Prognostic and predictive significance of MSI in stages II / III colon cancer

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Abstract
In colon cancer, classic disease staging remains the key prognostic and treatment determinant. Although adjuvant chemotherapy has an established role in stage III colon cancer patients, in stage II it is still a subject of controversy due to its restriction to a small subgroup of patients with high-risk histopathologic features. Patients with stage II tumors form a highly heterogeneous group, with five-year relative overall survival rates ranging from 58.4% (II A) to 87.5% (II C). Identifying those for whom adjuvant chemotherapy would be appropriate and necessary has been challenging, and prognostic markers which could serve in the selection of patients more likely to recur or benefit from adjuvant chemotherapy are eagerly needed. The stronger candidate in this category seems to be microsatellite instability (MSI). The recently reported European Society for Medical Oncology guidelines suggest that MSI should be evaluated in stage II colorectal cancer patients in order to contribute in treatment decision-making regarding chemotherapy administration. The hypothetical predictive role of MSI regarding its response to 5-fluorouracil-based adjuvant chemotherapy has proven a much more difficult issue to address. Almost every possible relation between MSI and chemotherapy outcome has been described in the adjuvant colon cancer setting in the international literature, and the matter is far from being settled. In this current report we critically evaluate the prognostic and predictive impact of MSI status in patients with stage II and stage III colon cancer patients.

Key words: Microsatellite instability; Stage II; Stage III; Colon cancer; Predictive; Prognostic

Core tip: Adjuvant chemotherapy in patients with stage II colon cancer is still a subject of controversy. Stage II tumors are highly heterogeneous, with five-year relative overall survival rates ranging from 58.4% to 87.5%. Recently reported European Society for Medical Oncology guidelines suggest that microsatellite instability (MSI) should be evaluated in stage II colorectal cancer patients in order to contribute in treatment decision-making regarding chemotherapy administration. The current report critically evaluates the prognostic and predictive impact of MSI status in patients with stage II and stage III colon cancer.

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INTRODUCTION
Colorectal cancer (CRC) remains a major public health
new cases in the western world, with an estimated 143397 cases and 51690 deaths occurring in 2012 in the United States alone[1].

In the adjuvant setting, after the oxaliplatin/fluorouracil (5-FU)/leucovorin (LV) era[2,3], we have reached a deadlock. Up until now, classic disease staging remained the key prognosis and treatment determinant. Based on that, adjuvant chemotherapy has an established role in stage III patients, where it is restricted to a small subgroup of patients with high-risk histopathologic features and stage II disease[4,5]. Adjuvant chemotherapy in patients with stage II colon cancer is still a subject of controversy. Stage II tumors are highly heterogeneous, with five-year relative overall survival (OS) rates ranging from 87.5% (II A) to 58.4% (II C). Several data suggest that chemotherapy is not mandatory for low risk stage II tumors (T3N0 without risk factors), while FOLFOX or XELOX should be considered as candidates for adjuvant treatment for stage II tumors with high risk factors (T4 or bowel obstruction, perforation, poorly differentiated tumor, < 10 or 12 examined lymph nodes, and/or histological signs of vascular, lymphatic, or perineural invasion).

Nevertheless, it is fair to admit that a significant percentage of adjuvant patients receive chemotherapy in vain. Identifying those for whom adjuvant chemotherapy would be appropriate and necessary has been challenging, and prognostic markers which could serve in the selection of patients more likely to recur or benefit from adjuvant chemotherapy are eagerly needed. Microsatellite instability (MSI), alongside 18q loss of heterozygosity[6,7], KRAS, BRAF, and TP53, are among the most investigated parameters[8,9]. While awaiting the fruits of considerable efforts being undertaken regarding the evaluation of the above mentioned markers in large prospective series, as well as the evaluation of multigene signatures on prognosis and prediction, the stronger candidate seems to be MSI. Nevertheless, it is worth noting that it has not yet found its place as a robust parameter, and it is only in the guidelines of the European Society for Medical Oncology[10] where MSI is advised to be evaluated in stage II CRC patients in order to contribute in treatment decision-making regarding chemotherapy administration.

