OUTCOMES OF ADJUVANT CAPECITABINE THERAPY IN HIGH-RISK STAGE II COLON CANCER: A SINGLE-CENTER ANALYSIS FROM VIETNAM

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The optimal adjuvant chemotherapy for high-risk Stage II colon cancer remains debated. In Vietnam, capecitabine monotherapy is often chosen for its convenience and tolerability. In this retrospective study, 96 high-risk Stage II (pT3-4,N0,M0)patients underwent R0 resection at Vietnam National Cancer Hospital (2016 – 2019) and received capecitabine (1,250 mg/m² twice daily on days 1 – 14 of a 21-day cycle) for eight cycles. After a median follow-up of 60.6 months (range: 22 – 79), 5-year disease-free survival (DFS) was 89.5% and overall survival (OS) was 91.1%. In multivariate Cox analysis, lymphovascular/perineural invasion independently predicted poorer 5-year DFS (HR = 5.21; 95% CI: 1.02 – 26.55; p = 0.047), while both pathologic Stage IIC (pT4b) (HR = 6.98; 95% CI: 0.88 – 55.06; p = 0.009) and lymphovascular/perineural invasion (HR = 5.21; 95% CI: 1.02 – 26.55; p = 0.027) were independent predictors of worse 5-year OS. Grade ≥ 3 toxicities were uncommon: hand–foot syndrome (5.2%), diarrhea (2.1%), and hematologic events (4.2%); three patients (3.1%) discontinued therapy due to adverse events.These findings indicate that adjuvant capecitabine provides favorable 5-year DFS and OS in high-risk Stage II colon cancer. Patients with lymphovascular/perineural invasion or pT4b status may benefit from intensified approaches.

Keywords: Capecitabine, adjuvant chemotherapy, colon cancer, stage II, high-risk factors, toxicity, Vietnam.

I. INTRODUCTION

Colon cancer incidence in Vietnam has increased over the past decade.[1] Surgical resection is curative for Stage II colon cancer (pT3–4, N0, M0), but 20 – 30% of patients experience recurrence.[2] Adjuvant chemotherapy aims to eradicate micrometastatic disease. International guidelines recommend adjuvant therapy for high-risk Stage II patients with features such as lymphovascular/perineural invasion, inadequate nodal evaluation, poor differentiation, mucinous histology, tumor budding, obstruction/perforation, positive margins, and T4 disease.[3,4]

Major phase III trials and pooled analyses have demonstrated that adjuvant fluoropyrimidine-based regimens reduce recurrence risk by 20 – 25% and mortality by roughly 15 – 20% in stage II–III colon cancer. The QUASAR trial (2007) revealed that adjuvant 5-fluorouracil (5-FU) plus leucovorin (LV) decreased recurrence risk by 22% and mortality by 18% compared with observation alone in patients with colorectal cancer [71% colon, 29% rectal; 91% stage II].[5] The ACCENT pooled analysis (2009) involving nearly 6,900 stage II colon cancer patients reported an

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absolute 8-years survival improvement of 5% with fluoropyrimidine-based adjuvant therapy (p = 0.026).[6] A 2020 meta-analysis found that adjuvant fluoropyrimidine-based chemotherapy significantly improved both DFS (p = 0.002) and OS (p < 0.001) in high-risk stage II colon cancer.[7]

Capecitabine monotherapy is widely used in Vietnam due to its oral administration and manageable toxicity. However, Vietnamese data on outcomes and toxicity in high-risk Stage II patients remain limited. This study examines survival outcomes, prognostic factors, and toxicity in high-risk Stage II colon cancer treated with adjuvant capecitabine at Vietnam National Cancer Hospital.

II. MATERIALS AND METHODS

1. Subjects

We performed a single-center,retrospective cohort analysis of 96 consecutive high-risk stage II colon adenocarcinoma patients (pT3-4, N0, M0) treated at K Hospital between January 2016 and December 2019. Patients were selected by convenience sampling based on treatment records.High-risk features (excluding T4) were defined as lymphovascular or perineural invasion, fewer than 12 lymph nodes examined, poor differentiation or mucinous histology, tumor budding, bowel obstruction or perforation, and positive resection margin. Patients with T4 tumors were included in survival analyses but not counted toward the high-risk feature tally.

