The differences on efficacy of oxaliplatin in locally advanced colon cancer between mucinous and nonmucinous adenocarcinoma

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Abstract

Until now, it remains unclear how to best use the histological subtype in clinical practice. This study aimed to compare differences in the efficacy of postoperative chemotherapy among different histological subtypes of colon adenocarcinomas. Using the Surveillance, Epidemiology, and End Results-Medicare database, 51,200 patients with stage II or III primary colon carcinomas who underwent resection for curative intent between 1992 and 2008 were included. The survival benefit was evaluated using a Cox proportional hazards model, interaction analyses, and propensity score-matched techniques. There was no significant difference in survival for low-risk stage II mucinous adenocarcinoma (MA) or nonmucinous adenocarcinoma (NMA) between 5-FU and oxaliplatin-treated groups ($P = 0.387$ for MA, $P = 0.629$ for NMA). Patients with high-risk stage II NMA who received the oxaliplatin chemotherapy regimen had significantly improved cancer-specific survival (CSS) compared with the 5-FU group ($P = 0.004$), while those with MA saw no improvement ($P = 0.690$). For stage III tumors, patients with NMA who received the oxaliplatin chemotherapy regimen had significantly improved CSS compared with the 5-FU group ($P < 0.001$), while those with MA saw no improvement ($P = 0.300$). There were significant interactions between chemotherapy regimen and histological subtype. For patients with resected colon cancer who received 5-FU-based postoperative chemotherapy, oxaliplatin chemotherapy prolongs CSS for stage III and high-risk stage II NMA. Conversely, there was no similar improvement with addition of oxaliplatin for patients with stage III or stage II MA.

Introduction

The use of histological subtype as a classification system for colorectal cancer was introduced by the World Health Organization in 1979. Carcinomas are categorized as traditional adenocarcinomas, mucinous adenocarcinomas (MA), signet-ring cell carcinomas (SC), and other, more infrequent, types [1, 2]. MA is a histological subtype of colon cancer in which the neoplastic cells secrete extensive extracellular mucins that form more than 50% of the tumor volume [3]. SC tumors are comprised of more than 50% signet-ring cells in which the nucleus is pushed to the
periphery by intracytoplasmic mucins of colon cancer [4]. This classification of histological subtype is routinely carried out during the postoperative pathological examination of colon cancer. However, how to this histological subtyping should best be used to aid in the clinical practice remains unclear.

In clinical practice, decision making regarding whether give or which regimen give adjuvant therapy to patients with stage II tumors remains controversial [5, 6]. For patients with stage III disease, although the preferred treatment options are FOLFOX or CapeOx, the side effects of oxaliplatin are indisputable. It has been reported that oxaliplatin might not be applicable for all patients, specifically the elderly population [7, 8]. Thus, it is important to find prognostic and predictive features to help assist with selecting appropriate and beneficial adjuvant therapy for patients considered. Histological subtype is not considered in the decision making for colon cancer adjuvant therapy in either the National Comprehensive Cancer Network (NCCN) [9] or the European Society for Medical Oncology (ESMO) [10]. In addition, no research has proposed that histological subtype could have an influence on chemotherapeutic effects in colorectal cancer patients. As for other types of cancer, Sugawa et al. [11] found a difference in chemotherapy effects between different histological subtypes in cervical cancer, and Itaya et al. [12] found histology-dependent differences of chemosensitivity in nonsmall cell lung cancer.

The aim of this study was to compare the efficacy of postoperative chemotherapy among different histological subtypes of colon cancer. We then tried to find the most suitable postoperative chemotherapy regimens for both major histological subtypes of colonic adenocarcinoma.

