1－4　冠動脈バイパス術（新鮮凍結血漿・Cグループ）

病院記号	入院件数（件）	使用頻度（%）	一件あたりの使用量（単位）（注1）	O/E値
-	77	78	7.69	2.26
-	31	45	4.16	1.77
-	7	29	1.71	0.93
-	0	－	－	－
-	0	－	－	－
-	0	－	－	－
-	0	－	－	－
-	8	38	3.25	1.04
-	10	30	1.80	0.79
-	19	5	0.74	0.27
-	36	42	4.39	1.14
-	47	19	0.98	0.28
-	72	72	12.50	4.42
-	24	46	3.83	1.43
-	0	－	－	－
-	20	80	10.00	4.82
-	58	31	9.45	2.59
-	51	14	1.41	0.59
-	28	14	1.86	0.66
-	63	32	3.40	1.06
-	35	20	6.17	1.36
-	16	31	10.88	4.47
-	0	－	－	－
-	9	67	13.33	3.87
-	20	80	16.50	4.44
-	44	34	3.14	0.91
-	27	19	2.00	0.49
-	17	12	1.53	0.45
-	77	48	3.27	1.02
-	0	－	－	－
-	12	50	4.83	1.87
-	0	－	－	－
-	0	－	－	－
-	0	－	－	－

（注1）：血液製剤が投与された患者一人あたりの使用量

1－4　冠動脈バイパス術（アルブミン製剤・A グループ）

病院記号	入院件数（件）	使用頻度（%） 20 %・25 %	使用頻度（%） 5 %	一件あたりの使用量（単位）（注1）	O/E 値
-	46	20	67.00	32.61	1.32
-	0	－	－	－	－
-	27	7	93.00	50.46	2.32
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	6	17	67.00	43.75	1.98
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	68	0	15.00	2.76	0.14
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	1	0	0.00	0.00	0.00
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－

（注1）：血液製剤が投与された患者一人あたりの使用量

1－4　冠動脈バイパス術（アルブミン製剤・Bグループ）

病院記号	入院件数（件）	使用頻度（%） 20 %・25 %	使用頻度（%） 5 %	一件あたりの使用量（単位）（注1）	O/E値
-	0	－	－	－	－
-	26	0	73.00	2.84	0.13
-	0	－	－	－	－
-	0	－	－	－	－
-	7	0	86.00	32.14	1.77
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	13	0	69.00	20.19	0.95
-	0	－	－	－	－
-	0	－	－	－	－
-	8	0	38.00	20.31	1.63
-	0	－	－	－	－
-	0	－	－	－	－
-	35	46	23.00	41.07	1.78
-	0	－	－	－	－
-	16	63	0.00	22.63	0.92
-	5	0	20.00	2.50	0.09
-	79	92	67.00	49.68	1.93
-	26	0	0.00	0.00	0.00
-	0	－	－	－	－
-	0	－	－	－	－
-	10	10	50.00	46.25	2.48
-	0	－	－	－	－
-	31	3	26.00	8.47	0.33
-	2	0	0.00	0.00	0.00
-	3	0	33.00	0.42	0.02
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	7	14	100.00	48.21	2.44

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（注1）：血液製剤が投与された患者一人あたりの使用量

病院記号	入院件数（件）	使用頻度（%） 20%・25%	使用頻度（%） 5%	一件あたりの使用量（単位）（注1）	O/E値
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	5	80	80.00	95.00	4.60
-	0	－	－	－	－
-	6	0	50.00	16.67	0.65
-	6	0	50.00	20.83	0.90

（注1）：血液製剤が投与された患者一人あたりの使用量

1－4　冠動脈バイパス術（アルブミン製剤・Cグループ）

病院記号	入院件数（件）	使用頻度（%） 20 %・25 %	使用頻度（%） 5 %	一件あたりの使用量（単位）（注1）	O/E 値
-	77	10	91.00	62.50	2.20
-	31	29	84.00	99.19	4.59
-	7	43	43.00	39.14	2.53
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－
-	8	38	38.00	17.19	0.80
-	10	0	70.00	26.25	1.48
-	19	21	53.00	37.50	1.72
-	36	8	67.00	58.33	2.62
-	47	2	34.00	9.04	0.32
-	72	78	21.00	55.14	2.54
-	24	58	63.00	49.48	2.31
-	0	－	－	－	－
-	20	10	15.00	5.00	0.24
-	58	14	14.00	11.85	0.47
-	51	10	35.00	27.70	1.37
-	28	4	18.00	8.48	0.38
-	63	35	51.00	32.54	1.49
-	35	3	63.00	15.36	0.78
-	16	0	50.00	17.97	0.91
-	0	－	－	－	－
-	9	44	0.00	13.89	0.75
-	20	25	25.00	18.25	0.86
-	44	41	68.00	32.61	1.49
-	27	7	89.00	60.74	2.22
-	17	0	6.00	1.18	0.05
-	77	10	69.00	50.16	1.99
-	0	－	－	－	－
-	12	33	0.00	13.54	0.40
-	0	－	－	－	－
-	0	－	－	－	－
-	0	－	－	－	－

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（注1）：血液製剤が投与された患者一人あたりの使用量

研究成果の刊行に関する一覧表

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Primary chemotherapy patterns for ovarian cancer treatment in Japan

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Abstract

Aims: Evidence-based clinical practices can improve patient outcomes, especially in the area of chemotherapy. In Japan, it is not known how well physicians adhere to evidence-based chemotherapy guidelines. This study aimed to assess physician compliance with national guidelines for ovarian cancer primary chemotherapy in Japan.

Methods: Using an administrative database, we analyzed 209 cases of surgical laparotomy without neoadjuvant chemotherapy as the primary intervention for adnexal cancer. Cases were identified across seven teaching hospitals between 2003 and 2006.