Inclusion and exclusion criteria

Included: age ≥ 18 years, pT3-4,N0,M0, R0 resection, adjuvant capecitabine.

Excluded: receipt of fewer than four capecitabine cycles, prior chemotherapy for another malignancy, synchronous cancers, missing follow-up.

2. Methods

Treatment Protocol: Adjuvant capecitabine was administered at 1,250 mg/m² orally twice daily on days 1 – 14 of each 21-day cycle for eight cycles. Dose reductions to 80 – 90% were implemented for CTCAE v4.0 grade 2 – 3 toxicities per institutional guidelines.

Data Collection & Outcomes

Covariates captured

- Demographics: age, sex, ECOG status
- Tumor: location, histologic grade, T stage, number of nodes examined, lymphovascular/ perineural invasion, mucinous histology, tumor budding, obstruction/perforation, margin status
- Treatment: surgical approach, time from surgery to chemotherapy (< 4 vs. 4 – 8 weeks),, capecitabine dose intensity, number of cycles completed
- Laboratory: pre- and post-chemotherapy CEA levels

DFS was defined as time from surgery to recurrence or death; OS as time from surgery to death. Toxicities were graded per CTCAE v4.0.

Follow-Up: Patients were assessed every 3 months for 2 years, every 6 months for years 3 – 5, and annually thereafter. Surveillance included physical exam, CEA measurement, chest imaging, abdominal imaging, and colonoscopy at 12 months postoperatively.

Statistical Analysis

Continuous variables are presented as median (range) and categorical variables as n (%). DFS and OS were estimated by Kaplan–Meier analysis and compared using the log-rank test. Variables with p < 0.10 on univariate analysis were included in multivariate Cox proportional hazards models (HR, 95% CI). A p ≤ 0.05 was considered statistically significant. Analyses were performed using SPSS v20.0.

3. Research ethics

This study was approved by the Ethics Board

of Hanoi Medical University (No. 5073/QD-DHYHN). All procedures conformed to routine clinical care; patient data were anonymized and maintained confidentially.

III. RESULTS

1. Patient Characteristics

Table 1. Patient characteristics (n = 96)

Characteristic	Category	n (%)
Age (years)	Median (range): 56.5 (22–71); ≥ 60	38 (39.6)
Gender	Male	49 (51.0)
	Female	47 (49.0)
ECOG Performance Status	0	53 (55.0)
	1	31 (32.0)
	2	12 (13.0)
Pathologic Stage	IIA (pT3)	43 (44.8)
	IIB (pT4a)	47 (49.0)
	IIC (pT4b)	6 (6.2)
Nodes Examined	< 12	54 (56.2)
	≥ 12	42 (43.8)
Lymphovascular/Perineural Invasion	Present	6 (6.2)
	Absent	90 (93.8)
*Number of High-Risk Factors**	0	27 (28.1)
	1	54 (56.2)
	≥ 2	15 (15.6)
Surgical Approach	Laparoscopic	29 (30.2)
	Open	67 (69.8)
Time to Chemo	< 4 weeks	64 (66.7)
	4 – 8 weeks	32 (33.3)
Capecitabine Dose Intensity	≥ 90%	23 (24.0)
	85 – 90%	20 (20.8)
	80 – 85%	53 (55.2)
Chemo Cycles Completed	8 cycles	93 (96.8)
	4 – 7 cycles	3 (3.2)

**High-risk factors excluding T4: lymphovascular/perineural invasion, < 12 nodes, poor differentiation/ mucinous, obstruction/perforation, positive margin, tumor budding*

Table 1 summarizes patient demographics and clinicopathologic features. The median age was 56.5 years old, with 40.0% aged ≥ 60. The gender distribution was nearly equal (male 51%, female 49%). ECOG performance status was 0 in 55.0%, 1 in 32.0%, and 2 in 13.0%. Regarding pathological stage, 44.8% were IIA (pT3 N0), 49.0% IIB (pT4a N0), and 6.2% IIC (pT4b N0). Lymphovascular and/or perineural invasion was present in 38.5%. Inadequate lymph node evaluation (< 12 nodes) occurred in 36.5%. The numbers of high-risk factors (excluding T4) were: 0 in 27.9%, 1 in 55.8%, and ≥ 2 in 16.3%. Bowel obstruction at presentation was documented in 12.5%.