| Table 1. Main effect variables in propensity score models. |
|------------------------------------------------------------|
| **NMA Patients in low-risk stage II**                     |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU compared with              |
| No-chemo                                                  |
| Gender, age at diagnosis, year at diagnosis, HCC         |
| risk score, race, marital status                          |
| **MA Patients in low-risk stage II**                     |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU compared with              |
| No-chemo                                                  |
| Gender, age at diagnosis                                  |
| **NMA Patients in high-risk stage II**                   |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU compared with              |
| No-chemo                                                  |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU plus oxaliplatin          |
| compared with 5-FU alone                                  |
| Gender, age at diagnosis, year at diagnosis, histological|
| grade, pT category, intestinal obstruction, HCC risk     |
| score, number of examined lymph node, level of education,|
| marital status, residence location                        |
| Age at diagnosis, year at diagnosis, pT category, number |
| of examined lymph node, median income, marital status    |
| **MA Patients in high-risk stage II**                    |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU compared with              |
| No-chemo                                                  |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU plus oxaliplatin          |
| compared with 5-FU alone                                  |
| Gender, age at diagnosis, year at diagnosis, pT category,|
| intestinal obstruction, HCC risk score, marital status,  |
| profit hospital                                           |
| Year at diagnosis, pT category, number of examined       |
| lymph node, profit hospital                              |
| **NMA Patients in stage III**                            |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU compared with              |
| No-chemo                                                  |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU plus oxaliplatin          |
| compared with 5-FU alone                                  |
| Gender, age at diagnosis, year at diagnosis, pT category,|
| pN category, intestinal obstruction, HCC risk score, level|
| of education, median income, race, marital status,       |
| residence location                                        |
| Age at diagnosis, year at diagnosis, pN category, number |
| of examined lymph node, level of education, median       |
| income, marital status                                    |
| **MA Patients in stage III**                             |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU compared with              |
| No-chemo                                                  |
| Variables that significantly related to the patients’    |
| probability of receiving 5-FU plus oxaliplatin          |
| compared with 5-FU alone                                  |
| Gender, age at diagnosis, year at diagnosis, pT category,|
| intestinal obstruction, HCC risk score, marital status   |
| Gender, age at diagnosis, year at diagnosis, pN category,|
| number of examined lymph node, median income, marital    |
| status                                                   |

MA, mucinous adenocarcinoma; NMA, nonmucinous adenocarcinoma; HCC, hierarchical condition categories; 5-FU, 5-fluorouracil.
Table 2. Clinicopathologic features of patients with different histological subtype.

|                | NMA          | MA          | P    |
|----------------|--------------|-------------|------|
| Gender         |              |             |      |
| Male           | 18,479 (42.0%) | 2665 (37.0%) | <0.001 |
| Female         | 25,519 (58.0%) | 4537 (63.0%) |      |
| Age at diagnosis, years |              |             |      |
| <70            | 6712 (15.3%)  | 1027 (14.3%) | 0.018 |
| 70–74          | 8840 (20.1%)  | 1411 (19.6%) |      |
| 75–79          | 10,066 (22.9%) | 1610 (22.4%) |      |
| 80–84          | 9205 (20.9%)  | 1563 (21.7%) |      |
| >84            | 9175 (20.9%)  | 1591 (22.1%) |      |
| Year at diagnosis |            |             |      |
| 1992–1996      | 8818 (20.0%)  | 1472 (20.4%) | 0.001 |
| 1997–2000      | 8393 (19.1%)  | 1421 (19.7%) |      |
| 2001–2004      | 14,410 (32.8%) | 2452 (34.0%) |      |
| 2005–2008      | 12,377 (28.1%) | 1857 (25.8%) |      |
| Histological grade |          |             |      |
| Well           | 2695 (6.1%)   | 658 (9.1%)   | <0.001 |
| Moderate       | 30,354 (69.0%) | 4470 (62.1%) |      |
| Poor           | 9707 (22.1%)  | 1475 (20.5%) |      |
| Undifferentiated | 503 (1.1%)   | 77 (1.1%)    |      |
| Unknown        | 739 (1.7%)    | 522 (7.2%)   |      |
| Postoperative chemotherapy |       |             | 0.396 |
| No             | 28,104 (63.9%) | 4563 (63.4%) |      |
| Yes            | 15,894 (36.1%) | 2639 (36.6%) |      |
| pT category    |              |             |      |
| T1             | 612 (1.4%)    | 57 (0.8%)    | <0.001 |
| T2             | 1504 (3.4%)   | 197 (2.7%)   |      |
| T3             | 35,209 (80.0%) | 5661 (78.6%) |      |
| T4a            | 4134 (9.4%)   | 787 (10.9%)  |      |
| T4b            | 2539 (5.8%)   | 500 (6.9%)   |      |
| pN category    |              |             | <0.001 |
| N0             | 24,869 (56.5%) | 4105 (57.0%) |      |
| N1a            | 6852 (15.6%)  | 1016 (14.1%) |      |
| N1b            | 6422 (14.6%)  | 992 (13.8%)  |      |
| N2a            | 3652 (8.3%)   | 604 (8.4%)   |      |
| N2b            | 2203 (5.0%)   | 485 (6.7%)   |      |
| Intestinal obstruction |       |             | <0.001 |
| No             | 34,677 (78.8%) | 5910 (82.1%) |      |
| Yes            | 9321 (21.2%)  | 1292 (17.9%) |      |
| Intestinal perforation |     |             | 0.463 |
| No             | 43,401 (98.6%) | 7112 (98.8%) |      |
| Yes            | 597 (1.4%)    | 90 (1.2%)    |      |
| HCC risk score |              |             | 0.001 |
| 1st quartile   | 11,575 (26.3%) | 1974 (27.4%) |      |
| 2nd quartile   | 10,846 (24.7%) | 1707 (23.7%) |      |
| 3rd quartile   | 10,892 (24.8%) | 1671 (23.2%) |      |
| 4th quartile   | 10,685 (24.3%) | 1850 (25.7%) |      |
| Number of examined lymph node |       |             | <0.001 |
| <12            | 20,747 (47.2%) | 3164 (43.9%) |      |
| ≥12            | 23,251 (52.8%) | 4038 (56.1%) |      |
| Level of education |         |             | 0.712 |
| 1st quartile   | 11,129 (25.3%) | 1845 (25.6%) |      |
| 2nd quartile   | 11,088 (25.2%) | 1828 (25.4%) |      |
| 3rd quartile   | 10,974 (24.9%) | 1772 (24.6%) |      |
| 4th quartile   | 8899 (20.2%)  | 1426 (19.8%) |      |
| Unknown        | 1908 (4.3%)   | 331 (4.6%)   |      |
with cancer. It is a population-based cancer registry covering approximately 28% of the US population across several disparate geographic regions [13]. Medicare is the primary health insurer for approximately 97% of the US population aged ≥ 65 years [14]. The unmentioned details of the database appeared elsewhere [15].

