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Differences in the Outcomes of Adjuvant Chemotherapy for Colon Cancer Administered by Physicians in Different Disciplines: A population-based study

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Short title: Patient Survival Cared by Different Disciplines

Differences in the Outcomes of Adjuvant Chemotherapy for Colon Cancer Administered by Physicians in Different Disciplines: A population-based study

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Abstract

Objectives: One feature unique to the Taiwanese healthcare system is the ability of physicians other than oncologists to administer systemic chemotherapy. This study investigated whether the care paths implemented by oncologists and non-oncologists differ with regard to patient outcomes.

Setting: Data from the Taiwan Cancer Registry and National Health Insurance Database were linked to identify colon cancer patients who underwent colectomy as first treatment within 3 months of diagnosis and adjuvant chemotherapy between 2005 and 2009.

Participants: A total of 7,846 among 20,678 postoperative patients underwent adjuvant chemotherapy. We further excluded patients with stage 4 disease, positive surgical margin, early disease recurrence, and patients whose cancer diagnosis were not ranked within the first-order branch. Variables included sex, age, comorbidities, disease stage, chemotherapy cycle, and changes in treatment regimen as well as the specialty of treatment providers and their performance as it pertains to disease recurrence and patient survival.

Results: We examined 3,534 patients who were administered adjuvant chemotherapy by physicians from different disciplines. In terms of 5-year disease-free survival, no significant difference was observed between the groups of oncologists or surgeons among patients with stage II (90.02% vs 88.99%) or stage III (77.64% vs 79.99%) diseases. Patients with changes in their chemotherapy regimens exhibited a recurrence rate (stage II: 95 confidence interval [CI] , 1.90% - 3.26%; stage III: 95% CI, 2.98% -11.97 %) higher than those who did not. Male patients exhibited a lower risk of disease recurrence than did their female counterparts (95% CI, 0.69%-0.98%). The blurring of professional boundaries may not be an idealistic collaboration of healthcare. Nonetheless, discipline-oriented healthcare is a reality in current single-payer systems.

Conclusions: The discipline of practitioners is seldom taken into account in most series. Further study will be required before coming to any conclusions.

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Keywords: discipline, collaboration, performance, boundary, refer, oncology

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Strengths and limitations of this study:

- From a western perspective, it is incomprehensible that surgeons would be responsible for the administration of chemotherapy. Differences among disciplines that provide cancer care has never been regarded as an influential factor worthy of inclusion in most studies. It is the first research to inspect the outcome difference of patients under different care paths. This is a novel finding that is generally underreported in the literature of most western countries.
- We excluded many ineligible patients based on strict criteria in the analysis and methodologically reduced the bias of confounding factors between two disciplines with propensity score matching.
- It is a study designed by linking two large national data sets of a large number of patients with records of long-term follow-up.
- Lacking the variations in dose intensity across providers and clinical information of patients is the limitation of this study. With a time constraint, we were also unable to examine the influence of advances in chemotherapy regimens in different paradigms during the period of study.

INTRODUCTION

Shared care refers to the joint participation of physicians in the planning of patient care. This approach has been shown to improve cancer outcomes by helping to coordinate care to ensure the timely administration of adjuvant chemotherapy and thereby extend survival [1, 2]. Innovations in healthcare have resulted in highly specialized treatment regimes. For example, coronary artery bypass grafts performed by cardiothoracic surgeons have been replaced with percutaneous catheterization intervention performed by cardiologists [3, 4]. This has led to the blurring of professional boundaries, such as the issues that has been discussed by the American Society of Gynecologic Oncology [5]. Another situation is the long-simmering conflict between breast surgeons or radiologists over who should perform ultrasound or stereotactic biopsies [6]. These disputes demonstrate the interprofessional boundary changes that have occurred in the healthcare workforce [7].

In most western countries, physicians tend to stay close to their areas of specialization and rarely violate interprofessional boundaries [8]. Surgeons and radiation oncologists play distinct roles in cancer treatment. Medical oncologists are a subspecialty dedicated to the “total management” of patients with cancer and tasked with coordinating a multidisciplinary approach from initial diagnosis through cure to end-of-life care [9]. Nurses prescribing medication is another example of the permeable role boundary of oncologists [10, 11]. It appears in studies that the reluctance on the part of surgeons to refer patients to oncologists or the disparities in receipt of adjuvant therapy has to do with the age and race of patients as well as their expressed preferences with regard to chemotherapy [8, 12]. In Taiwan, chemotherapy is reimbursed irrespective of the specialty of the provider. It has been assumed that this provides a financial incentive for the horizontal substitution of surgeons in performing the tasks normally assumed by oncologists. However, differences in outcomes among patients treated by different subspecialists must be elucidated before addressing this issue.

The formidable gastrointestinal side effects of chemotherapy and neutropenic fever have been greatly alleviated through the adoption of more efficient antiemetics and the granulocyte colony stimulation factor. These medical advances have improved outcomes and facilitated the administration of chemotherapy. This has opened the door to practitioners in other disciplines to move into areas conventionally regarded as the “turf” of oncologists. When neutropenia or infection is encountered after chemotherapy, the doses can be reduced or the schedule delayed; however, these changes tend to undermine tumor response due to a compromised dose intensity.

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Moreover, regimen changes in the form of omissions or replacement with new agents can also affect survival benefits [13-16]. The aforementioned skills and knowledge all fall within the discipline of oncology. Thus, the segregation of oncologists from the multidisciplinary team approach represents a deprofessionalization of oncologists as well as an example of poor collaboration and a threat to the quality of care.

From a logistical perspective, two distinctive forms of in-house cancer care can be observed in Taiwan: 1) surgeons consulting with oncologists in the administration of postoperative chemotherapy, and 2) surgeons administering adjuvant chemotherapy and conducting follow-up. In this study, we investigated whether there were any differences in outcomes among patients under these different care paths.

MATERIALS AND METHODS

Study Population

The sample included patients who were first diagnosed with American Joint Committee on Cancer (AJCC) stages I–III colon cancer (ICD-0-3 = C18) between January 2005 and December 2009 and had undergone colectomy. Patients with preexisting cancer or those younger than 20 years were excluded.

Data Sources

This study linked population-based data collected from two databases in Taiwan: the Taiwan Cancer Registry (TCR) and the National Health Insurance Research Database (NHIRD). The TCR collects cancer-specific data, including cancer type, cancer stage, surgical margin, and details of the surgical procedures used. The data are abstracted by trained cancer registrars at each hospital into a standard report form, submitted with supporting medical records, and passed through a computerized logic check. From NHIRD data, we retrieved the patient ID, date of ambulatory or inpatient care, disease classification codes (ICD-9-CM codes), physician ID, physician specialty, hospital ID, procedures performed (surgical and nonsurgical), and medications prescribed in each case. The two databases were linked to identify cases of cancer recurrence. The IDs of the patients, physicians, and hospitals were all encrypted using the same algorithm for the cross-linking data while protecting privacy. The protocol for this study was approved by the institutional review board of National Taiwan University (protocol # 201501053RINA).

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Patient Selection and Variables

Postoperative care paths were determined according to whether adjuvant chemotherapy administration and follow-up were performed by oncologists (path 1) or surgeons (path 2) until disease recurrence. The adjuvant chemotherapy regimen included either single-agent fluorouracil (5FU) or its combinations with or without leucovorin and oxaliplatin. Any cases of other oral chemotherapy, unconventional regimens and off-label usages were excluded.

To avoid the misclassification of adjuvant therapy, we considered only chemotherapy administered within a designated period. The period began after curative colectomy and ended 1) on the claims date after which no new treatment for colon cancer was received within 3 months, including surgery, chemotherapy, and radiation; 2) at the time of cancer recurrence; or 3) 12 months after surgery, whichever occurred first. Differentiating salvage chemotherapy for recurrence after adjuvant chemotherapy from true upfront chemotherapy in early recurrence (within 1 year of diagnosis) can be fraught with ambiguities. Thus, we adopted a strict criterion of ineligibility for all patients presenting early recurrence, which resulted in the exclusion of 613 patients from analysis. We also excluded 235 patients whose colon cancers were not ranked within the first-order branch in order to prevent the inclusion of other major comorbidities, such as pneumonia, diabetes, and myocardial infarction, which could otherwise confound analysis. The recommendations for chemotherapy were derived from clinical trials and guidelines outlined by Roswell Park, NSABP C-04 [17, 18], the Mayo Clinic [18, 19], and the Mosaic regimen [20-22]. A change in regimen was defined as either the addition of a new chemotherapeutic agent or the removal of an existing agent from the original protocol.

We controlled for disease stage, the age and sex of patients, and comorbidities. The designation of comorbidity was based on a version of the National Cancer Institute (NCI) Comorbidity Index, in which cases are classified according to comorbidity scores (i.e., 1, 2, or ≥ 3) [23]. The service volume of physicians was controlled by counting the annual number of patients newly diagnosed with colon cancer. Recurrence was defined as metastatic or recurrent disease before or after the completion of adjuvant treatment or within the follow-up period (>12 months). Cases of recurrence were defined using diagnostic codes (ICD 9 codes: 196.0–3, 196.5–6, 196.8–9, 197.0–8, 198.0–8, 199.0–1) or the implementation of a new treatment modality (e.g., surgery or radiotherapy) before the end of or 3 months after the last cycle of adjuvant chemotherapy during the follow-up period. Patients with secondary

malignancies were excluded from the analysis. Disease-free survival (DFS) was defined as the time between colectomy and disease recurrence. Billing codes were used to assign patients to the surgeon who performed the definitive surgery and administered systemic chemotherapy. For the oncological care path, patients were assigned to the medical oncologist who billed for most of the visits and oversaw adjuvant chemotherapy within one year after colectomy. The performance of the treatment provider was defined in terms of the number of patients on which the surgeon operated or who received systemic chemotherapy or care in a given year, as determined in quartiles of case volume (i.e., Q1, median, Q3, and Q4).

Statistical Analysis

Descriptive statistics were used to evaluate baseline characteristics, and the Fisher exact and chi-square tests were used for statistical analysis. The association between various care paths and patient DFS was examined using the Cox proportional hazard model and propensity score matching. The adjusted models included age at the time of diagnosis, sex, disease stage, comorbidities, chemotherapy, care paths, and performance of care provider. The results are reported as hazard ratios (HRs) in conjunction with 95% confidence intervals. The Kaplan–Meier method was used to estimate the DFS of patients with stage II and stage III colon cancer. We performed a log-rank test to test the difference in DFS between the care paths of oncologists and surgeons. All statistical tests were two sided, and a computed p value of 0.05 was considered significant.

RESULTS

A total of 25,005 patients with primary colon cancer were identified from the TCR data. Among these patients, 20,678 had undergone colectomy surgery. We further limited the cohort to stage I–III, class 1 and 2 patients with a histology of adenocarcinoma and who had undergone postoperative adjuvant chemotherapy (Fig. 1). This left a total of 3,534 patients eligible for analysis. The proportions of men and women were 54.2% and 45.8%, respectively (Table 1). Among them, 50.5% of patients were older than 60 years and 23.8% were elderly patients (>70 y/o). Patients with stage II and III colon cancer accounted for 26.1% and 72.5% of all cases, respectively. Of these patients, 59.1% had an NCI comorbidity score of 1 or 2.

A total of 1,767 patients received care from each discipline. No statistical

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differences were observed between patients receiving care from different professionals in terms of sex, age, disease stage, NCI score, or adjuvant chemotherapy (Table 1). Surgeons were slightly more likely than oncologists to change the treatment regimen ($p = .060$). Among the patients whose progress was at the lower end of the spectrum ($< Q1$ and $Q1$ to median), a greater proportion received postoperative chemotherapy from surgeons than from oncologists (34.0% vs 14.3%; 31.9% vs 17.2% respectively, $p < .0001$). Conversely, a greater proportion of those whose progress was at the upper end of the spectrum (median- $Q3$, $> Q3$) received adjuvant chemotherapy from oncologists than from surgeons (29.7% vs 20.9%; 38.8% vs 13.2% respectively).

Stage III colon cancer ($p < .0001$), female sex ($p = .025$), NCI score 3+ ($p = .029$), and more cycles of adjuvant chemotherapy ($p = .027$) were factors associated with a higher likelihood of disease recurrence (Table 2). Patients who underwent changes in their chemotherapeutic agents had a higher recurrence rate than did patients who maintained the same regimen ($p < .0001$). Other factors such as age, performance of treatment providers, and care paths had no significant influence on recurrence.

We also examined the impact of the other variables on patients with stage II and stage III colon cancer (Table 3). The recurrence rate of male patients with stage II cancer was lower than that of their female counterparts (HR = 0.783, $p = .009$). In contrast, the recurrence rate of male patients with stage III cancer was not significantly higher than that of their female counterparts (HR = 1.166, $p = .484$). Among patients who received more cycles of chemotherapy, the recurrence rate of those with stage II was significantly higher than that of patients with stage III cancer (HR = 1.015, $p = .034$; HR = 1.009, $p = .509$, respectively). Changes in chemotherapy regimen were strongly associated with disease recurrence among patients with stage II (HR = 2.492, $p < .0001$) as well as those with stage III cancer (HR = 5.971, $p < .0001$). Patients with stage III cancer who received care from surgeons with performance in the median to third quartile had the lowest recurrence (HR = 0.483, $p = .038$). Overall, we observed no significant differences in age, NCI score, or care paths in terms of recurrence among patients with stage II or III disease.