The current review concerns the prognostic and predictive significance of MSI status in patients with stage II colon cancer.

**BIOLOGY BEHIND THE MSI PHENOMENON**

**MSI in hereditary and sporadic colon cancer**

The abnormal shortening or lengthening of DNA by 1-6 repeating base pair units is a phenomenon caused by the inactivation of the DNA mismatch repair (MMR) system, and leads to the MSI phenotype[11]. Nearly all patients suffering from hereditary non-polyposis colon cancer (HNPCC) or Lynch Syndrome[12,13], as well as approximately 15%-20% of patients with sporadic early CRC[14], are identified as having the MSI phenotype, which reflects the absence of protein expression encoded by the corresponding MMR genes (hMLH1, hMSH2, hMSH6, or PMS2)[14,15,16]. It has also been shown that the incidence of MSI differs between stage II and stage III disease, and that its prognostic impact seems to be significantly stronger in stage II than in stage III. In its familial form, the genetic basis of instability is largely due to inherited germline mutations of the MMR genes (notably hMLH1 and hMSH2)[17,18], whereas, in its sporadic form, this is due to hMLH1 inactivation by epigenic hypermethylation of the promoter, and less frequently due to genetic alterations of hMSH2 and hMSH6 genes[19,20,21].

Since 1998, microsatellite genotyping of CRC patients for clinically applicable diagnosis is based on panels of specific microsatellite markers (loci containing mono- or di-nucleotide repeated sequences) and standard criteria, as published by Boland et al[22]. Usually the panels used consist of the five markers from the Bethesda reference panel, as well as some additional markers from the alternative panel suggested during the International Workshop on HNPCC in 1997[23]. Based on that, a locus is called unstable if unequivocal instabilities are seen in the tumor sample in comparison to the paired normal DNA in a given patient. MSI is graded as high (MSI-H) when 30% or more of the markers used are unstable, low when 10%-20% of the markers used are unstable, and stable (MSS) when all the markers used are stable.

**CLINICAL VALIDITY OF MSI IN STAGE II AND III COLON CANCER PATIENTS**

**Prognostic value of MSI in stage II colon cancer**

Since approximately 1998, we have known that the majority of MSI-H CRC patients form a unique subset characterized by a differential, less aggressive clinical behavior and a favorable prognosis compared to MSS CRC patients[24,25]. Recent large trials[26-34], a meta-analysis[35], as well as a number of earlier reported retrospective studies[13,36,37], support the favorable stage-adjusted prognosis of MSI-H compared to MSS CRC patients.

Initially, it was the study by Ribic et al[35] which described that patients with MSI-H tumors have a modestly better prognosis than those with MSS tumors. These findings were confirmed five years later when, in a pooled population of more than 500 untreated stage II and III patients, a clear improvement in 5-year disease free survival (DFS) rate was observed in favor of MSI-H patients. Nevertheless, in this report containing a respective number of 5-FU adjuvantly treated stage II and III patients, no significant differences were found between MSI and MSS[35]. Somewhat opposing this finding is the control 5-FU treated arm of the PETACC3 trial, where over 600 stage II and III patients displayed a significant difference in 5-year DFS between MSI and MSS (P = 0.0077), suggesting that MSI improved prognosis can be maintained under 5-FU[36,37].

