Survival Outcomes in High-Risk, Resected Colorectal Cancer with and without Maintenance Therapy

Miklos L. Auber[1], Sijin Wen[2], Francesca Farran[3] and Gerald M. Higa[1,3,*]

[1]*Department of Medicine/West Virginia University/Morgantown, WV, USA*

[2]*Department of Biostatistics/West Virginia University/Morgantown, WV, USA*

[3]*Department of Clinical Pharmacy/West Virginia University/Morgantown, WV, USA*

Abstract: *Introduction*: Deaths due to colorectal cancer are disproportionately higher than either breast or prostate cancers even though the majority of new cases are potentially curable at diagnoses. If only half of the losses is due to metastatic disease at diagnosis, then a share of the remaining deaths must be attributable to tumor recurrence after presumptively curative therapy of early-stage disease. If so, current management of the latter group is suboptimal for a considerable number of subjects, a perception which argues for an assessment of maintenance therapy. Moreover, most recurrences occur within 24 months after standard surgical and (neo)adjuvant therapies.

Objective: To assess relapse-free and overall survival among patients with high-risk, resected tumors who did and did not receive maintenance therapy following completion of treatment according to accepted guidelines.

Methods: Pertinent clinical details were collected on 85 subjects, 37 who were, and 48 who were not, treated with maintenance therapy. Descriptive statistical analyses related to survival outcomes were performed on accumulated data. Wilcoxon rank test and Fisher's exact test were used to examine the continuous and categorical variables, respectively. Kaplan-Meier method and log-rank test were used to analyze between-group relapse-free and overall survival.

Results: Of the entire cohort, 63 of 85 (74.1%) subjects have no evidence of disease, a median of 5 years from the end of adjuvant therapy. Kaplan-Meier analyses indicated statistically, but not necessarily clinically, non-significant differences in median 5-year relapse-free survival, 79.8% vs 69.2%, and overall survival, 87.8% vs 81.7% in the treated and untreated groups of patients, respectively. A total of 21 subjects died; three of seven (treated group) and all 14 (untreated group) due to cancer.

Conclusion: Obscured is the hint that maintenance therapy is clinically more effective than what the *p*-value intimates. The results of this retrospective data collection and analyses suggest that some patients with early-stage, high-risk disease, will derive survival benefits with maintenance therapy.

Keywords: Capecitabine, High-risk, Resected CRC, Maintenance therapy, RFS, OS.

INTRODUCTION

Recent published data estimate 153,000 new colorectal cancer (CRC) diagnoses in the United States (US) in 2023 [1]. Quantitatively, CRC is the fourth most common site-specific solid tumor (after breast, prostate and lung) but disease-related deaths are disproportionately higher than breast and prostate cancers. While the 5-year recurrence-free survival (RFS) rate approximates 70% following resection and (neo)adjuvant therapy, survival outcomes are not uniform among all subsets of stage 3, and stage 2, tumors [2]. Still, there is cautious optimism as a pragmatic analysis of global trends related to CRC indicated a decrease in mortality in countries, including the US, with high human development indices (HDI). Three components of the HDI associated with the improvement in survival include screening colonoscopy, molecular analysis (i.e., *KRAS,* gene methylation, microsatellite instability) and adjuvant systemic therapy [3]. Nonetheless, a proportion of patients with early-stage disease will not be cured despite these efforts. Furthermore, the inference that six months of adjuvant chemotherapy is only palliative for a significant number of subjects argues for an appraisal of extended systemic treatment.

It is important to note that the concept of maintenance therapy in CRC has been investigated, though only in patients with metastatic disease [4-7]. Variable results have been reported in this setting with the majority of studies showing some benefit. However, durable well-being was not observed.

If the belief that anticancer treatment modalities are more effective in early stage (low tumor burden) disease, then maintenance therapy should be of some benefit after standard adjuvant therapy. Nevertheless, potential favorable consequences must be balanced relative to the costs (physical, emotional and financial) associated with possible overtreatment.

The primary objective of this study is to analyze survival outcomes in subjects with high-risk, surgically-

*Address correspondence to this author at the Professor of Clinical Pharmacy, Clinical Professor Medicine (Adjunct), Schools of Pharmacy and Medicine, West Virginia University, Morgantown, WV 26506-9520, USA; Tel: 304-293-1461; Fax: 304-293-7672; E-mail: ghiga@hsc.wvu.edu

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resected CRC who received or did not receive maintenance treatment following adjuvant chemotherapy.

