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Original Article

Impact of Patient Sex on Adverse Events and Unscheduled Utilization of Medical Services in Cancer Patients Undergoing Adjuvant Chemotherapy: A Multicenter Retrospective Cohort Study

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Purpose The female sex is reported to have a higher risk of adverse events (AEs) from cytotoxic chemotherapy. Few studies examined the sex differences in AEs and their impact on the use of medical services during adjuvant chemotherapy. This sub-study aimed to compare the incidence of any grade and grade ≥ 3 AEs, healthcare utilization, chemotherapy completion rate, and dose intensity according to sex.

Materials and Methods This is a sub-study of a multicenter cohort conducted in Korea that evaluated the impact of healthcare reimbursement on AE evaluation in patients who received adjuvant chemotherapy between September 2013 and December 2016 at four hospitals in Korea.

Results A total of 1,170 patients with colorectal, gastric, or non–small cell lung cancer were included in the study. Female patients were younger, had fewer comorbidities, and experienced less postoperative weight loss of > 10%. Females had significantly higher rates of any grade AEs including nausea, abdominal pain, stomatitis, vomiting, and neutropenia, and experienced more grade ≥ 3 neutropenia, nausea, and vomiting. The dose intensity of chemotherapy was significantly lower in females, and they also experienced more frequent dose reduction after the first cycle. Moreover, female patients receiving platinum-containing regimens had significantly higher rates of unscheduled outpatient visits.

Conclusion Our study found that females experienced a higher incidence of multiple any-grade AEs and severe neutropenia, nausea, and vomiting, across various cancer types, leading to more frequent dose reductions. Physicians should be aware of sex differences in AEs for chemotherapy decisions.

Key words Sex characteristics, Adverse events, Adjuvant chemotherapy

Introduction

Sex may influence cancer risk, survival rates, and the efficacy of anticancer treatment [1]. Recent research suggests that chemotherapy drugs may affect males and females differently in terms of pharmacokinetics and pharmacodynamics [2]. Despite this, sex differences in cancer treatment are often disregarded in preclinical experiments, clinical trials, and actual clinical practice. To better address potential sex effects on chemotherapy-related adverse events (AEs) and outcomes, it is imperative that sex differences are taken into consideration in the design of cancer treatment plans.

Several studies indicate that females have a higher incidence of chemotherapy-related AEs to most anticancer drugs than men in various solid tumors [3,4]. Certain chemotherapeutic drugs exhibit sex-specific pharmacokinetics and toxicity, such as 5-fluorouracil (FU), paclitaxel, doxorubicin, cisplatin, and many other drugs [5]. For example, in 5-FU–based chemotherapy, which is commonly used to treat gastrointestinal cancers, female patients more frequently and severely experienced leukopenia, stomatitis, diarrhea, nausea, and vomiting compared to male patients [6-9]. Moreover, female patients treated with cisplatin-based therapy show substantially higher AEs such as nausea and vomiting than males

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[10]. These findings support that sex-specific pharmacokinetics and toxicity should be considered when administering anticancer treatment.

Adjuvant systemic therapy following curative-intent resection has been shown to have a significant impact on reducing the risk of cancer recurrence and overall mortality. However, AEs following adjuvant chemotherapy can result in premature treatment discontinuation or even death. In the Lung Adjuvant Cisplatin Evaluation (LACE) pooled analysis, it was revealed that 34% of patients could not complete the planned number of chemotherapy cycles due to toxicity, and 0.9% of patients experienced chemotherapy-related deaths within the first 6 months [11]. To optimize chemotherapy dosing and develop personalized care plans, it is crucial to conduct sex-specific analyses of chemotherapy toxicity and healthcare utilization, especially in the adjuvant setting where maintaining dose intensity is important for a cure.

However, few studies have examined sex differences in the occurrence of AEs for adjuvant chemotherapy settings across multiple cancer types, and there is scarce data on healthcare utilization or dose intensity according to sex in patients undergoing chemotherapy, with even fewer reports in Asian regions. Thus, this study aimed to explore the association between sex and the incidence and severity of chemotherapy-related AEs in patients undergoing adjuvant chemotherapy across multiple cancer types. Additionally, we aimed to investigate the unexpected use of medical services during chemotherapy in patients receiving various chemotherapy treatments.