Two-thirds (66.7%) of patients initiated capecitabine within 4 weeks of surgery, while 33.3% began between 4 and 8 weeks. Dose intensity was adjusted such that 55.2% received 80–85% of the standard dose, 20.8% received 85–90%, and 24.0% maintained ≥ 90%. Almost all patients (96.8%) completed all 8 planned cycles of chemotherapy; only 3 (3.2%) discontinued between cycles 4 and 7 due to toxicity.

2. Survival Outcomes

Table 2. Five- year Survival outcome (n = 96)

Outcome	5-Year Rate (%)
Disease-Free Survival (DFS)	89.5
Overall Survival (OS)	91.1

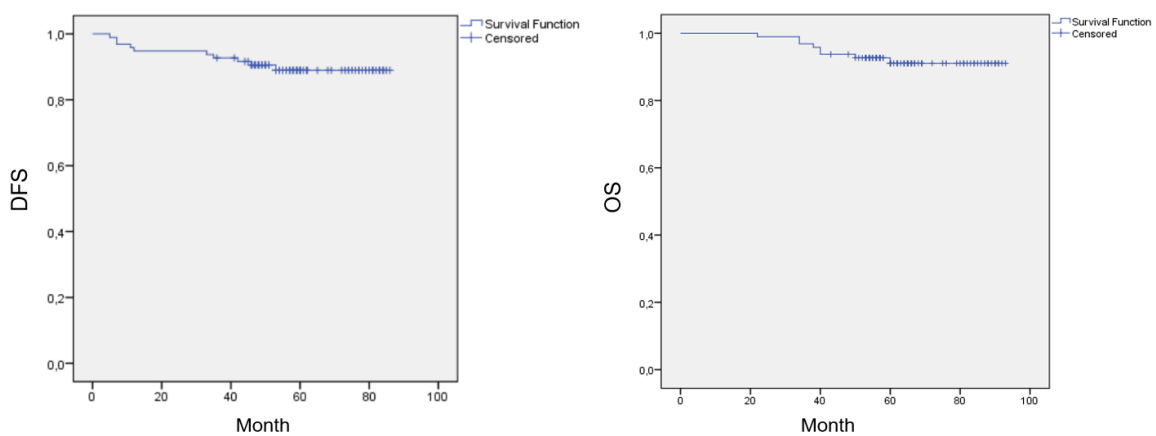

Chart 1. Five-Year Survival Outcomes

With a median follow-up of 60.6 months (95% CI: 22 – 79), 10 patients (10.4%) experienced disease recurrence (locoregional or distant), and 9 patients (9.4%) died. At 5 years, the overall DFS rate was 89.5% (95% CI: 83.1 – 95.9), and the OS rate was 91.1% (95% CI: 84.9 – 97.3) (Table 2; Chart 1).

3. Survival and Prognostic Factors

On univariate (log-rank) analysis (Table 3), lymphovascular and/or perineural invasion was significantly associated with worse 5-year DFS (66.7% vs. 91.0%, p = 0.047) and OS (66.7% vs. 92.7%, p = 0.014). Patients with ≥ 2 high-risk factors had inferior 5-year DFS (71.4% vs. 95.8% [1 factor] vs. 100% [0 factors], p < 0.001) and OS (71.4% vs. 94.7% [1 factor] vs. 100% [0 factors], p < 0.001). Advanced pathological stage also trended

toward poorer outcomes: 5-year DFS was 93.1% (IIA), 89.2% (IIB), and 66.7% (IIC) (p = 0.115); 5-year OS was 92.1% (IIA), 93.6% (IIB), and 66.7% (IIC) (p = 0.050)

