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Original Article

The impact of combination chemotherapy administration on prognostic outcomes in stage II and III gastric cancer: a comprehensive analysis utilizing propensity score matching

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Abstract: Objective: Limited data are available on the effects of combined and intravenous or oral chemotherapy on the survival of patients who have undergone D2 gastrectomy for cancer. Methods: This study involved 1314 patients who participated in a trial that followed D2 gastrectomy with adjuvant or neoadjuvant chemotherapy. Results: Following propensity score matching (PSM), the results indicated that contrary to expectations, combined chemotherapy administration was associated with poorer overall survival (OS) and progression-free survival (PFS) at the 5-year mark for stage II gastric cancer, with log-rank *P* values of 0.005 for OS (83.6% vs. 68.8%) and 0.005 for PFS (71.6% vs. 61.5%). Significant differences were observed in the recurrence rate ($P < 0.001$) and local-regional recurrence ($P = 0.009$), although no significant difference was found for distant metastasis ($P = 0.146$). For stage III gastric cancer, the Kaplan-Meier survival curves showed that the combination of oral and intravenous chemotherapy was inferior to single-modality chemotherapy for PFS ($P = 0.006$). However, it did not differ significantly from single therapy in OS ($P = 0.257$). Notable discrepancies were evident in the recurrence rate ($P < 0.001$), distant metastasis ($P < 0.001$), and local-regional recurrence ($P = 0.003$). Conclusions: The findings suggest that the concurrent use of oral and intravenous chemotherapy after D2 gastrectomy does not enhance the prognosis for gastric cancer patients compared to using either modality alone. Instead, it appears to increase the risk of disease progression for stage III patients and the likelihood of recurrence for both stages II and III of gastric cancer.

Keywords: Chemotherapy administration, gastric cancer, propensity score matching

Introduction

Gastric carcinoma, commonly known as stomach cancer, is a significant global health issue, ranking as the fifth most prevalent cancer worldwide and the third leading cause of cancer-related deaths [1]. In recent years, advancements in medical technology have led to significant improvements in the treatment of gastric cancer, mainly through the development of D2+ gastrectomy - a surgical procedure involving extensive lymph node dissection - and the increased efficacy of adjuvant chemotherapy. These advancements have improved overall survival rates for patients with gastric cancer [2, 3]. Despite these improvements, there is a continued need for further research to enhance long-term survival outcomes for patients [4]. For instance, studies have compared the chemotherapy regimens SOX and mFOLFOX6 for locally advanced gastric cancer and found them to have similar efficacy. However, the SOX regimen was associated with a lower risk of gastrointestinal adverse reactions compared to mFOLFOX6 [5]. Additionally, research has shown that the FOLFIRI and paclitaxel + carboplatin treatments have similar overall survival (OS), progression-free survival (PFS), and side effect profiles for the subsequent line treatment of Her-2-negative gastric cancer [6].

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Furthermore, the combination of taxanes with essential chemotherapy is superior to chemotherapy without taxanes as the first-line treatment for advanced gastric cancer patients [7]. Subgroup analysis has also suggested that adjuvant SOX may be more effective than CAPOX in male patients over the age of 60 with tumors in the gastric antrum and moderately differentiated tumors in terms of overall survival (OS) and progression-free survival (PFS) [8]. A previous study found that the inclusion of S-1 did not demonstrate a superior effect over the exclusion of S-1 in the prognosis of stage II and III gastric cancer patients. However, it was significantly associated with an increased risk of mortality in stage III gastric cancer patients [9].

Scientific literature has not extensively investigated the prognostic implications of employing various chemotherapy regimens in the treatment of gastric cancer. Concretely, although a variety of combined chemotherapy regimens - including SOX, XELOX, and XELOX plus Sintilimab - are commonly proposed as initial treatment options, evidence suggests that the survival benefits conferred by these combined approaches may not be significantly different when compared to monotherapy regimens. Additional studies are needed to clarify the optimal chemotherapy strategies for gastric cancer patients. Different chemotherapy administrations are extensively employed in both neoadjuvant and postoperative chemotherapy settings. Each method presents distinct characteristics. Oral administration, for instance, is noted for its superior medical compliance and minimal side effects compared to intravenous administration. Conversely, intravenous chemotherapy enables drugs to directly enter the bloodstream, thereby minimizing the variability in drug absorption among individuals and ensuring adequate systemic drug delivery. Despite these advantages, the impact of different chemotherapy regimens on survival outcomes remains an unresolved issue in oncology. This study aims to address this gap by investigating whether there are variations in prognosis and recurrence rates among advanced-stage cancer patients treated with either single or combination chemotherapy regimens. Through comparative analysis, the study seeks to provide critical insights into the efficacy of each treatment approach and potentially uncover significant differences in their effects on patient outcomes. The findings from this research endeavor can potentially guide healthcare professionals in making informed decisions regarding treating advanced-stage cancer patients. By enhancing our understanding of the comparative effectiveness of different chemotherapy strategies, this study contributes to improved prognostic outcomes and reduced recurrence rates in this vulnerable patient population.

Methods

Data collection

The study was a retrospective analysis of 1314 cancer patients who underwent gastrectomy in Shanxi Province, China, from 2002 to 2020. The patients were divided into 412 stage II and 902 stage III patients. The clinicopathological characteristics of the patients were analyzed, including age at operation, sex, number of positive lymph nodes, depth of tumor invasion, vascular invasion, nerve invasion, Lauren classification, largest tumor diameter, TNM stage, type of gastrectomy, surgical margins, multiple organ resection, chemotherapy regimen, chemotherapy administration, number of chemotherapy cycles, various metastases, retinal metastases, complications, Clavien-Dindo classification, overall survival (OS), and progression-free survival (PFS).

The inclusion criteria for the study were patients who had received adjuvant or neoadjuvant chemotherapy before radical gastrectomy, patients with histologically confirmed cancer, patients with no serious postoperative complications, patients with complete clinical pathology and follow-up records, and patients without any other malignant tumors or causes of death aside from cancer. The exclusion criteria included patients with incomplete clinical records, patients with different tumors, patients with non-gastric cancer, and patients who had undergone bypass or palliative surgery.