PATIENTS AND METHODS

A total of 85 patients included in this report had cancers of the colon or rectum classified pathologically, and clinically, as high-risk tumors. Eighty patients had disease staged 2B, 2C, 3A, 3B, or 3C. All subjects in these subsets with colon cancer underwent surgery followed by standard adjuvant chemotherapy; patients with rectal cancer received neo-adjuvant chemo-radiation therapy followed by surgery and adjuvant chemotherapy**.** Five patients were diagnosed with stage 4 tumors, two of who had extrahepatic metastases. The three subjects with liver metastases received neo-adjuvant radiofrequency ablation (RFA); one of these patients was also treated with intrahepatic arterial infusion of floxuridine (FUDR). All five subjects had no measurable disease following RFA +/- FUDR as mentioned, neo-adjuvant chemotherapy, surgery and systemic adjuvant therapy.

All subjects with stage 3 disease received standard adjuvant chemotherapy. Notably, post-surgery systemic treatment is also recommended for “high-risk” stage 2B and 2C tumors; those individuals who consented to adjuvant therapy were included in this analysis. Despite the proven clinical benefit of adjuvant therapy, disease relapse still occurs in a significant number of patients. However, current standard does not include treatment beyond completion of adjuvant therapy.

Appeal for Maintenance Therapy

Because of the uncertainty related to cancer recurrence, a number of patients expressed a preference for further treatment in order to reduce this risk. It was in this setting that the implications of maintenance therapy for resected CRC was contemplated. And weighing the elements of cost, route of administration, side effect profile, and quality of life, capecitabine was considered an appropriate, and reasonably tolerable, treatment option.

Plain and open discussion was paramount to ensure that all interested subjects were fully aware of the proposed intervention, the importance of their involvement in the decision-making process, the standard alternative, and potential risks associated with the proposed intervention; the possibility of relapse risk reduction was mentioned but not magnified. All of these discussion points form the basis of respect for persons, beneficence, and justice taken from the Belmont Report [8]. Only patients who gave verbal informed consent (which was witnessed by GMH and MLA and documented in their medical records) were treated with capecitabine as maintenance therapy with the understanding that treatment would be discontinued if the disease progressed, intolerable toxicity developed, or patient or physician decided to stop, whichever came first.

Design

Intervention group - the prescribed dose of capecitabine was 1,500 – 2,000 mg/m^2/day in divided doses for one week, every other week. A priori adjustments to this dosage were based on patient age, co-morbidities, and performance status. Kidney function did not influence drug dose though patients with calculated creatinine clearances <30 ml/min were not included; body surface area was capped at 2 m^2. The planned course of maintenance therapy was 60 months with the stipulation related to stopping mentioned previously.

Non-intervention group - routine follow-up for disease assessment

The co-primary endpoints were between-group relapse-free survival (RFS) and overall survival (OS). Relapse-free survival is defined as the time from the end of adjuvant therapy to relapse, institution of new therapy, or death, whichever occurred first; overall survival is defined as the length of time from diagnosis to death from any cause. The duration of follow-up is defined as the number of months from end of standard adjuvant therapy until the last follow-up visit or data cutoff.

Statistical Analyses

Descriptive statistical analyses were performed on the two cohorts to summarize data related to time from end of adjuvant therapy to last assessment, respective-group disease status, and RFS and OS at the time of this report including summary tables, and median and standard deviations. Wilcoxon rank test and Fisher’s exact test were used to examine the continuous variables and categorical variables, respectively. Kaplan-Meier method and log-rank test were used to examine RFS and OS between treatment groups.