**Patient selection**

All Medicare-registered patients diagnosed with incident malignant primary colon cancer (SEER cancer site codes: 18.0, 18.2–18.9) between 1992 and 2008 in a SEER area were considered for study inclusion. The study contained two histological types defined by WHO International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), codes: MA (8480) and nonmucinous adenocarcinomas (NMA) (8010, 8020–8022, 8140–8141, 8144–8145, 8210–8211, 8220–8221, 8230–8231, 8260–8263).

Patients were selected who underwent primary tumor resection with likely curative intent within 180 days of diagnosis. The No-chemo group was designated as no claim of postoperative chemotherapy within 9 months after operation. The 5-FU group consisted of patients who only received 5-FU/capecitabine chemotherapy within 9 months of surgery. The oxaliplatin group comprised patients with any record of oxaliplatin plus 5-FU/capecitabine within 9 months of surgery.

**Table 3. Results of patients subjected to different chemotherapy regimens.**

|                     | Number of patients | HR          | 95% CI      | P         |
|---------------------|--------------------|-------------|-------------|-----------|
| **Low-risk stage II** |                    |             |             |           |
| No-PSM-NMA (No-chemo vs. 5-FU) | 5958 | 961 | – | 0.735 | 0.604–0.893 | 0.002 |
| No-PSM-NMA (5-FU vs. oxaliplatin) | – | 961 | 94 | 0.462 | 0.146–1.465 | 0.179 |
| No-PSM-MA (No-chemo vs. 5-FU) | 1025 | 178 | – | 0.934 | 0.582–1.496 | 0.775 |
| No-PSM-MA (5-FU vs. oxaliplatin) | – | 178 | 13 | 0.045 | 0.001–0.843.46 | 0.346 |
| PSM-NMA (No-chemo vs. 5-FU) | 961 | 961 | – | 0.939 | 0.726–1.214 | 0.629 |
| PSM-MA (No-chemo vs. 5-FU) | 176 | 176 | – | 1.399 | 0.690–2.598 | 0.387 |
| **High-risk stage II** |                    |             |             |           |
| No-PSM-NMA (No-chemo vs. 5-FU) | 13,951 | 2664 | – | 0.826 | 0.758–0.901 | <0.001 |
| No-PSM-NMA (5-FU vs. oxaliplatin) | – | 2664 | 260 | 0.529 | 0.348–0.804 | 0.002 |
| No-PSM-MA (No-chemo vs. 5-FU) | 2028 | 443 | – | 0.749 | 0.598–0.938 | 0.011 |
| No-PSM-MA (5-FU vs. oxaliplatin) | – | 443 | 37 | 0.792 | 0.289–2.172 | 0.649 |
| PSM-NMA (No-chemo vs. 5-FU) | 2662 | 2662 | – | 1.003 | 0.894–1.125 | 0.961 |
| PSM-MA (5-FU vs. oxaliplatin) | – | 260 | 260 | 0.529 | 0.348–0.804 | 0.004 |
| **Stage III** |                    |             |             |           |
| No-PSM-NMA (No-chemo vs. 5-FU) | 7843 | 8188 | – | 0.551 | 0.525–0.578 | <0.001 |
| No-PSM-NMA (5-FU vs. oxaliplatin) | – | 8188 | 1826 | 0.583 | 0.522–0.625 | <0.001 |
| No-PSM-MA (No-chemo vs. 5-FU) | 1287 | 1360 | – | 0.566 | 0.503–0.637 | <0.001 |
| No-PSM-MA (5-FU vs. oxaliplatin) | – | 1360 | 258 | 0.74 | 0.569–0.962 | 0.023 |
| PSM-NMA (No-chemo vs. 5-FU) | 7841 | 7841 | – | 0.554 | 0.527–0.581 | <0.001 |
| PSM-MA (5-FU vs. oxaliplatin) | – | 1819 | 1819 | 0.621 | 0.543–0.710 | <0.001 |
| PSM-MA (No-chemo vs. 5-FU) | 1287 | 1287 | – | 0.567 | 0.502–0.639 | <0.001 |
| PSM-MA (5-FU vs. oxaliplatin) | – | 252 | 252 | 0.837 | 0.598–1.173 | 0.300 |