Results: Of the 136 patients receiving inpatient chemotherapy, 101 cases (74%) were treated with platinum–taxane therapy. In five hospitals, platinum–taxane therapy was used in more than 75% of patients, compared to 56% and 32% in the other two hospitals, respectively. The proportion of patients receiving paclitaxel and carboplatin concomitant therapy (TC therapy) was 67%, although significant variation was noted between hospitals (range 32% to 94%, $P < 0.001$). Of the 91 patients receiving TC therapy, 59 (65%) were given full-dose monthly regimens, while 32 cases (35%) were treated with divided doses weekly. Weekly TC therapy was more frequently provided in hospitals with a low volume of patients receiving TC therapy. Patients under the age of 65 receiving inpatient chemotherapy were more likely to receive full-dose regimens than patients 65 or older (68% vs 43%, $P = 0.005$). Adherence to standardized chemotherapy was comparable to rates in European countries, although rates among hospitals differed significantly.

Conclusions: Elderly patients were more likely to receive divided-dose regimens. Publication of national treatment guidelines did not appear to substantially impact chemotherapy practice patterns.

Key words: chemotherapy, guideline, ovarian cancer, pattern of care.

Introduction

Many studies have suggested that evidence-based practices can lead to improved clinical outcomes.[1–3] Effective implementation of such practices, however, requires the standardization of the behavior of physicians. Establishment of practice guidelines and clinical pathways are among the most widely employed methods of changing the behavior of physicians and standardizing patient care.[4] Because these methods are passive, however, they have not been fully effective in leading to widespread adoption of evidence-based practices.[5,6]

Ovarian cancer treatment guidelines developed in Europe and in the USA have recommended standard systemic chemotherapy for epithelial ovarian cancer.[7–10] By international consensus, first-line chemotherapy is combination taxane and platinum-based drugs. Most experts recommend concomitant paclitaxel (175 mg/m^2) and carboplatin therapy (AUC

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5–7.5), a regimen administered every 3 weeks. Systemic chemotherapy is currently not recommended for stage Ia and Ib cases with well-differentiated, low-grade tumors. In 2004, the Japanese Society of Gynecologic Oncology concurred with these guidelines, recommending taxane and platinum therapy (TC therapy) as primary chemotherapy for ovarian cancer.[11]

Prior studies have noted that Japanese physicians are often reluctant to implement standardized regimens for patient care, such that treatment approaches for administration of antibiotics or operative interventions for breast cancer, hip fracture and acute cholecystitis continue to vary widely.[12–15] Understanding this variability in baseline practice patterns is an important first step for disseminating and promoting standardized treatment approaches. Despite the establishment of evidence-based practice guidelines for chemotherapy, however, few studies have yet evaluated practice patterns in medical oncology.[16,17]

This study was designed to assess variations in treatment approaches for primary chemotherapy in ovarian cancer. Using an administrative database, we analyzed multiple variables across Japanese teaching hospitals, including choice of drug, schedule of administration, and choice to admit for inpatient care during chemotherapy administration.

Methods

Study patients

This study was approved by the Institutional Review Board of the Faculty of Medicine, Kyoto University Graduate School of Medicine, Japan. A total of 680 patients (2783 hospitalizations) with ovarian or fallopian tube cancers treated in 16 general hospitals between April 2003 and December 2006 were considered for analysis. The 16 hospitals selected are members of the Quality Indicator/(Improvement) Project (QIP). QIP is an initiative designed to improve clinical performance through analysis of administrative data. Most facilities participating in the project are located in urban areas across Japan, have more than 350 beds, provide tertiary care, and are certified for residency training. All participating hospitals provide QIP with administrative data for all discharged patients, including clinical information and claim data. Clinical information includes patient demographics, comorbidities on admission, dates of admission and discharge, oncological status (primary versus recurrence and International Union against Cancer [UICC] classification), and surgical history (date and type of the procedure). Claim data itemizes the type and quantity of all tests, medications, procedures, the use of intensive, specialized care or nursing services per day, as well as associated fees.

Using this database, we identified patients with adnexal cancer using the International Classification of Diseases 10th Version (ICD-10) codes of C56 (ovarian cancer), and C57.0 (fallopian tube cancer). From that patient pool, we then selected patients who had undergone a laparotomy as their primary treatment intervention. Patients that underwent staging laparotomy (salpingo-oophorectomy, total hysterectomy, omentectomy, and retroperitoneal lymph node dissection) were identified by ICD-9-CM codes 65.49, 65.61, 68.4, and 40.3, as well as Japanese classification system codes K888 and K889 (procedure for malignant adnexal tumor). We also used ICD-9-CM codes 54.11, 54.23, and 54.4 and Japanese classification system codes K636 (exploratory laparotomy) and K641 (omentectomy) to identify patients who underwent cytoreductive surgery. We used the Charlson co-morbidity index[18,19] for the assessment of a medical condition in a patient.

We excluded patients treated in hospitals with fewer than 10 recorded surgical procedures for adnexal cancer. Patients who had received multiple laparotomy procedures or neoadjuvant chemotherapy were also excluded from the study, as were patients with incomplete claim data (type of anti-cancer drug, amount of drug, and date of administration).

Extraction of information about chemotherapy and generation of variables

For each selected case, we extracted data on the type and dosage of anticancer drug, as well as the schedule of chemotherapy administration. Based on this information, we classified chemotherapy regimens into three groups: taxane-platinum therapy, platinum-based therapy alone, and non-platinum-based therapy. Taxane-platinum regimens included paclitaxel with carboplatin (TC), paclitaxel with cisplatin (TP), and docetaxel with carboplatin (DC). Platinum-based regimens included cyclophosphamide with adriamycin and cisplatin (CAP), cyclophosphamide with cisplatin (CP), and irinotecan with cisplatin (CPTP). We also identified the duration of chemotherapy administration, including initiation and completion dates.

To assess clinical outcomes, we collected data on all subsequent surgeries and hospitalizations. Identified data points included the dates of later surgical

interventions and the type of any accompanying chemotherapy regimens.