A 2011 study by Sinicrope et al[38] had the impressive inclusion of 2141 CRC patients and specimens from
various adjuvant trials randomized between 5-FU and no treatment or no 5-FU treatment. Of these, 344 patients had MSI tumors (164 stage II and 180 stage III tumors), and had an overall better prognosis compared to MSS tumor patients[28]. In the multivariate analysis of this article, MSI status was shown to be a statistically significant independent prognostic variable granting MSI CRC patients an improved TTR (P = 0.005), DFS (P = 0.035) and OS (P = 0.031) compared to MSS patients. Similarly to the PETACC3 authors[31], this improved prognosis was shown in both treated and untreated patients with stage II and stage III MSI CRC tumors, as it was highlighted by a statistically significant improved time to recurrence (P < 0.001), DFS, and OS (P = 0.004) compared to patients with MSS tumors. Similarly, a retrospective analysis of MSI status was reported from the QUASAR study[40], in which 1913 patients with stage II colon or rectal cancer were randomly assigned to receive or not receive 6 mo adjuvant treatment with 5FU/LV. The recurrence rate for dMMR tumors was significantly lower in comparison with that for MMR-proficient tumors [11% (25 of 218) vs 26% (438 of 1695) recurred; RR = 0.53; 95%CI: 0.40-0.70; P = 0.001]. Recently, Sinicrope et al[32] introduced primary tumor site as another parameter in the MSI equation; supporting the observation that MSI was found to be prognostic and conferring a favorable outcome only in patients with proximal primary tumors.

Predictive value of MSI in stage II and III colon cancer patients

The hypothetical predictive role of MSI regarding response to 5-FU-based adjuvant chemotherapy has been proven a much more difficult issue to address. Almost every possible relation between MSI and chemotherapy outcome has been described in the international literature. Before going into this subject in more detail and in an attempt to explain the controversies, we could hypothesize that among the reported articles are some based on older studies, with small patient populations and no randomization between treatment vs control, allowing for potential selection bias and other inherent pitfalls of non-randomized comparisons to occur. Although, as will be described, despite this not being the case with the newer larger series, contradictory results were still documented, stressing the possibility that such findings could occur by chance and thus need careful interpretation and validation before unwarranted restriction of chemotherapy in adjuvant stage III MSI-H patients is advocated[48].

As noted above, we have reports highlighting increased sensitivity of MSI patients to 5-FU treatment[47,50], while others are suggestive of no differential response related to MMR proficiency or deficiency[31]. Subsequently, a stronger and larger publication by Ribic et al[9], which incorporated data from randomized clinical trials of surgery only vs 5-FU-based treatment, showed that MSI patients not only did not seem to benefit from adjuvant chemotherapy, but were in fact possibly harmed by it in terms of OS. This notion seemed to be replicated in the second largest publication on the matter, where in a pooled analysis by Sargent et al[27] including a total of 1027 patients, no difference in 5-year DFS rate in favor of MSI patients was observed in the 512 treated stage II and stage III patients (contrary to what was observed in the untreated patient group), suggesting that the survival benefit of MSI patients was abolished by 5-FU treatment. In this article, a statistically significant improved DFS (P = 0.001) was observed in patients with stage III MSS tumors receiving adjuvant 5-FU chemotherapy, but no treatment effect was observed in patients with stage III MSI tumors. A non-statistically significant benefit of adjuvant therapy was observed in patients with stage II MSS tumors, whereas a trend towards worse outcome was observed in patients with stage II MSI tumors[27,48]. However, the authors of the original article, as well as those of the two accompanying editorials[42,53], were extremely careful in the interpretation of the results and did not suggest that stage III CRC patients should thereafter be excluded from standard 5-FU-based chemotherapy. Nevertheless this issue was still evident. Interestingly, in a 2011 article by Sinicrope et al[28] concerning 2141 CRC patients, a benefit of 5-FU treatment for stage III MSI CRC patients was observed, contrary to what was previously reported[27,39]. In addition, the authors went further, and added the germline vs sporadic MSI origin parameter, stating that the beneficial treatment outcome in stage III MSI CRC patients seemed to be restricted to tumors where MSI originated from a germline defect[28]. Unfortunately, Sinicrope et al[34] did not formally compare the predictive value of MSI status for DFS or survival in patients treated in adjuvant 5-FU-based clinical trials compared to untreated control groups in the available cohorts, nor did they perform a formal analysis of the treatment effect in stage II MSI CRC patients[43].