In terms of DFS, no statistical differences were observed in the outcomes of stage II or stage III patients who followed different care paths. The 5-year DFS rates in patients with stage II and stage III cancer who received care from surgeons and oncologists were 88.99% versus 90.02% and 79.99% versus 77.64% ($p = .628$ and p

= .137, respectively) (Figs. 2 and 3). Patients with stage I colon cancer were excluded from the analysis based on their favorable prognosis and relatively small sample size.

DISCUSSION

The number of cases of colon cancer newly diagnosed in Taiwan was 9,584 in 2005 and 15,140 in 2013 [24]. In the 1990s, adjuvant chemotherapy for colon cancer was reported to improve survival [17, 25]. At present, adjuvant chemotherapy for high-risk patients with stage II and stage III colon cancer is the standard. Surgeons in Taiwan typically administer adjuvant treatment themselves or refer the patient to an oncologist.

This study revealed a number of notable findings. First, we observed no difference in DFS despite differences in the care paths (Figs. 2 and 3). A similar result was observed in two early retrospective cohort studies that compared patient outcomes among different disciplines. The study by Silber applied a research design similar to that of our present study. They hypothesized that patients would benefit more with regard to postoperative survival when receiving chemotherapy from a medical oncologist rather than a gynecologic oncologist. Nonetheless, the two groups of patients presented equal survival results. They explained that their results could perhaps be attributed to the imperfect measurement of chemotherapy and the assignment of providers [26]. Earle reported that after adjustment for surgeon types and patient characteristics, gynecologic oncologists and general gynecologists achieved outcomes that were marginally superior to those of general surgeons. However, the details and jurisdiction of specialists in chemotherapy was not discussed. In addition, characterizing chemotherapy using a variable of all-or-none activity identified in billing claims can be detrimental to the findings [27]. Compared with the designs used in the aforementioned studies, the present study includes more details pertaining to the administration of chemotherapy.

Second, the effects of changing regimens or doses are significantly associated with disease recurrence. In this study, surgeons made more regimen changes than did oncologists; however, the patients under the care of surgeons did not have poorer survival results as would intuitively be inferred. This may be explained by the relatively mild impact that regimen changes had on the few patients to whom they were applied. The actual implications of this remain unclear due to the fact that the details of the chemotherapy they received and other clinical information pertaining to these patients are unknown.

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Third, we observed an equal range of chemotherapy cycles in the two paths. This differs from the report by Silber, in which medical oncologists were shown to administer chemotherapy for longer durations than did gynecologic oncologists. Anecdotal evidence suggests that medical oncologists may be referred a larger proportion of patients with refractory disease requiring more courses of salvage treatment. A wider range of cycles may stem from the various regimens employed under various treatment paradigms. We employed the unit of weeks from the billing data, which is less satisfactory than the unit of real cycles. Nonetheless, neither Silber nor we could verify the assumption that chemotherapy administered through dissimilar in-house logistics affects survival.

Fourth, multiple studies have confirmed the presence of a positive volume–outcome effect in colorectal cancer [28, 29]. However, colorectal surgery is a low-risk procedure, with incomplete staging lower than that observed in gynecological malignancies [30]. The results in most previous studies were in terms of short-term postoperative mortality and length of stay or costs. In those studies, adjuvant chemotherapy was seldom discussed [31]. It was not possible to compare most of the studies directly, due to differences in volume definitions and outcome measures [32, 33]. In our study, surgeons treated decreasing proportions of patients in each quartile: 34.0% (<Q1), 31.9% (Q1-median), 20.9% (median-Q3), and 13.2% (>Q3). What is interesting is that the number of patients that received chemotherapy is inversely proportional to surgeon performance but directly proportional to oncologist performance. Oncologists treated increasing proportions of patients in each quartile: 14.3% (<Q1), 17.2% (Q1-median), 29.7% (median-Q3), and 38.8% (>Q3). This finding implies but not validates the merits of close collaboration in terms of the high volume of patients shared by two specialists. One previous study reported a 5% improvement in survival for every additional patient shared between surgeons and oncologists [2]. However, these findings seem to imply a certain degree of spillover. When surgeons reached the maximum number of patients they could treat, some patients were referred to or voluntarily went to oncologists. One study on ovarian cancer reported that a surgeon’s volume of patients is not predictive of survival; however, a referral to a medical oncologist (or lack thereof) was a strong predictive factor [34]. The reasons for referring or not referring patients to oncologists remain to be investigated, particularly within a fee-for-service payment system [35].

Finally, our results support the supposition that adherence to clinical guidelines would have the same effect on survival, regardless of the practitioner [28, 36].

Nonetheless, adherence to clinical guidelines could be expected to promote trespassing of professional boundaries. Boundary blurring can be affected by any number of factors, such as culture, financial and nonfinancial incentives, scope of work, knowledge and skills, role and identity, and power status [7, 35, 37-39]. Collaboration between disciplines has numerous benefits in terms of patient outcomes. Nonetheless, in Taiwan the status of medical oncologists has been devalued despite international recognition of their contributions [40].

This study has a number of limitations. First, randomized controlled trials are the most reliable means of obtaining evidence in the field of medicine; however, conducting a prospective randomized trial to compare the outcomes of patients undergoing different care paths would be impossible. Furthermore, cross-boundary work is not a major concern in healthcare systems outside Taiwan. The only related retrospective studies have focused on the management of ovarian cancer, which has for decades involved a power struggle in the American Gynecology Society [5, 41].

Second, despite important advances in chemotherapy regimens during the period of this study, we were unable to examine the influence of these changes in various cohorts. Furthermore, we were unable to identify other influential factors, such as variations in dose intensity across providers, the physical frailty of patients, or treatment complications. Third, we focused exclusively on patients who received adjuvant chemotherapy based on strict eligibility criteria. As a result, we excluded a substantial number of patients who underwent paths other than those involving surgeons or oncologists as well as those who experienced recurrence within one year. Finally, our study results may not be generalizable to all stages of cancer or other malignancies.

CONCLUSION

The administering of systemic chemotherapy by non-oncologists is a common practice in the single-payer global healthcare system in Taiwan. This is the first study to address the fundamental question of whether the discipline of the care provider affects patient outcomes. Our analysis does not favor any path of care and our findings indicate no difference in patient survival, regardless of who oversaw the administration of chemotherapy. Nonetheless, one must not jump to any conclusions at this point with regard to the blurring of professionalism boundaries. Furthermore, these findings are not applicable to other malignancies or other disease stages. Further study using outcome measures other than survival time should be conducted

in the future.

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Fig. 1. Flowchart of cohort selection from 2005 to 2009

Fig. 2. Disease-free survival of patients with stage II cancer by different care paths

Fig. 3. Disease-free survival of patients with stage III cancer by different care paths

Table1. Clinical characteristics of patients, treatments, providers’ performance, recurrence, and survival according to different paths (chi-square test, $n = 3,534$)

	Total (%)	Care paths Oncologist n=1,767(%)	Surgeon n=1,767(%)	P value
<u>Characteristics</u>				
Sex				
Male	1917 (54.2)	935 (52.9)	982 (55.6)	.1125
Female	1617 (45.8)	832 (47.1)	785 (44.4)	
Age (years)				
<50	709 (20.1)	372 (21.0)	337 (19.1)	.0735
50–60	1039 (29.4)	523 (29.6)	516 (29.2)	
61–70	943 (26.7)	482 (27.3)	461 (26.1)	
>70	843 (23.8)	390 (22.1)	453 (25.6)	
Stage				
I	49 (1.4)	24 (1.4)	25 (1.4)	.2909
II	921 (26.1)	481 (27.2)	440 (24.9)	
III	2564 (72.5)	1262 (71.4)	1302 (73.7)	
NCI score				
0	1018 (28.8)	523 (29.6)	495 (28.0)	.2790
1	1309 (37.1)	641 (36.3)	668 (37.8)	
2	779 (22.0)	376 (21.3)	403 (22.8)	
3+	428 (12.1)	227 (12.8)	201 (11.4)	
<u>Adjuvant chemotherapy</u>				
Number of cycles		11.24±6.17	11.26±7.1	.2240
Change in regimen				
No	3313 (93.7)	1670 (94.5)	1643 (93)	.0607
Yes	221 (6.3)	97 (5.5)	124 (7)	
<u>Providers’ performance</u>				
<Q1	854 (24.2)	253 (14.3)	601 (34.0)	<.0001
Q1–median	866 (24.5)	303 (17.2)	563 (31.9)	
Median–Q3	895 (25.3)	525 (29.7)	370 (20.9)	
>Q3	919 (26.0)	686 (38.8)	233 (13.2)	
<u>Recurrence</u>				
No	2966 (83.9)	1475 (83.5)	1491 (84.4)	.4637
Yes	568 (16.1)	292 (16.5)	276 (15.6)	
<u>Disease-free survival</u>				
(months)		40.06	41.02	.6550

Table 2. Disease recurrence categorized by clinical characteristics of patients, treatments, care paths, and providers' performance (Cox regression model, $n = 3,534$)

	HR	P	95%CI	
<u>Characteristics</u>				
Sex				
Male	0.826	.0249	0.699	0.976
Female	ref			
Age (years)				
<50	ref			
50–60	1.052	.6786	0.827	1.340
61–70	0.928	.5612	0.72	1.196
>70	0.957	.7414	0.735	1.245
Stage				
I	1.023	.9602	0.414	2.526
II	ref			
III	2.054	<.0001	1.632	2.586
NCI score				
0	ref			
1	1.063	.5704	0.861	1.311
2	1.105	.4206	0.867	1.408
3+	1.370	.0288	1.033	1.817
<u>Adjuvant chemotherapy</u>				
Number of cycles	1.014	.0268	1.002	1.026
Change in regimen				
Yes	2.751	<.0001	2.148	3.523
No	ref			
<u>Care paths</u>				
Oncologists	ref			
Surgeons	0.876	.1479	0.732	1.048
<u>Providers' performance</u>				
<Q1	ref			
Q1–median	0.974	.8287	0.769	1.234
Median–Q3	0.948	.6673	0.744	1.208
>Q3	0.941	.6338	0.731	1.210

Table 3. Disease recurrence in patients with stage II or III colon cancer categorized by clinical characteristics, treatments, care paths, and providers’ performance

	Stage II (<i>n</i> =921)				Stage III (<i>n</i> =2,564)			
	HR	<i>P</i>	95%CI		HR	<i>P</i>	95%CI	
<u>Characteristics</u>								
Sex								
Male	0.783	.0089	0.652	0.94	1.166	.4836	0.759	1.79
Female								ref
Age (years)								
<50								ref
50–60	0.999	.9966	0.768	1.300	1.083	.8055	0.573	2.047
61–70	0.855	.2667	0.648	1.128	1.341	.3701	0.706	2.547
>70	0.880	.3839	0.661	1.173	0.309	.7200	2.827	0.880
NCI score								
0								ref
1	1.051	.6703	0.836	1.321	1.118	.6926	0.643	1.942
2	1.103	.4662	0.847	1.437	1.285	.4407	0.679	2.432
3+	1.316	.0829	0.965	1.796	1.612	.1978	0.779	3.334
<u>Adjuvant chemotherapy</u>								
Number of cycles	1.015	.0349	1.001	1.028	1.009	.5089	0.982	1.037
Change in regimen								
No								ref
Yes	2.492	<.0001	1.903	3.263	5.971	<.0001	2.98	11.965
<u>Care paths</u>								
Oncologists								ref
Surgeons	0.847	.1015	0.694	1.033	1.004	.9861	0.65	1.551
<u>Providers’ performance</u>								
<Q1								ref
Q1–median	0.943	.6622	0.726	1.225	1.315	.3456	0.744	2.322
Median–Q3	1.025	.8543	0.786	1.337	0.483	.0376	0.243	0.959
>Q3	0.918	.5538	0.693	1.218	1.159	.6134	0.654	2.051

Data sharing statement:

The access and release of all the data analyzed in this study was approved by the Department of Statistics. All authors did not have privilege to own or utilize the dataset. Researchers who are Interested in the data may also apply to the Department of Statistics, Ministry of Health and Welfare (Taiwan) via the contact personnel: Ms. Wu Tzu-Hui (stcarolwu@mohw.gov.tw) and Mr. Zongying Lin (st-zylin@mohw.gov.tw).

Author contributor ship statement:

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Data curation: CCL, RNK.