Analysis

Cases that satisfied both inclusion and exclusion criteria were used to analyze chemotherapy pattern practices by hospital. We first determined the proportion of cases for which in-patient postoperative chemotherapy was initiated. Of the cases where primary chemotherapy was employed, we then calculated the proportion of cases where platinum–taxane therapy was selected as the initial regimen. As a final analysis, we compared those cases using TC therapy across the following variables: proportion of cases initiating chemotherapy during hospitalization for the initial laparotomy, dosing schedule of chemotherapy (full or divided dose) and time interval between surgery and initial chemotherapy.

Across all participating hospitals, we also analyzed the association between patient age and type of chemotherapy regimen selected. By age group (<65 years, ≥65 years), we compared the numbers of patients treated with in-patient chemotherapy, the numbers of patients treated with platinum–taxane therapy, the chemotherapy dose regimen, and the interval between surgery and chemotherapy.

The Ovarian Cancer Treatment Guidelines were published by the Japanese Society of Gynecologic Oncology in October 2004. To evaluate the impact of practice guidelines on patterns of clinical care, we studied rates of in-patient chemotherapy administration before and after publication of the guidelines. Patients receiving in-patient chemotherapy were divided into two groups by date of admission for surgery: admission prior to 2005, and admission during or after 2005.

Statistical analyses were carried out using SPSS version 11 (SPSS Inc., Chicago, IL, USA). All continuous variables were reported using descriptive statistics, while categorical data were summarized with frequency counts and percentages. Inter-group comparisons were assessed with the two-tailed *t*-test and ANOVA for continuous variables; and Pearson's χ^2-test and Fisher's exact test were used for categorical variables. *P*-values <0.05 were considered to be statistically significant.

Results

A total of 309 patients received surgical treatment for adnexal cancer in the 16 selected hospitals between April 2003 and December 2006. Twenty-five patients from nine hospitals were excluded due to low surgical volumes at those institutions, as were 21 patients who received surgery for recurrences. After excluding an additional 54 patients who received multiple laparotomy procedures ($n = 4$), neoadjuvant chemotherapy ($n = 23$) or unspecified chemotherapy ($n = 27$), our study population included a total of 209 patients across seven hospitals. Of those 209 patients, 73 did not receive inpatient chemotherapy; analyses of chemotherapy administration patterns were therefore based on the remaining 136 patients. Baseline patient characteristics by hospital are displayed in Table 1. While statistically significant variation was found in the distribution of average Charlson scores among the hospitals ($P < 0.001$), the average patient age did not significantly vary by institution. Because UICC classification data were missing in a high percentage of cases, this parameter was excluded from additional analyses.

Variations of chemotherapy in hospitals

Of the 209 patients with surgical hospital records, we identified initial chemotherapy regimens for 136 patients (65%, Table 1). The majority of patients received inpatient chemotherapy, and rates of inpatient chemotherapy were similar across institutions (50%–76%, $P = 0.48$).

Seventy-four percent (101/136 cases) of patients receiving chemotherapy received platinum–taxane treatment. In five hospitals, platinum–taxane therapies were selected in more than 75% of cases. The remaining two hospitals selected platinum–taxane regimens in only 56% and 32% of the patients, respectively (Fig. 1).

Of all patients undergoing chemotherapy, 67% (91/136 cases) received TC therapy. The proportion of patients receiving TC therapy varied significantly between hospitals (range 32%–94%, $P < 0.001$). Chemotherapy was initiated at the time of surgery in 73% of cases (66/91) where TC therapy was selected, but the proportion of patients initiating chemotherapy during hospitalization for their primary operative intervention also varied significantly across institutions (range 0%–100%, $P < 0.001$). Full-dose TC chemotherapy at 3–4 week intervals was administered in 65% (59/91) of cases (monthly TC), while 35% (32/91) of cases received divided doses weekly (weekly TC). Weekly TC therapy sessions were more prevalent in hospitals with a low volume of patients receiving TC therapy. The mean interval between surgery and chemotherapy

Table 1 Patient characteristics by hospital

Hospital	A	B	C	D	E	F	G	All	*P*-value
Numbers of patients	25	13	8	35	28	42	58	209	
Age (year), mean (SD)	58.0 (12.6)	65.0 (14.6)	63.4 (14.4)	59.2 (11.2)	58.2 (11.8)	53.9 (17.1)	57.5 (16.5)	58.1 (14.8)	0.10
Charlson score, mean (SD)	0.7 (1.2)	2.2 (2.7)	0.5 (1.1)	1.3 (1.6)	0.2 (0.7)	0.3 (0.8)	0.7 (1.4)	0.8 (1.4)	<0.001
FIGO Stage									
Available data	8 (32%)	9 (69%)	4 (50%)	17 (49%)	20 (71%)	22 (52%)	44 (76%)	124 (59%)	
IA-IC	2	1	1	6	10	13	20	53	
IIA-IIC	1	1	1	1	3	0	2	9	
IIIA-IIIC	5	6	2	6	5	6	15	45	
IV	0	1	0	4	2	3	7	17	
In-patient chemotherapy	19 (76%)	9 (69%)	4 (50%)	18 (51%)	18 (64%)	28 (67%)	40 (69%)	136 (65%)	0.48
Regimen									
Platinum–taxane	19 (100%)	7 (78%)	4 (100%)	17 (94%)	10 (56%)	9 (32%)	35 (87%)	101 (74%)	<0.001
Platinum without taxane	0 (0%)	1 (11%)	0 (0%)	1 (6%)	6 (33%)	15 (54%)	2 (5%)	25 (19%)	
Non platinum	0 (0%)	1 (11%)	0 (0%)	0 (0%)	2 (11%)	4 (14%)	3 (8%)	10 (7%)	
Cases with TC therapy	14 (78%)	7 (78%)	3 (75%)	17 (94%)	6 (33%)	9 (32%)	35 (88%)	91 (67%)	<0.001
Initial chemotherapy in the same hospitalization with surgery (%)	9 (64%)	0 (0%)	3 (100%)	13 (76%)	4 (67%)	7 (78%)	30 (86%)	66 (73%)	<0.001
Dose									
Full (monthly TC)	13 (93%)	1 (14%)	1 (33%)	17 (100%)	1 (17%)	0 (%)	26 (74%)	59 (65%)	<0.001
Divided (weekly TC)	1 (7%)	6 (86%)	2 (67%)	0 (0%)	5 (83%)	9 (100%)	9 (26%)	32 (35%)	
Interval between surgery and chemotherapy in days, mean (SD)	22.5 (14.0)	31.9 (12.3)	14.0 (1.0)	16.5 (8.2)	17.0 (5.4)	17.6 (6.7)	17.9 (7.9)	19.2 (9.8)	0.008

FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation; TC, Paclitaxel with carboplatin chemotherapy.