Materials and Methods

1. Study populations

This study was a sub-study from a prior retrospective multicenter study that evaluated the impact of healthcare reimbursement of AE evaluation in patients receiving adjuvant or neoadjuvant chemotherapy between September 2013 and December 2016 at four tertiary hospitals in Korea [12]. The four centers included in this study were Asan Medical Center (Seoul, Korea), Ulsan University Hospital (Ulsan, Korea), Seoul National University Bundang Hospital (Seongnam, Korea), and Gangneung Asan Hospital (Gangneung, Korea). A total of 2,168 patients with breast cancer, colorectal cancer (CRC), gastric cancer (GC), or non–small cell lung cancer (NSCLC) were included in the analysis. To assess the impact of sex differences on anticancer therapy toxicity, patients with sex-dominant breast cancer were excluded from this study. Patients who received palliative surgery or adjuvant concurrent chemoradiation therapy, were lost to follow-up for reasons other than AEs, participated in clinical trials, and experienced disease progression during neoadjuvant or adjuvant chemotherapy were also excluded. Patients meeting inclusion criteria were extracted and matched using the 1:1 greedy method from the electronic medical record (EMR) database system. The pre-reimbursement group (September 2013 to August 2015, n=1,084) and post-reimbursement group (January 2016 to December 2016, n=1,084) were included in this study.

2. Clinical data and adverse events collection

Clinical data regarding baseline characteristics, treatment, and AEs were retrospectively collected using the EMR system. We also compared the rates of unscheduled outpatient department (OPD) and emergency room (ER) visits and hospitalizations between male and female patients during chemotherapy. Past and current medical history collected in this study included hypertension, diabetes mellitus, tuberculosis, hepatitis, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease. The Common Terminology Criteria for Adverse Events (CTCAE) scoring system was used to evaluate chemotherapy-related AEs that developed or worsened during the on-treatment period. Most participating hospitals have integrated a systematic toxicity assessment form (STAF) (S1 Fig.) containing common chemotherapy-related AE categories and severity grading into EMR systems to assist physicians in capturing and grading AEs. In addition to the AEs recorded in STAF, all AEs documented by physicians in medical records were also collected. The incidence of any grade and severe (grade ≥ 3) toxicity were analyzed.

3. Study variables and statistical analysis

The primary variable in this study was the comparison of the rates of any grade treatment-related AEs between male and female patients during all chemotherapy periods. The treatment periods were divided into the first cycle and late (since the second cycle) periods. Secondary variables included grade ≥ 3 AEs, chemotherapy completion rates, dose intensity, dose reduction rates, rates of unexpected utilization of medical services during chemotherapy including unexpected OPD or ER visits, and hospitalization rates. Subgroup analyses of AEs according to the regimen used (single-agent or platinum-containing regimen) were also performed. Differences in baseline characteristics, rates of AEs, and grade ≥ 3 AEs between males and females were compared using the chi-square test or Fisher's exact test, considering all therapy agents together. When analyzing the continuous variables, the mean and standard deviation were presented. If the data followed a normal distribution, a t test was applied. Alternatively, if the data did not follow a normal distribution, the median (interquartile range), or median (range) was present-

Table 1. Baseline characteristics of patients

Characteristic	Total (n=1,170)	Female (n=493)	Male (n=677)	p-value[a]
Age (yr)				
Median (range)	61 (17-84)	57 (17-84)	63 (29-83)	< 0.001
≥ 70 yr	221 (18.9)	69 (14.0)	152 (22.5)	< 0.001
ECOG PS				
0-1	1,155 (98.7)	486 (98.6)	669 (98.8)	0.721
≥ 2	15 (1.3)	7 (1.4)	8 (1.2)	
BMI (kg/m²), median (range)	22.7 (14.2-35.6)	22.6 (14.2-35.6)	22.7 (15.4-34.4)	0.314
Past or current medical history[b]				
Present	621 (53.1)	224 (45.4)	397 (58.6)	< 0.001
None	547 (46.8)	269 (54.6)	278 (41.1)	
Unknown	2 (0.2)	0	2 (0.3)	
Marriage				
Single	51 (4.4)	27 (5.5)	24 (3.5)	0.100[c]
Married	941 (80.4)	379 (76.9)	562 (83.0)	
Unknown	178 (15.2)	87 (17.6)	91 (13.4)	
Cancer type				
Colon	366 (31.3)	178 (36.1)	188 (27.8)	0.008
Stomach	387 (33.1)	147 (29.8)	240 (35.5)	
Lung	417 (35.6)	158 (34.1)	249 (36.8)	
Pathologic stage				
1-2	621 (53.1)	261 (52.9)	360 (53.2)	0.937
3-4	549 (46.9)	232 (47.1)	317 (46.8)	
Chemotherapy regimen[d]				
Single-agent	351 (30.0)	149 (30.2)	202 (29.8)	0.887
Platinum-containing	819 (70.0)	344 (69.8)	475 (70.2)	
Extensive surgery[e]	44 (3.8)	14 (2.8)	30 (4.4)	0.158
Postoperative weight loss > 10%	211 (18.0)	71 (14.4)	140 (20.7)	0.006