Formal analysis: CCL

Funding acquisition: KPC

Investigation: CIH

Methodology: CIH, RNK

Resources: RNK, KPC

Software: CCL

Supervision: RNK

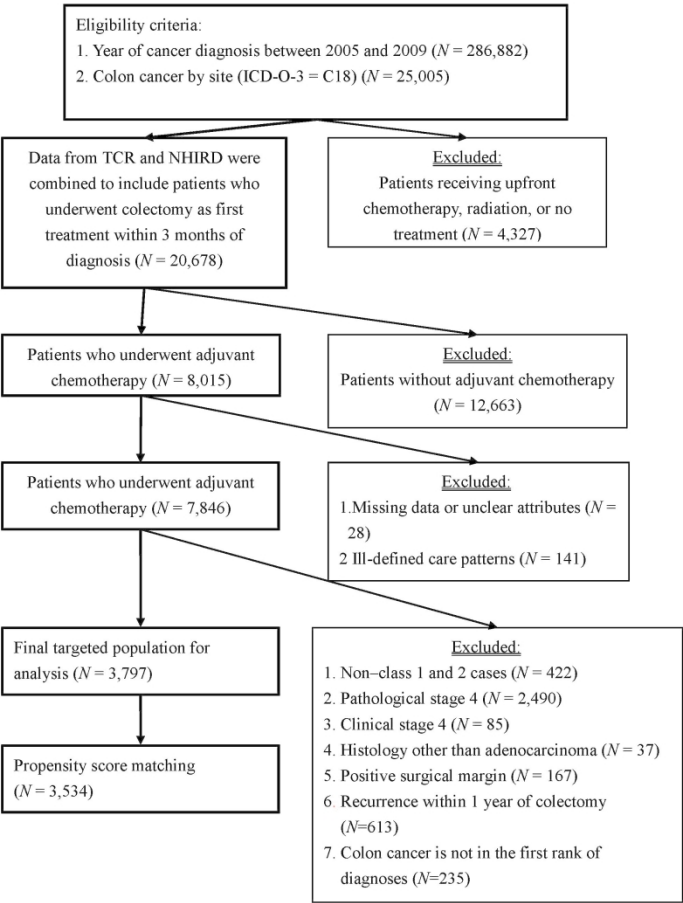
Validation: RNK, CCL

Writing - original draft: CIH

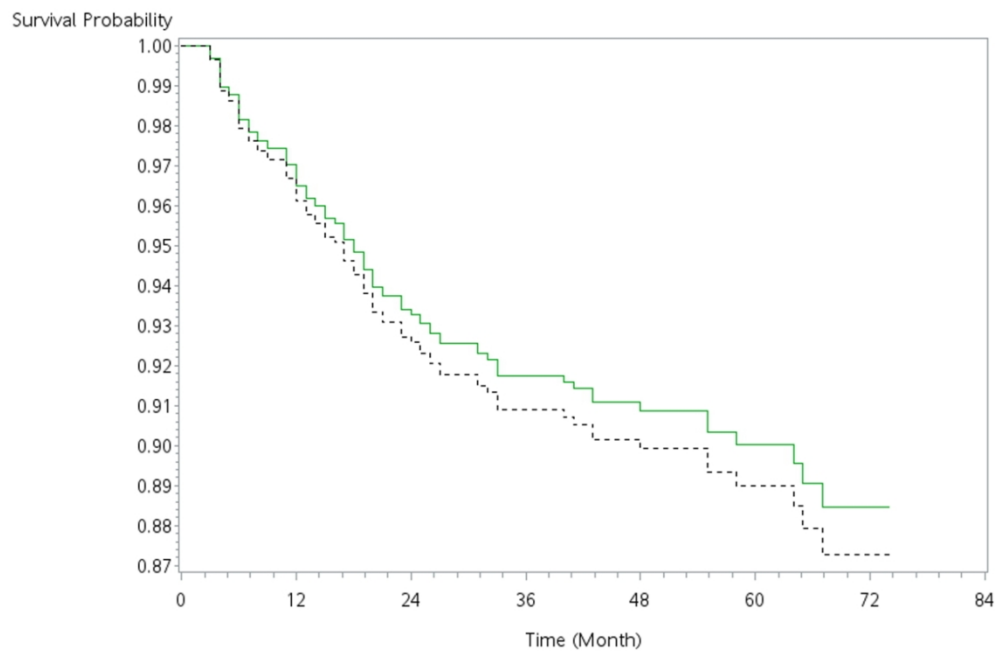
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All authors claim to have no competing interests.

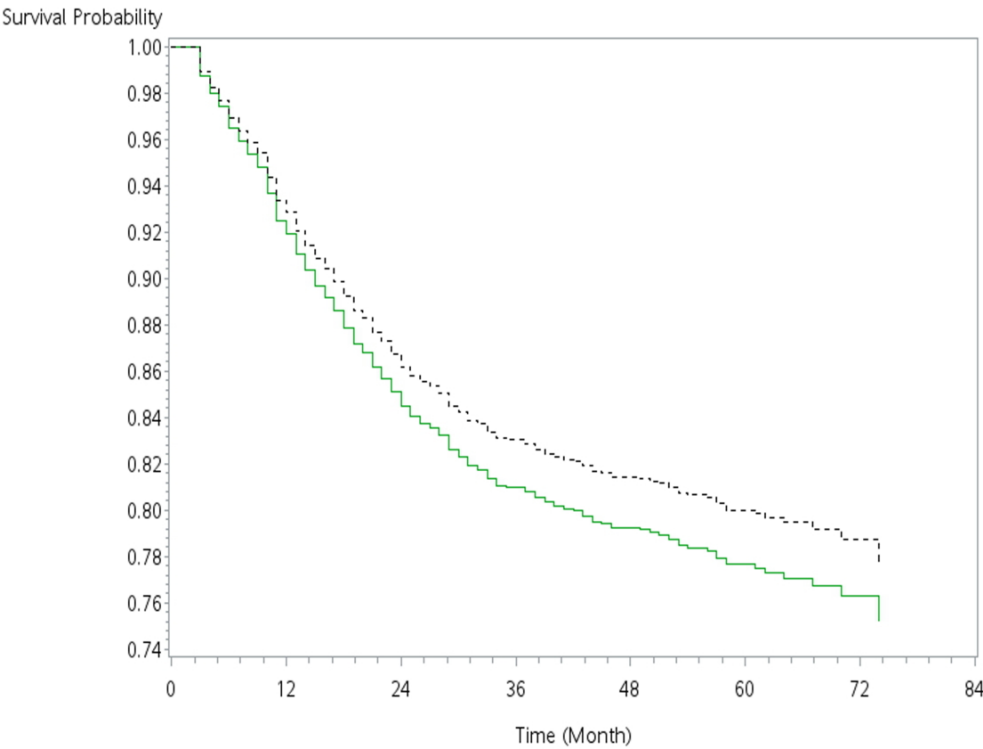


Flowchart of cohort selection
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Disease-free survival of patients with stage II cancer by different care paths

107x73mm (300 x 300 DPI)



Disease-free survival of patients with stage III cancer by different care paths
95x73mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1, 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	(N/A)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	(N/A)
		(c) Explain how missing data were addressed	Figure 1
		(d) If applicable, explain how loss to follow-up was addressed	(N/A)
		(e) Describe any sensitivity analyses	(N/A)
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	(N/A)
		(c) Summarise follow-up time (eg, average and total amount)	(N/A)
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(b) Report category boundaries when continuous variables were categorized	8-10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	(N/A)
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Differences in the Outcomes of Adjuvant Chemotherapy for Colon Cancer Prescribed by Physicians in Different Disciplines: A population-based study

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Differences in the Outcomes of Adjuvant Chemotherapy for Colon Cancer Prescribed by Physicians in Different Disciplines: A population-based study

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Short title: Patient Survival and Care in Different Disciplines

Abstract

Objectives: One feature unique to the Taiwanese healthcare system is the ability of physicians other than oncologists to prescribe systemic chemotherapy. This study investigated whether the care paths implemented by oncologists and non-oncologists differ with regard to patient outcomes.

Setting: Data from the Taiwan Cancer Registry and National Health Insurance Database were linked to identify colon cancer patients who underwent colectomy as first treatment within 3 months of diagnosis and adjuvant chemotherapy between 2005 and 2009.

Participants and methods: Postoperative patients underwent adjuvant chemotherapy were included in this study. We further excluded patients with stage IV disease, positive surgical margin, early disease recurrence, and patients whose cancer diagnosis were not ranked within the first-order branch. Variables included sex, age, comorbidities, disease stage, chemotherapy cycle, and changes in treatment regimen as well as the specialty of treatment providers and their case volume as it pertains to disease recurrence and patient survival. Cox regression models and Kaplan-Meier analysis were used to examine differences in outcomes in the matched cohorts.

Results: We examined 3,534 patients who were prescribed adjuvant chemotherapy by physicians from different disciplines. In terms of 5-year disease-free survival, no significant difference was observed between the groups of oncologists or surgeons among patients with stage II (90.02% vs. 88.99%) or stage III (77.64% vs. 79.99%) diseases. Patients with changes in their chemotherapy regimens exhibited a recurrence rate higher than those who did not.

Conclusions: The discipline of practitioners is seldom taken into account in most series. This is the first study to provide empirical evidence demonstrating that the outcomes of colon cancer patients do not depend on the treatment path, as long as the selection criteria for adjuvant chemotherapy is appropriate. Further study will be required before making any further conclusions.

Keywords: adjuvant treatment, medical specialization, professional boundaries, referral pattern, medical oncology

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Strengths and limitations of this study:

- In countries with a clear demarcation between specialties, surgeons do not cross professional boundaries; i.e., they do not engage in prescribing chemotherapy. Previous researchers have generally not treated differences among cancer care disciplines as a influence factor worthy of inclusion. This is the first study to examine the differential outcomes of cancer patients under different care paths. We found that the outcomes of colon cancer patients do not depend on the treatment path, as long as the selection criteria for adjuvant chemotherapy is appropriate. These findings are of particular importance in countries where cross-boundary cancer care is the norm.
- We excluded many ineligible patients based on strict criteria in the analysis and methodologically reduced the bias of confounding factors between two disciplines with propensity score matching.
- It is a study designed by linking two large national data sets of a large number of patients with records of long-term follow-up.
- Lacking the variations in dose intensity across providers and clinical information of patients is the limitation of this study. With a time constraint, we were also unable to examine the influence of advances in chemotherapy regimens in different paradigms during the period of study.

Introduction

Shared care refers to the joint participation of physicians in the planning of patient care. This approach has been shown to improve cancer outcomes by helping to coordinate care to ensure the timely administration of adjuvant chemotherapy and thereby extend survival^{1 2}. Innovations in healthcare have resulted in highly specialized treatment regimes. For example, coronary artery bypass grafts performed by cardiothoracic surgeons have been replaced with percutaneous catheterization intervention performed by cardiologists^{3 4}. This has led to the blurring of professional boundaries, such as the issues that has been discussed by the American Society of Gynecologic Oncology⁵. Another situation is the long-simmering conflict between breast surgeons or radiologists over who should perform ultrasound or stereotactic biopsies⁶. These disputes demonstrate the interprofessional boundary changes that have occurred in the healthcare workforce⁷.

In most western countries, physicians tend to stay close to their areas of specialization and rarely violate interprofessional boundaries⁸. Surgeons and radiation oncologists play distinct roles in cancer treatment. Medical oncologists are a subspecialty dedicated to the “total management” of patients with cancer and tasked with coordinating a multidisciplinary approach from initial diagnosis through cure to end-of-life care⁹. Nurses prescribing medication is another example of the permeable role boundary of oncologists^{10 11}. It appears in studies that the reluctance on the part of surgeons to refer patients to oncologists or the disparities in receipt of adjuvant therapy has to do with the age and race of patients as well as their expressed preferences with regard to chemotherapy^{8 12}. In Taiwan, chemotherapy is reimbursed irrespective of the specialty of the provider. It has been assumed that this provides a financial incentive for the horizontal substitution of surgeons in performing the tasks normally assumed by oncologists. However, differences in outcomes among patients treated by different subspecialists must be elucidated before addressing this issue.

The formidable gastrointestinal side effects of chemotherapy and neutropenic fever have been greatly alleviated through the adoption of more efficient antiemetics and the granulocyte colony stimulation factor. These medical advances have improved outcomes and facilitated the administration of chemotherapy. This has opened the door to practitioners in other disciplines to move into areas conventionally regarded as the “turf” of oncologists. When neutropenia or infection is encountered after

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chemotherapy, the doses can be reduced or the schedule delayed; however, these changes tend to undermine tumor response due to a compromised dose intensity. Moreover, regimen changes in the form of omissions or replacement with new agents can also affect survival benefits ¹³⁻¹⁶. The aforementioned skills and knowledge all fall within the discipline of oncology. Thus, the segregation of oncologists from the multidisciplinary team approach represents a deprofessionalization of oncologists as well as an example of poor collaboration and a threat to the quality of care.

Our objective in this study was to determine whether the care paths implemented by oncologists and non-oncologists differ with regard to patient outcomes. From a logistical perspective, two distinctive forms of in-house cancer care can be observed in Taiwan: 1) surgeons consulting with oncologists in the prescription of postoperative chemotherapy, and 2) surgeons prescribing adjuvant chemotherapy and conducting follow-up. From a practical perspective, it is impossible to conduct randomized clinical trial to compare the differences in outcomes among patients under different care paths. The results of this study are of particular relevance in regions facing a shortage of oncologists, or where there are concerns pertaining to the outcomes of patients receiving adjuvant treatment from clinicians other than oncologists.

Materials and methods

Study Population

The sample included patients who were first diagnosed with colon cancer according to the American Joint Committee on Cancer (AJCC) Stages I–III (ICD-0-3 = C18) between January 2005 and December 2009. All participants had undergone colectomy, as verified by the Taiwan Cancer Registry (TCR). The data was linked to the National Health Insurance Research Database (NHIRD) for follow up between Jan. 2005 and December 2012. Patients with preexisting cancer and those younger than 20 years were excluded from analysis.