The study was conducted following the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Shanxi Cancer Hospital. Patient information was anonymized and not disclosed to the public. Since

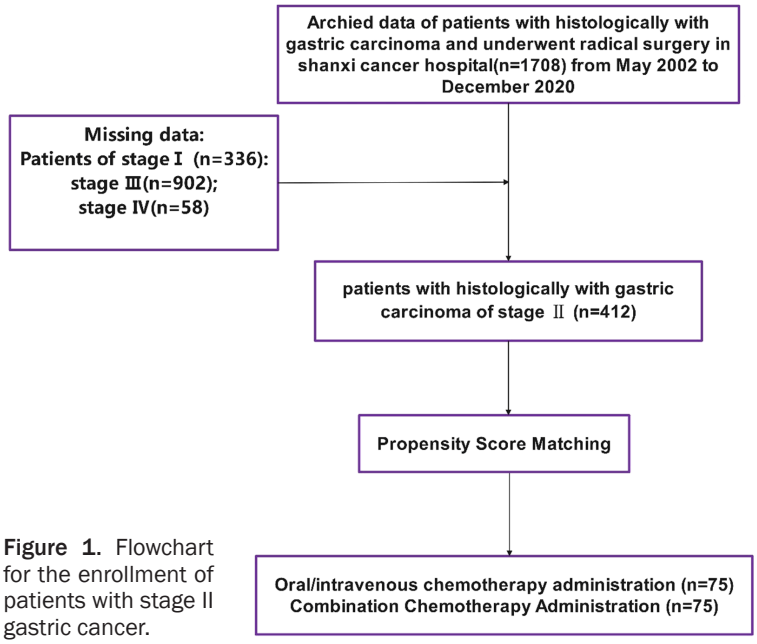

Figure 1. Flowchart for the enrollment of patients with stage II gastric cancer.

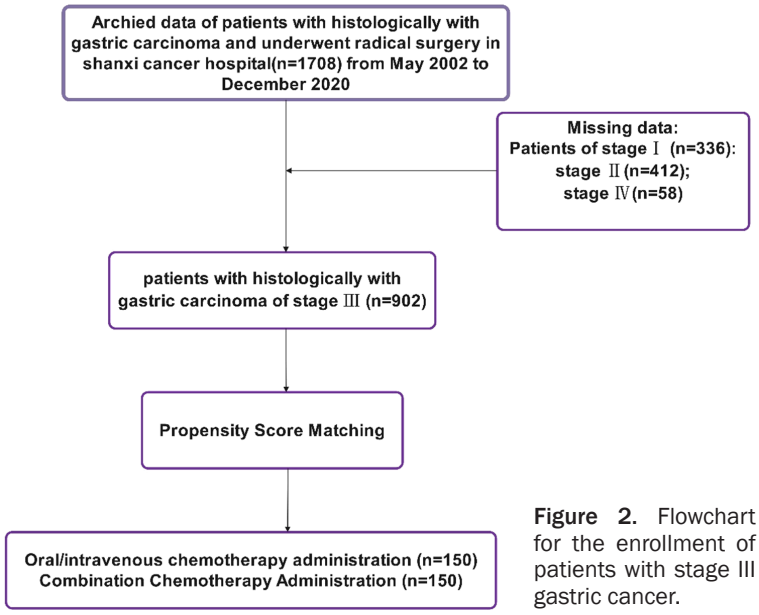

Figure 2. Flowchart for the enrollment of patients with stage III gastric cancer.

the study was retrospective, consent was not required from the patients. **Figure 1** provides a flowchart outlining the research process of stage II gastric cancer patients, and **Figure 2** for stage III.

Patient treatment

Patients included in this study have received postoperative chemotherapy regimens: (1) Oxaliplatin (130 mg/m^2) and S-1 (40-60 mg) are administered twice a day for two consecutive weeks, followed by a 7-day rest period. (2) S-1 (Gemeracil/Tegafur/Oataxil) is administered twice a day for two weeks, with a dosage determined based on the location of the disease (between 40-60 mg), followed by a 7-day rest period. (3) S-1 (40-60 mg) and Apatinib (500 mg) are administered continuously once a day for two weeks, followed by a 7-day rest period. (4) Folic acid combination (200 mg/m^2), folinic acid (200 mg/m^2), and FOLFOX (fluorouracil 2800 mg/m^2 and oxaliplatin 85 mg/m^2) are administered every three weeks. (5) XELOX (oxaliplatin and capecitabine) is administered intravenously. Oxaliplatin (150 mg/m^2) is administered on the first day of every three weeks, and capecitabine (1000 mg/m^2) is taken orally twice a day from day 1 to day 14, followed by a 7-day rest period. (6) Capecitabine (1000 mg/m^2) is taken orally twice daily for two consecutive weeks, followed by a 7-day rest period. (7) From day 1 to day 5, S-1+docetaxel, cisplatin, and fluorouracil (DCF) are administered orally twice daily. Docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) are administered from day 1 to day 5, and fluorouracil (750 mg/m^2) is administered from day 1 to day 5. S-1 (40-60 mg) is taken orally from day 1 to day 14, followed by a 7-day rest period. (8) Defluorouridine is orally administered at a recommended dosage of 1000 mg/m^2, taken twice daily for 28 days, followed by a 14-day rest period.

In the context of neoadjuvant chemotherapy, only a tiny proportion of patients (102 out of 1314) elected to receive this treatment approach. Notably, all these patients had been diagnosed with stage III cancer (out of a total of

902 patients with stage III disease). The specific regimens chosen for neoadjuvant chemotherapy included S-1 monotherapy (42 patients), SOX combination therapy (31 patients), and FOLFOX regimen (30 patients).

In simpler terms, chemotherapy treatments were categorized into two groups: 1) Oral/intravenous group: This group included chemotherapy regimens that could be taken orally (in the form of a pill) or administered intravenously (through a vein). Some specific regimens in this group were S-1 and capecitabine. Other regimens in this group were given entirely through intravenous infusion, such as FOLFOX and ECF. 2) Combination group: This group included oral and intravenous administration chemotherapy regimens. Examples of these regimens were SOX and XELOX. Multiple regimens in this group involved oral and intravenous administration in various ways.

Based on these criteria, the pathological stage of the patients and the degree of tumor regression were assessed. The treatment response to neoadjuvant chemotherapy was also evaluated. The specimens of the patients were dissected and examined thoroughly during the study. The evaluation was based on Ryan's criteria, which provided a grading system for assessing the level of tumor regression. Grade 0 indicated complete remission, where no residual tumor cells were found. Grade 1 referred to primary remission, with scattered tumor cells still present. Grade 2 denoted moderate remission, characterized by aggregated tumor cells and fibrosis. Finally, grade 3 indicated mild remission, in which tumor cells were frequently retained. By applying these grading criteria, the researchers could determine each patient's pathological stage and evaluate the effectiveness of neoadjuvant chemotherapy in terms of tumor regression and treatment response [6]. The method used to assess the toxicity of neoadjuvant chemotherapy was criterion 5.0, which refers to the Common Terminology Criteria for Adverse Events (CTCAE) [7].

Follow-up

As of December 2020, the follow-up period for stage II cancer patients was 41.51±21.18 months, while the follow-up period for stage III cancer patients was 43.56±24.45 months. Patients were followed up every three months during the first year after surgery. Followed up every six months within 2 to 5 years after surgery. Afterward, followed up once a year. Routine follow-up items included physical examination, chest X-ray, pelvic ultrasound, magnetic resonance imaging, computed tomography, and laboratory examination.