Another pending question open for debate is “which kind of adjuvant chemotherapy should be used in MSI CRC patients?” A trial by Bertagnolli et al[49] was suggestive of a positive effect of irinotecan-based adjuvant chemotherapy (CALGB 89803) in favor of MSI patients[54], which became only marginally significant in the updated trial[28] and was not replicated in PETACC-3[51].

CONCLUSION: ISSUES FOR FUTURE ELABORATION

We believe the prognostic value of MSI to be clearer than its predictive value. According to our opinion, MSI status should be evaluated in all stage II CRC patients in order to contribute in treatment decision-making regarding chemotherapy administration; indeed MSI-H patients can be spared adjuvant chemotherapy.

Although undoubtedly much progress has been made, pending questions, such as the differential impact of MSI status between stage II and stage III CRC patients and the potential harm of 5-FU treatment in stage II CRC MSI patients, still exist and remain largely unanswered[48].

A possible method of moving forward and resolving
the prognostic and predictive validity of such an easy to perform and relatively cheap biomarker in the controversial area of stage II colon cancer disease is to combine efforts. Patient series from large databases from Europe and the United States analyzed together and preferably having in their included trials patients randomized between treatment and no treatment, could allow a per stage stratification and open the field for strong and unambiguous answers regarding prognosis and prediction[30,45].

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]

2. Kuebler JP, Wiedand HS, O’Connell MJ, Smith RE, Colangelo LH, Yothers G, Petrelli NJ, Findlay MP, Sea TE, Atkins JK, Zapas JL, Goodwin JW, Fehrenbacher L, Ramanathan RK, Conley BA, Flynn PJ, Soori G, Colman LK, Levine EA, Lanier KS, Wolmark N. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007; 25: 2198-2204 [PMID: 17470851 DOI: 10.1200/JCO.2006.08.2974]

3. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingen P, Bridgewater J, Tabah-Fisch I, de Gramont A. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004; 350: 2343-2351 [PMID: 15175436 DOI: 10.1056/NEJMoa032709]

4. O’Connell MJ, Laurie JA, Kahn M, Fitzgibbons RJ, Erlichman C, Shepherd L, Moertel CG, Kocha WI, Pazdur R, Wiedand HS, Rubin J, Vukov AM, Donohue JH, Krook JE, Figueredo A. Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. J Clin Oncol 1998; 16: 295-300 [PMID: 9440756]

5. Morris EJ, Maughan NJ, Forman D, Quirke P. Who to treat with adjuvant therapy in Dukes B/stage II colorectal cancer: the need for high quality pathology. Gut 2007; 56: 1419-1425 [PMID: 17494107 DOI: 10.1136/gut.2006.116830]

6. Malmström K, Lohi J, Lindahl H, Pelkonen A, Kajosaari M, Sarna S, Malmberg LP, Mäkelä MJ. Longitudinal follow-up of bronchial inflammation, respiratory symptoms, and pulmonary function in adolescents after repair of esophageal atresia with tracheoesophageal fistula. J Pediatr 2008; 153: 396-401 [PMID: 18534205 DOI: 10.1016/j.jpeds.2008.03.034]

7. Bosman FT, Yan P, Teijpar S, Fiocca R, Van Cutsem E, Kennedy RD, Dietrich D, Roth A. Tissue biomarker development in a multicentre trial context: a feasibility study on the PETACC3 stage II and III colon cancer adjuvant treatment trial. Clin Cancer Res 2009; 15: 5528-5533 [PMID: 19690194 DOI: 10.1158/1078-0432.CCR-09-0741]

8. Ogino S, Nosho K, Irahara N, Shima K, Baba Y, Kirkner GJ, Meyerhardt JA, Fuchs CS. Prognostic significance and molecular associations of 18q loss of heterozygosity: a cohort study of microsatellite stable colorectal cancers. J Clin Oncol 2009; 27: 4591-4598 [PMID: 19704056 DOI: 10.1200/JCO.2009.22.8858]