RESULTS

Thirty-seven of the 85 subjects included in this report were, or continue to be, treated with capeci-tabine as maintenance therapy. Numbers of colon and

Table 1: Demographics of Treated and Untreated Subjects

Variables	Treated	Untreated
	n (%)	n (%)
Gender		
F	14 (37.8)	25 (52.1)
M	23 (62.2)	23 (47.9)
Stage (in detail)		
2B	0	1 (2.1)
2C	3 (8.1)	3 (6.2)
3A	3 (8.1)	5 (10.4)
3B	15 (40.5)	32 (68.7)
3C	12 (32.4)	6 (10.4)
4	4 (10.8)	1 (2.1)
Disease.status at time of data collection		
NED	29 (78.4)	34 (70.8)
Metastatic	8 (21.6)	14 (29.2)
Died from metastatic disease	3 (8.1)	14 (100)
	Median (range)	**Median (range)**
Age	59 (40, 87)	64 (40, 87)
SEER 5-year survival rate	0.33 (0.13, 0.73)	0.33 (0.13, 0.73)
Duration capecitabine (months)	27 (3, 60)	
Time, end of adjuvant therapy to last seen (years)	3.75 (0.42, 19)	8.46 (0.33, 23.83)

rectal cancer cases were 58 and 27, respectively. A summary of key data is shown in Table **1**.

Duration of follow-up from the end of adjuvant therapy is shown in Figure **1**. Median duration for the group as a whole was approximately 5 years, though the medians for the treated and untreated groups differed, 3.75 years and 8.46 years, respectively. Of the treated cohort, 29 subjects have no evidence of disease at their last clinic visit. Twenty of these 29

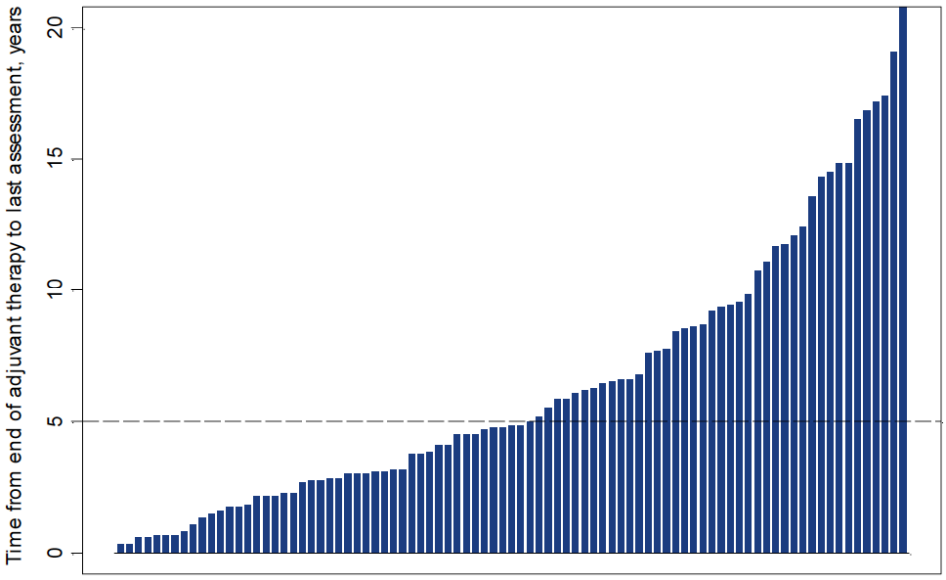

Figure 1: Water-fall plot of time from end of adjuvant therapy to last assessment (median 5 years).

patients received capecitabine ≥27 months, none of who relapsed; all eight of the relapses occurred within 24 months following the end of adjuvant therapy. Comparatively, there were 14 relapses in the untreated group, 10 of which occurred less than 24 months of ending adjuvant therapy. Based on Kaplan-Meier (K-M) method, 5-year RFS was 79.8% (95% CI: 67.5% - 94.4%) in the treated cohort and 69.2% (95% CI: 56.8% - 84.1%) in the untreated group (Figure **2**), p = 0.49; K-M estimates for 5-year OS were 87.8% (95% CI: 74.9% - 99.9%) in the treated group and 81.7% (95% CI: 71% - 94.1%) in the untreated group, p = 0.17 (Figure **3**).