Statistical analyses

The propensity score matching (PSM) analysis was conducted to account for potential confounding variables and match individuals with similar characteristics. This method involved a 1:1 nearest neighborhood matching approach, wherein each individual from the treated group was matched with the closest individual from the control group. The matching was performed without replacement, meaning each control individual could only be matched once. Calipers were adjusted for sample size and matching success to ensure successful matching. Calipers were used to set a threshold for the maximum difference in propensity scores between matched pairs. The analysis aimed to better balance between the treated and control groups by adjusting the calipers for sample size and matching success. The characteristics used for matching included gender, age at surgery, vascular invasion, nerve invasion, depth of tumor invasion, number of positive lymph nodes, Lauren classification, maximum tumor diameter, and type of gastrectomy. These variables were selected based on their potential association with the outcomes of interest. Once the patients were matched successfully, a correlation analysis was performed to investigate the relationship between the primary and secondary endpoints. The primary endpoints in this analysis were progression-free survival (PFS) and overall survival (OS), which are necessary measures of the effectiveness of the treatment. The secondary endpoints included tumor recurrence and metastasis, the occurrence of multiple metastases, and recurrence patterns. By examining the correlations between these endpoints, the analysis aimed to determine the impact of the treatment on the various aspects of disease progression and recurrence.

The log-rank comparison is a statistical test used to compare the survival rates between different groups. This analysis was used to generate Kaplan-Meier survival curves for each group, allowing for the visual representation of the differences in survival rates. Appropriate statistical tests were used to analyze categorical variables. These tests help determine if there are significant differences between groups regarding these variables. The significance level, or *P*-value, was set at 0.05. This means any observed differences between groups with a *P*-value less than 0.05 were considered statistically significant, indicating that they were unlikely to occur by chance alone. The return visit date was calculated by subtracting the surgery date from the last contact with the patient. This provides information on the time between the surgery and the last follow-up. Overall survival (OS) was calculated as the time between the surgery and death or the last follow-up. This measurement gives insight into the duration of survival after surgery. Progression-free survival (PFS) is the time between the surgery and the first recorded death or recurrence. It provides information on the time before disease progression or recurrence occurs. These measurements are essential for understanding the analyzed population's survival outcomes and disease progression. They help provide information on how long patients survive after surgery and how quickly disease progression or recurrence occurs.

Categorical variables were presented as percentages and analyzed using exact, Fisher, and chi-square tests. Continuous data, expressed as mean ± standard deviation, were analyzed using T-tests. Survival analysis for PFS and OS was conducted using the Kaplan-Meier method, and the results were compared using the log-rank test. Non-normally distributed parameters were analyzed using the Mann-Whitney test with the median. Subgroup analyses were done using Cox hazard regression models. Statistical significance was set at $P < 0.05$. Complete PSM was achieved through Hansen and Bowers's overall balance testing, which involved checking if the standardized average absolute deviation is less than 0.25 and using the relative multivariable imbalance L1 for testing. χ Square tests were used to compare differences between the two groups regarding local recurrence, recurrence, peritoneal metastasis, and distant metastasis. The data analysis in this study was performed using SPSS 25.0 software (IBM, Armonk, NY, USA).

Results

TNM stage II gastric cancer patients propensity score matching (PSM) analysis and subgroup analysis

In this study, we included 412 individuals with TNM stage II cancer for analysis. The variables examined for each patient included gender, age at the time of surgery, presence of vascular and nerve invasion, depth of tumor invasion, number of positive lymph nodes, Lauren classification, maximum tumor diameter, type of gastrectomy, and surgical margin. To account for differences in patient characteristics, we employed a 1:1 nearest-neighbor propensity score matching (PSM) without replacement with a caliper value of 0.2. **Table 1** shows a significant difference in the number of positive lymph nodes between the oral or intravenous chemotherapy administration group and the oral combined with intravenous chemotherapy administration group ($P = 0.048$). We then conducted PSM within these two groups and selected 150 patients, including 75 cases in each group. No apparent differences were found in any variables between the two groups after PSM ($P > 0.05$), indicating that the matched patients were well-balanced regarding these characteristics.

Of the 75 patients receiving oral or intravenous chemotherapy, the S-1 monotherapy and FOLFOX regimen were the primary treatments, accounting for 64.0% (48/75) and 25.3% (19/75) of cases, respectively. The remaining cases involved capecitabine monotherapy (8 patients). In the group receiving both oral and intravenous chemotherapy, 38.6% (29/75) were administered SOX, 2.9% (2/75) received XELOX, 16.0% (12/75) were on a combination of SOX and FOLFOX, and 5.3% (4/75) on S-1 plus FOLFOX. A further 28 patients were treated with multiple chemotherapy regimens. Following propensity score matching (PSM), the Hansen & Bowers overall balance test *P*-value was 1.0, significantly exceeding the threshold

Table 1. Patients' characteristics before and after propensity score matching (PSM) of chemotherapy administration for stage II cancer

Variables	Before PSM		P	After PSM		P
	Oral/Venous (n = 328)	Combination (n = 84)		Oral/Venous (n = 75)	Combination (n = 75)	
Gender			0.827			1.000
Male	270	70		62	62	
Female	58	14		13	13	
Age (years)	59.21±10.19	57.68±11.30	0.308	58.91±9.01	58.63±9.48	0.920
Depth of tumor invasion			0.456			0.675
T1	9	4		5	4	
T2	25	4		5	4	
T3	214	60		50	51	
T4	80	16		15	16	
Number of positive lymph nodes			0.048			0.599
0	196	40		36	37	
1-2	120	40		36	34	
3-6	7	2		3	2	
≥ 7	5	2		3	2	
Type of gastrectomy			0.805			0.656
Proximal	32	6		6	6	
Distal	103	31		24	27	
Total	193	47		45	42	
Vascular invasion			0.314			0.509
Negative	101	54		42	46	
Positive	137	30		33	29	
Neural invasion			0.617			0.615
Negative	205	50		48	45	
Positive	123	30		27	30	
Lauren classification			0.027			0.994
Intestinal	169	34		32	33	
Diffuse	69	16		15	13	
Mixed	90	34		28	29	
Maximum diameter of tumor (cm)			0.287			0.599
< 6	238	56		53	50	
≥ 7	90	28		22	25	
Surgical margin			0.744			0.65
Negative	322	82		72	73	
Positive	6	4		3	2	

of 0.05. The relative unbalanced L1 test values were 0.969 before PSM and 0.875 after PSM, indicating substantial balance. No variables had imbalances greater than |d| > 0.25 across all cases, and the distribution of variables between the two groups was primarily balanced.