Data Sources

This study linked population-based data collected from two databases in Taiwan: the Taiwan Cancer Registry (TCR) and the National Health Insurance Research Database (NHIRD). The TCR collects cancer-specific data, including cancer type, cancer stage, surgical margin, and details of the surgical procedures used. The data are abstracted by trained cancer registrars at each hospital into a standard report form, submitted with supporting medical records, and passed through a computerized logic

check. From NHIRD data, we retrieved the patient ID, date of ambulatory or inpatient care, disease classification codes (ICD-9-CM codes), physician ID, physician specialty, hospital ID, procedures performed (surgical and nonsurgical), and medications prescribed in each case. The two databases were linked to identify cases of cancer recurrence. The IDs of the patients, physicians, and hospitals were all encrypted using the same algorithm for the cross-linking data while protecting privacy.

Patient Selection and Variables

Postoperative care paths were determined according to whether adjuvant chemotherapy administration and follow-up were performed by oncologists (path 1) or surgeons (path 2) until disease recurrence. The adjuvant chemotherapy regimen included either single-agent fluorouracil (5FU) or its combinations with or without leucovorin and oxaliplatin. Any cases of other oral chemotherapy, unconventional regimens and off-label usages were excluded.

To avoid the misclassification of adjuvant therapy, we considered only chemotherapy prescribed within a designated period. The period began after curative colectomy and ended 1) on the claims date after which no new treatment for colon cancer was received within 3 months, including surgery, chemotherapy, and radiation; 2) at the time of cancer recurrence; or 3) 12 months after surgery, whichever occurred first. Differentiating salvage chemotherapy for recurrence after adjuvant chemotherapy from true upfront chemotherapy in early recurrence (within 1 year of diagnosis) can be fraught with ambiguities. Thus, we adopted a strict criterion of ineligibility for all patients presenting early recurrence, which resulted in the exclusion of 613 patients from analysis. We also excluded 235 patients whose colon cancers were not ranked within the first-order branch in order to prevent the inclusion of other major comorbidities, such as pneumonia, diabetes, and myocardial infarction, which could otherwise confound analysis. The recommendations for chemotherapy were derived from clinical trials and guidelines outlined by Roswell Park, NSABP C-04^{17 18}, the Mayo Clinic^{18 19}, and the Mosaic regimen²⁰⁻²². A change in regimen was defined as either the addition of a new chemotherapeutic agent or the removal of an existing agent from the original protocol.

The patient's sex, age, stage of cancer, comorbidities, and history of regimen changes were used for matching, and were also controlled in Cox regression models.

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The designation of comorbidity was based on a version of the National Cancer Institute (NCI) Comorbidity Index, in which cases are classified according to comorbidity scores (i.e., 1, 2, or ≥ 3)²³. The case volume of physicians was controlled by counting the annual number of patients newly diagnosed with colon cancer. Recurrence was defined as metastatic or recurrent disease before or after the completion of adjuvant treatment or within the follow-up period (>12 months). Cases of recurrence were defined using diagnostic codes (ICD 9 codes: 196.0–3, 196.5–6, 196.8–9, 197.0–8, 198.0–8, 199.0–1) or the implementation of a new treatment modality (e.g., surgery or radiotherapy) before the end of or 3 months after the last cycle of adjuvant chemotherapy during the follow-up period. Patients with secondary malignancies were excluded from the analysis. Disease-free survival (DFS) was defined as the time between colectomy and disease recurrence. Billing codes were used to assign patients to the surgeon who performed the definitive surgery and prescribed systemic chemotherapy. For the oncological care path, patients were assigned to the medical oncologist who billed for most of the visits and oversaw adjuvant chemotherapy within one year after colectomy. The case volume of the treatment provider was defined in terms of the number of patients on which the surgeon operated or who received systemic chemotherapy or care in a given year, as determined in quartiles of case volume (i.e., < 25%, 25-50%, 51-75%, > 75%).

Statistical Analysis

Descriptive statistics were used to evaluate baseline characteristics. We adopted propensity score methods similar to those described in previous studies^{24 25} to create a cohort of matched patients (i.e., sharing similar characteristics). The scores were calculated using logistic regression to estimate the probability of each patient receiving adjuvant chemotherapy on the basis of sex, age, stage, co-morbidities, and change in regimen. Patient cohorts on both paths were matched using a greedy-matching algorithm to formulate a 1:1 case-control match ratio using calipers with a width of < 0.2 standard deviations of the logit of propensity scores. The degree of balance in characteristics was compared using the Mantel-Haenszel test and generalized estimating equation (GEE) regression. The results are reported as hazard ratios (HRs) in conjunction with 95% confidence intervals. The Kaplan–Meier method was used to estimate the DFS of patients with stage II and stage III colon cancer. We performed a log-rank test to test the difference in DFS between the care

paths of oncologists and surgeons. All statistical tests were two sided, and a computed p value < 0.05 was considered significant.

Patient and public involvement

No patients or public were involved in the design and process of this study. Patients and public will be informed of the study results via peer-reviewed journals.

Results

A total of 25,005 patients with primary colon cancer were identified from the TCR data. Among these patients, 20,678 had undergone colectomy surgery. We further limited the cohort to stage I–III, class 1 and 2 patients with a histology of adenocarcinoma and who had undergone postoperative adjuvant chemotherapy (Fig. 1). This left a total of 3,534 matched patients eligible for analysis. The proportions of men and women were 54.2% and 45.8%, respectively (Table 1). Among them, 50.5% of patients were older than 60 years and 23.8% were elderly patients (>70 y/o). Patients with stage II and III colon cancer accounted for 26.1% and 72.5% of all cases, respectively. Of these patients, 59.1% had an NCI comorbidity score of 1 or 2.

A total of 1,767 patients received care from professionals in each discipline. After matching, no statistical differences were observed between patients receiving care from different professionals, in terms of sex, disease stage, comorbidities, or adjuvant chemotherapy (Table 1). Surgeons were slightly more likely than oncologists to change the treatment regimen ($p = .060$). A greater proportion of patients received postoperative chemotherapy from low-volume surgeons than from low-volume oncologists ($<25\%$: 34.0% vs 14.3%; 25–50%: 31.9% vs 17.1%, respectively, $p < .0001$).

As shown in Table 2, care paths did not have a significant influence on recurrence. Stage III colon cancer ($p < .0001$), NCI score 3+ ($p = .029$), and more cycles of adjuvant chemotherapy ($p = .027$) were factors associated with a higher likelihood of disease recurrence. Patients who underwent changes in their chemotherapeutic agents had a higher recurrence rate than did patients who maintained the same regimen ($p < .0001$).

We also conducted sensitivity analysis to examine the impact of treatment paths

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on recurrence among patients with stage II and stage III colon cancer (Table 3). We observed no significant differences between the care paths in terms of recurrence. Changes in chemotherapy regimen were strongly associated with disease recurrence among patients in stage II (HR = 5.97, $p < .0001$) as well as those in stage III (HR = 2.49, $p < .0001$).

In terms of disease free survival (DFS), no statistical differences were observed in the outcomes of stage II or stage III patients who followed different care paths (Fig. 2 and Fig. 3). The 5-year DFS rates in patients in stage II and stage III who received care from oncologists and surgeons were 90.02% versus 88.99% and 77.64% versus 79.99% ($p = .628$ and $p = .137$, respectively). Patients with stage I colon cancer were excluded from the analysis based on their favorable prognosis and relatively small sample size.

Discussion

The number of cases of colon cancer newly diagnosed in Taiwan was 9,584 in 2005 and 15,140 in 2013²⁶. In the 1990s, adjuvant chemotherapy for colon cancer was reported to improve survival^{17 27}. At present, adjuvant chemotherapy for high-risk patients with stage II and stage III colon cancer is the standard. Surgeons in Taiwan typically prescribed adjuvant treatment themselves or refer the patient to an oncologist.

To the best of our knowledge, this is the first study to investigate whether the care paths implemented by oncologists and non-oncologists differ in terms of patient outcomes. We observed no difference in DFS despite differences in the care paths (Figs. 2 and 3). A similar result was observed in two early retrospective cohort studies that compared patient outcomes among different disciplines. The study by Silber applied a research design similar to that of our present study. They hypothesized that patients would benefit more with regard to postoperative survival when receiving chemotherapy from a medical oncologist rather than a gynecologic oncologist. Nonetheless, the two groups of patients presented equal survival results. They explained that their results could perhaps be attributed to the imperfect measurement of chemotherapy and the assignment of providers²⁸. Earle reported that after adjustment for surgeon types and patient characteristics, gynecologic oncologists and general gynecologists achieved outcomes that were marginally superior to those of

general surgeons. However, the details and jurisdiction of specialists in chemotherapy was not discussed. In addition, characterizing chemotherapy using a variable of all-or-none activity identified in billing claims can be oversimplified and detrimental to the findings²⁹. Compared with the designs used in the aforementioned studies, the present study includes more details pertaining to the administration of chemotherapy.

Our results indicate that changes in regimen or dose are significantly associated with disease recurrence. Patients who were prescribed chemotherapy by surgeons underwent more regimen changes than did those who were prescribed chemotherapy by oncologists. Nonetheless, the survival of patients who were under the care of surgeons was no worse, as one may intuitively infer. Nonetheless, our study design cannot be used to determine whether surgeons made more change regimens, or to characterize the outcomes in cases where changes were made. We included regimen changes in our statistical models to control for confounding factors related to regimen changes, which are not necessarily observable in our data. We also conducted sensitivity analysis that included only patients who had not undergone regimen changes (Table 2). Our results revealed no statistical differences in disease recurrence among patients treated by oncologists or surgeons. The actual implications of these findings remain unclear, due to the fact that the details of the chemotherapy they received and other clinical information pertaining to these patients are unknown.

We also determined that the two paths were very similar in terms of the number of chemotherapy cycles (mean: 11.2 vs. 11.3, $p = 1.00$). This differs from the report by Silber, in which medical oncologists were shown to prescribe chemotherapy for longer durations than did gynecologic oncologists. Anecdotal evidence suggests that medical oncologists may be referred a larger proportion of patients with refractory disease requiring more courses of salvage treatment. A wider range of cycles may stem from the various regimens employed under various treatment paradigms. We employed the unit of weeks from the billing data, which is less satisfactory than the unit of real cycles. Nonetheless, neither Silber nor we could verify the assumption that chemotherapy prescribed through dissimilar in-house logistics affects survival.

We found that the case volume of patients managed by the health provider was not associated with disease recurrence. This contradicts the findings of previous studies, which reported a positive association between the volume of patients and colorectal cancer outcomes^{30 31}. However, colorectal surgery is a low-risk procedure, such that the incidence of incomplete surgical staging is lower than that observed in gynecological malignancies³². The results in most previous studies were in terms of

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short-term postoperative mortality and length of stay or costs. In those studies, adjuvant chemotherapy was seldom discussed³³. It was not possible to compare most of the studies directly, due to differences in volume definitions and outcome measures^{34 35}. In this study, the provider's patient volume was not associated with recurrence; however, we found that 65.9% of patients who received chemotherapy from surgeons were treated by professionals with low case volumes ($\leq 50\%$). Conversely, we found that 68.5% of patients who received chemotherapy from oncologists were treated by professionals with high case volumes ($> 50\%$). One previous study reported a 5% improvement in survival for every additional patient shared between surgeons and oncologists². However, these findings seem to imply a certain degree of spillover. When surgeons reached the maximum number of patients they could treat, some patients were referred to or voluntarily went to oncologists. One study on ovarian cancer reported that a surgeon's volume of patients is not predictive of survival; however, a referral to a medical oncologist (or lack thereof) was a strong predictive factor³⁶. The reasons for referring or not referring patients to oncologists remain to be investigated, particularly within a fee-for-service payment system³⁷.

Previous studies have shown that adherence to clinical guidelines in the administration of cancer treatment would have the same effect on survival, regardless of the speciality of the practitioner^{30 38}. Nonetheless, adherence to clinical guidelines could be expected to promote trespassing of professional boundaries. Boundary blurring can be affected by any number of factors, such as culture, financial and nonfinancial incentives, scope of work, knowledge and skills, role and identity, and power status^{7 37 39-41}. Collaboration between disciplines has numerous benefits in terms of patient outcomes. Nonetheless, in Taiwan the status of medical oncologists has been devalued despite international recognition of their contributions⁴².

This study has a number of limitations. First, randomized controlled trials are the most reliable means of obtaining evidence in the field of medicine; however, conducting a prospective randomized trial to compare the outcomes of patients undergoing different care paths would be impossible. Furthermore, cross-boundary work is not a major concern in healthcare systems outside Taiwan. The only related retrospective studies have focused on the management of ovarian cancer, which has for decades involved a power struggle in the American Gynecology Society^{5 43}. Second, we were unable to identify other influential factors, such as variations in dose intensity, the number of cycles across providers, the preferences of patients, the physical frailty of patients, or treatment complications. To mitigate the potential confounding effects of changes in treatment regimen, we performed sensitivity

analysis in which 221 patients who underwent regimen changes were excluded. The results were no different than those obtained using the entire sample. The dataset was the factor limiting our definitions of regimen changes. In the future, researchers should make an effort to take these unobserved factors into account. Third, we focused exclusively on patients who received adjuvant chemotherapy, based on strict eligibility criteria. This resulted in the exclusion of a substantial number of patients who underwent paths other than those involving surgeons or oncologists as well as those who experienced recurrence within one year.