A total of 21 subjects have died at the time of data analysis. Of the seven deaths in the treated group, four patients had no evidence of disease (NED) at the time of their passing. In contrast, all 14 deaths among the

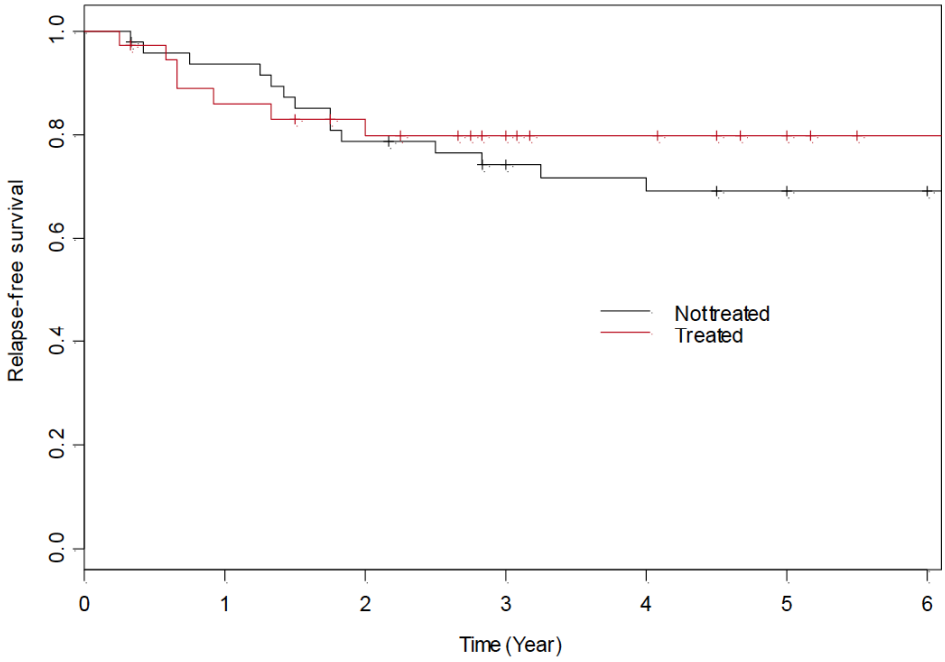

Figure 2: Comparative Kaplan-Meier plots of RFS between treated and untreated groups.

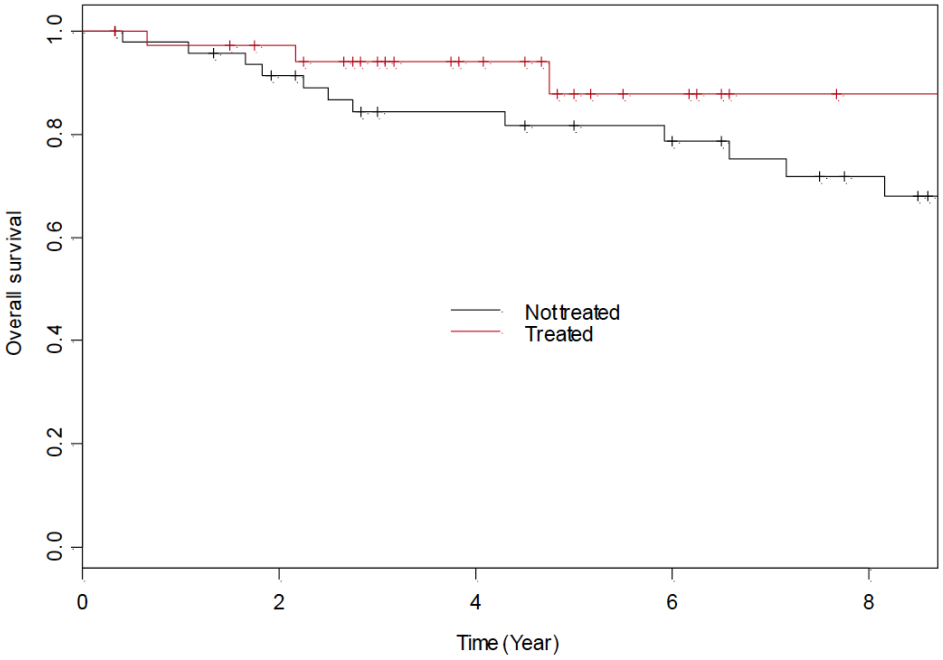

Figure 3: Comparative Kaplan-Meier plots of OS between treated and untreated groups.

untreated subjects were due to metastatic disease. Of note also, all five subjects with stage 4 disease at diagnosis were still alive with NED after more than four years of follow up. Four of the latter five patients received maintenance capecitabine for at least 48 months; the other subject was treated similarly for more than a year. The most common side effect observed was grade 1/2 hand-foot syndrome which occurred in nearly all of the treated subjects. The relatively low-grade toxicity responded to, or resolved with, dose reduction (500 mg of the total daily dose). None of the capecitabine-treated patients discontinued therapy due to drug intolerance.