Figure 3 demonstrates that after performing propensity score matching (PSM), there was no statistically significant difference in overall survival (OS) and progression-free survival (PFS) between the two groups (P > 0.05). However, it is essential to highlight that for patients with TNM stage II, research has shown that oral or intravenous chemotherapy administration is more effective regarding PFS than combined oral and intravenous chemotherapy. Before PSM, the median OS for oral or intravenous chemotherapy administration was 44 months,

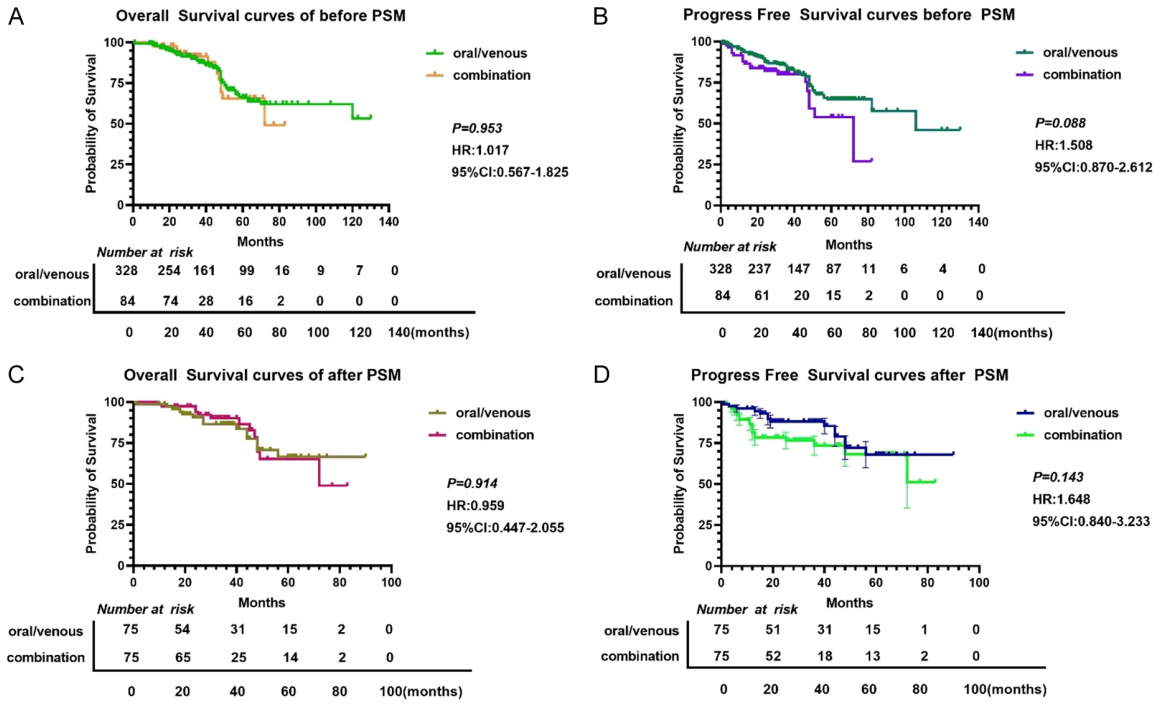

Figure 3. Comparison of overall survival (OS) and progression-free survival (PFS) before and after propensity score matching (PSM) in stage II gastric cancer patients. (A, B) Comparison of OS (A) and PFS (B) between the two groups based on chemotherapy administration before PSM; (C, D) Comparison of OS (C) and PFS (D) between the two groups based on chemotherapy administration after PSM.

while for oral plus intravenous chemotherapy administration, it was 49 months. The median PFS for oral or intravenous chemotherapy administration was 41 months; for oral plus intravenous chemotherapy administration, it was 36 months. After PSM, the 1-year, 3-year, and 5-year OS and PFS rates between the two groups were similar (P > 0.05). The median OS for oral or intravenous chemotherapy administration was not reached, while for oral plus intravenous chemotherapy administration, it was 72 months. The comparison of OS rates at one year, three years, and five years between the two groups revealed no statistically significant differences. Similarly, there were no significant differences in PFS rates between the groups. It is important to note that the median PFS for neither group has yet to be reached. Additionally, the incidence of recurrence with oral combined with intravenous chemotherapy administration was higher compared to oral or intravenous chemotherapy administration. The recurrence and local-regional recurrence rates were significantly different between the groups (P = 0.001 and P = 0.009, respectively), while the difference in distant metastasis was not statistically significant (P = 0.146).

In the comparison of oral plus intravenous chemotherapy administration with oral or intravenous administration alone, no significant differences were observed in overall survival (OS) (P = 0.555) and progression-free survival (PFS) (P = 0.15). However, subgroup interaction analysis revealed that tumors with a maximum diameter of 6 cm or larger were significantly associated with shorter OS (P for interaction = 0.016) and PFS (P for interaction = 0.003) when treated with oral plus intravenous chemotherapy (**Tables 2**, **3**; **Figure 4**). Compared to oral or intravenous chemotherapy alone, the hazard ratio (HR) for mortality was reduced by 26.8% (HR: 0.732, 95% CI: 0.202-2.467) for tumors less than 6 cm and by 24.4% (HR: 0.756, 95% CI: 0.290-1.973) for tumors 6 cm or more significant in the group receiving oral combined with intravenous chemotherapy (**Table 2**; **Figure 4**). Similarly, compared to oral combined with intravenous chemotherapy, the risk of disease progression increased by 81.4% (HR: 1.814, 95% CI: 0.637-5.165) for tumors less

Table 2. Subgroups analysis of overall survival (OS) by cox regression of chemotherapy administration for stage II cancer

Variables	Event	Total	HR	95% CI	P	P for interaction
Gender						0.784
Male	24	124	0.832	0.370-1.832	0.657	
Female	3	26	2.000	0.181-22.056	0.571	
Number of positive lymph nodes						0.192
0	14	71	1.812	0.605-5.428	0.288	
≥ 1	13	79	0.359	0.097-1.330	0.125	
Vascular invasion						0.387
Negative	16	88	1.353	0.397-3.679	0.554	
Positive	11	62	0.605	0.175-2.008	0.327	
Neural invasion						0.761
Negative	12	93	1.228	0.465-2.306	0.692	
Positive	12	57	0.665	0.209-2.115	0.490	
Lauren classification						0.599
Intestinal	12	65	1.267	0.712-2.253	0.421	
Diffuse	6	28	1.080	0.216-5.403	0.965	
Mixed	9	57	0.672	0.334-1.532	0.265	
Maximum diameter of tumor (cm)						0.016
< 6	10	103	0.732	0.202-2.467	0.634	
≥ 6	17	47	0.756	0.290-1.973	0.568	
Type of gastrectomy						0.685
Proximal	5	12	0.986	0.401-2.425	0.974	
Distal	7	51	0.293	0.057-1.512	0.142	
Total	15	87	1.400	0.830-2.363	0.207	

than 6 cm and by 29.9% (HR: 1.299, 95% CI: 0.519-3.248) for tumors 6 cm or more prominent in the single chemotherapy administration group (**Table 3**; **Figure 4**).

TNM stage III gastric cancer patients PSM analysis and subgroup analysis

All cases of TNM staging III (n = 902) underwent 1:1 nearest-neighbor propensity score matching without replacement, with a caliper value set at 0.2. Results from **Table 4** demonstrate a clear distinction between the administration of oral or intravenous chemotherapy and the combination of oral and intravenous chemotherapy in two key variables: age (P = 0.005) and depth of tumor invasion (P = 0.010). Propensity score matching was performed within each treatment group, selecting 300 patients - 150 in the oral or intravenous chemotherapy group and 150 in the combined oral chemotherapy group. Following matching, no variables significantly differed between the two groups (P > 0.05).