Conclusions

The prescribing of systemic chemotherapy by non-oncologists is a common practice in the single-payer global healthcare system in Taiwan. This is the first study to address the fundamental question of whether the discipline of the care provider affects patient outcomes. Our analysis does not favor any path of care and our findings indicate no difference in patient survival, regardless of who oversaw the administration of chemotherapy. Nonetheless, one must not jump to any conclusions at this point with regard to the blurring of professionalism boundaries. Furthermore, these findings are not applicable to other malignancies or other disease stages. Further study using outcome measures other than survival time should be conducted in the future.

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Figure captions

- Fig. 1. Flowchart of cohort selection from 2005 to 2009
- Fig. 2. Disease-free survival of patients with stage II cancer by different care paths
- Fig. 3. Disease-free survival of patients with stage III cancer by different care paths

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Tables

Table 1 Baseline characteristics of colon cancer patients following different care paths

	Before propensity score matching				After propensity score matching			
	Oncologist (N=1767) N (%)	Surgeon (N=2030) N (%)	Standardized difference, %	P value	Oncologist (N=1767) N (%)	Surgeon (N=1767) N (%)	Standardized difference, %	P value
Characteristics								
Sex				0.12				0.11
Male	935 (52.9)	1125 (55.4)	5.0		935 (52.9)	982 (55.6)	5.3	
Female	832 (47.1)	905 (44.6)			832 (47.1)	785 (44.4)		
Age, year								
Mean(SD)	59.14 (12.4)	59.76 (12.7)	4.9	0.13	59.14 (12.4)	59.99 (12.5)	4.9	0.04
<50	372 (21.1)	405 (20.0)	2.7		372 (21.1)	337 (19.1)	4.9	
50-60	523 (29.6)	582 (28.7)	2.0		523 (29.6)	516 (29.2)	0.9	
61-70	482 (27.3)	529 (26.1)	2.8		482 (27.3)	461 (26.1)	2.7	
>70	390 (22.1)	514 (25.3)	7.6		390 (22.1)	453 (25.6)	8.4	
Stage				0.07				0.17
I	24 (1.4)	29 (1.4)	0.6		24 (1.4)	25 (1.4)	0.5	
II	481 (27.2)	493 (24.3)	6.7		481 (27.2)	440 (24.9)	5.3	
III	1262 (71.4)	1508 (74.3)	6.4		1262 (71.4)	1302 (73.7)	5.1	
NCI comorbidity score				0.84				0.96
0	523 (29.6)	564 (27.8)	4.0		523 (29.6)	495 (28.0)	3.5	
1	641 (36.3)	765 (37.7)	2.9		641 (36.3)	668 (37.8)	3.2	
2	376 (21.3)	472 (23.3)	4.7		376 (21.3)	403 (22.8)	3.7	
3+	227 (12.8)	229 (11.3)	4.8		227 (12.8)	201 (11.4)	4.5	
Adjuvant Chemotherapy								
Numbers of cycles								
Mean(SD)	11.5 (6.2)	11.4 (7.1)	0.8	0.81	11.2 (6.2)	11.3 (7.1)	0.4	1.00
Change in regimen				0.06				0.06
No	1670 (94.5)	1889 (93.1)			1670 (94.5)	1643 (93.0)		
Yes	97 (5.5)	141 (6.9)	6.0		97 (5.5)	124 (7.0)	6.3	
Providers' case volume				<.0001				<.0001
<25%	253 (14.3)	695 (34.2)	47.8		253 (14.3)	601 (34.0)	47.3	
25-50%	303 (17.1)	644 (31.7)	34.4		303 (17.1)	563 (31.9)	34.7	
51-75%	525 (29.7)	426 (21.0)	20.2		525 (29.7)	370 (20.9)	20.3	

	Before propensity score matching				After propensity score matching*			
	Oncologist (N=1767) N (%)	Surgeon (N=2030) N (%)	Standardized difference, %	P value	Oncologist (N=1767) N (%)	Surgeon (N=1767) N (%)	Standardized difference, %	P value
>75%	686 (38.8)	265 (13.1)	61.5		686 (38.8)	233 (13.2)	61.1	
Recurrence								
No	1475 (83.5)	1704 (84.9)			1475 (83.5)	1491 (84.4)		
Yes	292 (16.5)	326 (16.1)			292 (16.5)	276 (15.6)		
Disease-free survival, month								
Mean(SD)	46.91 (19.2)	47.43 (19.2)			46.91 (19.2)	47.65 (19.1)		
Median(IQR)	45 (31-63)	47 (31-63)			45 (31-63)	47 (31-64)		

Abbreviations: SD, standard deviation; IQR, interquartile range; DFS, disease-free-survival; NCI, National Cancer Institute.
*Variables used for propensity score matching included sex, age, stage, 12 comorbid conditions of NCI comorbidity index, and history of regimen changes.
The standardized differences of the 12 comorbid conditions were between 0.3 and 4.6 in un-matched data and between 0 and 4.5 in matched data (data not shown).
P-values were obtained using the Mantel-Haenszel test for categorical variables and generalized estimating equations (GEE) regression for continuous variables.

Table 2. Disease recurrence categorized by clinical characteristics of patients, treatments, care paths, and the case volume of primary care providers (Cox regression models)

	Overall (N=3534)			No change regimens (N=3313)			Change regimens (N=221)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Characteristics									
Sex									
Male	Ref			Ref			Ref		
Female	0.83	(0.70 -0.98)	0.025	0.83	(0.69 -0.99)	0.042	0.77	(0.47 -1.26)	0.297
Age(years)									
<50	Ref			Ref			Ref		
50-60	1.05	(0.83 -1.34)	0.679	1.11	(0.85 -1.44)	0.458	0.78	(0.42 -1.45)	0.426
61-70	0.93	(0.72 -1.20)	0.561	1.04	(0.79 -1.37)	0.786	0.39	(0.18 -0.84)	0.016
>70	0.96	(0.74 -1.25)	0.741	0.99	(0.74 -1.32)	0.943	0.94	(0.48 -1.85)	0.862
Stage									
I	1.02	(0.41 -2.53)	0.960	0.72	(0.23 -2.27)	0.569	2.32	(0.47 -11.4)	0.299
II	Ref			Ref			Ref		
III	2.05	(1.63 -2.59)	<.0001	2.21	(1.73 -2.82)	<.0001	1.06	(0.53 -2.13)	0.862
NCI score									
0	Ref			Ref			Ref		
1	1.06	(0.86 -1.31)	0.570	0.97	(0.77 -1.22)	0.780	1.77	(0.96 -3.26)	0.067
2	1.11	(0.87 -1.41)	0.421	1.04	(0.80 -1.34)	0.794	1.66	(0.78 -3.53)	0.186
3+	1.37	(1.03 -1.82)	0.029	1.25	(0.92 -1.68)	0.150	2.89	(1.19 -7.03)	0.019
Adjuvant Chemotherapy									
Numbers of cycles	1.01	(1.00 -1.03)	0.027	1.01	(1.00 -1.02)	0.133	1.03	(0.99 -1.08)	0.101
Change in regimen									
No	Ref			—			—		
Yes	2.75	(2.15 -3.52)	<.0001	—			—		
Care paths									
Oncologists	Ref			Ref			Ref		
Surgeons	0.88	(0.73 -1.05)	0.148	0.87	(0.72 -1.06)	0.165	0.94	(0.56 -1.59)	0.820
Providers' case volume									
<25%	Ref			Ref			Ref		
25-50%	0.97	(0.77 -1.23)	0.829	0.98	(0.76 -1.26)	0.850	1.05	(0.55 -2.00)	0.889
51-75%	0.95	(0.74 -1.21)	0.667	0.94	(0.72 -1.21)	0.609	0.89	(0.44 -1.80)	0.740

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>75%	0.94	(0.73 -1.21)	0.634	0.89	(0.68 -1.16)	0.381	1.66	(0.80 -3.45)	0.175
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Table 3. Disease recurrence in patients with stage II or III colon cancer, categorized according to clinical characteristics, treatments, care paths, and case volume of primary care providers

Characteristics	Stage II (N=921)			Stage III (N=2564)		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex						
Male	Ref			Ref		
Female	1.17	(0.76 -1.79)	0.484	0.78	(0.65 -0.94)	0.009
Age(years)						
<50	Ref			Ref		
50-60	1.08	(0.57 -2.05)	0.806	1.00	(0.77 -1.30)	0.997
61-70	1.34	(0.71 -2.55)	0.370	0.86	(0.65 -1.13)	0.267
>70	1.43	(0.72 -2.83)	0.309	0.88	(0.66 -1.17)	0.384
NCI score						
0	Ref			Ref		
1	1.12	(0.64 -1.94)	0.693	1.05	(0.84 -1.32)	0.670
2	1.29	(0.68 -2.43)	0.441	1.10	(0.85 -1.44)	0.466
3+	1.61	(0.78 -3.33)	0.198	1.32	(0.97 -1.80)	0.083
Adjuvant chemotherapy						
Numbers of cycles	1.01	(0.98 -1.04)	0.509	1.02	(1.00 -1.03)	0.035
Change in regimen						
No	Ref			Ref		
Yes	5.97	(2.98 -11.97)	<.0001	2.49	(1.90 -3.26)	<.0001
Care paths						
Oncologists	Ref			Ref		
Surgeons	1.00	(0.65 -1.55)	0.986	0.85	(0.69 -1.03)	0.102
Providers' case volume						
<25%	Ref			Ref		
25-50%	1.32	(0.74 -2.32)	0.346	0.94	(0.73 -1.23)	0.662
51-75%	0.48	(0.24 -0.96)	0.038	1.03	(0.79 -1.34)	0.854
>75%	1.16	(0.65 -2.05)	0.613	0.92	(0.69 -1.22)	0.554

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Footnotes

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Provenance and peer review: Not commissioned; externally peer reviewed.

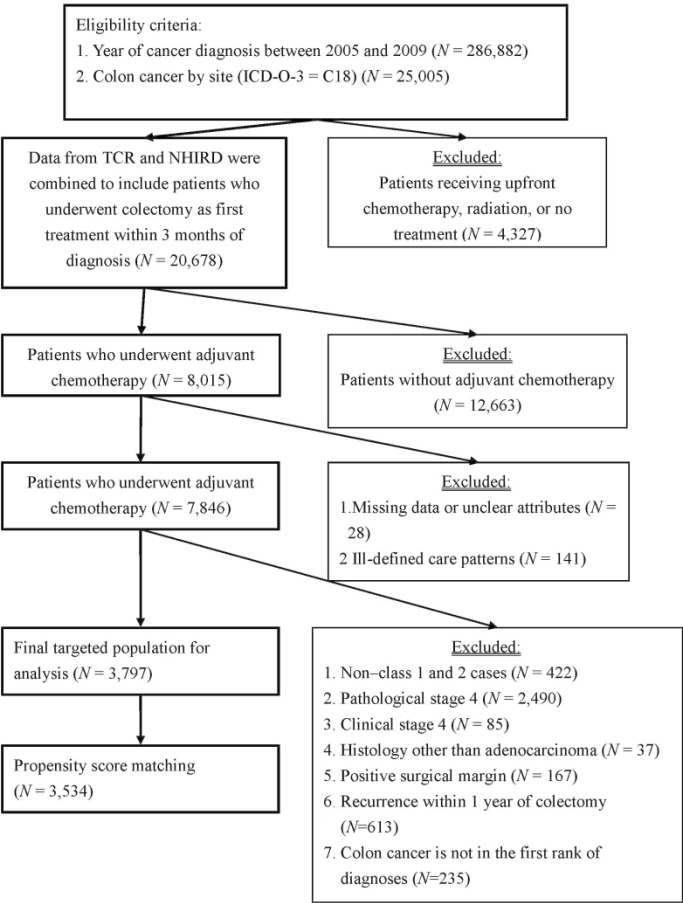
Data sharing statement: Additional unpublished data are not publicly available. The authors are authorized to use the data in this study; however, we do not own the datasets and cannot prevent access to them. All requests for data access must be approved by the Department of Statistics, Ministry of Health and Welfare (Taiwan). Researchers who are interested in the data may also apply to the Department of Statistics, Ministry of Health and Welfare (Taiwan) by contacting Ms. Wu Tzu-Hui (stcarolwu@mohw.gov.tw) or Mr. Zongying Lin (st-zylin@mohw.gov.tw).

