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Irinotecan and Oxaliplatin Might Provide Equal Benefit as Adjuvant Chemotherapy for Patients with Resectable Synchronous Colon Cancer and Liver-confined Metastases: A Nationwide Database Study

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Abstract. *Background: Although irinotecan and oxaliplatin are both standard treatments for advanced colon cancer, it remains unknown whether either is effective for patients with resectable synchronous colon cancer and liver-confined metastasis (SCCLM) after curative surgery. Patients and Methods: A population-based cohort of patients diagnosed with de novo SCCLM between 2004 and 2009 was established by searching the database of the Taiwan Cancer Registry and the National Health Insurance Research Database of Taiwan. Patients who underwent curative surgery as their first therapy followed by chemotherapy doublets were classified into the irinotecan group or oxaliplatin group accordingly. Patients who received radiotherapy or did not receive chemotherapy doublets were excluded. Results: We included 6,533 patients with de novo stage IV colon cancer. Three hundred and nine of them received chemotherapy doublets after surgery; 77 patients received irinotecan and 232 patients received oxaliplatin as adjuvant chemotherapy. The patients in both groups exhibited similar overall survival (median: not reached vs. 40.8 months, p=0.151) and time to the next line of treatment (median: 16.5 vs. 14.3 months, p=0.349) in both univariate and multivariate analyses. Additionally, patients with resectable SCCLM had significantly shorter median overall survival than patients with stage III colon cancer who underwent curative surgery and subsequent adjuvant chemotherapy, but longer median overall survival than patients with de novo stage IV colon cancer who underwent surgery only at the primary site followed by standard systemic chemotherapy (p<0.001). Conclusion: Irinotecan and oxaliplatin exhibited similar efficacy in patients who underwent curative surgery for resectable SCCLM.*

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Colorectal cancer (CRC) is the third most prevalent type of cancer worldwide and the leading type of cancer in Taiwan (1, 2). Approximately 50-60% of patients with metastatic CRC develop liver metastases, and approximately 20% of patients with CRC have liver metastases at the time of diagnosis (3, 4). Because of the unique biology and anatomy of this type of cancer, surgery can still be performed on many patients with CRC and liver-confined metastasis. These patients have been demonstrated to exhibit much more favourable prognoses than patients with extensive metastasis. However, 75% of patients who undergo surgery both at the primary site and the site of liver metastases eventually develop recurrent disease, and thus postoperative chemotherapy is a key concern (3, 5-7).

Postoperative chemotherapy is suggested for patients who have undergone curative surgery for metastatic CRC and liver-confined metastasis, but the optimal chemotherapy

regimen for these patients remains unclear. By definition, these patients have stage IV disease, for which both irinotecan- or oxaliplatin-based regimens are offered (8-10). However, no clinical trials have been conducted to compare irinotecan- and oxaliplatin-based regimens in these patients. Biologically, whether such a disease should be considered stage IV CRC and either irinotecan- or oxaliplatin-based regimens can be freely chosen, or should be considered resected CRC and oxaliplatin-based regimens are to be preferred also remains unclear.

We used national databases to compare the efficacy of irinotecan and oxaliplatin in patients who had undergone curative surgery for synchronous colon cancer and liver-confined metastasis (SCCLM). Notably, both irinotecan and oxaliplatin were accompanied by 5-fluorouracil (5-FU) or its analogues. This study compared the efficacy and survival benefit of irinotecan- and oxaliplatin-based chemotherapy doublet regimens after curative surgery.

Patients and Methods

Data source. Three national databases were used in this retrospective population-based cohort study. Patient demographics, tumour histology, and disease stage were retrieved from the Taiwan Cancer Registry (TCR), which is managed by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan (2, 11). All major cancer care providers in Taiwan are obliged to input patient data into the TCR database. Subsequently, the Taiwan National Health Insurance (NHI) Research Database was accessed to obtain records of patient prescriptions and surgical procedures. The NHI is a mandatory health insurance system covering more than 99% of the residents of Taiwan (12). Finally, dates of death were collected from the National Death Registry database.

All personal data were encrypted and analyzed anonymously, such that any results that applied to fewer than 3% of the targeted group were not allowed to be processed. The release of all data used in our study was approved by the Data Release Review Board of the Collaboration Center of Health Information Application, Ministry of Health and Welfare, Executive Yuan, Taiwan (MOST-103-2314-B-002-181-MY2). The protocol for our study was approved by the Research Ethics Committee of National Taiwan University Hospital.