In the cohort receiving chemotherapy, 52.0% (78/150) were administered S-1 alone, while 23.3% (35/150) received various regimens. Two individuals were treated with S-1 and apatinib, and 35 patients underwent FOLFOX treatment. Among those receiving a mix of oral and intravenous chemotherapy, 21.3% (32/150) were prescribed capecitabine as a single agent, while 1.3% (2/150) received XELOX, 6.7% (10/150) were given SOX+FOLFOX, and 4.0% (6/150) were treated with S-1+FOLFOX. The remaining 100 patients in this category were treated with a combination of multiple chemotherapy regimens.

After applying the propensity score matching, the overall balance test by Hansen and Bowers yielded a *P*-value of 0.938, which significantly exceeded the threshold of 0.05. The relative unbalanced Logistic regression (L1) test indicated a decrease in the L1 value from 0.954 to 0.927 post-PSM. Importantly, no variable exhibited an absolute standardized difference |d| greater than 0.25 in all instances. The dis-

Table 3. Subgroups analysis of progression-free survival (PFS) by cox regression of chemotherapy administration for stage II cancer

Variables	Event	Total	HR	95% CI	P	P for interaction
Gender						0.432
Male	29	124	1.383	0.660-2.895	0.390	
Female	5	26	4.679	0.521-42.109	0.168	
Number of positive lymph nodes						0.230
0	14	71	1.997	0.665-5.998	0.218	
≥ 1	20	79	1.361	0.551-3.363	0.504	
Vascular invasion						0.263
Negative	18	88	1.718	0.661-4.469	0.488	
Positive	16	62	1.549	0.573-4.190	0.563	
Neural invasion						0.205
Negative	19	93	2.027	0.795-5.166	0.139	
Positive	15	57	1.280	0.457-3.585	0.639	
Lauren classification						0.194
Intestinal	14	65	2.032	0.679-6.085	0.205	
Diffuse	6	28	1.212	0.244-6.011	0.814	
Mixed	14	57	1.493	0.533-4.362	0.463	
Maximum diameter of tumor (cm)						0.003
< 6	15	103	1.814	0.637-5.165	0.265	
≥ 6	19	47	1.299	0.519-3.248	0.576	
Type of gastrectomy						0.763
Proximal	5	12	0.894	0.147-5.433	0.903	
Distal	11	51	1.075	0.328-3.525	0.905	
Total	18	87	2.720	1.009-7.334	0.048	

tribution of variables across the two groups was primarily balanced.

Figure 5 illustrates that for patients with TNM stage III, there were similar overall survival (OS) and progression-free survival (PFS) outcomes between those receiving oral or intravenous chemotherapy and those receiving oral plus intravenous chemotherapy. Before propensity score matching (PSM), the median OS for the two groups were 44 and 49 months, respectively, while the median PFS were 41 and 36 months. After PSM, the 1-year, 3-year, and 5-year OS and PFS rates between the groups were comparable. The median OS for oral or intravenous chemotherapy administration was 46 months. For oral plus intravenous chemotherapy administration, it was 49 months, with corresponding 1-year, 3-year, and 5-year OS rates showing no significant differences between the groups. Similarly, the median PFS for the two groups were 42 and 36 months, respectively, with no statistically significant differences in the 1-year and 3-year PFS rates but a borderline significance at five years. Furthermore, the incidence of recurrence and various recurrence patterns differed significantly between the two groups, with oral or intravenous chemotherapy administration showing a lower recurrence ratio (25.33% vs. 62.00%). The disparity in local-regional metastasis, recurrence, and distant metastasis between the two groups was remarkable, while differences in peritoneal metastasis were not statistically significant. Regarding recurrence patterns, the proportion of peritoneal metastasis, local-regional metastasis, and distant metastasis differed between the two groups. For oral or intravenous chemotherapy administration, the proportion of peritoneal metastasis, local-regional metastasis, and distant metastasis were 47.36%, 2.63%, and 50.00%, respectively. In contrast, for oral plus intravenous chemotherapy administration, the proportions were 40.86%, 6.45%, and 52.69%, respectively. Oral or intravenous chemotherapy

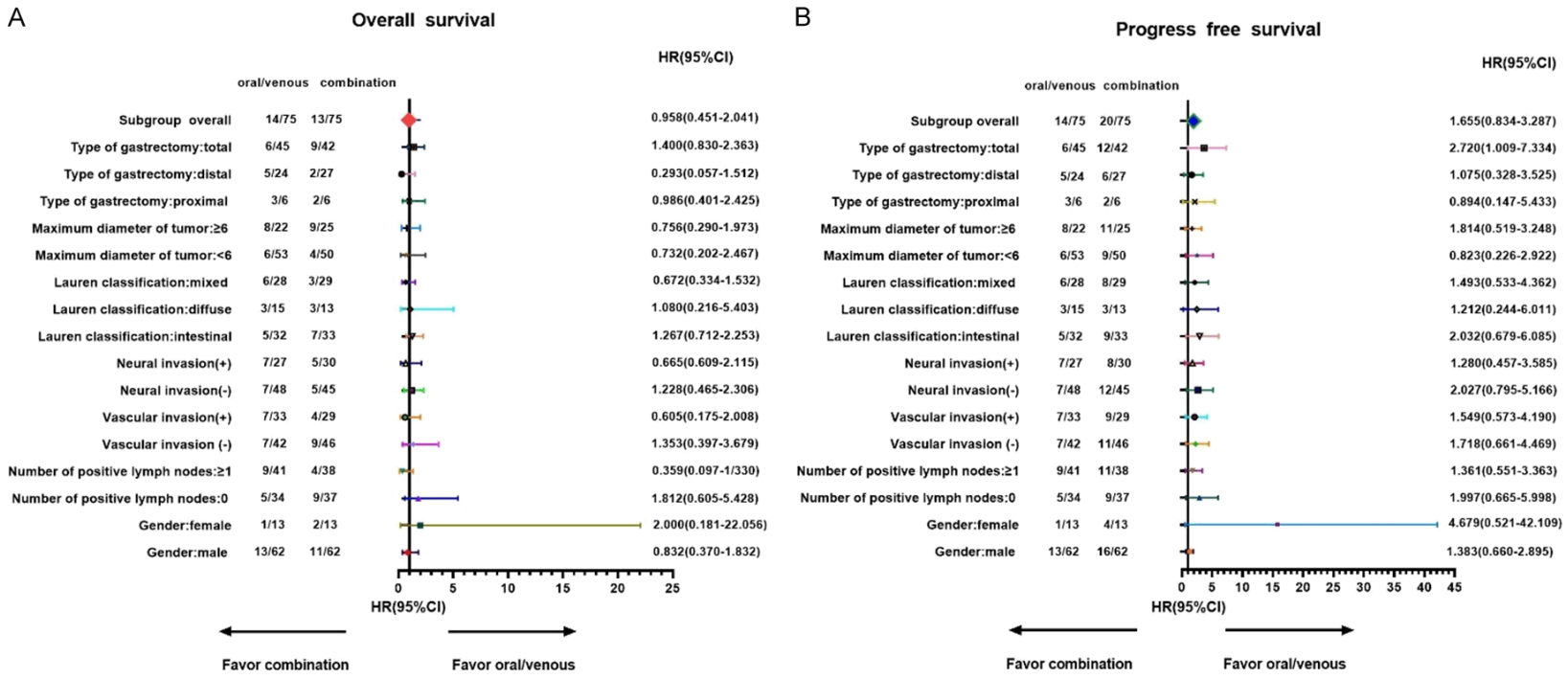

Figure 4. Subgroup analyses of overall survival (OS) and progression-free survival (PFS) based on different chemotherapy administration in stage II gastric cancer patients. A: OS; B: PFS.