Table 3. Univariate Analysis of 5-Year DFS and OS

Factor	Category	5-Year DFS (%)	p-Value (PFS)	5-Year OS (%)	p-value (OS)
Lymphovascular/Perineural Invasion	Present	66.7	0.047	66.7	0.014
	Absent	91.0		92.7	
Stage	IIA	93.1	0.115	92.1	0.050
	IIB	89.2		93.6	
	IIC	66.7		66.7	
High-Risk Factors*	0	100.0	< 0.001	100.0	< 0.001
	1	95.8		94.7	
	≥ 2	71.4		71.4	

**High-risk factors excluding T4: lymphovascular/perineural invasion, < 12 nodes, poor differentiation/ mucinous, obstruction/perforation, positive margin, tumor budding.*

Table 4. Multivariate Cox Regression Analysis of Factors Associated with 5-Year DFS and OS

Factor	5-year DFS		5-year OS	
	HR (95% CI)	p	HR (95% CI)	p
Stage IIB vs. IIA	1.76 (0.42 – 7.39)	0.443	1.76 (0.42 – 7.39)	0.736
Stage IIC vs. IIA	6.98 (0.88 – 55.06)	0.065	6.98 (0.88 – 55.06)	0.009
Lymphovascular/perineural invasion (Yes vs. No)	5.21 (1.02 – 26.55)	0.047	5.21 (1.02 – 26.55)	0.027
Bowel obstruction or perforation (Yes vs. No)	1.40 (0.22 – 8.77)	0.718	1.40 (0.22 – 8.77)	0.349
Number of lymph nodes examined (< 12 vs. ≥ 12)	2.01 (0.51 – 7.50)	0.322	2.01 (0.51 – 7.50)	0.076

On multivariate analysis (Table 4), Stage IIC (HR = 6.98; p = 0.009) and lymphovascular/ perineural invasion (HR = 5.21; p = 0.027) emerged as independent predictors of poorer 5-year overall survival. Lymphovascular/ perineural invasion was significantly associated with reduced 5-year DFS.

4. Treatment-Related Toxicity

Overall, capecitabine was well tolerated (Table 5): most hematologic and biochemical abnormalities were Grade 1–2 only (anemia 30.2%, AST/ALT elevation 13.5%, creatinine elevation 4.2%), with just one Grade 3 thrombocytopenia (1.0%). Hand–foot syndrome

occurred in 51.0% (49.0% Grade 1–2, 2.0% Grade 3), while diarrhea (10.4%) and nausea/vomiting (5.2%) were almost exclusively low grade. No Grade 4 events were observed, and severe (Grade 3) toxicities affected fewer than 5% of patients, supporting capecitabine's favorable safety profile.

Table 5. Toxicities Graded According to CTCAE Version 4.0 (n = 96)

Adverse Event	Total n (%)	Grade 1–2 n (%)	Grade 3–4 n (%)
Anemia	29 (30.2)	29 (30.2)	0
Leukopenia	4 (4.2)	4 (4.2)	0
Thrombocytopenia	2 (2.0)	1 (1.0)	1 (1.0)
AST/ALT Elevation	13 (13.5)	13 (13.5)	0
Creatinine Elevation	4 (4.2)	4 (4.2)	0
Hand-Foot Syndrome	49 (51.0)	47 (49.0)	2 (2.0)
Diarrhea	10 (10.4)	9 (9.4)	1 (1.0)
Nausea/Vomiting	5 (5.2)	5 (5.2)	0

Percentages refer to proportion of the 96 total patients

IV. DISCUSSION

In this single-center cohort of 96 high-risk Stage II colon cancer patients treated with adjuvant capecitabine, univariate analysis identified several factors significantly associated with poorer 5-year outcomes. Most notably, lymphovascular/perineural invasion correlated with substantially lower disease-free survival (66.7% vs. 91.0%, p = 0.047) and overall survival (66.7% vs. 92.7%, p = 0.014). This finding echoes prior studies showing that microscopic tumor infiltration into vascular or neural structures signals a biologically aggressive phenotype, leading to earlier recurrence despite node-negative status.[8,9]

Pathologic stage also influenced univariate survival. Although the difference did not reach statistical significance for DFS (93.1% in IIA vs. 89.2% in IIB vs. 66.7% in IIC, p = 0.115), overall survival was significantly worse in Stage IIC (66.7%) compared to IIA (92.1%) and IIB (93.6%) (p = 0.050). These data suggest that tumors penetrating adjacent organs (pT4b) carry a higher relapse risk, consistent with literature recommending more intensive regimens for T4b patients.[10] In practice, this stage-dependent survival gradient underscores the need to consider adding oxaliplatin or enrolling T4b patients in clinical trials rather than relying on capecitabine alone.