Study population and variables. The TCR was reviewed and all patients who fit all of the following criteria were included in this study: i) Diagnosis of histology-proven primary colon cancer (ICD-O-3 C180 to C189) between January 1, 2004 and December 31, 2009; ii) age ≥18 years; iii) initially diagnosed with stage IV colon cancer; and iv) underwent both hepatectomy and radical surgery at the tumour origin, not earlier than 1 month before and not later than 3 months after, diagnosis. Patients with missing clinical data, a diagnosis of haematological malignancies or Kaposi's sarcoma (ICD-O-3 morphology code 9140, 9590-9989), a diagnosis of more than one type of primary cancer, and patients who received any radiotherapy within 3 months before or after surgeries were all excluded.

In order to compare the efficacy of postoperative chemotherapy, patients were required to have received their first dose of chemotherapy within 3 months following curative surgery. Patients were assigned to the irinotecan or oxaliplatin group according to their postoperative chemotherapy regimen. However, the following patients were excluded: Those who had received any chemotherapy agent before each surgery, those who received both or neither irinotecan and oxaliplatin, those who received irinotecan or oxaliplatin without combination with 5-FU or its analogues, those with rectal cancer (because patients with this type of cancer should usually receive radiotherapy), those who received radiotherapy, and those with recurrent liver metastases from previously treated colon cancer.

Extended cohort population and comparison. In order to compare the survival of our study cohort to that of other patients with a similar disease status, we conducted an extended cohort survey. Another three cohorts were established with similar inclusion and exclusion criteria for staging and epidemiological status. The first cohort consisted of patients with *de novo* stage III colon cancer who underwent radical surgery at the primary sites and subsequent adjuvant chemotherapy within 3 months of surgery; notably, adjuvant chemotherapy was limited to oxaliplatin with 5-FU or its oral analogues. The second cohort consisted of patients with *de novo* stage IV colon cancer who underwent radical surgery only at the primary tumour and subsequent salvage chemotherapy within 3 months of surgery. The third cohort consisted of patients with *de novo* stage IV colon cancer who did not undergo any tumour surgery and received only salvage chemotherapy within 3 months of diagnosis. Patients who underwent radiotherapy were excluded from the cohorts of patients who underwent surgery. Treatment in the cohorts of patients who received chemotherapy involved either irinotecan or oxaliplatin accompanied by 5-FU or its oral analogues.

Statistical analysis. The mean of continuous variables was compared using two-sample *t*-tests or the Wilcoxon rank-sum test, whereas the frequency of categorical variables was compared using the chi-squared test or Fisher's exact test when appropriate. Overall survival (OS) was calculated from the date of diagnosis of stage IV colon cancer to the date of death or 31st December 2013, whichever came first; the data were considered censored if patients survived beyond December 31, 2013. Additionally, the time to the next line of treatment (TNT) was calculated, and defined as the time from the date of enrolment to the date when the first dose of the next line of chemotherapy for metastatic colon cancer was prescribed. OS and TNT were both estimated using the Kaplan–Meier method, and the log-rank test was subsequently used to compare differences between the groups. Two-sided *p*-values less than 0.05 were considered statistically significant. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics. We identified 6,533 patients with *de novo* stage IV colon cancer, 777 (11.9%) of whom underwent curative surgery for resectable SCCLM. Among them, 309 patients received either irinotecan- or oxaliplatin-based chemotherapy after surgery and were included in this study (Figure 1). The median age was 61 years, and 23.6% of the patients were older than 70 years; the majority (57.0%) of the patients were male (Table I). The irinotecan group had 77 (24.9%) patients, and the oxaliplatin group had 232 (75.1%) patients. Because targeted therapy agents, such as bevacizumab and cetuximab, were not reimbursed by the