Table 4. Patients' characteristics before and after propensity score matching (PSM) of chemotherapy administration of stage III cancer

Variables	Before PSM		P	After PSM		P
	Oral/Venous (n = 745)	Combination (n = 157)		Oral/Venous (n = 150)	Combination (n = 150)	
Gender			0.909			1.000
Male	582	122		118	118	
Female	123	35		32	32	
Age (years)	59.21±10.19	56.87±9.40	0.005	58.17±8.29	57.59±8.75	0.525
Depth of tumor invasion			0.01			0.531
T2	1	1		0	0	
T3	173	51		43	48	
T4	571	105		107	102	
Number of positive lymph nodes			0.602			0.924
0	4	0		0	0	
1-2	123	27		26	26	
3-6	188	35		32	33	
≥ 7	430	95		92	91	
Type of gastrectomy			0.062			0.745
Proximal	37	15		9	14	
Distal	198	45		46	42	
Total	510	97		95	94	
Vascular invasion			0.471			0.422
Negative	179	42		34	40	
Positive	566	115		116	110	
Neural invasion			0.961			0.903
Negative	253	53		52	51	
Positive	492	104		98	99	
Lauren classification			0.999			0.602
Intestinal	149	30		31	30	
Diffuse	385	83		83	79	
Mixed	213	44		36	41	
Maximum diameter of tumor (cm)			0.244			0.084
< 6	370	86		68	83	
≥ 7	375	71		82	67	
Surgical margin			0.143			0.556
Negative	687	150		145	143	
Positive	58	7		5	7	

administration showed favorable outcomes regarding recurrence and recurrence patterns compared to oral plus intravenous chemotherapy administration in patients with TNM stage III.

The administration of oral or intravenous chemotherapy showed similar outcomes in overall survival (OS) when compared to the combined oral and intravenous chemotherapy approach (P = 0.257) (refer to **Table 5** and **Figure 6**). However, it marginally preceded the combined approach in terms of progression-free survival (PFS) (P = 0.007) (**Table 6** and **Figure 6**). Within male subgroups, particularly those with deep tumor invasion (T3), number positive lymph nodes < 7, vascular invasion, nerve invasion, maximum tumor diameter of 6 cm or more, and who underwent distal gastrectomy, the combined oral and intravenous chemotherapy was

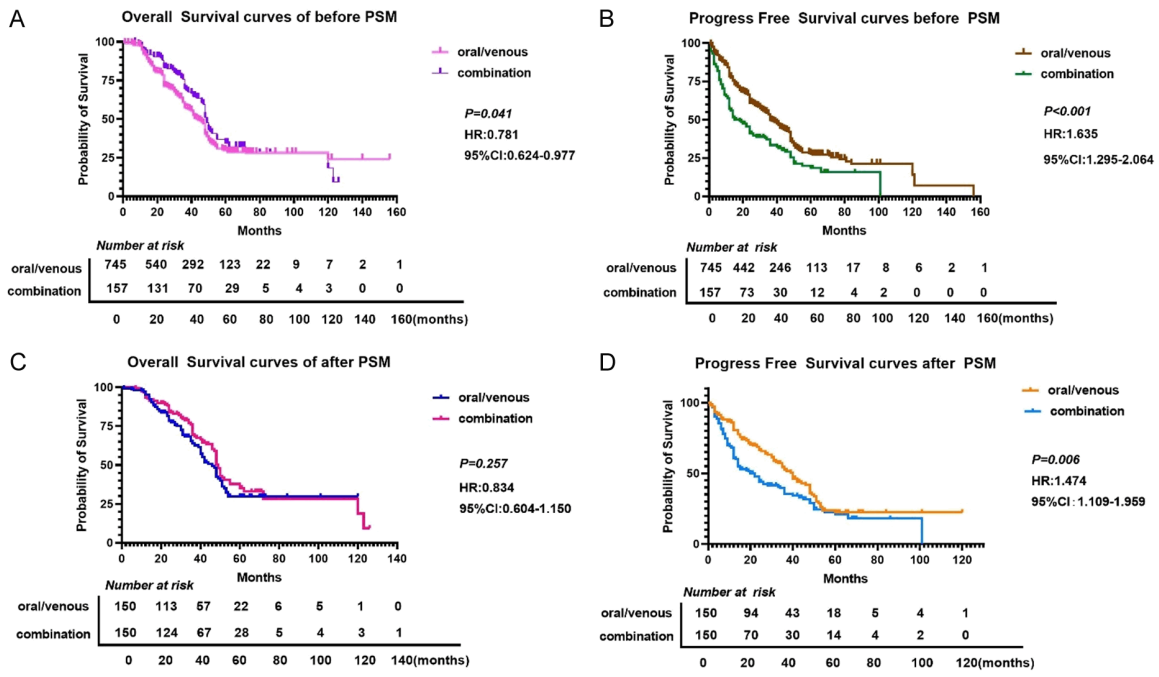

Figure 5. Comparison of overall survival (OS) and progression-free survival (PFS) before and after propensity score matching (PSM) in stage III gastric cancer patients. (A, B) Comparison of OS (A) and PFS (B) between the two groups based on chemotherapy administration before PSM; (C, D) Comparison of OS (C) and PFS (D) between the two groups based on chemotherapy administration after PSM.

less effective than single-modality chemotherapy. These factors were significantly associated with a reduced PFS ($P < 0.05$).

Further subgroup analysis revealed that patients with at least seven positive lymph nodes faced a higher risk of disease progression when receiving oral or intravenous chemotherapy compared to the combined therapy (hazard ratio [HR] = 1.652, 95% confidence interval [CI] = 1.171-2.331). Similarly, those with vascular invasion (HR = 1.714, 95% CI = 0.898-3.269), neural invasion (HR = 1.493, 95% CI = 0.888-2.509), who had undergone distal gastrectomy (HR = 1.991, 95% CI = 1.140-3.476), and those with a tumor diameter of 6 cm or more (HR = 1.734, 95% CI = 1.171-2.569) also exhibited a higher risk of disease progression in the oral or intravenous chemotherapy group, as opposed to the combined therapy group (**Table 6**).