PSM, propensity score matched; MA, mucinous adenocarcinoma; NMA, nonmucinous adenocarcinoma; HR, hazard ratio; CI, confidential intervals; 5-FU, 5-fluorouracil; No-chemo, without postoperative chemotherapy.
Patients were eliminated from the study population if they (1) received any preoperative adjuvant treatment; (2) received postoperative radiotherapy; (3) had prior noncolon cancer; (4) had incomplete histological subtype or pathological stage entries; (5) died within 30 days after tumor resection; (6) had stage I or stage IV tumors; (7) histological subtype was signet-ring cell carcinoma, as this population represented too small a sample size (0.9%).

**Variables**

Subjects were categorized by age at diagnosis, year of diagnosis, gender, race, marital status, residence (rural
or urban), median household income, level of education (percentage of people aged >25 years with <12 years of education), and the type of hospital in which they received care (teaching or nonteaching). To control for the effects of comorbidities, analyses were adjusted by the Centers for Medicare and Medicaid Services Hierarchical Condition Category (HCC) based on Medicare outpatient and inpatient claims for miscellaneous comorbidities within the 12 months before colon cancer diagnosis. The HCC risk score summarizes the healthcare problems and forecasts the future healthcare cost of a population compared with the average Medicare beneficiary [16].

Postoperative pathological stage was designated via the seventh edition of the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system [17]. Other covariates included histological grade, histological subtype, intestinal obstruction, intestinal perforation, and the number of lymph nodes examined.

**Statistical analysis**

The chi-square test was used to compare demographics and tumor characteristics between the different groups. In the univariate survival analysis, cancer-specific survival (CSS) was analyzed by the Kaplan–Meier method. Comparison of survival curves was carried out using the log-rank test. Because treatment choice estimates are likely confounded by factors related to treatment selection, a propensity score (PS)-matched analysis was performed to compare the effect of treatment on survival among patients of similar risk profiles as assessed by measured known confounders [18, 19]. Propensity score matching is a statistical procedure for reducing this bias by assembling a sample in which confounding factors are balanced between treatment groups. Univariate logistic regression was used to find factors related to treatment selection ($P < 0.05$). Multivariate logistic regression was used to estimate the propensity scores in each group (Table 1). The propensity score-matched sample would then be constructed using...

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**Figure 2.** Kaplan–Meier comparison of cancer-specific survival among patients who received different postoperative treatment stratified by histological subtype. (A) NMA in high-risk stage II (No-chemo vs. 5-FU); (B) MA in high-risk stage II (No-chemo vs. 5-FU); (C) NMA in high-risk stage II (5-FU vs. oxaliplatin); (D) MA in high-risk stage II (5-FU vs. oxaliplatin).
“psmatch2” software package in STATA 14.0. A Cox proportional hazards model was also used in the adjusted analysis. The covariates included all variables that were identified to be significantly related to survival in the univariate analysis.

All statistical analyses and graphics were performed using SAS 9.4 (SAS Institute, Cary, NC), STATA 14.0 software (STATA, College Station, TX), and PASW Statistics 20.0 software (SPSS, Inc., Somers, NY). For all analyses, a $P$ value < 0.05 was considered statistically significant.

Results

Patient characteristics

Selected 51,200 individuals were stratified into two analysis groups: NMA ($n = 43,998$) and MA ($n = 7202$). Demographic characteristics of patients are depicted in Table 2. Compared with NMA, MA was more common in women ($P < 0.001$), individuals aged >80 years ($P = 0.018$), year at diagnosis before 2004 ($P < 0.001$), well histological grade ($P < 0.001$), T1–T3 category ($P < 0.001$), N2 category ($P < 0.001$), nonintestinal obstruction ($P < 0.001$), number of examined lymph nodes $\geq 12$ ($P < 0.001$), white race ($P < 0.001$), widowed ($P = 0.006$).