9. Roth AD, Teijpar S, Delorenzi M, Yan P, Fiocca R, Klingbeil D, Dietrich D, Biesmans B, Bodoky G, Barone C, Aranda E, Nordlinger B, Cisar L, Tabernero J, Cunningham D, Van Cutsem E, Bosman F. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC3-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol 2010; 28: 466-474 [PMID: 20008840 DOI: 10.1200/JCO.2009.23.3452]

10. Russo A, Bazan V, Iacopetta B, Kerr D, Soussi T, Gebbia N. The TP53 colorectal cancer international collaborative study on the prognostic and predictive significance of p53 mutation: influence of tumor site, type of mutation, and adjuvant treatment. J Clin Oncol 2005; 23: 7518-7528 [PMID: 16172461 DOI: 10.1200/JCO.2005.04.471]

11. Teijpar S, Bertagnolli M, Bosman F, Lenz HJ, Harraway L, Woldman F, Warren R, Bild A, Collins-Brennan D, Hahn H, Harkin DP, Kennedy R, Ilyas M, Morreau H, Proutski V, Swanton C, Tohlinson I, Delorenzi M, Fiocca R, Van Cutsem E, Roth A. Prognostic and predictive biomarkers in resected colon cancer: current status and future perspectives for integrating genomics into biomarker discovery. Oncologist 2010; 15: 390-404 [PMID: 20350999 DOI: 10.1634/theoncologist.2009-0233]

12. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Gilmelius B, Haustermans K, Nordlinger B, van de Velde CJ, Balmana J, Regula J, Nagtegaal ID, Beets-Tan RG, Arnold D, Ciardiello F, Hoff P, Kerr D, Kohnke CH, Labianca R, Price T, Scheithauer W, Sorebro A, Tabernero J, Adlerka D, Barroso S, Bodoky G, Douillard JY, El Ghazy H, Gallardo J, Garin A, Glynnes-Jones R, Jordan K, Meshcheryakova Y, Papamichail D, Pfeiffer P, Souglakos I, Turhal S, Cervantes A. ESMO Consensus Guidelines for management of patients with colon and rectal cancer, a personalized approach to clinical decision making. Ann Oncol 2012; 23: 2479-2516 [PMID: 23012255 DOI: 10.1016/S0929-1021(11)70062-5]

13. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993; 260: 816-819 [PMID: 8484122]

14. Aaltonen LA, Peltomäki P, Mecklin JP, Järvinen H, Jass JR, Green JS, Lynch HT, Watson P, Talkvist G, Juhola M. Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients. Cancer Res 1994; 54: 1645-1648 [PMID: 8137274]

15. Aaltonen LA, Peltomäki P, Leach FS, Sistonen P, Pylkänen L, Mecklin JP, Järvinen H, Powell SM, Jen J, Hamilton SR. Clues to the pathogenesis of familial colorectal cancer. Science 1993; 260: 812-816 [PMID: 8484121]

16. Thibodeau SN, French AJ, Cunningham JM, Tester D, Burkart L, Roche PC, McDonnell SK, Schaid DJ, Vocke CW, Michels VV, Farr GH, O’Connell M. Microsatellite instability in colorectal cancer: different mutator phenotypes and the principal involvement of hMLH1. Cancer Res 1998; 58: 1713-1718 [PMID: 9563488]

17. Popat S, Hubbard R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 2005; 23: 609-618 [PMID: 15659508 DOI: 10.1200/JCO.2005.03.086]

18. Peltomäki PT. Genetic basis of hereditary nonpolyposis colorectal carcinoma (HNPCC). Ann Med 1994; 26: 215-219 [PMID: 8074840]

19. Leach FS, Nicolaides NC, Papadopoulos N, Liu B, Jen J, Parsons R, Peltomäki P, Sistonen P, Aaltonen LA, Nyström-Lahti M. Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer (HNPCC). Am J Hum Genet 1997; 61: 808-811 [PMID: 9041175]