Discussion

Oral administration of chemotherapy presents high medication adherence and minimal side effects, making it a preferred choice for many outpatients with gastric cancer. Drugs such as S-1, capecitabine, and apatinib are commonly used in this context. Extensive research in Japan has examined various aspects of S-1 administration, including optimal timing, suitability for the elderly, recurrence management, and its efficacy as an adjuvant chemotherapy for gastric cancer [10-14]. Capecitabine, used for treating breast, colorectal, and gastric cancers, offers the convenience of oral administration and enhanced patient compliance. It is converted to 5-FU in tumor tissues, enabling targeted cancer treatment and reducing systemic toxicity compared to continuous intravenous 5-FU infusion. This localized conversion enhances anticancer effects and has been shown to prolong overall survival (OS) and reduce gastrointestinal toxicity in advanced gastric cancer among Asian populations [15-17]. Comparative studies indicate no significant difference in OS between capecitabine-based and S-1-based chemotherapy as first-line treatments for advanced or inoperable gastric cancer in China. However, capecitabine-based regimens are recommended for gastric cancer patients with peritoneal metastases [18]. A European study found capecitabine-based che-

Table 5. Subgroups analysis of overall survival (OS) by Cox regression of chemotherapy administration of stage III cancer

Variables	Event	Total	HR	95% CI	P	P for interaction
Gender						0.708
Male	116	236	0.875	0.675-1.262	0.474	
Female	33	64	0.628	0.314-1.255	0.188	
Depth of tumor invasion						0.419
T3	25	91	1.155	0.524-2.546	0.722	
T4	124	209	0.769	0.540-1.097	0.147	
Number of positive lymph nodes						0.490
≤ 6	47	117	1.037	0.579-1.856	0.903	
≥ 7	102	183	0.731	0.494-1.083	0.118	
Vascular invasion						0.539
Negative	30	74	0.897	0.436-1.844	0.767	
Positive	119	226	0.789	0.548-1.137	0.204	
Neural invasion						0.548
Negative	41	103	0.865	0.467-1.601	0.644	
Positive	108	197	0.838	0.572-1.277	0.364	
Lauren classification						0.341
Intestinal	31	61	1.095	0.766-1.567	0.617	
Diffuse	92	162	0.661	0.435-1.004	0.052	
Mixed	26	77	1.051	0.714-1.548	0.800	
Maximum diameter of tumor (cm)						0.286
< 6	66	151	0.726	0.478-1.259	0.304	
≥ 6	83	149	0.926	0.600-1.431	0.731	
Type of gastrectomy						0.970
Proximal	12	23	0.664	0.371-1.180	0.163	
Distal	37	88	0.915	0.673-2.459	0.446	
Total	100	189	0.844	0.726-1.078	0.224	

motherapy superior to S-1-based chemotherapy in terms of OS in advanced gastric cancer [19]. Intravenous chemotherapy, such as the FLOT4 and FOLFOX regimens, can maintain a consistent drug concentration and stabilize therapeutic effects. The FLOT4 regimen has been validated in numerous studies for its effectiveness in advanced gastric cancer and preoperative neoadjuvant therapy, making it a first-line treatment for postoperative chemotherapy [20, 21]. Similarly, the FOLFOX regimen is a first-line therapy for advanced gastric cancer patients with peritoneal metastasis post-adjuvant therapy. It is typically used as a second-line regimen for postoperative adjuvant chemotherapy [22, 23]. Combination oral and intravenous chemotherapy regimens, such as SOX and XELOX, have also been studied. Japanese research supports the SOX regimen as a viable first-line treatment for locally advanced gastric cancer due to its efficacy and safety [24]. A Chinese study confirmed the clinical effectiveness of the SOX regimen in patients with advanced gastric cancer-producing alpha-fetoprotein (AFP) and liver metastases, recommending specific dosages of oxaliplatin and S-1 [25]. However, surgery during SOX chemotherapy for these patients may not significantly improve disease control rates and could increase adverse effects. The XELOX regimen, verified as safe and effective by multiple studies, is often used as a second-line treatment post-surgery. A Chinese study comparing the SOX and XELOX regimens after D2 gastrectomy found no significant difference in disease-free survival (DFS) and OS, with similar adverse effect incidences [26]. Another study compared S-1 monotherapy with the SOX/XELOX regimen as postoperative adjuvant chemotherapy in gastric cancer patients after D2 resection,

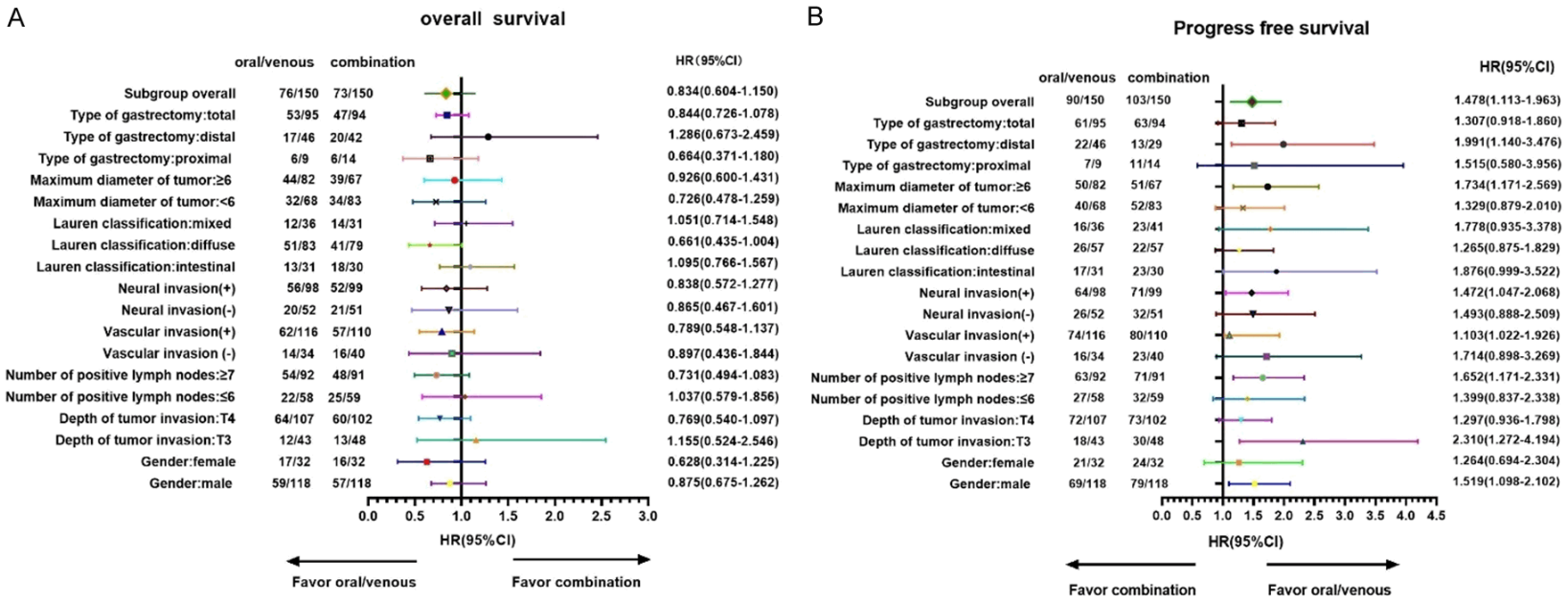

Figure 6. Subgroup analyses of overall survival (OS) and progression-free survival (PFS) for different chemotherapy administration in stage III gastric cancer patients. (A, B) Subgroup analyses of OS (A) and PFS (B) based on chemotherapy administration.