Values are presented as number (%) unless otherwise indicated. BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status. [a]p-values were calculated using Pearson's chi-squared test or Fisher's exact test as appropriate on the percentage difference of female vs. male patients, [b]Medical history included hypertension, diabetes mellitus, tuberculosis, hepatitis, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease, [c]p-value after excluding unknown and including only single and married, [d]Single-agent: 5-fluorouracil (5-FU), S-1, capecitabine; platinum-containing chemotherapy: FOLFOX (5-FU+oxaliplatin), XELOX (capecitabine+oxaliplatin), vinorelbine+cisplatin, paclitaxel+cisplatin, paclitaxel+carboplatin, [e]Extensive surgery included total gastrectomy, total colectomy, and pneumonectomy.

ed and compared using the Mann-Whitney U test. Multivariable logistic regression was used to assess the association between sex and the risk of chemotherapy agent-related AEs while adjusting for potential confounding factors such as age, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status, history of extensive surgery, and cancer type. The extensive surgery included total colectomy, total gastrectomy, and pneumonectomy. We compared the completion rates, dose intensity, and dose modification of chemotherapy, as well as the rates of unexpected OPD or ER visits and hospitalization per patient between the male and female groups. Statistical significance was set at a two-sided p-value of less than 0.05. All analyses were performed using the SPSS software ver. 26 (IBM Corp., Armonk, NY).

Results

1. Patient characteristics

A total of 1,170 patients with lung cancer, GC, or CRC who received adjuvant chemotherapy between September 2013 and December 2016 were compared between males and females. The median age of all patients was 61 years (range, 17 to 84 years), and 42.1% of the patients were female. Patients with CRC (n=366, 31.3%), GC (n=387, 33.1%), or NSCLC (n=417, 35.6%) were included in the analyses. The types of chemotherapy regimens for each cancer type and the number of total cycles for each regimen according to sex are shown in S2 Table. There were no differences between male and female patients in median body mass index, ECOG performance sta-

Table 2. Adverse events occurring in at least 10% of patients in either group

	Female (n=493)		Male (n=677)		p-value	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Anemia	343 (69.6)	4 (0.8)	455 (67.2)	11 (1.6)	0.391	0.222
Neutropenia	302 (61.3)	87 (17.6)	316 (46.7)	88 (13.0)	< 0.001	0.028
Anorexia	188 (38.1)	8 (1.6)	255 (37.7)	8 (1.2)	0.871	0.521
Nausea	169 (34.3)	34 (6.9)	164 (24.2)	27 (4.0)	< 0.001	0.027
Peripheral neuropathy	159 (32.3)	3 (0.6)	210 (31.0)	1 (0.1)	0.654	0.316
Thrombocytopenia	136 (27.6)	4 (0.8)	214 (31.6)	4 (0.6)	0.138	0.727
AST elevation	126 (25.6)	1 (0.2)	117 (17.3)	5 (0.7)	0.001	0.410
Diarrhea	125 (25.2)	5 (1.0)	185 (27.3)	9 (1.3)	0.405	0.624
Fatigue	113 (22.9)	2 (0.4)	154 (22.7)	2 (0.3)	0.944	> 0.99
Hand-foot syndrome	109 (22.1)	2 (0.4)	154 (22.7)	0	0.796	0.177
Abdominal pain	106 (21.5)	13 (2.6)	99 (14.6)	12 (1.8)	0.002	0.313
ALT elevation	105 (21.3)	3 (0.6)	110 (16.2)	6 (0.9)	0.028	0.741
Stomatitis	83 (16.8)	2 (0.4)	67 (9.9)	2 (0.3)	< 0.001	> 0.99
Skin rash	78 (15.8)	2 (0.4)	92 (13.6)	3 (0.4)	0.285	> 0.99
Vomiting	68 (13.8)	25 (5.1)	39 (5.8)	9 (1.3)	< 0.001	< 0.001
Hyperbilirubinemia	55 (11.2)	1 (0.2)	98 (14.5)	1 (0.1)	0.096	> 0.99
Constipation	51 (10.3)	0	61 (9.0)	0	0.444	-

Values are presented as number (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase.