20. Kane MF, Loda M, Gaida GM, Lippman J, Mishra R, Goldstein H, Jessup JM, Kolodner R. Methylation of the hMLH1 promoter correlates with lack of expression of hMLH1 in sporadic colon tumors and mismatch repair-defective human tumor cell lines. Cancer Res 1997; 57: 808-811 [PMID: 9041175]

21. Cunningham JM, Kim CY, Christensen ER, Tester DJ, Parc Y, Burgart LJ, Halling KC, McDonnell SK, Schaid DJ, Walsh Vockley C, Kubly V, Nelson H, Michels VV, Thibodeau SN. The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. Am J Hum Genet 2001; 69: 780-790 [PMID: 11524701 DOI: 10.1086/323658]

22. Cunningham JM, Christensen ER, Tester DJ, Kim CY, Roche PC, Burgart LJ, Thibodeau SN. Hypermethylation
of the hMLH1 promoter in colon cancer with microsatellite instability. Cancer Res 1998; 58: 3455-3460 [PMID: 9699680]

23 Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Grivestava S, A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998; 58: 5248-5257 [PMID: 9823339]

24 Roth AD, Delorenci M, Tejpar S, Yan P, Klingbiel D, Fiocca R, d’Ario G, Cíceri L, Labianca R, Cunningham D, Nordlinger B, Bosman F, Van Cutsem E. Integrated analysis of molecular and clinical prognostic factors in stage II/III colon cancer. J Natl Canc Inst 2012; 104: 1635-1646 [PMID: 23104212 DOI: 10.1093/jnci/djs427]

25 Merok MA, Ahlquist T, Rayrýk EC, Tufeland KF, Hektoen M, Sjo OH, Måla T, Svindland A, Lothe RA, Nesbakken A. Microsatellite instability has a positive prognostic impact on stage II colorectal cancer after complete resection: results from a large, consecutive Norwegian series. Ann Oncol 2013; 24: 1274-1282 [PMID: 23235802 DOI: 10.1093/annonc/mds614]

26 Bertagnolli MM, Redston M, Compton CC, Niedzwicki D, Mayer RJ, Goldberg RM, Colacchio TA, Saltz LB, Warren RS. Microsatellite instability and loss of heterozygosity at chromosomal location 18q: prospective evaluation of biomarkers for stages II and III colon cancer—a study of CALGB 9581 and 9803. J Clin Oncol 2011; 29: 3153-3162 [PMID: 21747089 DOI: 10.1200/JCO.2010.33.0092]

27 Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR, French AJ, Kabat B, Foster NR, Torri V, Ribic C, Grothey A, Moore M, Zaniboni A, Seitz JF, Sinicrope FA, Gallinger S. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010; 28: 3219-3226 [PMID: 20498593 DOI: 10.1200/JCO.2009.27.1825]

28 Sinicrope FA, Foster NR, Thibodeau SN, Marsoni S, Monges G, Labianca R, Kim GP, Yothers G, Allegre C, Moore MJ, Gallinger S, Sargent DJ. DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy. J Natl Cancer Inst 2011; 103: 863-875 [PMID: 21597022 DOI: 10.1093/jnci/djr153]

29 Kerr D, Gray R, Quirke P. A quantitative multigene RT-PCR assay for prediction of recurrence in stage II colon cancer: Selection of the genes in four large studies and results of the independent, prospectively designed QUASAR validation study. J Clin Oncol 2009; 27 (suppl; abstr 4000): 15s

30 Roth AD, Tejpar S, Yan P. Correlation of molecular markers in colon cancer with stage-specific prognosis: Results of the translational study on the PETACC3 - EORTC 40993-SAKK 60-00 trial. ASCO Gastrointestinal Cancers Symposium; 2009 Jan 15-17; San Francisco, CA. 2009 (abstr 288)

31 Tejpar S, Bosman F, Delorenci M. Microsatellite instability (MSI) in stage II and III colon cancer treated with 5FU-LV or 5FU-LV and irinotecan (PETACC 3-EIORTC 40993-SAKK 60/00 trial). J Clin Oncol 2009; 27 (suppl; abstr 4001): 15s