DISCUSSION

Randomized clinical trials demonstrate near doubling of relative disease-free survival with the addition of oxaliplatin to fluorouracil-based adjuvant therapy for colon cancer [9,10]. And though arguable, some oncologists prefer an oxaliplatin-based regimen for all patients with resected rectal cancer, an approach consistent with the National Comprehensive Cancer Network guidelines. In addition, oxaliplatin-containing adjuvant therapy has also been reported to be associated with improved survival in real-world community-based settings of older and ethnically-diverse subjects who were treated at the discretion of treating clinicians [11-14]. Still, the number of annual CRC deaths is approximately a third of the annual incidence, a percentage that is more than double the mortality rates of breast and prostate cancers in their respective incident populations. While differences in tumor biology may partially explain the poorer disease outcomes, extended duration systemic therapy may also impact survival endpoints. It has been clearly shown that addition of adjuvant endocrine therapy has improved disease-free and overall survival in patients with operable hormone-sensitive breast cancer [15,16]. Indeed, durations of endocrine therapy exceeding five years confer even greater survival benefits. Furthermore, patient age, anatomic stage, tumor size, lympho-vascular invasion, extent of nodal involvement, tumor grade, and genomic signature are used to identify women with estrogen receptor-positive tumors, some of who will benefit from addition of chemotherapy. Significant benefit in prostate cancer-specific survival has also been observed with longer hormone deprivation therapy [17,18].

Consistent with previous reports was the finding in our study that most recurrences occurred within the first two years after completion of standard therapy. Of the 22 recurrences in the entire population, 18 (81.8%) occurred within 24 months. And even though not statistically significant, the numerical difference between the two groups (8, treated group; 14, untreated group) may be inherently meaningful. For example, that disease relapse has not been observed among subjects who received capecitabine exceeding two years with a follow-up approaching four years suggest that some of the early (and even late) recurrences may be pre-empted. Support for this belief comes from the common dataset of the German Cancer Society restricted to patients with colorectal cancer. In this large retrospective population-based cohort study, investigators detected significantly better recurrence-free and overall survival in women compared with men [19]. These outcomes are even more telling when considering that right-sided tumors were more common, tumors were of higher grade and stage, and treatment with chemotherapy occurred less frequently among women. Of note, this particular finding is consistent with the lower recurrence rate in women compared to men, 20% and 39.1%, respectively, among the untreated subjects in our study. What is particularly interesting is if female gender is innately advantageous, then, logically, women should derive less benefit from maintenance therapy. This logic is corroborated by the finding of a very modest difference (regarding recurrence) between females in the treated and untreated cohorts, 18.8% and 20%, respectively, again, in our study population. Conversely, a lower recurrence rate (and greater benefit) was observed among males in the treated and untreated groups, 22.7% and 39.1%, respectively. Because gender may impact survival outcomes, the question whether the greater number of women in the untreated cohort could have affected RFS is not a rhetorical one.

Another comparable finding relates to the 5-year RFS (69.2%) in the absence of maintenance therapy in our study which is nearly identical to the 70% reported by other investigators [20]. In addition, while the 10% between-group difference (79.8%, treated vs 69.2%, untreated) from our data is not significant statistically, this may not be the case clinically when applied to a larger population of patients. Notable also is the perceptibly greater benefit of capecitabine on OS although it is not statistically significant due to the small sample size. In this context, even though between-group number of deaths (7, treated; 14, untreated) did not differ significantly, the number of cancer-related deaths were appreciably lower with maintenance therapy (i.e. 3 of 7, treated; 14 of 14, untreated).