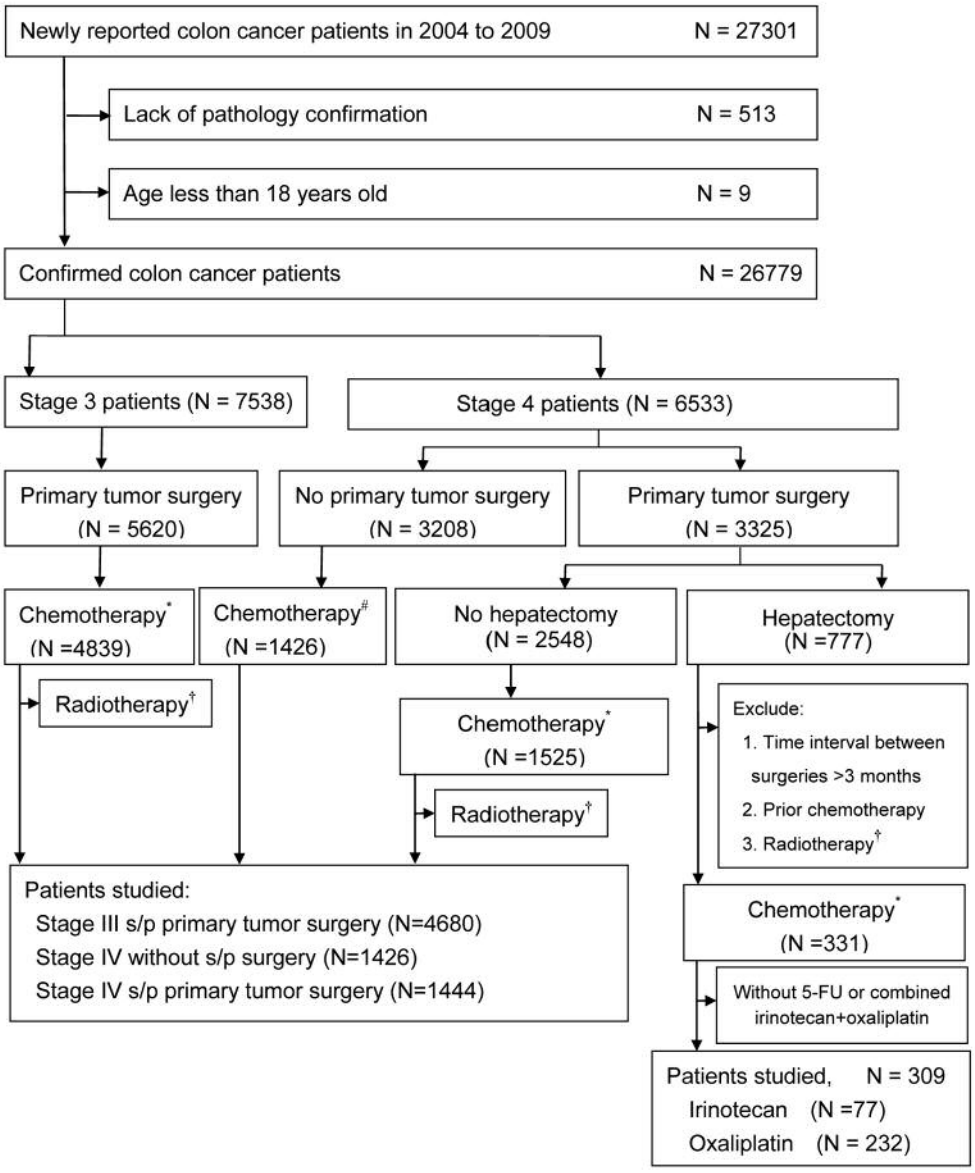


Figure 1. *Flow chart illustrating the process of evaluating patients for inclusion in study.*Irinotecan or oxaliplatin started within 3 months after surgery; #irinotecan or oxaliplatin started within 3 months after cancer diagnosis; †radiotherapy within 3 months after surgery.*

NHI during the study period, patients receiving these treatments were not included in our study.

No significant difference was observed between the irinotecan and oxaliplatin groups regarding gender, age, primary site of metastasis, the use of 5-FU or its analogues, or pathological stage (Table I). Although some heterogeneity was noted in the distribution of the year of diagnosis, no obvious trends existed. The median treatment duration was 5.1 months for the irinotecan group and 5.0 months for the oxaliplatin group, and approximately 60% of patients in both groups received subsequent lines of chemotherapy.

Survival. As of December 31st, 2013, with a median follow-up period of 45.5 months, 193 (62.5%) patients had died. The median OS of patients overall was 47.7 months [95% confidence interval (CI): 37.1-52.2 months]. The 1-, 3-, and 5-year survival rate was 88%, 57%, and 41%, respectively.

The irinotecan group exhibited similar OS (median: not reached, 95% CI: not reached) to the oxaliplatin group (median=40.8 months, 95% CI=32.5-50.2 months) (p=0.151; Figure 2A). The irinotecan group also exhibited similar TNT (median=16.5 months, 95% CI=12.7-41.3 months) to the oxaliplatin group (median=14.3 months, 95% CI=12.0–17.1