Stage II patients were further divided into low-risk stage II and high-risk stage II groups. We designated the cohort of patients with high-risk stage II using features of poor prognosis referred to in the NCCN [9], including T4 tumors, poorly differentiated histology, bowel obstruction, bowel perforation, and inadequate sampled nodes ($<$12 lymph nodes). The number of patients and the results of each analysis and treatment chemotherapy effect analysis are summarized in Table 3.

CSS in low-risk stage II adenocarcinoma

There was a significant difference in survival for NMA patients with low-risk stage II cancer between the no-chemo and 5-FU groups ($P = 0.002$, Fig. 1A), while those with MA saw no difference ($P = 0.775$, Fig. 1B). There was no significant difference in NMA and MA patients
with low-risk stage II cancer between the 5-FU and oxaliplatin groups (Fig. 1C and D).

A PS-matched cohort was generated using related variables which may interfere with the chemotherapy decision (Table 1). The aforementioned general results were recalculated in the PS-match cohorts. There was no significant difference in survival for patients with low-risk stage II NMA between the no-chemo and 5-FU groups ($P = 0.629$, Fig. 1E), while those with MA again saw no difference ($P = 0.387$, Fig. 1F). Another PS-matched cohort was generated using related variables which may interfere with the choice of chemotherapy regimen. However, its sample size is too small to recalculate aforementioned results.

### CSS in high-risk stage II adenocarcinoma

There was a significant difference in survival for patients with high-risk stage II NMA between the no-chemo and 5-FU groups ($P < 0.001$, Fig. 2A), while those with MA again saw a difference ($P = 0.011$, Fig. 2B). Patients with NMA who received the oxaliplatin chemotherapy regimen had significantly improved CSS ($P = 0.002$, Fig. 2C) compared with the 5-FU group, while those with MA saw no improvement ($P = 0.649$, Fig. 2D).

Then, we used the PS-match cohorts to recalculate the aforementioned general results. There was no significant difference in survival for patients with high-risk stage II NMA between the no-chemo and 5-FU groups ($P = 0.961$, Fig. 3A), while those with MA again saw no difference ($P = 0.754$, Fig. 3B). Patients with NMA who received the oxaliplatin chemotherapy regimen had significantly improved CSS ($P = 0.004$, Fig. 3C).
Table 5. Univariate prognostic analysis stratified by histological subtype.

| NMA in stage III | HR  | 95% CI     | P   |
|------------------|-----|------------|-----|
| Age at diagnosis, years |     |            |     |
| <70              | 1   |            |     |
| 70–74            | 1.070 | 0.991–1.155 | 0.082 |
| 75–79            | 1.217 | 1.130–1.311 | <0.001 |
| 80–84            | 1.468 | 1.361–1.583 | <0.001 |
| >84              | 2.021 | 1.875–2.179 | <0.001 |
| Year at diagnosis |     |            |     |
| 1992–1996        | 1   |            |     |
| 1997–2000        | 1.000 | 0.934–1.070 | 0.989 |
| 2001–2004        | 0.925 | 0.870–0.984 | 0.014 |
| 2005–2008        | 0.850 | 0.794–0.910 | <0.001 |
| HCC risk score   |     |            |     |
| 1st quartile     | 1   |            |     |
| 2nd quartile     | 0.838 | 0.787–0.891 | <0.001 |
| 3rd quartile     | 0.905 | 0.850–0.964 | 0.002 |
| 4th quartile     | 1.117 | 1.050–1.189 | <0.001 |
| Number of examined lymph node |     |            |     |
| <12              | 1   |            |     |
| ≥12              | 0.890 | 0.851–0.930 | <0.001 |
| pT category      |     |            |     |
| T1               | 1   |            |     |
| T2               | 1.240 | 0.994–1.547 | 0.057 |
| T3               | 2.804 | 2.311–3.401 | <0.001 |
| T4a              | 4.124 | 3.375–5.039 | <0.001 |
| T4b              | 7.451 | 6.087–9.120 | <0.001 |
| Intestinal perforation |     |            |     |
| No               | 1   |            |     |
| Yes              | 2.259 | 1.928–2.648 | <0.001 |
| Intestinal obstruction |     |            |     |
| No               | 1   |            |     |
| Yes              | 1.549 | 1.473–1.629 | <0.001 |
| Marital status   |     |            |     |
| Single           | 1   |            |     |
| Married          | 0.793 | 0.733–0.858 | <0.001 |
| Widowed          | 1.007 | 0.930–1.091 | 0.864 |
| Others           | 0.926 | 0.802–1.070 | 0.299 |
| Chemotherapy regimen |     |            |     |
| 5-FU             | 1   |            |     |
| Oxaliplatin      | 0.583 | 0.522–0.652 | <0.001 |
| Histological grade |     |            |     |
| Well             | 1   |            |     |
| Moderate         | 1.264 | 1.123–1.422 | <0.001 |
| Poor             | 1.801 | 1.595–2.034 | <0.001 |
| Undifferentiated | 1.902 | 1.550–2.334 | <0.001 |
| Unknown          | 1.223 | 0.993–1.507 | 0.059 |
| Median income    |     |            |     |
| 1st quartile     | 1   |            |     |
| 2nd quartile     | 0.938 | 0.881–0.997 | 0.041 |
| 3rd quartile     | 0.905 | 0.850–0.963 | 0.002 |
| 4th quartile     | 0.858 | 0.803–0.918 | <0.001 |
| Unknown          | 1.027 | 0.919–1.148 | 0.639 |
| pN category      |     |            |     |
| N1a              | 1   |            |     |
| N1b              | 1.417 | 1.337–1.503 | <0.001 |
| N2a              | 2.000 | 1.877–2.131 | <0.001 |
| N2b              | 3.272 | 3.056–3.503 | <0.001 |