In defining "high-risk features," we adhered to NCCN and ESMO guidelines, which include T4 tumors, lymphovascular or perineural invasion, poor differentiation, examination of fewer than 12 lymph nodes, bowel obstruction or perforation, and positive resection margins. However, for the purpose of isolating the prognostic impact of non-T4 high-risk factors, we excluded T4 status from the cumulative risk count used in our subgroup analysis. While patients with T4 tumors were included in the

overall cohort and survival analyses, they were not counted toward the total number of high-risk features in this specific stratification.

When stratified by the number of high-risk features (excluding T4), patients with ≥ 2 factors (e.g., < 12 lymph nodes examined plus poor differentiation) had markedly lower 5-year DFS (71.4%) and OS (71.4%) compared to those with one (95.8% and 94.7%, respectively) or no additional factors (100% and 100%; $p < 0.001$ for both). Although this univariate association does not distinguish which individual risk element drives outcome, it supports existing guidelines that accumulating risk features identify a subgroup at substantially higher relapse risk who may benefit from intensified adjuvant therapy.[11]

Inadequate lymph node harvest (< 12 nodes) trended toward worse univariate survival (DFS 87.0% vs. 92.9%, $p = 0.337$; OS 87.0% vs. 96.0%, $p = 0.064$). This reinforces the concept that suboptimal nodal evaluation may understate true stage, potentially leaving micrometastatic disease unaddressed.[12] While not statistically significant here, we advocate for continued efforts to achieve ≥ 12 nodes in every colectomy specimen.

In our multivariate analysis, pathologic Stage IIC (HR = 6.98; 95% CI: 0.88 – 55.06; $p = 0.009$) and lymphovascular/perineural invasion (HR = 5.21; 95% CI: 1.02 – 26.55; $p = 0.027$) were independently associated with worse 5-year OS, underscoring the particularly high risk in these subgroups. Notably, lymphovascular/perineural invasion also predicted poorer DFS (HR = 5.21; $p = 0.047$). These findings suggest that patients with Stage IIC disease or evidence of microinvasion may benefit from intensified adjuvant regimens.

Regarding toxicity, data confirmed that capecitabine-related adverse events were predominantly low grade: anemia (30.2%), AST/ALT elevation (13.5%), creatinine elevation (4.2%), and hand–foot syndrome (51.0%, mostly Grades 1–2). Serious (Grade 3) toxicities were rare (< 5% overall), enabling 96.8% of patients to complete all eight cycles. These findings mirror other East Asian experiences, which report low incidence of severe toxicity with capecitabine in Stage II–III disease.[13]

In summary, our analysis highlights lymphovascular/perineural invasion, Stage IIC (pT4b), multiple risk features, and suboptimal nodal count as markers of poorer 5-year survival. Capecitabine monotherapy achieved high completion rates and manageable toxicity, but patients exhibiting these risk factors may warrant consideration of more aggressive adjuvant regimens such as the addition of oxaliplatin. Future prospective studies incorporating molecular profiling will be valuable to refine risk stratification further.

V. CONCLUSION

Adjuvant capecitabine monotherapy in high-risk Stage II colon cancer at a Vietnamese center yielded 5-year DFS of 89.5% and OS of 91.1% with minimal grade ≥ 3 toxicity. Nonetheless, lymphovascular/perineural invasion and pT4b status independently predicted poorer survival, suggesting these patients may require intensified regimens or trial enrollment. Future prospective studies with molecular profiling are essential to personalize adjuvant therapy in high-risk Stage II colon cancer.

Declarations

Conflicts of Interest: The authors have no competing interests to declare.

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Data Availability: The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

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