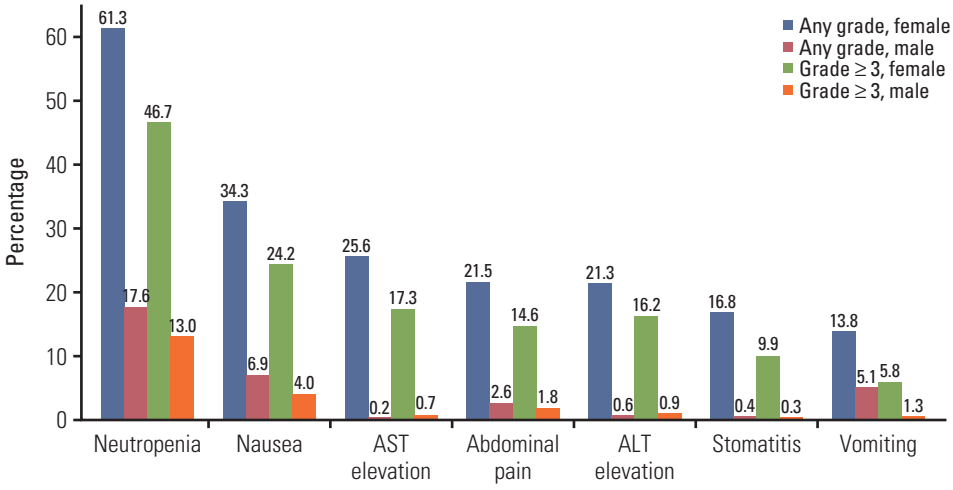

Fig. 1. The percentage of patients who experienced any grade/grade ≥ 3 adverse events with significant differences ($p < 0.05$) between males and females. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

tus, pathologic stage, number of patients undergoing extensive surgery, and use of single-agent chemotherapy or platinum-containing chemotherapy. However, female patients were younger (86.0% of females were under 70 years old vs. 77.5% of males, $p < 0.001$), had fewer comorbidities (45.4% of females had at least one comorbidity vs. 58.6% of males, $p < 0.001$), had more CRC (36.1% of females vs. 27.8% of males, p=0.008) and experienced less postoperative weight loss of > 10% (14.4% of females vs. 20.7% of males, p=0.006) compared to male patients (Table 1).

2. Incidence of common adverse events according to sex

Overall, females were more likely to experience both non-hematologic and hematologic AEs of all grades compared to male patients. Neutropenia was the most commonly observed AE (61.3% in females vs. 46.7% in males, $p < 0.001$), followed by nausea (34.3% vs. 24.2%, $p < 0.001$), aspartate transaminase (AST) elevation (25.6% vs. 17.3%, p=0.001),

Table 3. Adjusted odds ratio (95% CI) for all-grade adverse events

	Female events/total (%)	Male events/total (%)	Odds ratio[a] (95% CI)	p-value
AST elevation				
All regimens	126/493 (25.6)	117/677 (17.3)	1.58 (1.15-2.16)	0.004
Single-agent	35/149 (23.5)	36/202 (17.8)	1.44 (0.84-2.48)	0.186
Platinum-containing regimen	91/344 (26.5)	81/475 (17.1)	1.65 (1.13-2.42)	0.010
ALT elevation				
All regimens	105/493 (21.3)	110/667 (16.2)	1.28 (0.93-1.75)	0.127
Single-agent	31/149 (20.8)	32/202 (15.8)	1.38 (0.78-2.42)	0.269
Platinum-containing regimen	74/344 (21.5)	78/475 (16.4)	1.24 (0.85-1.81)	0.272
Abdominal pain				
All regimens	106/493 (21.5)	99/677 (14.6)	1.61 (1.16-2.23)	0.004
Single-agent	55/149 (36.9)	55/202 (27.2)	1.53 (0.96-2.46)	0.075
Platinum-containing regimen	51/344 (14.8)	44/475 (9.3)	1.68 (1.06-2.65)	0.027
Arthralgia				
All regimens	20/493 (4.1)	10/677 (1.5)	1.84 (1.43-2.38)	< 0.001
Single-agent	4/149 (2.7)	1/202 (0.5)	5.19 (0.55-49.13)	0.151
Platinum-containing regimen	16/344 (4.7)	9/475 (1.9)	2.37 (1.02-5.47)	0.044
Nausea				
All regimens	169/493 (34.3)	164/677 (24.2)	1.80 (1.36-2.36)	< 0.001
Single-agent	48/149 (32.2)	51/202 (25.2)	1.51 (0.93-2.45)	0.098
Platinum-containing regimen	121/344 (35.2)	113/475 (23.8)	1.94 (1.38-2.71)	< 0.001
Stomatitis				
All regimens	83/493 (16.8)	67/677 (9.9)	1.83 (1.29-2.62)	0.001
Single-agent	27/149 (18.1)	26/202 (12.9)	1.37 (0.75-2.51)	0.305
Platinum-containing regimen	56/344 (16.3)	41/475 (8.6)	2.20 (1.41-3.44)	0.001
Vomiting				
All regimens	68/493 (13.8)	39/677 (5.8)	2.80 (1.81-4.35)	< 0.001
Single-agent	10/149 (6.7)	9/202 (4.5)	1.42 (0.54-3.73)	0.480
Platinum-containing regimen	58/344 (16.9)	30/475 (6.3)	3.29 (2.00-5.42)	< 0.001
Neutropenia				
All regimens	302/493 (61.3)	316/677 (46.7)	1.84 (1.43-2.38)	< 0.001
Single-agent	88/149 (59.1)	78/202 (38.6)	2.22 (1.42-3.45)	< 0.001
Platinum-containing regimen	214/344 (62.2)	238/475 (50.1)	1.68 (1.23-2.29)	0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval. [a]Adjusted for age, Eastern Cooperative Oncology Group performance status, body mass index, extensive surgery, and the type of cancer.