(Continues)
compared with the 5-FU group, while those with MA saw no improvement ($P = 0.690$, Fig. 3D). This result was also verified by a Cox proportional hazards model (Table 4 and 5).

An interaction analysis was performed between chemotherapy regimen (5-FU or oxaliplatin) and histological type for patients with high-risk stage II adenocarcinoma. No significant interaction effects were found in the test ($P = 0.750$).

**CSS in stage III adenocarcinoma**

The prognosis for patients with stage III NMA in the no-chemo group was significantly worse than the 5-FU group ($P < 0.001$, Fig. 4A). Similar results were also found for MA patients ($P < 0.001$, Fig. 4B). Patients with NMA who received the oxaliplatin chemotherapy regimen had significantly improved CSS ($P < 0.001$, Fig. 4C) compared with the 5-FU group. Likewise, we found a survival benefit for patients with stage III MA receiving oxaliplatin compared to the 5-FU group ($P = 0.023$, Fig. 4D).

The aforementioned results were recalculated in the PS-matched cohorts. The prognosis of patients with stage III MA was significantly worse than that of the 5-FU group ($P < 0.001$, Table 5).
NMA in the no-chemo group was significantly worse than in the 5-FU group \( (P < 0.001, \text{Fig. 5A}) \). Similar results were also seen for MA patients \( (P < 0.001, \text{Fig. 5B}) \). Patients with NMA who received the oxaliplatin chemotherapy regimen had significantly improved CSS \( (P < 0.001, \text{Fig. 5C}) \) compared with the 5-FU group. However, we did not find a similar survival benefit for patients with stage III MA between the oxaliplatin and 5-FU groups \( (P = 0.300, \text{Fig. 5D}) \). This result was also verified by a Cox proportional hazards model (Table 5 and 6). The result of the interaction analysis showed that there was a significant interaction effect seen in the test \( (P = 0.040) \).

**FOLFOX versus CapeOx**

We found no difference in survival between the FOLFOX and CapeOx group for NMA \( (HR: 0.817, 95\% \text{ CI: 0.190–3.518, } P = 0.786) \) and MA \( (HR: 0.042, 95\% \text{ CI: 0.001–92710.202, } P = 0.512) \) in high-risk stage II patients. Similar results were found for NMA \( (HR: 1.128, 95\% \text{ CI: 0.750–1.695, } P = 0.562) \) and MA \( (HR: 0.746, 95\% \text{ CI: 0.234–2.382, } P = 0.618) \) in stage III patients. Detailed information is shown in Table 7.

**Discussion**

Mucinous adenocarcinoma is a relatively common histological subtype of colon adenocarcinoma, yet the clinical significance of its histological designation remains unclear. The rate of MA was 14.1\% in our study and 20–30\% in previous studies \[20, 21\]. Moreover, other studies reported that MA occurred in 10–20\% cases of colon cancer \[22, 23\]. The reason may be that the definition of MA has not been consistent across studies \[24\]. In our study, MA was defined according to the MORPHOLOGY CODE of SEER (ICD-O-3: 8480). Most previous studies demonstrated worse survival in MA patients compared with NMA \[25, 26\]. However, this is contradicted by other research \[22\]. MA is more often discovered in the proximal colon \[27\], and in females \[23\], and it generally has a more
advanced stage at presentation [27]. Whether MA should be considered as an independent prognostic factor is still controversial. To the best of our knowledge, there is no difference in treatment prescribed between NMA and MA. At present, the main treatment for locally advanced colon cancer is curative resection plus chemotherapy.