Table 6. Subgroups analysis of progression-free survival (PFS) by Cox regression of chemotherapy administration of stage III cancer

Variables	Event	Total	HR	95% CI	P	P for interaction
Gender						0.056
Male	148	236	1.519	1.098-2.102	0.012	
Female	45	64	1.264	0.694-2.304	0.443	
Depth of tumor invasion						0.216
T3	48	91	2.310	1.272-4.194	0.006	
T4	145	209	1.297	0.936-1.798	0.118	
Number of positive lymph nodes						< 0.001
≤ 6	59	117	1.399	0.837-2.338	0.200	
≥ 7	134	183	1.652	1.171-2.331	0.004	
Vascular invasion						0.007
Negative	39	74	1.714	0.898-3.269	0.102	
Positive	154	226	1.103	1.022-1.926	0.036	
Neural invasion						0.001
Negative	58	103	1.493	0.879-2.010	0.130	
Positive	135	197	1.472	1.047-2.068	0.026	
Lauren classification						0.183
Intestinal	40	61	1.876	0.999-3.522	0.050	
Diffuse	114	162	1.265	0.875-1.829	0.201	
Mixed	39	77	1.778	0.935-3.378	0.079	
Maximum diameter of tumor (cm)						0.001
< 6	92	151	1.329	0.478-1.259	0.178	
≥ 6	101	149	1.734	1.171-2.569	0.006	
Type of gastrectomy						0.021
Proximal	18	23	1.515	0.580-3.956	0.397	
Distal	51	88	1.991	1.140-3.476	0.015	
Total	124	189	1.307	0.918-1.860	0.138	

noting a tendency for improved PFS with SOX/XELOX but no significant OS benefit [27, 28].

The SOX regimen continues to dominate as the primary treatment option for gastric cancer. A phase II study revealed promising long-term results for patients with high-risk gastric cancer who underwent two cycles of neoadjuvant chemotherapy with S-1 and oxaliplatin, followed by D2 gastrectomy [29]. Additionally, combining SOX with sintilimab in the perioperative management of locally advanced gastric cancer demonstrated improved patient pathological response rates [30]. Another study found that combining apatinib with the SOX regimen for conversion therapy in advanced gastric cancer patients resulted in higher overall survival rates [31]. For patients with peritoneal metastatic gastric cancer, the combination of intraperitoneal high-dose paclitaxel and systemic SOX proved to be a highly effective and well-tolerated first-line treatment [32]. In a real-world study, the albumin-bound paclitaxel+S-1 regimen outperformed SOX chemotherapy, especially for patients with peritoneal metastasis of the Lauren diffuse type [33]. The prognosis of stage III gastric cancer after D2 gastrectomy was improved with the addition of S-1 maintenance chemotherapy following SOX regimen chemotherapy, according to a 5-year analysis [34]. In Chinese patients with pathological stage II or III gastric cancer after D2 gastrectomy, the XELOX chemotherapy regimen demonstrated similar survival benefits when compared to the SOX regimen [27]. Conversely, a randomized phase II study found that capecitabine+docetaxel (TX) resulted in significantly longer progression-free survival and overall survival rates than the XELOX group for patients with ascites [35]. For patients with

poorly differentiated adenocarcinoma and liver metastasis, the EOX regimen (epirubicin, oxaliplatin, and capecitabine) showed considerably longer overall survival rates and a trend toward longer progression-free survival rates compared to the XELOX group [36].

Scientific literature has long acknowledged the influence of different chemotherapy regimens on the prognosis of gastric cancer patients. However, limited research has specifically focused on the nuanced effects of combined chemotherapy administration - both oral and intravenous - versus the use of chemotherapy via a single route. Our investigation represents a pioneering effort to meticulously compare the collective impact of combined chemotherapeutic approaches against their individual application, thus challenging conventional perspectives on the efficacy of dual-route therapy. These findings underscore the importance of conducting further clinical trials to systematically assess diverse chemotherapy delivery methods' unique advantages and limitations.

Previous literature has notably lacked comprehensive investigation into the effects of post-D2 gastrectomy chemotherapy delivery methods on patient survival. Our investigation revealed that the concurrent use of both oral and intravenous chemotherapy regimens offers no survival benefit over monotherapy for stage II and III gastric cancer patients and may elevate the risk of disease progression in stage III patients. Furthermore, this dual-route administration approach was associated with a heightened likelihood of recurrence in stage II and III gastric cancer patients. Conversely, the application of combined chemotherapy regimens has shown certain advantages. These include the potential for increased anticancer efficacy due to higher drug concentrations and the possibility of reduced drug toxicity. However, such regimens are also linked to an increased incidence of adverse effects, including alopecia, immunosuppression, nausea, vomiting, and diarrhea, as well as exacerbated psychological symptoms such as anxiety. Therefore, there is an urgent need to clarify the role of combined oral and intravenous chemotherapy in the management of advanced gastric cancer. In the stage II gastric cancer cohort, our research revealed a significant correlation between tumor size and treatment efficacy, precisely when comparing combined oral and intravenous chemotherapy regimens to monotherapy. Notably, patients whose tumors measured 6 cm or more in diameter exhibited a higher risk of mortality when opting for a combined treatment approach (HR: 0.756, 95% CI: 0.290-1.973). Conversely, those with tumors smaller than 6 cm seemed to be at a greater risk of disease progression when receiving only oral or intravenous chemotherapy (HR: 1.814, 95% CI: 0.637-5.165). This inverse correlation between tumor size and treatment response is a novel finding in the context of gastric cancer chemotherapy administration.

The current study, while retrospective and confined to a single center, does have its limitations. One significant drawback is the potential for selection bias, which the researchers attempted to address through propensity score matching. While this method can reduce bias, it does not eliminate it, and thus, the results may not be entirely generalizable. Additionally, the lack of standardization in the chemotherapy regimens and the various indications for their use could have led to differences in treatment outcomes, complicating any analysis of the effects of different chemotherapy protocols.

Despite these shortcomings, the study offers important observations into the relationship between chemotherapy administration and various factors such as vascular and neural invasion and tumor size on overall survival (OS) and progression-free survival (PFS). These insights fill a gap in the existing literature and provide a basis for further investigation and potential improvements in treatment strategies.

Conclusions

In summary, combining oral and intravenous administration of chemotherapy did not improve the prognosis of gastric cancer stage II and III compared to using only oral or intravenous administration. It led to a significantly increased risk of disease progression in stage III and an increased chance of recurrence in both stages of gastric cancer.

Disclosure of conflict of interest

None.

Abbreviations

PFS, progression-free survival; PSM, propensity score matching; OS, overall survival.

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