Lastly, all five subjects with metastatic disease (at diagnosis) and NED >5 years from end of adjuvant therapy suggest that this outcome may be partially attributable to continued systemic therapy. Despite this small number, it is important to emphasize that median overall survival of patients with metastatic colorectal cancer (mCRC) is approximately 30 months. [21]

Although a formal quality of life tool was not utilized, none of the subjects had their treatment discontinued because of unmanageable side effects. One other concern of maintenance therapy relates to the development of second malignancies. A single institution reported a small number of patients treated for CRC who were subsequently diagnosed with acute leukemia or myelodysplasia [22]. However, limited data precluded any conclusive statement regarding a causal relationship between prior therapy and incident hematologic malignancies. Instead, the authors speculated that incorporation of oxaliplatin, rather than fluorouracil, may be the link between anticancer therapy and latent marrow aberrances. Adding further credence to their notion regarding the lack of culpability of the fluoropyrimidine is the absence of any reported premalignant marrow findings or leukemogenic effect associated with capecitabine therapy.

A number of study limitations were considered in conjunction with the assessment of the clinical data. First, retrospective data collection using medical records frequently limits access to all facets related to patient care. However, the subjects in this report were patients of only one oncologist. Meticulous accounting of patient-related information including date of, and stage at, diagnosis, all anticancer treatments, blood and radiographic assessments, and follow-up visits support the accuracy of the data collected. Nonetheless, some information such as the cause of the unexpected deaths regarding four treated subjects (NED) was not available. Even so, CRC patients tend to be elderly and many of them have assorted comorbidities and competitive risks of death. Second, while subjects who received capecitabine were "selected" based on having tumors with high-risk features for relapse and provision of verbal consent to receive maintenance therapy the results were not biased by selection based on "best" individual outcomes. Third, a relapse-free interval of 5 years generally approximates cure. While the majority of patients in the untreated group met this endpoint, only 35% (13 of 37) of the treated patients met this criterion. Still, 31 (83.7%) of the latter group have follow-ups exceeding two years, a cardinal numeric in that tumor recurrences in patients occur most frequently within 24 months. Fourth, the selection of a lower than FDA-approved dose (i.e., 2,500 mg/m^2/day) was justified based on clinical experience that most patients were unable to tolerate this dosage regimen. Furthermore, a dose-response relationship has not been established for capecitabine; and lower drug dose is not only associated with a better therapeutic index [23] but may also inhibit angiogenesis and immune escape [24]. Fifth, the small sample size precludes making any definitive statement regarding therapeutic efficacy. Even so, the data in this report related to patients receiving standard therapy only are remarkably similar to other previously studies; even the modest benefits observed among our treated group are consistent with findings involving maintenance capecitabine in triple negative breast cancer [25].

CONCLUSION

While the role of maintenance therapy has been established in several cancers, testing of the same concept has not occurred in patients with surgically-resected, high-risk CRC. Because of its approval for the treatment of mCRC, capecitabine could be also beneficial after standard adjuvant therapy. The initial results of this retrospective analysis suggest that some patients with early-stage, low-tumor burden but high-risk disease, will derive survival benefits with extended duration systemic therapy. Even though the optimal dose and duration is not known, the use of capecitabine, at reduced doses, following standard adjuvant therapy is practicable, tolerable, and potentially life-sustaining.

STATEMENT OF ETHICS

Retrospective collection of clinical outcomes data for analysis received full approval of the Institutional Review Board of West Virginia University (IRB Protocol Notice: Protocol 2009110099 Approved). Relevant patient-specific data were accessed from electronic medical records (*Epic* Hyperspace^R). Since this was not a formal clinical trial, written informed consent forms were not mandated. Still, all subjects in this report gave fully informed consent for treatment as indicated in the Patients and Methods section.

CONFLICT OF INTEREST

The authors do not have any relationship, financial or otherwise (i.e., support in the form of employment, consultancies, honoraria, stock ownership and options,

expert testimony, grants or patents received or pending, or royalties) with the manufacturer of the agent described that influenced the writing of this manuscript.

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AUTHOR CONTRIBUTIONS

MLA contributed to study concept, data acquisition, and manuscript review, editing and approval. SW and FF contributed to data analyses and manuscript review. GMH contributed to study concept, data acquisition and interpretation, and presided over writing and editing the manuscript. The authors approved the final draft of the manuscript and are accountable for all aspects of the work including its accuracy and integrity and their involvement in this submitted paper.