Most of the benefit of postoperative chemotherapy is reported in the patients with stage III disease. The benefit of chemotherapy for stage II disease is very controversial. In our study, there was no significant difference in survival for NMA and MA patients with stage II cancer between the no-chemo and 5-FU groups. For patients with stage III, adjuvant chemotherapy after primary surgical treatment is usually recommended [28]. As would be expected, we found a survival benefit for MA and NMA patients with stage III receiving 5-FU compared to the no-chemo group.

Oxaliplatin is a platinum analogue that blocks DNA replication and transcription. It has been permitted in the European Union since 1999 and in the United States since 2002 [29, 30]. FOLFOX had proven to be highly efficient in treatment of gastrointestinal cancer, which had enabled significant progress in clinical oncology in recent years [31]. Studies have found that the 10-year OS of patients with stage III disease receiving FOLFOX was significantly increased compared with those receiving 5-FU alone [32]. However, oxaliplatin causes severe side effects which should not be ignored. These include peripheral neuropathy and gastrointestinal side effects. The primary safety concern with oxaliplatin use is peripheral neuropathy, a cumulative dose-related toxicity which affects 90% of all treated patients [33]. Incidence of grade 3 peripheral sensory neuropathy was 12.4% for patients receiving FOLFOX and only 0.2% for patients receiving 5-FU. Moreover, Andre et al. [34] found that neuropathy was still present in 15.4% of examined patients at 4 years post-treatment, suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients.

It is quite important to identify which patients could optimally benefit from oxaliplatin treatment. This study found that patients with locally advanced colon cancer whose histological type is NMA can benefit from

![Graphs showing cancer-specific survival comparison](image)
| Race          | HR    | 95% CI         | P    |
|---------------|-------|----------------|------|
| White         | 1     |                |      |
| Black         | 1.076 | 0.952–1.215    | 0.240|
| Asian         | 0.806 | 0.664–0.977    | 0.028|
| Others        | 0.975 | 0.821–1.157    | 0.771|
| Level of education | | | |
| 1st quartile  | 1     |                |      |
| 2nd quartile  | 1.041 | 0.939–1.154    | 0.445|
| 3rd quartile  | 1.148 | 1.025–1.286    | 0.017|
| 4th quartile  | 1.270 | 1.111–1.452    | <0.001|
| Gender        |       |                |      |
| Male          | 1     |                |      |
| Female        | 0.970 | 0.897–1.049    | 0.445|

| Chemotherapy regimen | HR    | 95% CI         | P    |
|----------------------|-------|----------------|------|
| 5-FU                 | 1     |                |      |
| Oxaliplatin          | 0.851 | 0.611–1.185    | 0.340|

| Year at diagnosis | HR    | 95% CI         | P    |
|-------------------|-------|----------------|------|
| 1992–1996         | 1     |                |      |
| 1997–2000         | 0.867 | 0.685–1.098    | 0.236|
| 2001–2004         | 0.939 | 0.755–1.167    | 0.570|
| 2005–2008         | 0.707 | 0.510–0.981    | 0.038|

| HCC risk score | HR    | 95% CI         | P    |
|----------------|-------|----------------|------|
| 1st quartile  | 1     |                |      |
| 2nd quartile  | 1.066 | 0.476–2.386    | 0.876|
| 3rd quartile  | 1.356 | 1.048–1.756    | 0.036|
| 4th quartile  | 1.663 | 1.259–2.193    | 0.001|

| Number of examined lymph node | HR    | 95% CI         | P    |
|------------------------------|-------|----------------|------|
| <12                          | 1     |                |      |
| ≥12                          | 0.705 | 0.596–0.834    | <0.001|

| pT category | HR    | 95% CI         | P    |
|-------------|-------|----------------|------|
| T1          | 1     |                |      |
| T2          | 1.066 | 0.476–2.386    | 0.876|
| T3          | 2.038 | 1.048–3.965    | 0.036|
| T4a         | 3.166 | 1.589–6.308    | 0.001|
| T4b         | 4.793 | 2.358–9.742    | <0.001|

| Intestinal perforation | HR    | 95% CI         | P    |
|------------------------|-------|----------------|------|
| No                     | 1     |                |      |
| Yes                    | 1.258 | 1.021–1.549    | 0.031|

| Marital status | HR    | 95% CI         | P    |
|----------------|-------|----------------|------|
| Single         | 1     |                |      |
| Married        | 0.846 | 0.624–1.148    | 0.284|
| Widowed        | 0.888 | 0.645–1.222    | 0.465|
| Others         | 1.561 | 0.951–2.560    | 0.078|