Figure 1 Proportion of different chemotherapy regimens by hospital. White areas in the graph represent the proportion of patients within each hospital who underwent taxane-platinum chemotherapy regimens, grey areas represent the proportion of patients who underwent platinum without taxane treatments and the black areas represent the proportion of patients who underwent non-platinum chemotherapy treatments.

was 19.2 days (standard deviation 9.8), but statistically significant variation was noted across hospitals ($P = 0.008$).

Variation in chemotherapy practice patterns by patient age

We assessed the impact of patient age on chemotherapy practice patterns by comparing the chemotherapy regimen, interval between surgery and initial chemotherapy, and dosing schedule across younger (<65 years) and older (≥65 years) patient groups (Table 2).

Similar proportions of patients in each group received first-line platinum–taxane therapy ($P = 0.91$). Sixty-eight percent (63/92) of patients in the younger group were treated with full-dose chemotherapy, as compared to 43% (19/44) of patients in the older group. The interval between surgery and initial chemotherapy was not significantly different between the groups ($P = 0.20$).

Clinical practice guidelines and change in practice patterns of chemotherapy

The 209 cases with surgical histories were divided according to the date of hospitalization for initial surgical intervention: prior to 2005 ($n = 56$), and during or after 2005 ($n = 153$). Selection of chemotherapy regimens did not significantly differ between the two groups, and a similar proportion of patients in each group received platinum–taxane therapy ($P = 0.51$). All other examined outcomes were also found to be similar before and after publication of the Japanese

Table 2 Comparison of chemotherapy practice patterns by age group

Age group	<65 years	≥65 years	*P*-value
Numbers of patients	141	68	
Charlson score, mean (SD)	0.6 (1.2)	1.1 (1.7)	**0.019**
% receiving inpatient chemotherapy	65% (92/141)	65% (44/68)	0.939
Regimen			
Platinum–taxane	75% (69/92)	73% (32/44)	0.906
Platinum without taxane	17% (16/92)	20% (9/44)	
Non-platinum	8% (7/92)	7% (3/44)	
Dosing schedule			
% receiving full-dose regimens (monthly)	68% (63/92)	43% (19/44)	**0.005**
% receiving divided regimens (weekly)	32% (29/92)	57% (25/44)	
Interval between surgery and chemotherapy in days, mean (SD)	16.8 (9.2)	19.4 (13.3)	0.198

SD, standard deviation.

Table 3 Impact of treatment guidelines publication on chemotherapy practice patterns

Year of admission	<2005	≥2005	*P*-value
Numbers of patients	56	153	
Age in years, mean (SD)	55.7 (14.9)	59 (14.7)	0.164
Charlson score, mean (SD)	0.5 (1.1)	0.9 (1.5)	0.092
% receiving inpatient chemotherapy	66% (37/56)	65% (99/153)	0.854
Regimen			
Platinum–taxane	70% (26/37)	76% (75/99)	0.510
Platinum without taxane	24% (9/37)	16% (16/99)	
Non-platinum	6% (2/37)	8% (8/99)	
Dosing schedule			
% receiving full-dose regimens (monthly)	59% (22/37)	61% (60/99)	0.903
% receiving divided regimens (weekly)	41% (15/37)	39% (39/99)	
Interval between surgery and chemotherapy in days, mean (SD)	15.5 (9.0)	18.5 (11.2)	0.159

SD, standard deviation.

practice guidelines: rate of in-patient chemotherapy administration, choice of full-dose chemotherapy regimens, and interval between surgery and chemotherapy (Table 3).

Discussion

Several European research groups have evaluated compliance with practice guidelines by studying rates of platinum–taxane therapy administration as first-line chemotherapy for ovarian cancer. In Germany, researchers reported a 77.6% rate of compliance with chemotherapy guidelines for advanced cases of ovarian cancer,[20] while a similar study in Scotland found that the platinum–taxane combination was used in 64% of cases reported.[21] Our study showed that of patients receiving chemotherapy, platinum–taxane therapy was used as initial chemotherapy in 74.3% of cases. Moreover, chemotherapy regimens were fairly standardized across institutions, even among unspecialized hospitals in rural areas.

Nevertheless, not all hospitals succeeded in standardizing chemotherapy regimens, with one hospital reporting that only 32% of chemotherapy-treated patients received platinum–taxane therapy. While use of standardized regimens is not always indicated for ovarian cancer, for example in patients with established drug sensitivities, it is unlikely that those exceptions

would account for a large proportion of the non-standardized regimens used. The variation in standardization therefore constitutes a problem in quality of care. Previous studies have examined barriers to physician compliance with practice guidelines, which include lack of awareness, lack of familiarity, lack of consensus around the guidelines, inertia and external barriers.[5,6] Our study suggests that while adherence to standard chemotherapy regimens for ovarian cancer in Japan is comparable to that of other countries, universal adoption of such guidelines is still lacking. In Japanese hospitals using non-standardized regimens of care, lack of adherence may be attributable to any one of the identified barriers. More research will be needed to clarify Japanese attitudes toward practice guidelines and barriers to adherence. Widespread dissemination and adoption of guidelines will likely require additional effort and development of implementation strategies.[22–24]

In some hospitals, CPTP therapy was preferentially used over platinum–taxane therapy. This regimen is included as one option for primary chemotherapy in the Japanese guidelines, as are several other regimens put forth as options for specific patient populations. DC therapy, for example, is described as the treatment of choice for patients at risk of development of peripheral neuropathy.[11] Clear indications for use, however, have not been specified for all alternative regimens. Physicians may therefore be more likely to choose regimens based on histology results or the prior response of a patient to a given regimen. Those decisions are left to individual physicians, resulting in wide variations in selection of chemotherapy protocols.