abdominal pain (21.5% vs. 14.6%, p=0.002), alanine transaminase elevation (21.3% vs. 16.2%, p=0.028), stomatitis (16.8% vs. 9.9%, p < 0.001), and vomiting (13.8% vs. 5.8%, p < 0.001). Grade ≥ 3 AEs occurring significantly more frequently in females included neutropenia (17.6% vs. 13.0%, p=0.028), nausea (6.9% vs. 4.0%, p=0.027), and vomiting (5.1% vs. 1.3%, p < 0.001) (Table 2, Fig. 1). Although females experienced more frequent and severe neutropenia, there was no difference in the incidence of neutropenic fever between male and female patients (1.6% vs. 1.2%, p=0.565).

3. Association between sex and adverse events/chemotherapy regimen-related toxicities

To assess the impact of sex on toxicities, the adjusted associations between AEs and sex according to treatment regimen are shown in Tables 3 and 4. Irrespective of the treatment regimen, female patients had a significantly higher likelihood of experiencing any grade of vomiting (odds ratio [OR], 2.80; p < 0.001), neutropenia (OR, 1.84; p < 0.001), arthralgia (OR, 1.84; p < 0.001), stomatitis (OR, 1.83; p=0.001), nausea (OR, 1.80; p < 0.001), abdominal pain (OR, 1.61; p=0.004), and AST elevation (OR, 1.58; p=0.004) compared to male patients. Furthermore, female patients were more likely to experience grade ≥ 3 nausea (OR, 1.72; p=0.050) and vomiting (OR, 3.45; p=0.002) compared to male patients. When stratified by chemotherapy regimen, females who received platinum-based doublet chemotherapy had a significantly increased risk of all-grade vomiting (OR, 3.29; p < 0.001),

Table 4. Adjusted odds ratio (95% CI) for grade ≥ 3 adverse events

	Female events/total (%)	Male events/total (%)	Odds ratio[a] (95% CI)	p-value
Nausea				
All regimens	34/493 (6.9)	27/677 (4.0)	1.72 (1.00-2.97)	0.050
Single-agent	1/149 (0.7)	4/202 (2.0)	0.37 (0.04-3.45)	0.385
Platinum-containing regimen	33/344 (9.6)	23/475 (4.8)	1.99 (1.12-3.54)	0.019
Vomiting				
All regimens	25/493 (5.1)	9/677 (1.3)	3.45 (1.55-7.66)	0.002
Single-agent	1/149 (0.7)	0/202 (0.0)	-	-
Platinum-containing regimen	24/344 (7.0)	9/475 (1.9)	3.30 (1.48-7.37)	0.004
Neutropenia				
All regimens	87/493 (17.6)	88/677 (13.0)	1.36 (0.97-1.90)	0.076
Single-agent	14/149 (9.4)	9/202 (4.5)	1.86 (0.76-4.53)	0.176
Platinum-containing regimen	73/344 (21.2)	79/475 (16.6)	1.28 (0.89-1.84)	0.186