Table I. *Clinical characteristics of patients.*

Variable		Total n (%)	Irinotecan group n (%)	Oxaliplatin group n (%)	*p*-Value
Patient number		309 (100.0)	77 (100.0)	232 (100.0)	
Gender	Male	176 (57.0)	47 (61.0)	129 (55.6)	0.404
	Female	133 (43.0)	30 (39.0)	103 (44.4)	
Mean age, years	Mean (SD)	60.28 (12.02)	59.05 (12.87)	60.68 (11.73)	0.626
Age, years	<50	49 (15.9)	14 (18.2)	35 (15.1)	0.809
	50-70	187 (60.5)	45 (58.4)	142 (61.2)	
	70+	73 (23.6)	18 (23.4)	55 (23.7)	
Primary side	Left/other[#]	166 (53.7)	44 (57.1)	122 (52.6)	0.487
	Right	143 (46.3)	33 (42.9)	110 (47.4)	
Pathology T-stage	≤T3	221 (71.5)	50 (64.9)	171 (73.7)	0.139
	T4	88 (28.5)	27 (35.1)	61 (26.3)	
Pathology N-stage	N0	62 (20.1)	18 (23.4)	44 (19.0)	0.402
	≥N1	247 (79.9)	59 (76.6)	188 (81.0)	
Year of diagnosis	2004	22 (7.1)	13 (16.9)	9 (3.9)	0.002
	2005	49 (15.9)	14 (18.2)	35 (15.1)	
	2006	39 (12.6)	12 (15.6)	27 (11.6)	
	2007	54 (17.5)	9 (11.7)	45 (19.4)	
	2008	60 (19.4)	12 (15.6)	48 (20.7)	
	2009	85 (27.5)	17 (22.1)	68 (29.3)	
5-FU use[†]	Intravenous 5-FU	286 (92.6)	72 (93.5)	214 (92.2)	0.714
	Oral analogs	49 (15.9)	10 (13.0)	39 (16.8)	0.321
Next line of treatment		201 (65.0)	46 (59.7)	155 (66.8)	

SD: Standard deviation; 5-FU: 5-fluorourocil. [#]Other primary sites were incorporated into the left side because they were observed in fewer than 3% of cases. [†]Some patients received both intravenous 5-FU and other 5-FU analogs.

Table II. *Cox proportional hazards models of factors predicting overall survival and time to next line of treatment.*

Variable		Overall survival			Time to next line of treatment		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Postoperative adjuvant treatment	Oxaliplatin	1.00		0.458	1.00		0.272
	Irinotecan	0.88	0.62-1.25		0.82	0.58-1.17	
Gender	Female	1.00		0.197	1.00		0.017
	Male	1.22	0.90-1.63		1.42	1.07-1.89	
Age, years	<50	1.00		0.138	1.00		0.008
	50-70	0.70	0.47-1.05		0.59	0.41-0.86	
	70+	0.90	0.57-1.41		0.51	0.32-0.81	
Side	Right	1.00		0.048	1.00		0.019
	Left/other[#]	0.75	0.56-1.00		0.71	0.54-0.95	
Pathology T-stage	≤T3	1.00		0.734	1.00		0.074
	T4	1.06	0.76-1.47		1.33	0.97-1.81	
Pathology N-stage	N0	1.00		0.966	1.00		0.896
	≥N1	0.99	0.69-1.43		0.98	0.68-1.40	
Year of diagnosis	2004	1.00		0.270	1.00		0.562
	2005	1.97	0.94-4.11		1.24	0.64-2.41	
	2006	2.47	1.15-5.30		1.02	0.50-2.08	
	2007	2.38	1.13-4.98		1.40	0.72-2.69	
	2008	1.94	0.92-4.10		0.98	0.50-1.91	
	2009	1.98	0.97-4.08		1.34	0.71-2.52	

HR: Hazard ratio; CI: Confidence interval. [#]Other primary sites were incorporated into the left side because they were observed in fewer than 3% of cases.