We found that the proportion of patients receiving TC therapy by divided dosing schedules was 35% (32/91). The Japanese guidelines, uniquely among other guidelines for treatment of ovarian cancer, suggest that divided dosing of TC therapy (weekly TC) is an option for primary chemotherapy. Only a single study currently supports the effectiveness of weekly TC, as compared to full-dose, monthly TC therapy.[25] In our study, weekly TC treatment was performed more frequently in hospitals with low volumes of patients receiving TC therapy. Administering divided-dose chemotherapy is both more burdensome for patients, who must undergo repeated hospitalizations at shorter intervals, and more expensive for the health care system. For many clinical areas,[26,27] including chemotherapy,[28,29] volume-outcome relationships are well established. While most Japanese patients can easily access hospital-based health care, it is more difficult to access specialized care in high-volume centers. Many hospitals providing specialized medical care to only a few patients, therefore, may also yield variations in treatment regimens.

Sundararajan *et al.* reported that chemotherapy was used less frequently in patients aged over 65 with advanced ovarian cancer than in younger patients.[30] Similarly, Maas *et al.* demonstrated that even in the absence of existing co-morbidities, standard combination chemotherapy was prescribed significantly less often for elderly patients.[31] Concern around side-effect profiles may have contributed to the growing tendency for physicians to treat elderly patients with single sequential anti-cancer agents.[32] While Cloven *et al.* showed that patients over 80 years of age who undergo debulking surgery have higher operative morbidity and prolonged hospitalizations,[33] most patients were ultimately discharged and were able to receive post-operative chemotherapy. Villella *et al.* reported that patients older than 70 years were more likely to have chemotherapy doses reduced, although lower dosages remained within the standard protocol range.[34] Villella also demonstrated that elderly patients tolerated therapeutic doses, and that platinum–taxane combination therapy was effective in older patient populations.[34]

Although no statistical association between age and choice of chemotherapy regimen was noted in this study, elderly patients in Japan are more likely to receive divided-dose chemotherapy than younger patients. This finding may support the theory that elderly cancer patients are less likely to receive optimal treatment than younger patients. This may be due to physician concerns that adverse chemotherapeutic side-effects from standard treatment regimens could develop with higher frequencies in elderly cancer patients.[35] Despite age-related variation in dosing schedules, patient age appeared not to be a significant predictor of the chemotherapy agents selected.

Our study demonstrated that the choice of chemotherapy agents and dosing intervals varies widely among hospitals. Universal compliance with guidelines for treatment has not yet been achieved, and there is room for more work in promoting dissemination and awareness of the guidelines. It is important to note, however, that while there were high percentages of hospitals reporting using standardized regimens across the entire study period, the publication of the guidelines in 2004 did not significantly impact those percentages. The interval between surgery and chemotherapy tends to be longer in hospitals where post-operative chemotherapy is not initiated during

hospitalization for the surgical intervention. While it is known that delayed adjuvant chemotherapy for ovarian cancer is associated with poor prognoses, data for the appropriate interval between surgery and chemotherapy is currently lacking. Because the Japanese Ovarian Cancer Treatment Guidelines do not recommend a particular interval, the observed variation in intervals is likely a natural result of insufficient guidance. Further studies will be needed to establish an optimal interval.

Our study has several important limitations. First, some of the subgroup analyses involve small numbers of patients per group, which may therefore bias our statistical results. For seventy-three (39%) of the 209 patients, there was no information regarding inpatient chemotherapy. For our study, it is relevant to know what kind of treatment had been performed for these 73 cases. We classified the 73 cases into four groups: patients at surgical stages Ia,b, Grade 1 for whom subsequent treatment had been omitted, outpatients who have undergone platinum–taxane chemotherapy, outpatients who have undergone chemotherapy other than platinum–taxane, and patients with no subsequent treatment for any reason, even though adjuvant chemotherapy was recommended. According to the International Federation of Gynecology and Obstetrics (FIGO) Annual Report,[36] 13% of ovarian cancer patients are at surgical stages Ia & b, and a few more than 20 of the 209 cases are those with a well-differentiated histology who avoided adjuvant chemotherapy. If approximately 20 patients receive appropriate treatment, then at least 50 of the 73 cases were candidates for chemotherapy. Even though there were a few patients who either refused treatment or could not receive chemotherapy due to extremely poor health, it is likely that nearly 50 cases have received some outpatient chemotherapy. The proportion of patients who underwent outpatient platinum–taxane chemotherapy influenced the overall proportion of those who underwent platinum–taxane therapy. Those who receive outpatient chemotherapy cannot easily receive the complicated multidrug chemotherapy and regimen, as it requires massive infusion. We therefore assumed that these patients were treated with either TC therapy or single agent chemotherapy instead. As such, the proportion of those who receive TC therapy as outpatient chemotherapy may be higher than that as inpatient chemotherapy. However, as the target hospitals in this study are not highly specialized, there may be more patients who receive single agent therapy and whose treatment was inappropriately omitted, as compared to cases from cancer centers. It is unclear whether inclusion of these patients in our analysis could have either over- or underestimated the proportion of patients receiving standardized treatment regimens.

In addition, the data provided in administrative records was not always complete, particularly concerning histology, cancer staging, co-morbidities and complication rates. Some of these factors may be correlated to the use of alternative treatment regimens, emphasizing the need for stricter standards and improvements in database quality. Accurate and consistent tracking of these data points, including cancer staging and comorbidity scores, is critical to establishing a feedback loop whereby participating hospitals can improve the quality of subsequent databases and the accuracy of analyses based on them. For those hospitals where yearlong data could not be provided, it is possible that our results were subject to information bias. Because most chemotherapy regimens are initiated shortly after surgery, however, the likelihood of missing data regarding chemotherapy is small.