CI, confidence interval. [a]Adjusted for age, Eastern Cooperative Oncology Group performance status, body mass index, extensive surgery, and cancer type.

arthralgia (OR, 2.37; p=0.044), stomatitis (OR, 2.20; p=0.001), nausea (OR, 1.94; p < 0.001), neutropenia (OR, 1.68; p < 0.001), abdominal pain (OR, 1.68; p=0.027), and AST elevation (OR, 1.65; p=0.010). In addition, they had a significantly increased risk of grade ≥ 3 vomiting (OR, 3.30; p=0.004) and nausea (OR, 1.99; p=0.019). Among patients receiving single-agent chemotherapy, neutropenia (OR, 2.22; p < 0.001) was the only AE with a significantly increased incidence in female patients compared to male patients.

4. Association between sex and adverse events in each cancer type

Since cancer type was significantly different between males and females, we compared the incidence rate of AEs according to sex within each cancer type (S3-S5 Tables). In the patients with CRC, it was observed that females exhibited a higher incidence of any grade neutropenia, AST elevation, nausea, abdominal pain, and vomiting. In patients with GC, higher incidence of any grade neutropenia, nausea, thrombocytopenia, vomiting, and peripheral neuropathy was observed. A higher incidence of grade ≥ 3 AEs was observed in females, specifically in the occurrence of vomiting among patients with CRC and neutropenia and vomiting in GC. Nevertheless, within patient with NSCLC, there was no statistically significant disparity observed in the occurrence of grade ≥ 3 AEs between male and female patients.

5. Completion rates, dose intensity, and dose modification of chemotherapy

Overall, male and female patients showed similar completion rates of chemotherapy as planned (87.1 vs 87.6%, p=0.808). However, there was a significant difference in dose intensity, with female patients having a lower dose intensity than male patients (0.78±0.23 vs. 0.80±0.24, p=0.048). With regard to dose modification, there was no significant difference in the initial dose reduction from the first cycle between female and male patients (21.9% vs. 19.2%, p=0.257). However, more female patients underwent subsequent dose reductions after the first cycle compared to male patients (43.0% vs. 34.3%, p=0.001). When stratified by chemotherapy regimen, only the platinum-containing regimen showed a consistent difference between male and female patients. In this group, female patients received chemotherapy with a significantly lower dose intensity compared to male patients (0.80±0.21 vs. 0.83±0.23, p=0.012), and a higher proportion of female patients underwent dose modification after the first cycle (46.2% vs. 37.7%, p=0.014) (Table 5).

6. Unscheduled OPD and ER visits and hospitalization rates

Table 6 summarizes the incidence of unexpected medical service utilization per patient during chemotherapy. Overall, there were no significant differences observed between females and males in the rates of ER visits (13.4% in females vs. 13.1% in males, p=0.904) and hospitalizations (6.5% vs. 9.2%, p=0.097). However, there was a trend towards a higher rate of unscheduled visits to the OPD in female patients (14.0% vs. 10.5%, p=0.068). In patients treated with platinum-containing regimens, females had a significantly higher rate of unscheduled OPD visits than males (15.1% vs. 9.1%, p=0.007), whereas there were no significant differences between the two groups in the rates of OPD visits, ER visits, and hospitalizations in patients receiving single-agent chemotherapy. When we analyzed those patients who had an unscheduled outpatient visit and received a platinum-containing regimen, there were no differences in baseline

Table 5. Administration of chemotherapy between male and female patients by chemotherapy regimen

	All regimens			Single-agent			Platinum-containing		
	Female (n=493)	Male (n=677)	p-value	Female (n=149)	Male (n=202)	p-value	Female (n=344)	Male (n=475)	p-value
Total cycles completion as planned	432 (87.6)	590 (87.1)	0.808	120 (80.5)	165 (81.7)	0.786	312 (90.7)	425 (89.5)	0.565
Dose intensity	0.78±0.23	0.80±0.24	0.048	0.75±0.26	0.77±0.26	0.875	0.80±0.21	0.83±0.23	0.012
Dose reduction									
Initially from cycle 1	108 (21.9)	130 (19.2)	0.257	23 (15.4)	22 (10.9)	0.208	85 (24.7)	108 (22.7)	0.512
Subsequently	212 (43.0)	232 (34.3)	0.001	53 (35.6)	53 (26.2)	0.060	159 (46.2)	179 (37.7)	0.014

Values are presented as number (%) or median±standard deviation.

