticosteroid. Two-drug combination: a $5\text{-}HT_3$ antagonist and a corticosteroid

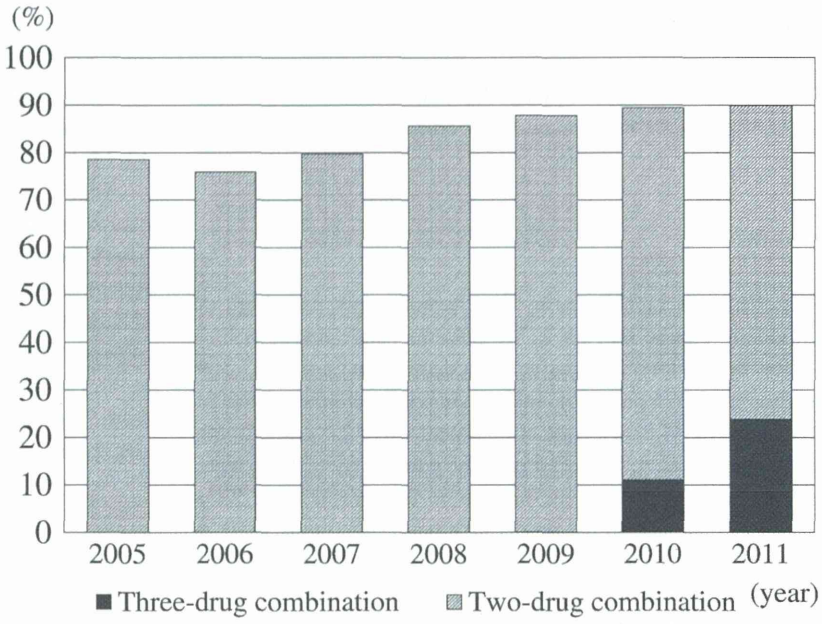

Fig. 2 Antiemetic therapy trends for moderate emetic risk patients. Three-drug combination: aprepitant, a 5-HT_3 antagonist, and a corticosteroid. Two-drug combination: a 5-HT_3 antagonist and a corticosteroid

methotrexate for their chemotherapy. The recent study by Rapoport et al. [10] shows that the aprepitant regimen is effective in the treatment of CINV in a broad range of chemotherapy patients with moderate emetic risk for both no-vomiting and no-rescue medications. While this gradual increase appeared before the publication of Japan's guidelines, the guidelines may contribute to the increase in antiemetic prescriptions.

With this increase in prescriptions for antiemetic drugs, improvements to the antiemetic regimen for the high emetic risk group in Japan should be considered. Only 60.1 % of the high emetic risk group were prescribed the recommended three-drug combination. Previous studies report that nonprescribing of an NK_1 antagonist (e.g., aprepitant) was the common reason for nonadherence to the guidelines, reflecting the economic constraints of hospitals and government payers [9, 15]. Aapro et al. [20] report the efficacy of aprepitant for preventing CINV in a wide range of tumor types. Furthermore, recent studies find that this efficacy is consistent across races and ethnicities. Japanese studies also report similarity in plasma pharmacokinetics of aprepitant between Japanese and non-Japanese patients [21] and the efficacy for preventing CINV in Japanese patients [22]. This recent evidence supports the use of aprepitant for chemotherapy patients.

On the other hand, some argue against the routine use of aprepitant as an antiemetic drug. First, aprepitant is simultaneously a substrate, moderate inducer, and moderate inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4). Patients should not take aprepitant with pimozide, terfenadine, astemizole, or cisapride, because these combinations may cause serious or life-threatening reactions [6]. Second, a second-generation 5-HT_3 antagonist (e.g., palonosetron) was introduced in 2010. This new 5-HT_3 antagonist is considered far more effective than a first-generation 5-HT_3 antagonist (e.g., ondansetron) [23–26]. The additional use of an NK_1 antagonist with a two-drug regimen of dexamethasone and palonosetron may not provide an incremental effect [27]. Third, there is a problem of cost. Aprepitant is more expensive than other drugs, such as steroids. It adds a financial burden to cancer patients who must continue chemotherapy for long periods. Moore et al. [28] report that aprepitant provides modest incremental benefits compared to conventional management of CINV. However, in Japan, high-dose cisplatin is usually administered in an inpatient setting to manage CINV and to ensure adequate hydration [29]. Furukawa et al. [29] find that if high emetic risk drugs are prescribed with an aprepitant and sufficient oral hydration in an outpatient setting, then CINV and nephrotoxicity are controllable. This approach would reduce total treatment cost and improve patients' quality of life.