Conclusion

This study descriptively analyzed practice patterns of primary chemotherapy for ovarian cancer in Japan. Standardized chemotherapy regimens were used at a comparable rate to that of European countries, but compliance rates varied greatly among hospitals. The choice of chemotherapy regimen did not differ across age groups, although elderly patients were more likely to be treated with divided doses. The provision of chemotherapy with divided doses may be more frequent in low-volume chemotherapy practices. The publication of national treatment guidelines did not appear to substantially impact chemotherapy practice patterns.

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Risk-adjusted increases in medical resource utilization associated with healthcare-associated infections in gastrectomy patients

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Abstract

Rationale, aims and objectives Quantifying the impact of health care-acquired infections (HAIs) on medical resource utilization is necessary for payers and providers to appropriately allocate limited resources for interventions. However, previous studies tend to involve single institutions and do not take into account patient and practice variations between several hospitals. The objective of this study was to conduct a multi-institutional risk-adjusted comparison of HAI-associated impact on medical resources in gastrectomy patients in Japan.

Methods Health care-acquired infections were identified using a combination of International Classification of Diseases-10 codes and antibiotic utilization patterns in 1058 gastrectomy patients from 10 Japanese hospitals. Multiple linear regression models and risk adjustment were used to analyse the impact of HAIs on: (1) total hospital costs; (2) antibiotic costs; and (3) post-surgical length of stay (LOS).

Results Overall HAI incidence for the database was 20.3%, with a range of 8.8–29.6% among the 10 hospitals. Regression models showed that HAIs were significantly associated with increases in all three indicators. Risk-adjusted comparisons revealed that HAIs were associated with an increase of US$2767 (range: US$1035–6513) in overall hospital cost, US$202 (US$98.8–764.6) antibiotic costs and 10.6 (4.7–24 days) post-surgical LOS days.

Conclusions Even after adjusting for patient characteristics and other variables, there was still a high degree of variation observed in the impact of HAIs on total hospital costs and antibiotic costs from a third-party payer's perspective and post-surgical LOS among the 10 hospitals. This information can increase the efficiency of allocation of resources for interventions to reduce HAIs.

Introduction

The control of health care-acquired infections (HAIs) is a particularly important yet elusive goal for increasing the quality of health care. In addition to decreased quality of life [1,2] and increased morbidity and mortality [3], HAIs represent potentially preventable increases in medical resource utilization [4–7]. These increases in resource utilization must first be quantified in order for providers and payers to decide how to appropriately allocate limited resources for preventive measures.

While studies that estimate the impact of HAIs on resource utilization generally involve data from one or two hospitals [8–12], a multi-institutional comparison would provide a wider contextual backdrop in which to interpret the results of each hospital. However, risk adjustments must first be conducted in order to account for practice variations and patient characteristics before meaningful comparisons can be made. To the best of our knowledge, there is no current risk-adjusted multi-institutional comparison of the impact of HAIs on medical resource utilization in a Japanese setting.

The aforementioned studies generally involved chart reviews [8,9] or prospective studies [10–12]. However, these methods are extremely labour-intensive and tend to be self-limiting in terms of population sample size and study period duration. An alternative approach is the use of reimbursement data or administrative data, which provides a standardized and detailed database that can be

used for multi-institution comparative studies. The hospital payment system in Japan uses an identical reimbursement schedule for all acute-care hospitals, and it is required for hospitals to produce data in similar formats. Therefore, these data are easily obtained, analysed and used to compare multiple institutions in a Japanese setting.

Infection identification using administrative data can be conducted by the use of International Classification of Diseases (ICD) codes. However, the use of these codes alone to identify HAIs has been found to have poor identification capability [13,14]. In order to improve identification capability, we chose to complement ICD code-based identification with the use of antibiotic utilization patterns as a clinically relevant indicator of infection incidence.

The objective of this study was to quantify increases in medical resource utilization associated with infections in gastrectomy patients from several Japanese hospitals, and to conduct a risk-adjusted comparison of performance between the hospitals.

Methods

Patient selection

Patient information was obtained from hospitals enrolled in the Quality Indicator/Improvement Project (QIP), a database of 16 Japanese hospitals (at the time of study) that consists of clinical and claims data on discharged patients. We selected patients with gastric cancer who were hospitalized for the purpose of gastrectomy as our target population as gastric cancer occurs with very high incidence in Japan [15]. By focusing on patients who had only undergone gastrectomies, we reduced the intrinsic variation associated with procedural differences.

Data were obtained on patients who were admitted from April 2004 to January 2007. Total and subtotal gastrectomies for gastric cancer performed were identified using the Diagnostic Procedure Combination coding system for reimbursement, a national fee schedule introduced into Japan in 2003. The sampled hospitals had a bed size ranging from 280 to 1106 beds, with a mean of 561 beds.

Patients were excluded if they fulfilled any of the following criteria: (1) patients who had died during admission; (2) patients who were given antibiotics before the day when gastrectomy was performed; (3) patients who had other surgeries before gastrectomy; (4) patients admitted directly from the emergency ward; and (5) patients with missing data with regards to antibiotic payments and anaesthesia time. Finally, hospitals with fewer than 30 cases were excluded from analysis.

Clinical diagnoses were conducted using ICD-10 (10th revision of ICD codes). Pre-existing co-morbidity conditions were analysed using the Charlson co-morbidity index (Dartmouth–Manitoba version) [16,17].

Identification of post-surgical HAI

Antibiotic utilization patterns were discerned using daily drug claims data, which allowed us to identify antibiotic administration, type of antibiotic and dosage on a day-to-day basis. We used antibiotic utilization patterns that would not occur in the simple pre-surgical prophylaxis observed in uninfected patients. Patients were deemed to have HAIs if they fell into any of the following categories: (1) post-admission complications with ICD-10 codes indicating HAI, adapted from the Pennsylvania Health Care Cost Containment Council (PHC4) [18]; (2) the use of three or more different types of antibiotics during their hospital stay; (3) the use of two types of antibiotics in which a second antibiotic type was added or changed midway through the course; (4) more than 1 day of antibiotics given in a separate time frame in which no surgery was conducted; and (5) the use of more than 3 days of antibiotics starting from the day of surgery. The final sample size (N) used for analysis was 1058 patients from 10 hospitals.