Author contributorship statement

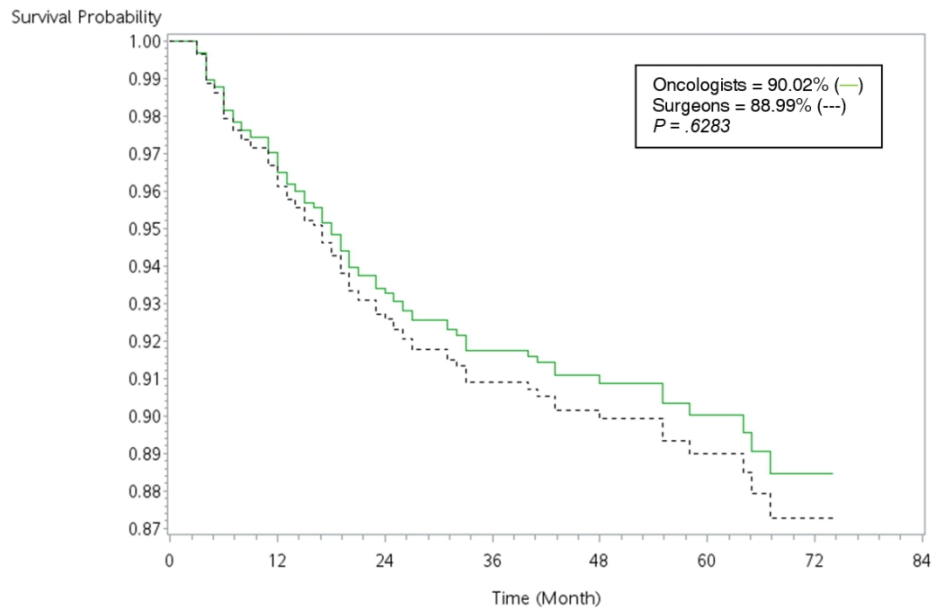
- Conceptualization: CIH, RNK
- Data curation: CCL, RNK.
- Formal analysis: CCL, HYT
- Funding acquisition: KPC
- Investigation: CIH
- Methodology: CIH, RNK
- Resources: RNK, KPC
- Software: CCL, HYT
- Supervision: RNK
- Validation: RNK, CCL, HYT
- Writing - original draft: CIH

Writing - review & editing: CIH, RNK

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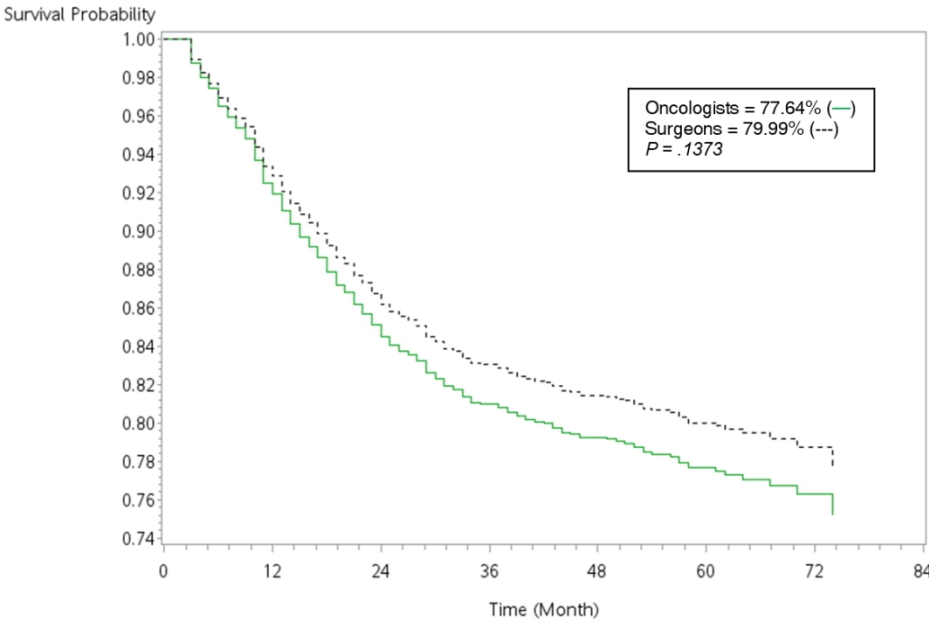


Flowchart of cohort selection
210x297mm (300 x 300 DPI)



Disease-free survival of patients with stage II cancer by different care paths

106x69mm (300 x 300 DPI)



Disease-free survival of patients with stage III cancer by different care paths

106x69mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1, 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	(N/A)
		(c) Explain how missing data were addressed	Figure 1
		(d) If applicable, explain how loss to follow-up was addressed	(N/A)
		(e) Describe any sensitivity analyses	Table 3
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	(N/A)
		(c) Summarise follow-up time (eg, average and total amount)	(N/A)
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(b) Report category boundaries when continuous variables were categorized	8-10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	(N/A)
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

Differences in the Outcomes of Adjuvant Chemotherapy for Colon Cancer Prescribed by Physicians in Different Disciplines: a population-based study in Taiwan

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Keywords:	adjuvant treatment, medical specialization, professional boundaries, medical oncology, referral pattern

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Differences in the Outcomes of Adjuvant Chemotherapy for Colon Cancer Prescribed by Physicians in Different Disciplines: a population-based study in Taiwan

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Short title: Patient Survival and Care in Different Disciplines

Abstract

Objectives: One feature unique to the Taiwanese healthcare system is the ability of physicians other than oncologists to prescribe systemic chemotherapy. This study investigated whether the care paths implemented by oncologists and non-oncologists differ with regard to patient outcomes.

Setting: Data from the Taiwan Cancer Registry and National Health Insurance Database were linked to identify colon cancer patients who underwent colectomy as first treatment within three months of diagnosis and adjuvant chemotherapy between 2005 and 2009.

Participants and methods: Postoperative patients who underwent adjuvant chemotherapy were included in this study. The exclusion criteria included patients with stage-IV disease, a positive surgical margin, and early disease recurrence. Among the patients presenting with multiple primary cancers, we also excluded patients who were diagnosed with colon cancer but for whom this was not the first primary cancer. The variables included sex, age, comorbidities, disease stage, chemotherapy cycle, and changes in treatment regimen as well as the specialty of treatment providers and their case volume. Cox regression models and Kaplan-Meier analysis were used to examine differences in outcomes in the matched cohorts.

Results: We examined 3,534 patients who were prescribed adjuvant chemotherapy by physicians from different disciplines. In terms of 5-year disease-free survival, no significant difference was observed between the groups of oncologists or surgeons among patients with stage II (90.02% vs. 88.99%) or stage III (77.64% vs. 79.99%) diseases. Patients who were subjected to changes in their chemotherapy regimens presented recurrence rates higher than those who were not.

Conclusions: The discipline of practitioners is seldom taken into account in most series. This is the first study to provide empirical evidence demonstrating that the outcomes of colon cancer patients do not depend on the treatment path, as long as the selection criteria for adjuvant chemotherapy is appropriate. Further study will be required before making any further conclusions.

Keywords: medical specialization, professional boundaries, referral pattern, medical oncology, case volume

Strengths and limitations of this study:

- This is the first study to examine the differential outcomes of cancer patients under different care paths, which are of particular importance in countries where adjuvant chemotherapy prescribed by physicians from different disciplines is the norm.
- We excluded many ineligible patients based on strict analysis criteria, and used propensity score matching to reduce the bias of confounding factors between two groups.
- The study design links two large national data sets covering a large number of patients with records related to long-term follow-up.
- The primary limitation of this study was our inability to obtain data pertaining to variations in dose intensity across providers and clinical information of patients.

Introduction

Shared care refers to the joint participation of physicians in the planning of patient care. This approach has been shown to improve cancer outcomes by helping to coordinate care to ensure the timely administration of adjuvant chemotherapy and thereby extend survival^{1,2}. Innovations in healthcare have resulted in highly specialized treatment regimes. For example, coronary artery bypass grafts performed by cardiothoracic surgeons have been replaced with percutaneous catheterization intervention performed by cardiologists³. This has led to the blurring of professional boundaries, as discussed by the American Society of Gynecologic Oncology⁵. Another situation is the long-simmering conflict between breast surgeons or radiologists over who should perform an ultrasound or stereotactic biopsies⁶. These disputes demonstrate the interprofessional boundary changes that have occurred in the healthcare workforce⁷.

In most western countries, physicians stay close to their areas of specialization and rarely violate interprofessional boundaries⁸. Surgeons and radiation oncologists play distinct roles in cancer treatment. Medical oncologists are a subspecialty dedicated to the “total management” of patients with cancer and tasked with coordinating a multidisciplinary approach from initial diagnosis through cure to end-of-life care⁹. Nurses prescribing medication is another example of the permeable role boundary of oncologists^{10,11}. The literature indicates that a reluctance on the part of surgeons to refer patients to oncologists or the disparities in receipt of adjuvant therapy has to do with the age and race of patients as well as their expressed preferences with regard to chemotherapy^{8,12}. In Taiwan, chemotherapy is reimbursed irrespective of the specialty of the provider. It has been assumed that this provides a financial incentive for the horizontal substitution of surgeons in performing the tasks normally assumed by oncologists. However, differences in outcomes among patients treated by different subspecialists must be elucidated before addressing this issue.

The formidable gastrointestinal side effects of chemotherapy and neutropenic fever have been greatly alleviated through the adoption of more efficient antiemetics and granulocyte colony stimulation factor. These medical advances have improved outcomes and facilitated the administration of chemotherapy, which has in turn opened the door to practitioners in other disciplines to move into areas conventionally regarded as the “turf”

of oncologists. When neutropenia or infection is encountered after chemotherapy, the doses can be reduced or the schedule delayed; however, these changes tend to undermine tumor response due to a compromised dose intensity. Moreover, regimen changes in the form of omissions or replacement with new agents can also affect survival benefits ¹³⁻¹⁶. The aforementioned skills and knowledge all fall within the discipline of oncology. Thus, the segregation of oncologists from the multidisciplinary team approach represents a deprofessionalization of oncologists as well as an example of poor collaboration and a threat to the quality of care.

Our objective in this study was to determine whether the care paths implemented by oncologists and non-oncologists differ with regard to patient outcomes. From a logistical perspective, two distinctive forms of in-house cancer care can be observed in Taiwan: 1) surgeons consulting with oncologists in the prescription of postoperative chemotherapy, and 2) surgeons prescribing adjuvant chemotherapy and conducting follow-up. From a practical perspective, it is impossible to conduct randomized clinical trials to compare the differences in outcomes among patients following different care paths. The results of this study are of particular relevance in regions facing a shortage of oncologists, and in regions where there are concerns pertaining to the outcomes of patients receiving adjuvant treatment from clinicians other than oncologists.

Materials and methods

Study Population

The sample included patients who were first diagnosed with colon cancer according to the American Joint Committee on Cancer (AJCC) Stages I–III (ICD-0-3 = C18) between January 2005 and December 2009. All participants had undergone colectomy, as verified by the Taiwan Cancer Registry (TCR). The data was linked to the National Health Insurance Research Database (NHIRD) for follow up between Jan. 2005 and December 2012. Patients with pre-existing cancer and those younger than 20 years were excluded from analysis.

Data Sources

This study linked population-based data collected from two databases in Taiwan: the Taiwan Cancer Registry (TCR) and the National Health Insurance Research Database (NHIRD). The TCR collects cancer-specific data, including cancer type, cancer stage,

surgical margin, and details of the surgical procedures used. The data are abstracted into a standard report form by trained cancer registrars at each hospital, before being submitted with supporting medical records and passed through a computerized logic check. From the NHIRD, we retrieved the patient ID, date of ambulatory or inpatient care, disease classification codes (ICD-9-CM codes), physician ID, physician specialty, hospital ID, procedures performed (surgical and nonsurgical), and medications prescribed in each case. The two databases were linked to identify cases of cancer recurrence. The IDs of the patients, physicians, and hospitals were all encrypted using the same algorithm to enable the cross-linking of data, while protecting privacy.

Patient Selection and Variables

Postoperative care paths were determined according to whether adjuvant chemotherapy administration and follow-up were performed by oncologists (path 1) or surgeons (path 2) until disease recurrence. The adjuvant chemotherapy regimen included either single-agent fluorouracil (5FU) or in combination with or without leucovorin and oxaliplatin. Any cases of other oral chemotherapy, unconventional regimens, and off-label usages were excluded.

To avoid the misclassification of adjuvant therapy, we considered only chemotherapy prescribed within a designated period. The period began after curative colectomy and ended 1) on the claims date after which no new treatment for colon cancer was received within 3 months, including surgery, chemotherapy, and radiation; 2) at the time of cancer recurrence; or 3) 12 months after surgery, whichever occurred first. Differentiating salvage chemotherapy for recurrence after adjuvant chemotherapy from true upfront chemotherapy in early recurrence (within 1 year of diagnosis) can be fraught with ambiguities. Thus, we adopted a strict criterion of ineligibility for all patients presenting early recurrence, which resulted in the exclusion of 613 patients from analysis. We also excluded 235 patients who were diagnosed with colon cancer but for whom this was not the first primary cancer (in the sequence of malignant and non-malignant neoplasms over the lifetime of the patient). The recommendations for chemotherapy were derived from clinical trials and guidelines outlined by Roswell Park, NSABP C-04^{17 18}, the Mayo Clinic^{18 19}, and the Mosaic regimen²⁰⁻²². A change in the regimen was defined as either the addition of a new chemotherapeutic agent or the removal of an existing agent from the original protocol.

The patient’s sex, age, stage of cancer, comorbidities, and history of regimen changes were used for matching, and were also controlled in Cox regression models. The designation of comorbidity was based on a version of the National Cancer Institute (NCI) Comorbidity Index, in which cases are classified according to comorbidity scores (i.e., 1, 2, or ≥ 3)²³. The case volume of physicians was controlled by counting the annual number of patients newly diagnosed with colon cancer. Recurrence was defined as a metastatic or recurrent disease before or after the completion of adjuvant treatment or within the follow-up period (>12 months). Cases of recurrence were defined using diagnostic codes (ICD 9 codes: 196.0–3, 196.5–6, 196.8–9, 197.0–8, 198.0–8, 199.0–1) or the implementation of a new treatment modality (e.g., surgery or radiotherapy) before the end of a cycle of adjuvant chemotherapy or three months or more after the completion of this adjuvant chemotherapy. Patients with secondary malignancies were excluded from the analysis. Disease-free survival (DFS) was defined as the time between colectomy and disease recurrence. Billing codes were used to assign patients to the surgeon who performed the definitive surgery and prescribed systemic chemotherapy. For the oncological care path, patients were assigned to the medical oncologist who billed for most of the visits and oversaw adjuvant chemotherapy within one year after colectomy. The case volume of the treatment provider was defined in terms of the number of patients on which the surgeon operated or who received systemic chemotherapy or care in a given year, as determined in quartiles of case volume (i.e., $< 25\%$, $25\text{--}50\%$, $51\text{--}75\%$, $> 75\%$).