The prescription rate for the antiemetic drugs in our study was higher than the prescription rate found in our previous study during the same period of time [19]. Since we derived data for this study from the employees' insurance, the sample tended to be younger and to include more females, who are recognized as high risk for CINV. These differences in sample characteristics may have influenced the prescribing patterns for antiemetic drugs.

Our study has several limitations. First, exact prescription dates were not available from the insurance claim data, since the claim data accumulates all services and drugs provided in a month. We cannot exclude the possibility that the antiemetic drugs were administered after the occurrence of CINV and that patients might have received a corticosteroid to alleviate other

symptoms. Therefore, the prescription rate in this study may be overestimated. Nevertheless, the trend observed in this study is valid, since such influence would have affected the rates across the study period. Second, the exact drug dosages and the body surface area of patients were not available from the claims data. For example, certain doses were listed as ranges (e.g., methotrexate 250–1,000 mg/m^2), for which we classified all prescriptions as moderate emetic risk. However, in our sample, few patients used methotrexate for chemotherapy and other drugs were usually prescribed at the moderate risk dose. We expect that the influence of this limitation was minimal. Finally, our sample was derived from 20 employee's health insurance societies. This sample may not be generalizable to all Japanese patients. Despite these limitations, this study illustrated an increased use of antiemetic therapy in Japan by using insurance claim data from a wide variety of health-care providers. Insurance claims data is useful to capture physicians' adherence to evidence-based practices and clinical guidelines.

Conclusion

A gradual increasing trend was identified in the rate of prescribing antiemetic drugs to cancer patients in both the high and moderate emetic risk groups from 2005 to 2011, using the insurance claim data from a wide variety of health-care providers. Only 60.1 % of patients in the high emetic risk group received a three-drug combination with an NK_1 antagonist in 2011. Our study also provided an example of practice monitoring. Further research should build on our system to evaluate patients' experiences with chemotherapy and the effectiveness of prophylactic antiemetic therapies for cancer treatment and patients' quality of life.

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Conflict of interest The authors have declared no conflicts of interest.

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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

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

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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.

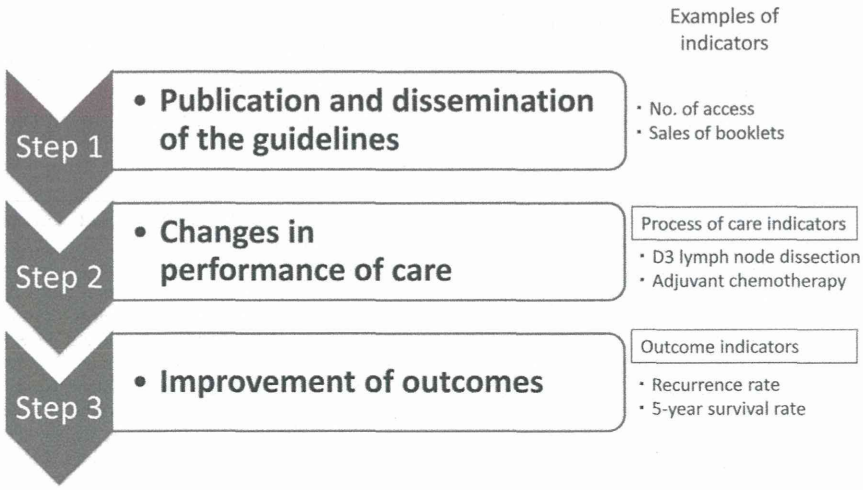

Figure 1. Three important steps for improving the quality of cancer care.