Resource utilization indicators

Total hospital costs and antibiotic costs from a third-party payer's perspective, as well as post-surgical length of stay (LOS), were used as indicators of medical resource utilization.

Statistical analysis

Analyses were performed using Dr. SPSS VER. II 11.0.1J (••); [1] P-values reported were two-tailed and the level of significance was set at $P < 0.05$.

Multiple linear regression models were developed to estimate the impact of HAIs on medical resource utilization. Total hospital costs, antibiotic costs and post-surgical LOS were natural logarithm transformed before being used as dependent variables in the regression models. The independent variables used were age (equal to and above 70 years), gender, post-surgical infection, co-morbidities, pre-surgical LOS, type of gastrectomy (total or partial), number of surgeries, surgery duration and hospital stratification. The age of 70 years was selected as preliminary analysis showed that the proportions of patients above and below this age were approximately equal, and univariate analysis showed highly significant association with HAI presence/absence (data not shown). Anaesthesia time (minutes) was used as a proxy indicator for surgery duration.

Hierarchal regression models were developed, with covariates grouped into patient characteristics, co-morbidities and surgery-associated factors. The first model for each dependent variable excluded the use of hospitals as dummy variables, while the second model included hospital stratification.

Risk-adjusted values were obtained using the first regression models as described previously, but with hospital stratification and post-surgical infection status excluded as variables. These regression models were then used to produce predicted values for each of the three medical resource utilization indicators. As the dependent variables were logarithmic transformed before analysis, the exponentials of the predicted values were calculated in order to obtain expected values with units of Japanese Yen and days. Duan's smearing coefficient was applied to correct for retransformation bias [19,20]. Risk adjustment was conducted by dividing each hospital's mean observed value (O) by the mean expected value (E), and multiplying the result by the mean value of the entire data set.

Final estimates were adjusted for inflation using the Japanese consumer price index (to adjust all values to the 2007 Yen value) and then converted to US dollars using Purchasing Power Parities (Japanese 100 Yen = US$0.85; April 2007) [21].

Results

The distribution of patient characteristics and gastrectomy type are presented in Table 1. The population was skewed towards an older patient population, with 47.9% of the subjects equal or more than 70 years of age. In all, 9.7% of the study population suffered from diabetes, and 9.5% exhibited metastatic cancer. There were more patients (64.2%) who underwent subtotal gastrectomies than those who underwent total gastrectomies.

Figure 1 shows HAI incidence in total and at the hospital level. In general, there was an infection incidence of 20.3% (215 cases) in our sample population, and a range from 8.8% (Hospital A) to 29.6% (Hospital E). A breakdown of infection cases by identification method shows that the use of ICD-10 codes resulted in 85 cases (8.03%) identified. In all, 72 of these cases were also identified by antibiotic utilization. Of the cases identified by ICD codes, 70% were 'unspecified infections following a procedure', 20% were specified as 'surgical site infections' (SSIs), and the remaining 10% consisted of unspecified pneumonia, septicaemia and urinary tract infections. There were an additional 130 patients identified by antibiotic utilization alone.

Furthermore, while 'the use of >3 days of antibiotics starting from the day of surgery' was included as a criterion for infection identification, all of the cases that were identified as infected patients by this particular criterion were also identified by at least one of the other four criteria.

The regression models used are shown in Table 2. Cases with post-surgical HAIs showed highly significant association in all three indicators of increased medical resource utilization ($P < 0.001$) in all of the six models constructed.

The first regression model constructed was able to account for 60.7% of variation observed in total hospital costs. With hospital stratification, the model accounted for 64.3% of variation. Age and all surgery-associated factors were significantly associated with total hospital costs, while gender was not. Congestive heart failure was the only co-morbid condition that was consistently significant in both models for total hospital costs, and diabetes showed significance when hospital stratification was included in analysis.

Table 1 Distribution of patients, patient characteristics and type of gastrectomy by hospital and in total

Hospital	A	B	C	D	E	F	G	H	I	J	Total	%
N	57	31	85	222	81	37	93	220	159	73	1058	100
Patient characteristics												
Female	16	8	30	61	28	12	31	74	59	24	343	32.4
Age (≥70 years)	24	16	52	102	41	15	30	102	92	33	507	47.9
Acute myocardial infarction	2	0	1	0	4	0	1	2	5	0	15	1.4
Congestive heart failure	0	1	0	0	1	1	0	0	4	0	7	0.7
Peripheral vascular disease	1	0	0	1	0	0	0	1	0	1	4	0.4
Cerebral vascular disease	3	1	3	7	7	0	3	3	6	2	35	3.3
Pulmonary disease	2	1	4	13	3	1	1	6	8	1	40	3.8
Peptic ulcer	3	2	8	7	2	1	0	9	13	9	54	5.1
Liver disease	0	0	0	3	1	0	0	1	1	0	6	0.6
Diabetes	10	4	10	30	3	2	4	16	21	3	103	9.7
Diabetes w/complications	0	1	0	1	7	0	0	1	2	0	12	1.1
Renal disease	2	0	0	2	1	0	2	1	7	1	16	1.5
Metastatic cancer	8	3	5	15	1	13	1	38	12	4	100	9.5
Gastrectomy type												
Subtotal	37	19	42	153	54	23	69	148	99	35	679	64.2

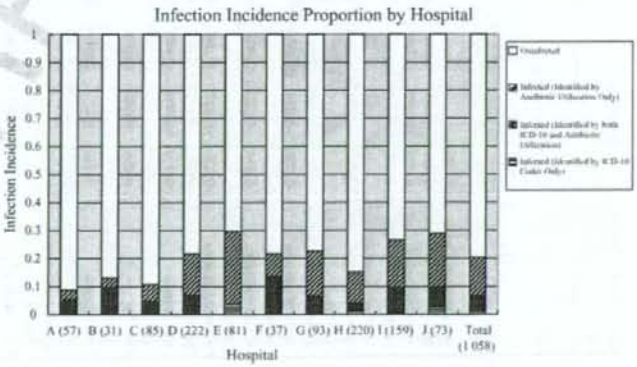

Figure 1 Infection incidence proportion by hospital and in total. White sections represent patients uninfected with HAIs; sections with diagonal lines represent infected patients identified by antibiotic utilization only; sections with dots represent infected patients identified by both International Classification of Diseases (ICD)-10 codes and antibiotic utilization; sections with horizontal lines represent infected patients identified by ICD-10 codes only (only in Hospitals E, H, I and J).