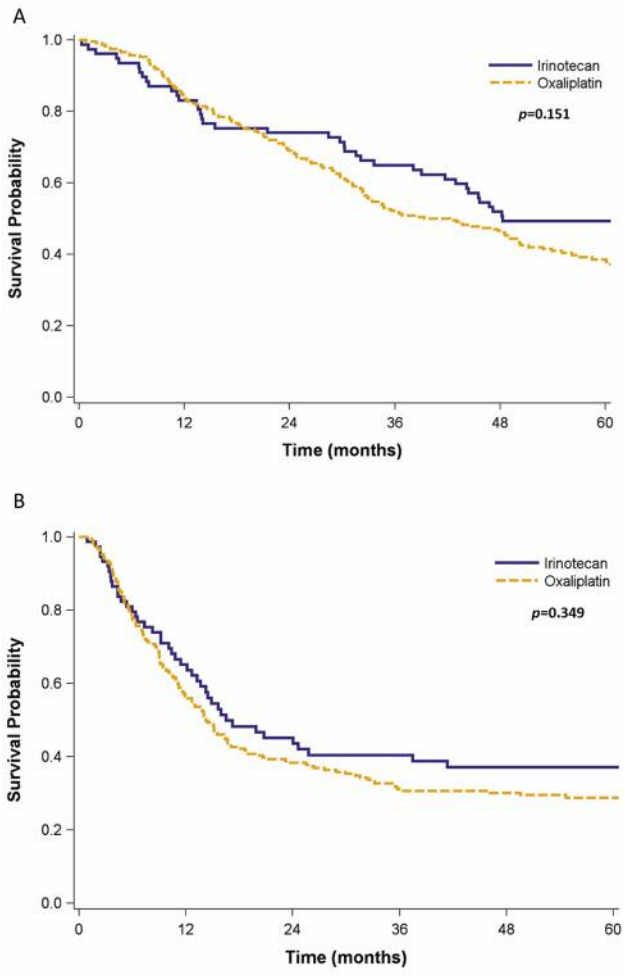


Figure 2. *Kaplan–Meier plots showing overall survival (A) and time to next line of treatment (B) according to treatment regimen. The p-values were determined using the log-rank test.*

months) (p=0.349; Figure 2B). Moreover, the subgroup analyses for OS and TNT revealed no significant differences across subgroups, including age, gender, and primary disease site (Figures 3 and 4).

In the multivariate analyses adjusted for age, gender, primary site, pathology staging, and year of diagnosis, the use of irinotecan or oxaliplatin still displayed no significant association with OS and TNT (Table II). Patients with right-sided primary cancer exhibited significantly shorter TNT than did those with left-sided primary cancers [hazard ratio (HR)=0.71, p=0.019] and OS (HR=0.75, p=0.048). In addition, female patients exhibited significantly longer TNT than male patients (p=0.017), but similar OS (p=0.197), whereas young (<50 years old) patients exhibited significantly shorter TNT than did older patients (p=0.008) although having a non-significant difference in OS (p=0.138).

Comparison between stage III, resectable SCCLM, and unresectable stage IV disease. We then examined the prognoses of patients with resectable SCCLM to determine whether it was more similar to stage III disease or unresectable stage IV disease. In addition to the SCCLM cohort, we established three other cohorts: patients with stage III colon cancer who underwent curative surgery and subsequent adjuvant chemotherapy (n=4,680), patients with *de novo* stage IV colon cancer who underwent surgery only at the primary site and standard systemic chemotherapy (n=1,444), and patients with *de novo* stage IV colon cancer who received standard systemic chemotherapy without cancer surgery (n=1,426).

As illustrated in Figure 5, these four cohorts exhibited significantly different OS (p<0.001). The patients who underwent curative surgery for SCCLM had poorer prognoses (median OS=47.7 months, 5-year survival=41%) than the patients who underwent curative surgery and adjuvant chemotherapy for stage III colon cancer (median OS: not reached, 5-year survival=69%), but they had more favourable prognoses than those who had a diagnosis of stage IV disease and underwent subsequent surgery at the primary cancer site (median OS=21.7 months, 5-year survival=21%) or chemotherapy alone (median OS=13.0 months, 5-year survival=14%) (Figure 5).

Discussion

In this study, we demonstrated that patients with resectable SCCLM obtained similar benefits from irinotecan and oxaliplatin when either treatment was combined with 5-FU or its analogues. In addition, resectable SCCLM was determined to be a unique disease entity with poorer prognosis than stage III colon cancer, but a more favourable prognosis than other types of metastatic colon cancer.

There was no consensus on the choice of chemotherapy regimen for patients with resectable SCCLM. Previous studies focusing on chemotherapy regimens for these patients were heterogeneous in design and patient population (13, 14), and most were retrospective (13, 15-17). Some researchers examined perioperative chemotherapy (18, 19), and others recruited patients with metachronous liver metastasis (16). In our study, we used the most stringent criteria to establish a more homogeneous population. All patients had to have synchronous liver metastasis and to have undergone curative surgery at both sites within 3 months. Patients receiving either neoadjuvant or perioperative chemotherapy were excluded to prevent the inclusion of borderline resectable SCCLM. Radiotherapy was also not allowed because of concerns that the surgeries may not have been of a curative intent or might not have achieved R0 resection. We are confident that we obtained a relatively homogeneous patient cohort with resectable SCCLM, which renders the results more convincing.