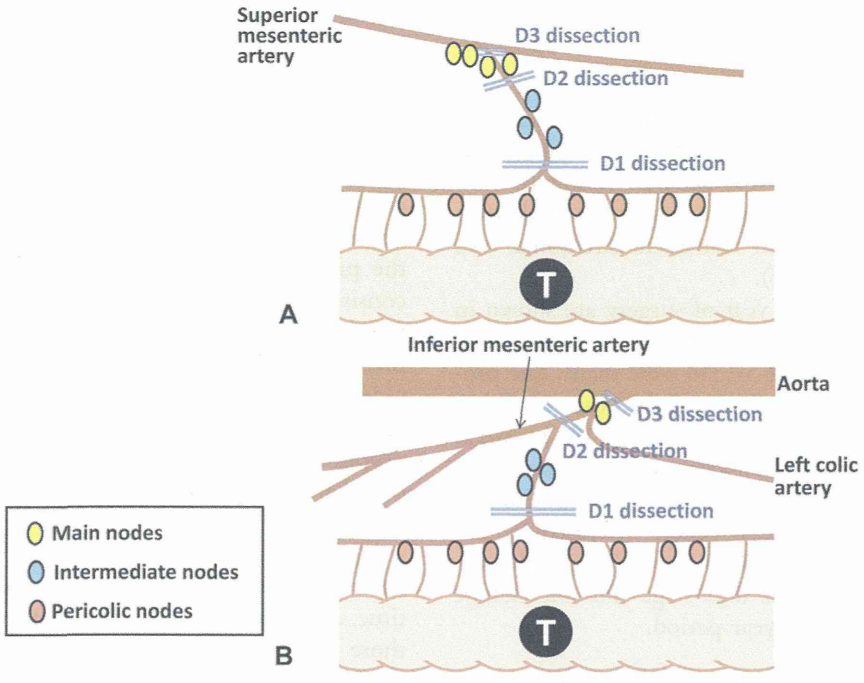

Figure 2. Scope of lymph node dissection in Japan. (A) Right-sided colon. (B) Left-sided and rectosigmoid colon. The double, parallel blue lines indicate transection points for the vessels.

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

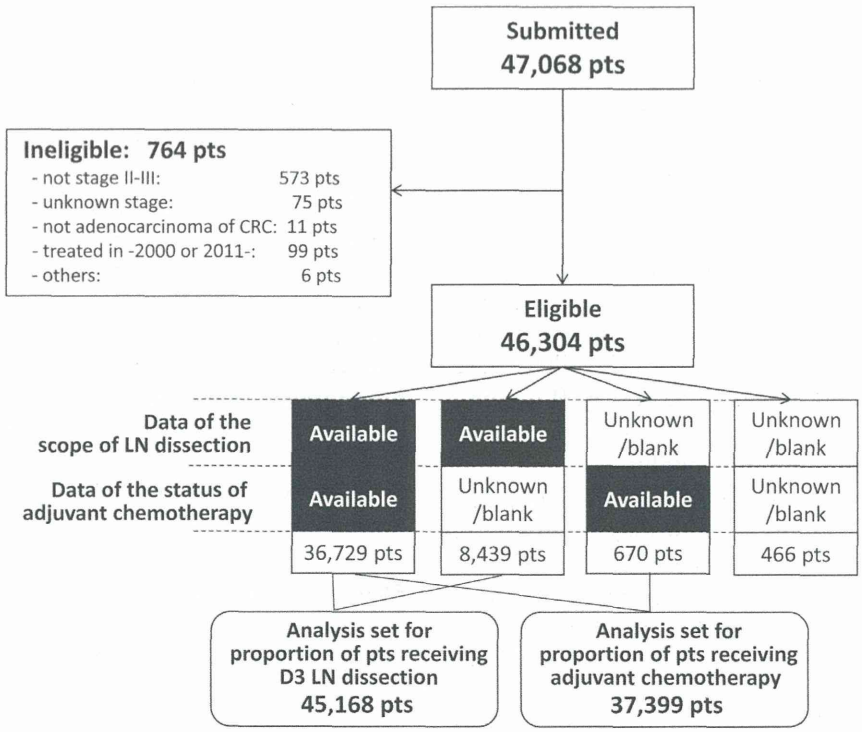

Figure 3. Subject flow diagram. CRC, colorectal cancer; LN, lymph node; pts, patients.

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