Table 2 Regression models showing association between patient characteristics, co-morbid conditions, surgery associated factors and hospital stratification on total hospital costs, antibiotic costs, and post-surgical length of stay

Models	Total hospital costs 1			Total hospital costs 2			Antibiotic costs 1			Antibiotic costs 2			Post-surgical length of stay 1			Post-surgical length of stay 2		
	0.607			0.643			0.349			0.661			0.282			0.322		
R^2	Beta	*B*	*P*-value	Beta	*B*	*P*-value	Beta	*B*	*P*-value	Beta	*B*	*P*-value	Beta	*B*	*P*-value	Beta	*B*	*P*-value
Patient characteristics																		
Age (≥70 years)	0.061	0.032	0.002	0.064	0.034	0.001	0.009	0.023	0.713	0.008	0.020	0.662	0.083	0.078	0.002	0.072	0.068	0.007
Gender	0.006	0.003	0.779	−0.002	−0.001	0.929	−0.015	−0.039	0.546	−0.004	−0.010	0.835	0.053	0.053	0.049	0.045	0.046	0.084
Post-surgical infection	0.325	0.216	>0.001	0.315	0.209	>0.001	0.580	1.716	>0.001	0.593	1.755	>0.001	0.404	0.473	>0.001	0.401	0.469	>0.001
Co-morbid conditions																		
Acute myocardial infarction	0.022	0.050	0.252	0.010	0.022	0.597	−0.050	−0.502	0.047	−0.023	−0.232	0.208	0.025	0.099	0.343	0.013	0.051	0.619
Congestive heart failure	0.057	0.189	0.004	0.055	0.182	0.004	−0.027	−0.397	0.286	0.021	0.311	0.253	0.047	0.276	0.075	0.043	0.247	0.103
Peripheral vascular disease	−0.008	−0.035	0.679	−0.007	−0.029	0.720	0.013	0.256	0.596	0.014	0.280	0.425	0.009	0.072	0.719	0.013	0.099	0.614
Cerebral vascular accident	0.014	0.022	0.462	0.008	0.011	0.682	0.000	0.003	0.984	0.016	0.105	0.389	−0.004	−0.010	0.882	−0.009	−0.025	0.716
Pulmonary disease	−0.023	−0.032	0.246	−0.014	−0.020	0.447	0.013	0.081	0.606	0.000	−0.002	0.986	0.005	0.013	0.842	0.009	0.022	0.724
Peptic ulcer	−0.002	−0.003	0.905	0.000	0.000	0.988	−0.034	−0.181	0.184	−0.024	−0.127	0.202	−0.004	−0.009	0.881	−0.006	−0.014	0.808
Liver disease	0.016	0.056	0.420	0.021	0.075	0.254	0.002	0.033	0.933	−0.002	−0.024	0.933	0.021	0.132	0.423	0.023	0.141	0.378
Diabetes	0.024	0.021	0.228	0.037	0.034	0.046	0.020	0.079	0.436	0.000	−0.001	0.989	0.026	0.042	0.318	0.034	0.054	0.187
Diabetes w/complications	0.035	0.089	0.073	0.024	0.061	0.206	−0.021	−0.234	0.410	0.034	0.387	0.064	0.060	0.265	0.024	0.038	0.168	0.151
Renal disease	0.032	0.071	0.097	0.025	0.054	0.191	−0.046	−0.453	0.065	−0.043	−0.418	0.019	0.012	0.045	0.658	0.007	0.025	0.799
Metastatic cancer	0.007	0.006	0.723	0.036	0.033	0.064	0.036	0.145	0.164	0.051	0.209	0.007	0.010	0.016	0.718	0.031	0.050	0.243
Surgery associated factors																		
Pre-surgical LOS	0.333	0.019	>0.001	0.325	0.019	>0.001	0.069	0.018	0.006	−0.026	−0.007	0.175	0.090	0.009	0.001	0.065	0.006	0.018
Gastrectomy type	0.359	0.200	>0.001	0.352	0.196	>0.001	0.061	0.152	0.020	0.058	0.145	0.003	0.144	0.142	>0.001	0.132	0.129	>0.001
No. of surgeries	0.194	0.071	>0.001	0.221	0.081	>0.001	−0.039	−0.064	0.144	0.031	0.051	0.154	0.070	0.046	0.012	0.121	0.079	>0.001
Surgery duration	0.148	0.000	>0.001	0.136	0.000	>0.001	0.010	0.000	0.707	0.043	0.001	0.040	0.091	0.000	0.001	0.070	0.000	0.018
Hospitals																		
B				0.023	0.036	0.316				−0.255	−1.801	>0.001				0.118	0.329	>0.001
C				0.030	0.029	0.309				0.218	0.954	>0.001				0.058	0.100	0.153
D				−0.075	−0.049	0.043				0.256	0.749	>0.001				−0.016	−0.018	0.758
E				0.067	0.067	0.019				−0.161	−0.719	>0.001				0.119	0.211	0.002
F				−0.068	−0.099	0.006				−0.212	−1.372	>0.001				−0.103	−0.265	0.003
G				0.137	0.129	>0.001				0.126	0.529	>0.001				0.069	0.115	0.082
H				−0.014	−0.009	0.700				0.238	0.698	>0.001				0.096	0.111	0.057
I				0.050	0.038	0.139				0.065	0.215	0.051				0.123	0.162	0.009
J				0.036	0.038	0.195				−0.105	−0.493	>0.001				0.030	0.055	0.434

Beta refers to standardized coefficients and B refers to unstandardized coefficients.