REFERENCES

[1] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer Statistics, 2023. CA Cancer Journal for Clinicians 2023; 73: 17-48. https://doi.org/10.3322/caac.21763

[2] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer 2017; pp. 252-54.

[3] Benson AB, Venook AP, Cederquist L, Chan E, Chen Y-J, Cooper HS, *et al*. Colon Cancer, Version 1.2017. Journal of the National Comprehensive Cancer Network 2017; 15(3): 370-98. https://doi.org/10.6004/jnccn.2017.0036

[4] Aparicio T, Ghiringhell F, Boige V, Malicot KL, Taieb J, Bouché O, *et al.*, PRODIGE 9 Investigators. Bevacizumab Maintenance Versus No Maintenance During Chemotherapy-free Intervals in Metastatic Colorectal Cancer: A Randomized Phase III Trial (PRODIGE 9). Journal of Clinical Oncology 2018; 36(7): 674-81. https://doi.org/10.1200/JCO.2017.75.2931

[5] Goey KKH, Elias SG, van Tinteren H, Laclé MM, Willems SM, Offerhaus JA, *et al*. Maintenance Treatment with Capecitabine and Bevacizumab Versus Observation in Metastatic Colorectal Cancer: Updated Results and Molecular Subgroup Analyses of the Phase 3 CAIRO3 study. Annals of Oncology 2017; 28(9): 2128-34. https://doi.org/10.1093/annonc/mdx322

[6] Luo H-Y, Li Y-H, Wang W, Wang Z-Q, Yuan X, Ma D, *et al*. Single-agent Capecitabine as Maintenance Therapy after Induction of XELOX (or FOLFOX) in First-line Treatment of Metastatic Colorectal Cancer: Randomized Clinical Trial of Efficacy and Safety. Annual of Oncology 2016; 27(6): 1074-81. https://doi.org/10.1093/annonc/mdw101

[7] Hegewisch-Becker S, Graeven U, Lerchenmüller CA, Killing B, Depenbusch R, Steffens C-C, *et al*. Maintenance Strategies after First-line Oxaliplatin plus Fluoropyrimidine plus Bevacizumab for Patients with Metastatic Colorectal Cancer (AIO 0207): A Randomised, Non-inferiority, Open-label, Phase 3 Trial. Lancet Oncology 2015; 16(13): 1355-69. https://doi.org/10.1016/S1470-2045(15)00042-X

[8] Department of Health, Education, and Welfare. Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.. Federal Register 1979; 82(12): 7149-274.

[9] André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, *et al*. Improved Overall Survival with Oxali¬platin, Fluorouracil, and Leucovorin as Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial. Journal of Clinical Oncology 2009; 27(10): 3109-16. https://doi.org/10.1200/JCO.2008.20.6771

[10] Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, *et al*. Oxaliplatin Combined with Weekly Bolus Fluorouracil and Leucovorin as Surgical Adjuvant Chemo¬therapy for Stage II and III Colon Cancer: Results from NSABP C-07. Journal of Clinical Oncology 2007; 25(16): 2198-2204. https://doi.org/10.1200/JCO.2006.08.2974

[11] Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare Data: Content, Research Applications, and Generalizability to the United States Elderly Population. Medical Care 2002; 40(8 suppl): IV-3-IV-18. https://doi.org/10.1097/01.MLR.0000020942.47004.03

[12] Romanus D, Weiser MR, Skibber JM, Veer AT, Niland JC, Wilson JL, *et al*. Concordance with NCCN Colorectal Cancer Guidelines and ASCO/NCCN Quality Measures: An NCCN Institutional Analysis. Journal of the National Comprehensive Cancer Network 2009; 7(8): 895-904. https://doi.org/10.6004/jnccn.2009.0059

[13] Ayanian JZ, Chrischilles EA, Fletcher RH, Fouad MN, Harrington DP, Kahn KL, *et al*. Understanding Cancer Treatment and Outcomes: The Cancer Care Outcomes Research and Surveillance Consortium. Journal of Clinical Oncology 2004; 22(15): 2992-6. https://doi.org/10.1200/JCO.2004.06.020