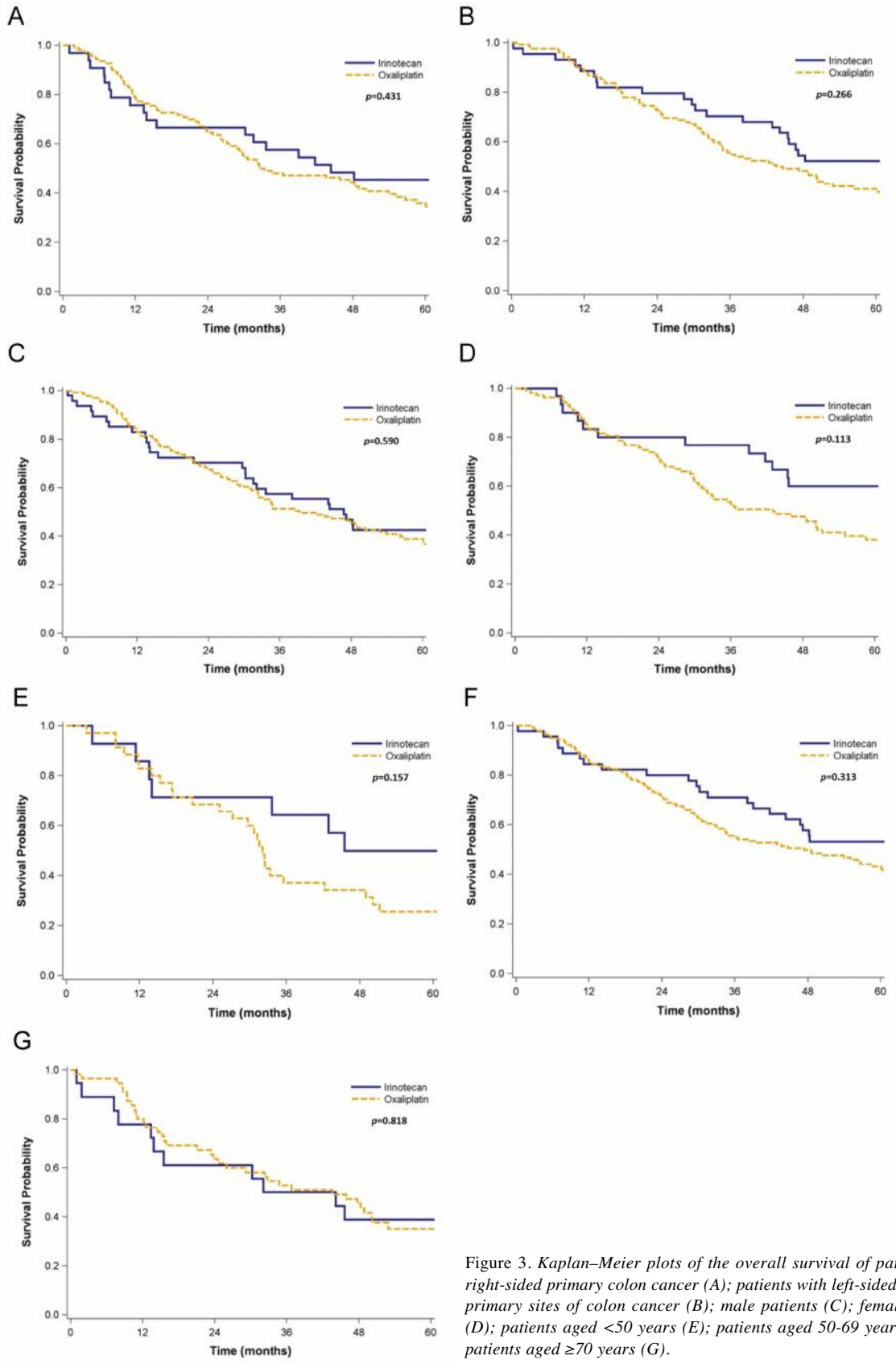


Figure 3. *Kaplan–Meier plots of the overall survival of patients with right-sided primary colon cancer (A); patients with left-sided and other primary sites of colon cancer (B); male patients (C); female patients (D); patients aged <50 years (E); patients aged 50-69 years (F); and patients aged ≥70 years (G).*