Statistical Analysis

Descriptive statistics were used to evaluate baseline characteristics. We adopted propensity score methods similar to those described in previous studies^{24 25} to create a cohort of matched patients (i.e., sharing similar characteristics). The scores were calculated using logistic regression to estimate the probability of each patient receiving adjuvant chemotherapy on the basis of sex, age, stage, co-morbidities, and change in regimen. Patient cohorts on both paths were matched using a greedy-matching algorithm to formulate a 1:1 case-control match ratio using calipers with a width of < 0.2 standard deviations of the logit of propensity scores. The degree of balance in characteristics was compared using the Mantel-Haenszel test and generalized estimating equation (GEE)

regression. The association between various care paths and patient DFS was examined using the Cox proportional hazards model. The results are reported as hazard ratios (HRs) in conjunction with 95% confidence intervals. The Kaplan–Meier method was used to estimate the DFS of patients with stage II and stage III colon cancer. We performed a log-rank test to test the difference in DFS between the care paths of oncologists and surgeons. All statistical tests were two-sided, and a computed p -value < 0.05 was considered significant.

Patient and public involvement

No patients or members of the public were involved in the design or implementation of this study. Patients and the general public will be informed of the study results via peer-reviewed journals.

Results

A total of 25,005 patients with primary colon cancer were identified from the TCR data. Among these patients, 20,678 had undergone colectomy surgery. We further limited the cohort to stage I–III, class 1 and 2 patients with a histology of adenocarcinoma who had undergone postoperative adjuvant chemotherapy (Fig. 1). This left a total of 3,534 matched patients eligible for analysis. The proportions of men and women were 54.2% and 45.8%, respectively (Table 1). Among them, 50.5% of patients were older than 60 years and 23.8% were elderly patients (>70 y/o). Patients with stage II and III colon cancer accounted for 26.1% and 72.5% of all cases, respectively. Of these patients, 59.1% had an NCI comorbidity score of 1 or 2.

A total of 1,767 patients received care from professionals in each discipline. After matching, no statistical differences were observed between patients receiving care from different professionals, in terms of sex, disease stage, comorbidities, or adjuvant chemotherapy (Table 1). Surgeons were slightly more likely than oncologists to change the treatment regimen ($p = .060$). A greater proportion of patients received postoperative chemotherapy from low-volume surgeons than from low-volume oncologists ($<25\%$: 34.0% vs 14.3%; 25–50%: 31.9% vs 17.1%, respectively, $p < .0001$).

As shown in Table 2, care paths did not have a significant influence on recurrence. Stage III colon cancer ($p < .0001$), NCI score 3+ ($p = .029$), and more cycles of adjuvant chemotherapy ($p = .027$) were factors associated with a higher likelihood of disease recurrence. Patients who underwent changes in their chemotherapeutic agents had a higher recurrence rate than did patients who maintained the same regimen ($p < .0001$).

We also conducted sensitivity analysis to examine the impact of treatment paths on recurrence among patients with stage II and stage III colon cancer (Table 3). We observed no significant differences between the care paths in terms of recurrence. Changes in chemotherapy regimen were strongly associated with disease recurrence among patients in stage II (HR = 5.97, $p < .0001$) as well as those in stage III (HR = 2.49, $p < .0001$).

In terms of disease-free survival (DFS), no statistical differences were observed in the outcomes of stage-II or stage-III patients who followed different care paths (Fig. 2 and Fig. 3). The 5-year DFS rates in patients in stage II and stage III who received care from oncologists and surgeons were 90.02% versus 88.99% and 77.64% versus 79.99% ($p = .628$ and $p = .137$, respectively). Patients with stage-I colon cancer were excluded from analysis due to their favorable prognosis and relatively small sample size.

Discussion

The number of cases of colon cancer newly diagnosed in Taiwan was 9,584 in 2005 and 15,140 in 2013 ²⁶. In the 1990s, adjuvant chemotherapy for colon cancer was shown to improve survival ^{17 27}. At present, adjuvant chemotherapy for high-risk patients with stage II and stage III colon cancer is the standard. Surgeons in Taiwan typically prescribed adjuvant treatment themselves or refer the patient to an oncologist.

To the best of our knowledge, this is the first study to investigate whether the care paths implemented by oncologists and non-oncologists differ in terms of patient outcomes. We observed no difference in DFS despite differences in the care paths (Figs. 2 and 3). A similar result was observed in two early retrospective cohort studies that compared patient outcomes among different disciplines. The study by Silber applied a research design similar to that of the current study. They hypothesized that patients would benefit more (in terms of postoperative survival) when receiving chemotherapy from a medical oncologist rather

than a gynecologic oncologist. Nonetheless, the two groups of patients presented equal survival results. They explained that their results could perhaps be attributed to the imperfect measurement of chemotherapy and the assignment of providers²⁸. Earle reported that after adjusting for surgeon types and patient characteristics, gynecologic oncologists and general gynecologists achieved outcomes that were marginally superior to those of general surgeons. However, the details and jurisdiction of specialists in chemotherapy were not discussed. In addition, characterizing chemotherapy using a variable of all-or-none activity identified in billing claims tends toward oversimplification and can be detrimental to overall findings²⁹. Compared with the designs used in the aforementioned studies, the present study included more details pertaining to the administration of chemotherapy.

Our results indicate that changes in regimen or dose are significantly associated with disease recurrence. Patients who were prescribed chemotherapy by surgeons underwent more regimen changes than did those who were prescribed chemotherapy by oncologists. Nonetheless, the survival of patients who were under the care of surgeons was no worse, as one may intuitively infer. Nonetheless, our study design cannot be used to determine whether surgeons made more change regimens, or to characterize the outcomes in cases where changes were made. We included regimen changes in our statistical models to control for confounding factors related to regimen changes, which are not necessarily observable in our data. We also conducted sensitivity analysis that included only patients who had not undergone regimen changes (Table 2). Our results revealed no statistical differences in disease recurrence among patients treated by oncologists or surgeons. The actual implications of these findings remain unclear, due to the fact that clinical information of the patients and details of the chemotherapy they received are unknown.

We also determined that the two paths were very similar in terms of the number of chemotherapy cycles (mean: 11.2 vs. 11.3, $p = 1.00$). This differs from the report by Silber, in which it was reported that medical oncologists prescribed chemotherapy for longer durations than did gynecologic oncologists. Anecdotal evidence suggests that medical oncologists may be referred a larger proportion of patients with a refractory disease requiring more courses of salvage treatment. A wider range of cycles may stem from the various regimens employed under various treatment paradigms. We employed the unit of weeks from the billing data, which is less satisfactory than the unit of real cycles. Nonetheless, neither Silber nor we could verify the assumption that chemotherapy prescribed through dissimilar in-house logistics affects survival.

We found that the case volume of patients managed by the health provider was not associated with disease recurrence. This contradicts the findings of previous studies, which reported a positive association between the volume of patients and colorectal cancer outcomes^{30 31}. However, colorectal surgery is a low-risk procedure, such that the incidence of incomplete surgical staging is lower than that observed in gynecological malignancies³². The results in most previous studies were in terms of short-term postoperative mortality and length of stay or costs. In those studies, adjuvant chemotherapy was seldom discussed³³. It was not possible to compare most of the studies directly, due to differences in volume definitions and outcome measures^{34 35}. In this study, the provider's patient volume was not associated with recurrence; however, we found that 65.9% of patients who received chemotherapy from surgeons were treated by professionals with low case volumes ($\leq 50\%$). Conversely, we found that 68.5% of patients who received chemotherapy from oncologists were treated by professionals with high case volumes ($> 50\%$). One previous study reported a 5% improvement in survival for every additional patient shared between surgeons and oncologists². However, these findings seem to imply a certain degree of spillover. When surgeons reached the maximum number of patients they could treat, some patients were referred to or voluntarily went to oncologists. One study on ovarian cancer reported that a surgeon's volume of patients is not predictive of survival; however, a referral to a medical oncologist (or lack thereof) was a strong predictor³⁶. The reasons for referring or not referring patients to oncologists remain to be investigated, particularly within a fee-for-service payment system³⁷.

Previous studies have shown that adherence to clinical guidelines in the administration of cancer treatment would have the same effect on survival, regardless of the specialty of the practitioner^{30 38}. Nonetheless, adherence to clinical guidelines could be expected to promote the trespassing of professional boundaries. Boundary blurring can be affected by any number of factors, such as culture, financial and nonfinancial incentives, the scope of work, knowledge, and skills, role and identity, and power status^{7 37 39-41}. Collaboration between disciplines has numerous benefits in terms of patient outcomes. Nonetheless, in Taiwan, the status of medical oncologists has been devalued despite international recognition of their contributions⁴².

This study has a number of limitations. First, randomized controlled trials are the most reliable means of obtaining evidence in the field of medicine; however, conducting a prospective randomized trial to compare the outcomes of patients undergoing different care paths would be impossible. Furthermore, cross-boundary work is not a major concern in

healthcare systems outside Taiwan. The only related retrospective studies have focused on the management of ovarian cancer, which has for decades involved a power struggle in the American Gynecology Society^{5 43}. Second, we were unable to identify other influential factors, such as variations in dose intensity, the number of cycles across providers, the preferences of patients, the physical frailty of patients, or treatment complications. To mitigate the potential confounding effects of changes in the treatment regimen, we performed sensitivity analysis in which 221 patients who underwent regimen changes were excluded. The results were no different than those obtained using the entire sample. The dataset was the factor limiting our definitions of regimen changes. In the future, researchers should make an effort to take these unobserved factors into account. Third, we focused exclusively on patients who received adjuvant chemotherapy, based on strict eligibility criteria. This resulted in the exclusion of a substantial number of patients who underwent paths other than those involving surgeons or oncologists as well as those who experienced recurrence within one year.

Conclusions

The prescribing of systemic chemotherapy by non-oncologists is a common practice in the single-payer global healthcare system in Taiwan. This is the first study to address the fundamental question of whether the discipline of the care provider affects patient outcomes. Our analysis does not favor any path of care and our findings indicate no difference in patient survival, regardless of who oversaw the administration of chemotherapy. Nonetheless, one must not jump to any conclusions at this point with regard to the blurring of professionalism boundaries. Moreover, these findings are not applicable to other malignancies or other disease stages. Further study using outcome measures other than survival time should be conducted in the future.

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Figure captions

- Fig. 1. Flowchart of cohort selection from 2005 to 2009
- Fig. 2. Disease-free survival of patients with stage II cancer by different care paths
- Fig. 3. Disease-free survival of patients with stage III cancer by different care paths

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Tables

Table 1 Baseline characteristics of colon cancer patients following different care paths

Characteristics	Before propensity score matching				After propensity score matching*			
	Oncologist (N=1767) N (%)	Surgeon (N=2030) N (%)	Standardized difference, %	P value	Oncologist (N=1767) N (%)	Surgeon (N=1767) N (%)	Standardized difference, %	P value
Characteristics								
Sex				0.12				0.11
Male	935 (52.9)	1125 (55.4)	5.0		935 (52.9)	982 (55.6)	5.3	
Female	832 (47.1)	905 (44.6)			832 (47.1)	785 (44.4)		
Age, year								
Mean(SD)	59.14 (12.4)	59.76 (12.7)	4.9	0.13	59.14 (12.4)	59.99 (12.5)	4.9	0.04
<50	372 (21.1)	405 (20.0)	2.7		372 (21.1)	337 (19.1)	4.9	
50-60	523 (29.6)	582 (28.7)	2.0		523 (29.6)	516 (29.2)	0.9	
61-70	482 (27.3)	529 (26.1)	2.8		482 (27.3)	461 (26.1)	2.7	
>70	390 (22.1)	514 (25.3)	7.6		390 (22.1)	453 (25.6)	8.4	
Stage				0.07				0.17
I	24 (1.4)	29 (1.4)	0.6		24 (1.4)	25 (1.4)	0.5	
II	481 (27.2)	493 (24.3)	6.7		481 (27.2)	440 (24.9)	5.3	
III	1262 (71.4)	1508 (74.3)	6.4		1262 (71.4)	1302 (73.7)	5.1	
NCI comorbidity score				0.84				0.96
0	523 (29.6)	564 (27.8)	4.0		523 (29.6)	495 (28.0)	3.5	
1	641 (36.3)	765 (37.7)	2.9		641 (36.3)	668 (37.8)	3.2	
2	376 (21.3)	472 (23.3)	4.7		376 (21.3)	403 (22.8)	3.7	
3+	227 (12.8)	229 (11.3)	4.8		227 (12.8)	201 (11.4)	4.5	
Adjuvant Chemotherapy								
Numbers of cycles								
Mean(SD)	11.5 (6.2)	11.4 (7.1)	0.8	0.81	11.2 (6.2)	11.3 (7.1)	0.4	1.00
Change in regimen				0.06				0.06
No	1670 (94.5)	1889 (93.1)			1670 (94.5)	1643 (93.0)		
Yes	97 (5.5)	141 (6.9)	6.0		97 (5.5)	124 (7.0)	6.3	
Providers' case volume				<.0001				<.0001
<25%	253 (14.3)	695 (34.2)	47.8		253 (14.3)	601 (34.0)	47.3	
25-50%	303 (17.1)	644 (31.7)	34.4		303 (17.1)	563 (31.9)	34.7	
51-75%	525 (29.7)	426 (21.0)	20.2		525 (29.7)	370 (20.9)	20.3	
>75%	686 (38.8)	265 (13.1)	61.5		686 (38.8)	233 (13.2)	61.1	
Recurrence								

	Before propensity score matching				After propensity score matching*			
	Oncologist (N=1767) N (%)	Surgeon (N=2030) N (%)	Standardized difference, %	P value	Oncologist (N=1767) N (%)	Surgeon (N=1767) N (%)	Standardized difference, %	P value
No	1475 (83.5)	1704 (84.9)			1475 (83.5)	1491 (84.4)		
Yes	292 (16.5)	326 (16.1)			292 (16.5)	276 (15.6)		
Disease-free survival, month								
Mean(SD)	46.91 (19.2)	47.43 (19.2)			46.91 (19.2)	47.65 (19.1)		
Median(IQR)	45 (31-63)	47 (31-63)			45 (31-63)	47 (31-64)		

Abbreviations: SD, standard deviation; IQR, interquartile range; DFS, disease-free-survival; NCI, National Cancer Institute.
*Variables used for propensity score matching included sex, age, stage, 12 comorbid conditions of NCI comorbidity index, and history of regimen changes.
The standardized differences of the 12 comorbid conditions were between 0.3 and 4.6 in un-matched data and between 0 and 4.5 in matched data (data not shown).
P-values were obtained using the Mantel-Haenszel test for categorical variables and generalized estimating equations (GEE) regression for continuous variables.