[14] Kahn KL, Adams JL, Weeks JC, Chrischilles EA, Schrag D, Ayanian JZ, *et al*. Adjuvant Chemotherapy Use and Adverse Events Among Older Patients with Stage III Colon Cancer. Journal of the American Medical Association 2010; 303(11): 1037-45. https://doi.org/10.1001/jama.2010.272

[15] Gnant M, Fitzal F, Rinnerthaler G, Steger GG, Greil-Ressler S, Balic M, *et al*., Austrian Breast and Colorectal Cancer Study Group. Duration of Adjuvant Aromatase-Inhibitor Therapy in Postmenopausal Breast Cancer. New England Journal of Medicine 2021; 385(5): 395-405. https://doi.org/10.1056/NEJMoa2104162

[16] Tjan-Heijnen V, van Hellemond IEG, Peer PGM, Swinkels ACP, Smorenburg CH, van der Sangen MJC, *et al*., Dutch Breast Cancer Research Group (BOOG) for the DATA Investigators. Extended Adjuvant Aromatase Inhibition after Sequential Endocrine Therapy (DATA): A Randomised, Phase 3 Trial. Lancet Oncology 2017; 18(11): 1502-11. https://doi.org/10.1016/S1470-2045(17)30600-9

[17] Nabid A, Carrier N, Martin A-G, Bahary J-P, Lemaire C, Vass S. Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III Trial. European Urology 2018; 74(4): 432-41. https://doi.org/10.1016/j.eururo.2018.06.018

[18] Bolla M, de Reijke TM, Tienhoven GV, Van den Bergh ACM, Oddens J, Poortmans PMP, *et al*. EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. Duration of androgen suppression in the treatment of prostate cancer. New England Journal of Medicine 2009; 360(24): 2516-27. https://doi.org/10.1056/NEJMoa0810095

[19] Schmuck R, Gerken M, Teegen E-M, Krebs I, Klinkhammer-Schalke M, Aigner F. Gender Comparison of Clinical, Histopathological, Therapeutic and Outcome Factors in 185,967 Colon Cancer Patients. Langenbeck's Archives of Surgery 2020; 405: 71-80. https://doi.org/10.1007/s00423-019-01850-6

[20] Tsikitis VL, Larson DW, Huebner M, Lohse CM, Thompson PA. Predictors of Recurrence Free Survival for Patients with Stage II and III Colon Cancer. BMC Cancer 2014; 14: 336. https://doi.org/10.1186/1471-2407-14-336

[21] Ulanja MB, Rishi M, Beutler BD, Sharma M, Patterson DR, Gullapalli N, Ambika S. Colon Cancer Sidedness, Presentation, and Survival at Different Stages. Journal of Oncology 2019; 21: 4315032. https://doi.org/10.1155/2019/4315032

[22] Stein EM, Pareek V, Kudlowitz D, Douer D, Tallman MS. Acute Leukemias Following a Diagnosis of Colorectal Cancer: Are They Therapy-related? Blood 2012; 120(21): 1453. https://doi.org/10.1182/blood.V120.21.1453.1453

[23] Hennessy BT, Gauthier AM, Michaud LB, Hortobagyi G, Valero V. Lower Dose Capecitabine has a More Favorable Therapeutic Index in Metastatic Breast Cancer. Retrospective Analysis of Patients Treated at M. D. Anderson Cancer Center and a Review of Capecitabine Toxicity in the Literature. Annals of Oncology 2005; 16(8): 1289-96. https://doi.org/10.1093/annonc/mdi253

[24] Pasquier E, Kavallaris M, André N. Metronomic Chemotherapy: New Rationale for New Directions. Nature Reviews. Clinical Oncology 2010; 7(8): 455-65. https://doi.org/10.1038/nrclinonc.2010.82

[25] Wang X, Wang S-S, Huang H, Cai L, Zhao L, Peng R-J, *et al*. for the South China Breast Cancer Group (SCBCG). Effect of Capecitabine Maintenance Therapy Using Lower Dosage and Higher Frequency vs Observation on Disease-free Survival Among Patients with Early-stage Triple-negative Breast Cancer Who Had Received Standard Treatment: The SYSUCC-001 Randomized Clinical Trial. Journal of the American Medical Association 2021; 325(1): 50-8. https://doi.org/10.1001/jama.2020.23370

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