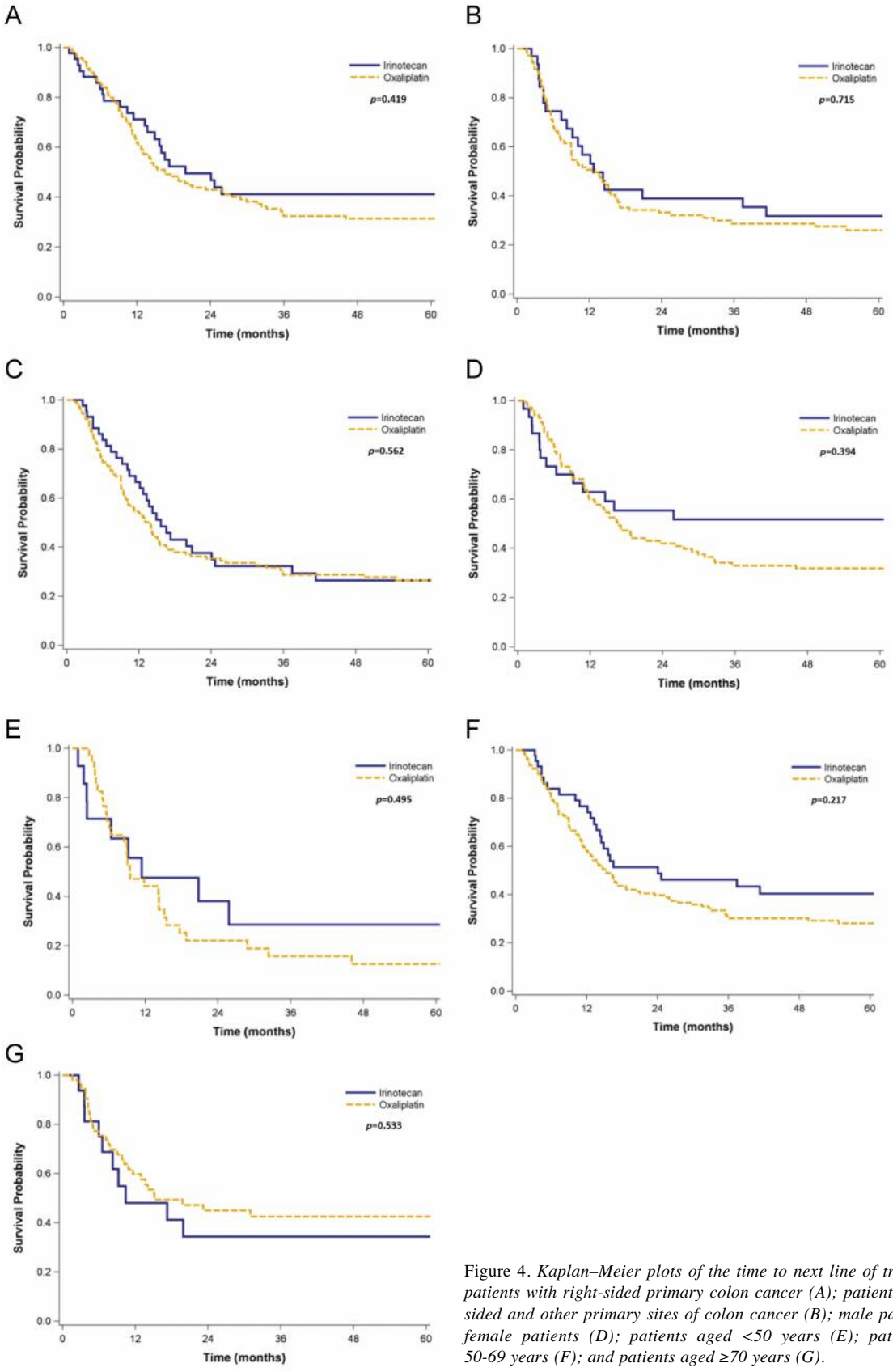
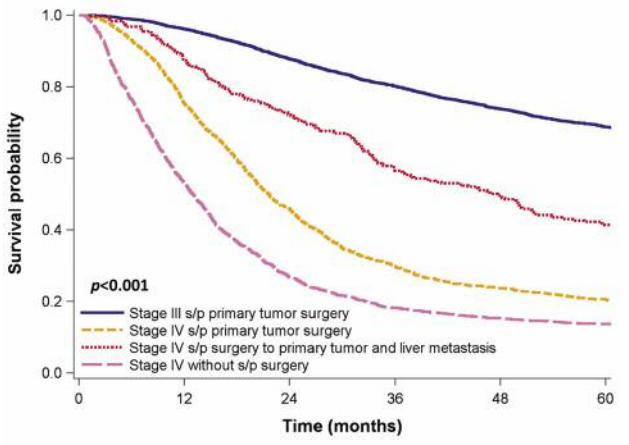


Figure 4. *Kaplan–Meier plots of the time to next line of treatment of patients with right-sided primary colon cancer (A); patients with left-sided and other primary sites of colon cancer (B); male patients (C); female patients (D); patients aged <50 years (E); patients aged 50-69 years (F); and patients aged ≥70 years (G).*