32 Sinicrope FA, Mahoney MJ, Smyrk TC, Thibodeau SN, Warren RS, Bertagnolli MM, Nelson GD, Goldberg RM, Sargent DJ, Alberts SR. Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy. J Clin Oncol 2013; 31: 3664-3672 [PMID: 24019539 DOI: 10.1200/JCO.2013.48.9591]

33 Gafà R, Maestri I, Matteuzzi M, Santini A, Ferretti S, Cavazzini L, Lanza G. Sporadic colorectal adenocarcinomas with high-frequency microsatellite instability. Cancer 2000; 89: 2025-2037 [PMID: 11066042]

34 Gryfe R, Kim H, Hsieh ET, Aronson MD, Holowaty EJ, Bull SB, Redston M, Gallinger S. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. N Engl J Med 2002; 346: 69-77 [PMID: 10631274 DOI: 10.1056/NEJM200101313420201]

35 Halling KC, Foss G, McDonnell SK, Burgardt LJ, Schaid DJ, Peterson BJ, Moon-Tasson L, Mahoney MR, Sargent DJ, O’Connell MJ, Witzig TE, Farr GH, Goldberg RM, Thibodeau SN. Microsatellite instability and 5p allelic imbalance in stage B2 and C colorectal cancers. J Natl Cancer Inst 1999; 91: 1295-1303 [PMID: 10436318]

36 Kakar S, Aksoy S, Burgardt LJ, Smyrk TC. Mucinous carcinoma of the colon: correlation of loss of mismatch repair enzymes with clinicopathologic features and survival. Mod Pathol 2004; 17: 696-700 [PMID: 15017435 DOI: 10.1038/modpathol.3800093]

37 Lanza G, Gafà R, Santini A, Maestri I, Guezzoni L, Cavazzini L. Immunohistochemical test for MLH1 and MSH2 expression predicts clinical outcome in stage II and III colorectal cancer patients. J Clin Oncol 2006; 24: 2559-2567 [PMID: 16710035 DOI: 10.1200/JCO.2005.02.433]

38 Lothe RA, Peltomäki P, Meling GI, Aaltenen LA, Nyström-Lahti M, Pylväkänén L, Heimdal K, Andersen TI, Møller P, Rognum T. Genomic instability in colorectal cancer: relationship to clinicopathological variables and family history. Cancer Res 1999; 59: 5849-5852 [PMID: 8261392]

39 Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, Hamilton SR, Laurent-Puig P, Gryte R, Shepherd LE, Tu D, Redston M, Gallinger S. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003; 349: 247-257 [PMID: 12867608 DOI: 10.1056/NEJMoa022289]

40 Samowitz WS, Curtin K, Ma KN, Schaffer D, Coleman LW, Leppert M, Slattery ML. Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. Cancer Epidemiol Biomarkers Prev 2001; 10: 917-923 [PMID: 11535541]

41 Sinicrope FA, Rego RL, Halling KC, Foster N, Sargent DJ, LaPlant B, French AJ, Laurie JA, Goldberg RM, Thibodeau SN, Witzig TE. Prognostic impact of microsatellite instability and DNA ploidy in human colon carcinoma patients. Gastroenterology 2006; 131: 729-737 [PMID: 16952542 DOI: 10.1053/j.gastro.2006.06.005]

42 Bubb VJ, Curtis LJ, Cunningham C, Dunlop MG, Carothers AD, Morris RG, White S, Bird CC, Wyllie AH. Microsatellite instability and the role of MSI-H in sporadic colorectal cancer. Oncogene 1996; 12: 2641-2649 [PMID: 8700523]

43 Lukish JR, Muro K, DeNobile J, Katz R, Williams J, Cruesse DF, Drucker W, Kirsch I, Hamilton SR. Prognostic significance of DNA replication errors in young patients with colorectal cancer. Ann Surg 1998; 227: 51-56 [PMID: 9445110]