| Histological grade | HR    | 95% CI         | P    |
|--------------------|-------|----------------|------|
| Well               | 1     |                |      |
| Moderate           | 1.160 | 0.975–1.381    | 0.094|
| Poor               | 1.461 | 1.221–1.749    | <0.001|
| Undifferentiated   | 1.575 | 1.143–2.172    | 0.006|
| Unknown            | 1.209 | 0.887–1.649    | 0.231|

| Median income | HR    | 95% CI         | P    |
|---------------|-------|----------------|------|
| 1st quartile  | 1     |                |      |
| 2nd quartile  | 1.085 | 0.982–1.199    | 0.107|
| 3rd quartile  | 1.150 | 1.028–1.286    | 0.014|
| 4th quartile  | 1.155 | 1.006–1.326    | 0.041|

| pN category | HR    | 95% CI         | P    |
|-------------|-------|----------------|------|
| N1a         | 1     |                |      |
| N1b         | 1.286 | 1.025–1.614    | 0.030|
| N2a         | 2.176 | 1.718–2.756    | <0.001|
| N2b         | 3.046 | 2.381–3.897    | <0.001|

| Intestinal obstruction | HR    | 95% CI         | P    |
|------------------------|-------|----------------|------|
| No                     | 1     |                |      |
| Yes                    | 1.258 | 1.021–1.549    | 0.031|

| Marital status | HR    | 95% CI         | P    |
|----------------|-------|----------------|------|
| Single         | 1     |                |      |
| Married        | 0.846 | 0.624–1.148    | 0.284|
| Widowed        | 0.888 | 0.645–1.222    | 0.465|
| Others         | 1.561 | 0.951–2.560    | 0.078|

| pN category | HR    | 95% CI         | P    |
|-------------|-------|----------------|------|
| N1a         | 1     |                |      |
| N1b         | 1.286 | 1.025–1.614    | 0.030|
| N2a         | 2.176 | 1.718–2.756    | <0.001|
| N2b         | 3.046 | 2.381–3.897    | <0.001|

| Intestinal perforation | HR    | 95% CI         | P    |
|------------------------|-------|----------------|------|
| No                     | 1     |                |      |
| Yes                    | 1.443 | 0.705–2.955    | 0.316|

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In spite of this, we still could not clearly define a reason for our findings. However, we elaborated upon this phenomenon to provide some preliminary data for markers identifying the efficiency of oxaliplatin in MA, and it is important to continue researching its specific mechanism in future studies.

Our findings should be interpreted in the context of several limitations. The information on perineural, vascular, and lymphatic invasion was not available in the SEER-Medicare database. To the best of our best knowledge, no studies to date evaluated the impact of perineural, vascular, and lymphatic invasion on the sensitivity of oxaliplatin, and no definite conclusions could be made because of limited data. Therefore, more studies are necessary to address this problem more conclusively.

The nonavailability of the microsatellite instability (MSI) status in the SEER-Medicare database was a major limitation. It was reported that 27% of MA patients were in MSI-H status and only 12% of NMA patients were in the MSI-H status [35]. In addition, Kim reported the prognosis of MA associated with the MSI-H status [36]. It is well known that patients with MSI-H stage II colon cancer do not benefit from 5-FU therapy in survival [9]. In contrast, whether the MSI status can affect FOLFOX efficacy in stage III patients remains controversial. A previous study found no difference between pMMR and dMMR in survival of patients with stage III colon cancer undergoing FOLFOX adjuvant chemotherapy [37]. In contrast, another study indicated that survival was significantly higher in patients undergoing FOLFOX with dMMR tumors compared to those with pMMR tumors [38]. Whether the MSI status interacted with the influence of MA on the efficacy of FOLFOX needs to be better studied.

In addition, few patients were aged <65 years at the time of diagnosis in our study (3.2%), which may limit the application of these findings to younger patients with colon cancer. It was reported that the efficacy of oxaliplatin was poor for older adults [8]. Therefore, we took age into account when recruiting the population for the PS-Match analysis. Moreover, it could be also a major confounding point, in that MSI and mucinous patients seem more frequent in older population. Since that, it is important to continue researching this problem in future studies.

Finally, although both a PS-matched technique and a Cox proportional hazards model were used to eliminate known relevant confounders, the potential for confounding based on patients selection could not be eliminated completely, as it was a retrospective exploratory study. Further prospective study was needed to verify our findings in future.

In summary, for patients with resected colon cancer who received 5-FU-based postoperative chemotherapy, oxaliplatin chemotherapy prolongs CSS for patients with stage III and high-risk stage II NMA. Conversely, adding oxaliplatin to 5-FU in postoperative chemotherapy did not improve CSS for patients with stage III or high-risk stage II MA.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Consent

The manuscript was approved by SEER-Medicare for anonymity prior to submission for publication. Because the SEER-Medicare data are de-identified and are based on registry data, no prior informed consent was required.

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