Table 2. Disease recurrence categorized by clinical characteristics of patients, treatments, care paths, and the case volume of primary care providers (Cox regression models)

	Overall (N=3534)			No change regimens (N=3313)			Change regimens (N=221)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Characteristics									
Sex									
Male	Ref			Ref			Ref		
Female	0.83	(0.70 -0.98)	0.025	0.83	(0.69 -0.99)	0.042	0.77	(0.47 -1.26)	0.297
Age(years)									
<50	Ref			Ref			Ref		
50-60	1.05	(0.83 -1.34)	0.679	1.11	(0.85 -1.44)	0.458	0.78	(0.42 -1.45)	0.426
61-70	0.93	(0.72 -1.20)	0.561	1.04	(0.79 -1.37)	0.786	0.39	(0.18 -0.84)	0.016
>70	0.96	(0.74 -1.25)	0.741	0.99	(0.74 -1.32)	0.943	0.94	(0.48 -1.85)	0.862
Stage									
I	1.02	(0.41 -2.53)	0.960	0.72	(0.23 -2.27)	0.569	2.32	(0.47 -11.4)	0.299
II	Ref			Ref			Ref		
III	2.05	(1.63 -2.59)	<.0001	2.21	(1.73 -2.82)	<.0001	1.06	(0.53 -2.13)	0.862
NCI score									
0	Ref			Ref			Ref		
1	1.06	(0.86 -1.31)	0.570	0.97	(0.77 -1.22)	0.780	1.77	(0.96 -3.26)	0.067
2	1.11	(0.87 -1.41)	0.421	1.04	(0.80 -1.34)	0.794	1.66	(0.78 -3.53)	0.186
3+	1.37	(1.03 -1.82)	0.029	1.25	(0.92 -1.68)	0.150	2.89	(1.19 -7.03)	0.019
Adjuvant Chemotherapy									
Numbers of cycles	1.01	(1.00 -1.03)	0.027	1.01	(1.00 -1.02)	0.133	1.03	(0.99 -1.08)	0.101
Change in regimen									
No	Ref			—			—		
Yes	2.75	(2.15 -3.52)	<.0001	—			—		
Care paths									
Oncologists	Ref			Ref			Ref		
Surgeons	0.88	(0.73 -1.05)	0.148	0.87	(0.72 -1.06)	0.165	0.94	(0.56 -1.59)	0.820
Providers' case volume									
<25%	Ref			Ref			Ref		
25-50%	0.97	(0.77 -1.23)	0.829	0.98	(0.76 -1.26)	0.850	1.05	(0.55 -2.00)	0.889
51-75%	0.95	(0.74 -1.21)	0.667	0.94	(0.72 -1.21)	0.609	0.89	(0.44 -1.80)	0.740
>75%	0.94	(0.73 -1.21)	0.634	0.89	(0.68 -1.16)	0.381	1.66	(0.80 -3.45)	0.175

Table 3. Disease recurrence in patients with stage II or III colon cancer, categorized according to clinical characteristics, treatments, care paths, and case volume of primary care providers

Characteristics	Stage II (N=921)			Stage III (N=2564)		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex						
Male	Ref			Ref		
Female	1.17	(0.76 -1.79)	0.484	0.78	(0.65 -0.94)	0.009
Age(years)						
<50	Ref			Ref		
50-60	1.08	(0.57 -2.05)	0.806	1.00	(0.77 -1.30)	0.997
61-70	1.34	(0.71 -2.55)	0.370	0.86	(0.65 -1.13)	0.267
>70	1.43	(0.72 -2.83)	0.309	0.88	(0.66 -1.17)	0.384
NCI score						
0	Ref			Ref		
1	1.12	(0.64 -1.94)	0.693	1.05	(0.84 -1.32)	0.670
2	1.29	(0.68 -2.43)	0.441	1.10	(0.85 -1.44)	0.466
3+	1.61	(0.78 -3.33)	0.198	1.32	(0.97 -1.80)	0.083
Adjuvant chemotherapy						
Numbers of cycles	1.01	(0.98 -1.04)	0.509	1.02	(1.00 -1.03)	0.035
Change in regimen						
No	Ref			Ref		
Yes	5.97	(2.98 -11.97)	<.0001	2.49	(1.90 -3.26)	.0001
Care paths						
Oncologists	Ref			Ref		
Surgeons	1.00	(0.65 -1.55)	0.986	0.85	(0.69 -1.03)	0.102
Providers' case volume						
<25%	Ref			Ref		
25-50%	1.32	(0.74 -2.32)	0.346	0.94	(0.73 -1.23)	0.662
51-75%	0.48	(0.24 -0.96)	0.038	1.03	(0.79 -1.34)	0.854
>75%	1.16	(0.65 -2.05)	0.613	0.92	(0.69 -1.22)	0.554

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Funding acquisition: KPC

Investigation: CIH

Methodology: CIH, RNK

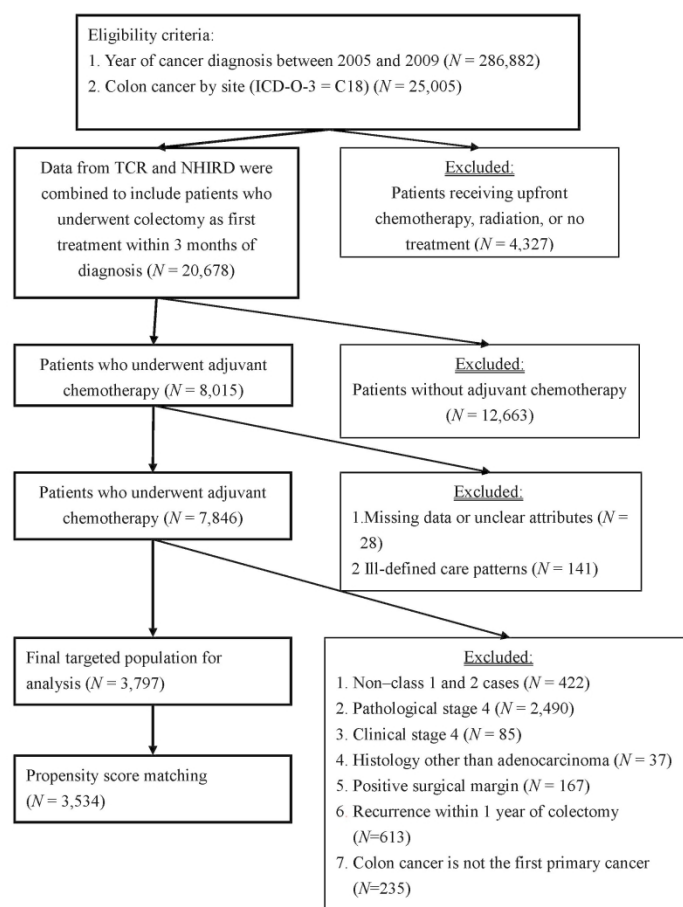
Resources: RNK, KPC

Software: CCL, HYT

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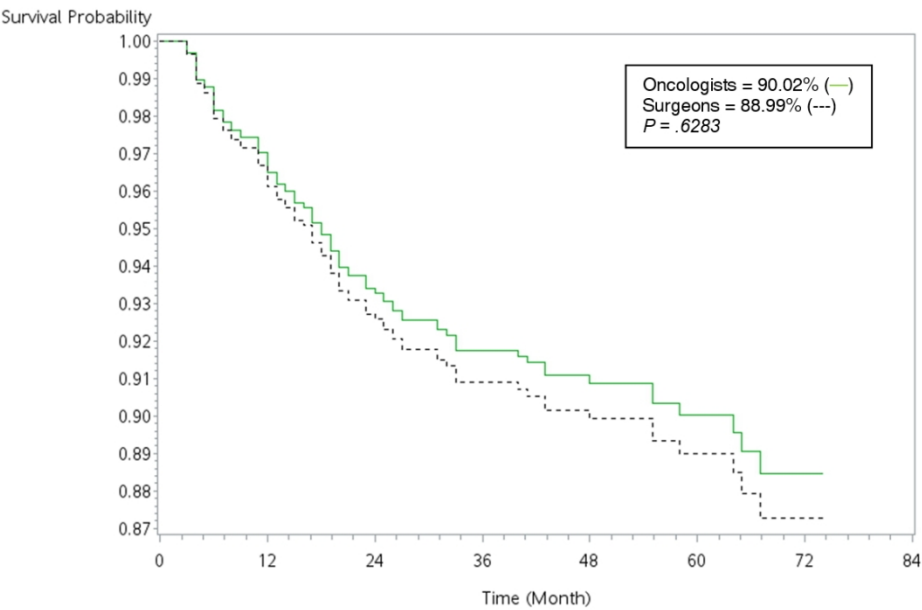
Supervision: RNK
Validation: RNK, CCL, HYT
Writing - original draft: CIH
Writing - review & editing: CIH, RNK

For peer review only



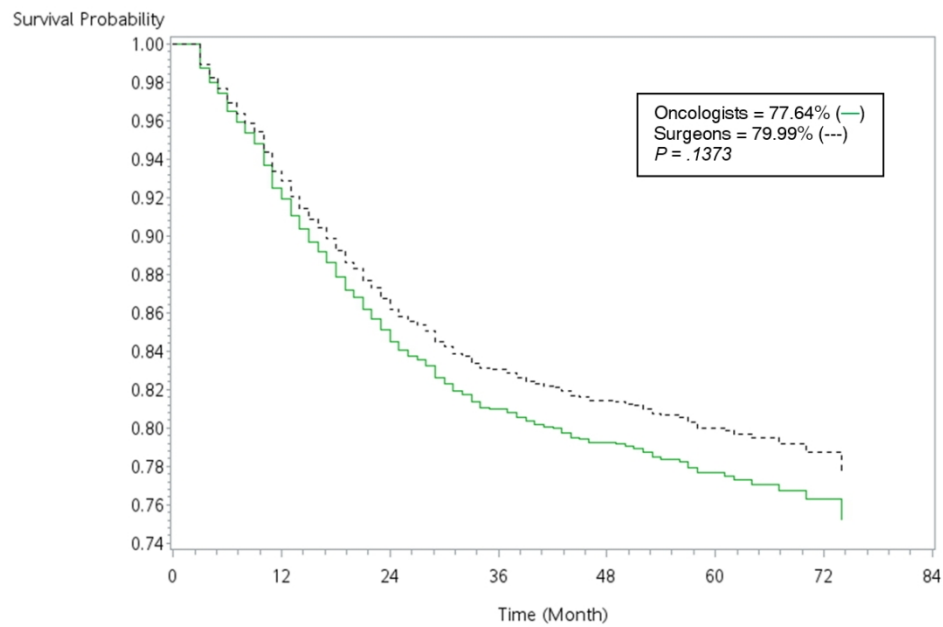
Flowchart of cohort selection from 2005 to 2009

210x297mm (300 x 300 DPI)



Disease-free survival of patients with stage II cancer by different care paths

106x69mm (300 x 300 DPI)



Disease-free survival of patients with stage III cancer by different care paths

106x69mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1, 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	(N/A)
		(c) Explain how missing data were addressed	Figure 1
		(d) If applicable, explain how loss to follow-up was addressed	(N/A)
		(e) Describe any sensitivity analyses	Table 3
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	6-7
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	(N/A)
		(c) Summarise follow-up time (eg, average and total amount)	(N/A)
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(b) Report category boundaries when continuous variables were categorized	8-10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	(N/A)
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.