44 Wright CM, Dent OF, Barker M, Newland RC, Chapuis PH, Bokey EL, Young JP, Leggett BA, Jass JR, Macdonald GA. Prognostic significance of extensive microsatellite instability in sporadic colorectal cancer. Br J Surg 2000; 87: 1197-1202 [PMID: 10971428 DOI: 10.1056/j.bjs.2000.01508.x]

45 Tejpar S, Saridaki Z, Delorenci M, Bosman F, Roth AD. Microsatellite instability, prognosis and drug sensitivity of stage II and III colorectal cancer: more complexity to the puzzle. J Natl Cancer Inst 2011; 103: 841-844 [PMID: 21597023 DOI: 10.1093/jnci/djq017]

46 Hutcheson G, Southward K, Handley K, Magill L, Beaumont C, Stahlshmidt J, Richman S, Chambers P, Seymour M, Kerr D, Gray R, Quirke P. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. J Clin Oncol 2011; 29: 1261-1270 [PMID: 21385284 DOI: 10.1200/JCO.2010.30.1366]

47 Elsheh H, Joseph D, Grieu F, Zeps N, Spyr N, Iacopetta B. As...
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Association of tumour site and sex with survival benefit from adjuvant chemotherapy in colorectal cancer. *Lancet* 2000; 355: 1745-1750 [PMID: 10832824 DOI: 10.1016/S0140-6736(00)02261-3]

Elsaleh H, Powell B, Soonttrapornchai P, Joseph D, Goria F, Spry N, lacopetta B. p53 gene mutation, microsatellite instability and adjuvant chemotherapy: impact on survival of 388 patients with Dukes’ C colon carcinoma. *Oncology* 2000; 58: 52-59 [PMID: 10644941]

Hemminki A, Mecklin JP, Järvinen H, Aaltonen LA, Joensuu H. Microsatellite instability is a favorable prognostic indicator in patients with colorectal cancer receiving chemotherapy. *Gastroenterology* 2000; 119: 921-928 [PMID: 11040179]

Jover R, Zapater P, Castells A, Llor X, Andreu M, Cubiella J, Balaguer F, Sempere L, Nicola RM, Bujanda L, René JM, Clofent J, Bessa X, Morillas JD, Nicolás-Pérez D, Pons E, Payá A, Alenda C. The efficacy of adjuvant chemotherapy with 5-fluorouracil in colorectal cancer depends on the mismatch repair status. *Eur J Cancer* 2009; 45: 365-373 [PMID: 18722765 DOI: 10.1016/j.ejca.2008.07.016]

Kim GP, Colangelo LH,Wieand HS, Paik S, Kirsch IR, Wolkmark N, Allegra CJ. Prognostic and predictive roles of high-degree microsatellite instability in colon cancer: a National Cancer Institute-National Surgical Adjuvant Breast and Bowel Project Collaborative Study. *J Clin Oncol* 2007; 25: 767-772 [PMID: 17228023 DOI: 10.1200/JCO.2006.05.8172]

Ng K, Schrag D. Microsatellite instability and adjuvant fluorouracil chemotherapy: a mismatch? *J Clin Oncol* 2010; 28: 3207-3210 [PMID: 20498398 DOI: 10.1200/JCO.2010.28.9314]

Kerr DJ, Midgley R. Defective mismatch repair in colon cancer: a prognostic or predictive biomarker? *J Clin Oncol* 2010; 28: 3210-3212 [PMID: 20498404 DOI: 10.1200/JCO.2010.28.9322]

Bertagnolli MM, Niedzwiecki D, Compton CC, Hahn HP, Hall M, Damar B, Jewell SD, Mayer RJ, Goldberg RM, Saltz LB, Warren RS, Redston M. Microsatellite instability predicts improved response to adjuvant therapy with irinotecan, fluorouracil, and leucovorin in stage III colon cancer: Cancer and Leukemia Group B Protocol 89803. *J Clin Oncol* 2009; 27: 1814-1821 [PMID: 19273709 DOI: 10.1200/JCO.2008.18.2071]

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