Table 6. Rates of unexpected utilization of medical services per patient by chemotherapy regimen

	All regimens			Single-agent			Platinum-containing		
	Female (n=493)	Male (n=677)	p-value	Female (n=149)	Male (n=202)	p-value	Female (n=344)	Male (n=475)	p-value
Unscheduled OPD visit	69 (14.0)	71 (10.5)	0.068	17 (11.4)	28 (13.9)	0.497	52 (15.1)	43 (9.1)	0.007
ER visit	66 (13.4)	89 (13.1)	0.904	18 (12.1)	22 (10.9)	0.729	48 (14.0)	67 (14.1)	0.951
Hospitalization	32 (6.5)	62 (9.2)	0.097	7 (4.7)	19 (9.4)	0.096	25 (7.3)	43 (9.1)	0.361

Values are presented as number (%). ER, emergency room; OPD, outpatient department.

characteristics between the sex (data not shown). However, the significant difference in incidence of any grade stomatitis was observed between female and male patients (15.8% vs. 2.1%, p=0.002) (S6 Table).

Discussion

In this multicenter retrospective cohort study, female patients receiving adjuvant chemotherapy experienced a higher incidence of all-grade non-hematological and hematological AEs, despite being younger and having fewer comorbidities. Moreover, female patients had a significantly higher incidence of grade ≥ 3 AEs, particularly neutropenia, nausea, and vomiting. A higher proportion of female patients underwent subsequent dose reductions after the first cycle and had a lower dose intensity. Additionally, they still had more unscheduled OPD visits during chemotherapy than male patients.

Most previous studies reported on the sex differences in AEs within a single cancer type. The ACCENT database, which analyzed 34,640 patients with colon cancer undergoing 5-FU single agent, with or without oxaliplatin, capecitabine as a single agent, or in combination with oxaliplatin, and 5-FU/leucovorin/irinotecan (FOLFIRI) regimens, found that females experienced significantly higher toxicity than males, particularly in terms of severe neutropenia and leukopenia [13]. A study conducted by Yamada et al. [14] investigated sex-related differences in the safety of S-1 plus oxaliplatin and S-1 plus cisplatin in 663 metastatic GC patients. The study revealed that female patients treated with S-1 plus oxaliplatin exhibited a greater susceptibility to leukopenia, neutropenia, nausea, and vomiting than male patients, while female patients treated with S-1 plus cisplatin had a higher incidence of vomiting and stomatitis compared to male patients. With regard to NSCLC, the E1594 trial [15] evaluated 1,157 advanced NSCLC patients who received one of four different platinum doublet chemotherapy regimens and found that females were more likely to experience nausea, vomiting, alopecia, and neurosensory deficits. Similarly, Yamamoto et al. [16], reported that females with NSCLC who were treated with carboplatin and paclitaxel had a higher incidence of severe leukopenia and a lower median leukocyte nadir. Overall, these findings are in line with our study and suggest that female patients receiving cytotoxic chemotherapy are at an increased risk of experiencing chemotherapy-related AEs, regardless of the type of cancer they have. Additionally, we analyzed the association between sex and AEs in each specific type of cancer, and our findings are consistent with prior studies. Of note, our study analyzed the differences in the risks of AEs between sexes based on chemotherapy regimens, and we found that the higher risks of AEs in female patients compared to male patients were more pronounced in platinum-based doublet regimens than

in monotherapy. This suggests that potential differences in the risks of AEs between sexes would be more apparent in chemotherapy regimens with more severe and frequent AEs.

It is important to note that AEs during chemotherapy can often interfere with completing the planned treatment if not managed appropriately. AEs can also diminish patients' quality of life and increase healthcare utilization and costs [17]. Several reports have compared the actual incidences of chemotherapy-related AEs between sexes, but few studies have addressed their impact on healthcare utilization [18,19]. Abdel-Rahman and Ahmed [20] conducted a pooled analysis of four randomized studies of 5-FU–based chemotherapy in metastatic CRC to identify predictors of toxicity-related hospitalization. They found that older age and poorer performance status were associated with a higher risk of hospitalization, but they did not consider sex as a factor influencing the risk of hospitalization. In contrast, our study demonstrated that female patients showed a tendency for higher rates of unscheduled OPD visits during chemotherapy. Moreover, in patients who received platinum-containing regimens, female patients visited unscheduled outpatient clinics and experienced more frequent any-grade stomatitis compared to male patients. This suggests that proper management of stomatitis in female patients can help reduce healthcare service costs. Our finding indicates that considering sex is important when analyzing unscheduled utilization of medical services during chemotherapy.