Group	Survival rate (%) 1-year	3-year	5-year	Survival time (months) Median (95% CI)
Stage III s/p primary tumor surgery	96	80	69	Not reached
Stage IV s/p primary tumor surgery	75	30	21	21.66 (20.52-22.79)
Stage IV s/p surgery to primary tumor and liver metastasis	88	57	41	47.70 (37.05-52.23)
Stage IV without s/p surgery	53	18	14	12.98 (12.20-13.90)

Figure 5. *Kaplan–Meier plots of overall survival according to treatment cohort. All patients received standard chemotherapy. The p-value was determined using the log-rank test. 95% CI: 95% Confidence interval. s/p: status post.*

The regimen that is more effective following curative surgery for patients with resectable SCCLM remains debatable. Although 5-FU-based regimens have demonstrated a survival benefit after surgical resection, they are not the standard for stage IV diseases (5, 20). According to the European Society for Medical Oncology (ESMO) guideline, 5-FU or 5-FU analogue singlet treatment postoperatively was not suggested (21). Although the evidence is limited, the ESMO guideline still suggested postoperative oxaliplatin-based doublet chemotherapy as preferred regimen (21). In the European Organisation for Research and Treatment of Cancer 40983 trial, Nordlinger *et al.* determined that perioperative therapy with folinic acid, fluorouracil and oxaliplatin (FOLFOX) improved OS compared with surgery alone for patients with SCCLM, but the difference was not significant (22). Similarly, Ychou *et al.* argued that the addition of irinotecan to postoperative 5-FU improved the disease-free survival rate in patients with resectable SCCLM; however, the difference was not significant and the OS was similar (23). A head-to-head comparison of the irinotecan-based and oxaliplatin-based chemotherapy doublets is not currently available under the prospective randomised clinical trial setting. As mentioned previously, the heterogeneity of patients in these trials made it difficult to draw definitive conclusions about the optimal chemotherapy for patients who underwent curative surgery for SCCLM. Our study employed a large database population, despite being retrospective, and implies that postoperative chemotherapy regimens for stage IV diseases are still effective for patients who underwent curative surgery for SCCLM.

Our study also demonstrated that resectable SCCLM is a unique disease entity, dissimilar from both stage III and other stage IV diseases. Overall, the patients with resectable SCCLM had significantly worse prognoses than patients with stage III colon cancer. This might explain why irinotecan demonstrated similar efficacy to oxaliplatin in our study, because the patients with resectable SCCLM were revealed to have distinct prognoses from those of patients with stage III colon cancer.

Our study had a few limitations. Firstly, we were unable to obtain data on prescriptions that were not subsidised by the NHI, such as drugs paid for by patients themselves or provided in clinical trials; information regarding *KRAS* and *BRAF* mutations was also not available. Secondly, family histories of major illness associated with the prognosis, such as Lynch syndrome, were also unavailable because of patient privacy protection. Thirdly, the clinical course of our study population was in the early 21st century but selection of this period was because we preferred to have adequate follow-up in order to detect any long-term survival difference. Even so, the median OS of the irinotecan group was not reached, which implies that a longer follow-up was needed. Furthermore, we did not enroll patients who received postoperative 5-FU or 5-FU analogue alone or patients who received no treatment after curative surgery for comparison. As mentioned above, a chemotherapy doublet should be the standard for postoperative treatment (21). Therefore, there might be an enormous selection bias in this retrospective setting study enrolling patients who received no treatment or only singlet 5-FU treatment postoperatively because this population might be too old or too weak to receive chemotherapy doublet. Finally, our study population only received chemotherapy; the efficacy of other targeted therapies in this population, such as bevacizumab or cetuximab, remains to be explored.

In conclusion, for the patients who underwent curative surgery for resectable SCCLM, both irinotecan- and oxaliplatin-based regimens provided similar efficacy as postoperative chemotherapy.

Ethics Approval and Consent to Participate

The release of all data used in our study was approved by the Data Release Review Board of the Collaboration Center of Health Information Application, Ministry of Health and Welfare, Executive Yuan, Taiwan. The protocol for our study was approved by the Research Ethics Committee of National Taiwan University Hospital. All personal data were encrypted and analysed anonymously.

Availability of Data and Materials

These three national databases were stored separately and are available only to researchers who officially send applications (2, 12). Requests for copies of the dataset should be made directly to the authorities (2, 12).

Conflicts of Interests

The Authors declare that they have no competing interests in regard to this study.

Acknowledgements

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