In our study, we found that even though the total cycle completion rates were similar, female patients achieved lower dose intensity and experienced a higher incidence of subsequent dose reduction beyond the first cycle of doublet chemotherapy. It is well established that a lower dose intensity of adjuvant chemotherapy is associated with an increased risk of recurrence. For example, in early breast cancer, patients who received less than 85% of the relative dose intensity had a 57% increase in the risk of disease recurrence at 10 years [21]. Therefore, our study underscores the significance of assessing and managing the AEs of chemotherapy to complete the planned cycles of adjuvant chemotherapy at the appropriate dose to prevent a recurrence, given its recommended curative intent. More personalized supportive care may be necessary for female patients to maintain the dose intensity of chemotherapy and mitigate adverse events.

Sex-based differences in the incidence of chemotherapy-related AEs can be attributed to the pharmacokinetics and pharmacodynamics of various anticancer drugs. In both GC and CRC, 5-FU–based treatment is a cornerstone of adjuvant chemotherapy. Females have a reduced capacity to eliminate fluorouracil, resulting in higher drug levels in their bloodstream compared to males when dosed based on body surface area (BSA) [6,22]. This difference may be attributed to sex-specific variations in the dihydropyrimidine dehydrogenase enzyme [8,23]. Furthermore, females have a lower DNA repair capacity, which may explain the toxicity associated with platinum-based chemotherapy, making them more susceptible to the AEs of platinum agents that work through DNA adduct formation [24,25]. In addition, female patients with solid tumors have a 20% lower elimination of paclitaxel than male patients, leading to higher drug exposure and potentially higher rates of AEs [26].

Several studies have suggested other potential explanations for the increased AEs observed in females after certain chemotherapeutic agents. One possible reason is that females have a slower rate of gastric emptying and larger distribution volumes of lipophilic drugs, which can result in elevated AEs. Furthermore, females tend to have more body fat and less lean body mass, leading to increased plasma drug levels compared to males. BSA-based dosing methods may not account for these pharmacokinetics and body composition differences, potentially resulting in overdosing of females [3]. Additionally, females may be more susceptible to gastrointestinal and mucosal toxicity from drugs such as 5-FU. It has also been suggested that females may over-report symptoms of morbidity and disability compared to males, potentially introducing a bias in reported rates of drug toxicity [27,28].

This study is, to our knowledge, the largest study conducted among Korean populations that examined the incidence of chemotherapy AEs according to sex in patients with CRC, GC, or NSCLC who received adjuvant chemotherapy. The strength of our study includes a large number of patients with homogenous treatment received and real-world reflection. As such, the study only included patients who received adjuvant chemotherapy, thereby excluding any cancer-related adverse events from the analysis. The weakness of our study is in its retrospective nature, which may have resulted in underreporting of AE. However, most participating hospitals adopted STAF to systematically collect AEs, and the rates of AEs are comparable to other prospective study data or clinical trial data, suggesting that AEs were collected well in our study [29]. Additionally, the study period was from 2013-2016, which may reflect different supportive care from the current standard. Also, we could not assess the association between reduced dose intensity in females and recurrence and survival outcome, because we did not collect data on the recurrence and survival in the main study, which would have given valuable insight on the consequence of sex differences. This warrants further investigation in a larger prospective cohort. Despite its limitations, we showed that females experience greater all grades and severe AEs from chemotherapy in a relatively large number of patients undergoing adjuvant chemotherapy, and this increase in toxicity leads to more frequent unscheduled OPD visits and dose

reductions in females. Further investigation is warranted to determine whether reduced dose intensity in females would lead to poor survival or recurrence.

In conclusion, our study found that females receiving adjuvant chemotherapy for CRC, GC, or NSCLC experienced higher rates of multiple all-grade AEs and grade ≥ 3 neutropenia, nausea, and vomiting, and had reduced dose intensity and more frequent unscheduled OPD visits. As personalized medicine becomes more prevalent, physicians need to consider sex-based differences in AEs when making chemotherapy decisions for their patients.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Institutional Review Board of each participating center (IRB No. for Asan Medical Center: 2017-1139; IRB No. for Ulsan University Hospital: UUH 2018-10-008; IRB No. for Seoul National University Bundang Hospital: B-1810-499-110; IRB No. for Gangneug Asan Hospital: GNAH 2018-10-012), and the requirement of informed consent has been waived because of the retrospective nature of this study. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Author Contributions

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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