Research Article

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Mismatch Repair/Microsatellite Instability Testing and Genetic Consult Referral Practice Patterns for Colorectal Cancer in a Community Hospital Based Cancer Center in Rural Central Nebraska.

Christina Ternent, Whitney Wedel, Soe Min Tun, Shari Fiala, Tonya Peterson, Bronson Reily, Charles Kelly Simpson, Adam Horn, Nicholas Lintel, Carlene Springer, Leslie Robbins, Mehmet Sitki Copur.

***Corresponding author**

Mehmet Sitki Copur, MD,FACP,
Medical Director of Oncology,Medical Oncology/Hematology Professor, University of Nebraska Medical Center, Adjunct Faculty,Omaha,
Mary Lanning Healthcare,Morrison Cancer Center
815 N Kansas Ave Hastings, NE 68901.
O: 402/460-5899 ext. 5068
C: 308/390-3493
F: 402/460-5898
E-mail : mehmet.copur@marylanning.org

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ABSTRACT

Background : MMR protein deficient colorectal cancer (CRC) has distinctive clinical and pathologic features which can be either sporadic or inherited. Mismatch Repair (MMR), Microsatellite Instability (MSI) testing of CRC tumor tissue for absent MMR proteins and BRAF (V600E) mutation has become a routine practice in most tertiary cancer centers. We sought to examine the utilization of MMR and BRAF testing and genetic consultation referral pattern in the diagnostic evaluation and management of CRC patients in a community hospital-based cancer center in rural central Nebraska.

Methods : All pathologically confirmed CRC patients diagnosed between January 2018 and December 2023 at Morrison Cancer Center in central rural Nebraska were evaluated. Data on age, gender, tumor location, stage, tumor testing for MMR, BRAF (V600E) and genetic consultation referrals were collected and analyzed. The independent sample t-test, and Fisher's exact tests were used to look at the association of patient characteristics based on the MMR status.

Results: Among a total of 272 patients (137 female, 135 male, median age 71), seventy-nine percent (215/272)were non-metastatic and twenty-one percent (57/272)) were metastatic CRC. Overall, 75% (205/272) of patients had MMR/MSI testing done and 32% (86/272) had BRAF V600E testing performed. Fifteen percent (42/272) of all CRC patients had deficient MMR (dMMR) and 60% (163/272) had proficient MMR (pMMR) while 67/272 (25%) patients did not have MMR testing. Thirty-nine percent (107/272) of all CRC patients were referred for genetic consultation but only 12% (33/272) of them followed through with their appointment. Four patients (4/272,1.4%) were diagnosed with Lynch Syndrome. Among 205 patients who had MMR/MSI testing, metastatic CRC patients were more likely to have dMMR status than non-metastatic CRC patients [4/47 (8.5%) vs 38/158 (2.4%)], p=0.023. More patients with dMMR status than pMMR status had BRAF mutation [22/28 (78%) vs 6/28 (21%)], p=0.0001. Genetic consultation referrals and Lynch syndrome were more likely in dMMR CRC group than pMMR group.

Conclusions: We present a real world rural community hospital based cancer center data from central Nebraska. Our data provides a glimpse of universal molecular testing and genetic consultation referral practice pattern for CRC patients in a rural community-based cancer center. Efforts to enhance the accessibility and integration of universal molecular testing and genetic counseling services into routine cancer care at the rural community oncology settings are crucial to ensure equitable cancer care for all patients, regardless of their geographic location.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer related deaths in the United States with an estimated 152,810 new diagnoses and 53,010 deaths for 2024. [1] CRCs with microsatellite instability (MSI) occur as a result of deficient mismatch repair (dMMR) proteins and account for

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approximately 16 % of newly diagnosed CRCs with the highest prevalence among stage I-II tumors.[2] dMMR commonly arises because of a loss of MMR protein function, which is caused by germline and/or somatic mutations including copy-number loss of MMR genes MLH1, MSH2, MSH6, or PMS2 or somatic hypermethylation of the MLH1 promoter. MMR deficiency leads to an accumulation of unrepaired errors in short repetitive DNA microsatellites.[3] MMR protein deficient CRC can be either sporadic or inherited as part of Lynch Syndrome. Sporadic dMMR is caused by the hypermethylation of the promoters of mismatch repair (MMR) genes, in hereditary form (Lynch syndrome) it is due to germline mutations of MMR or EPCAM genes. MSI CRC has distinctive clinical and pathologic features.

The three most widely used methods to screen and guide management for patients with MSI CRC are MMR protein staining by immunohistochemistry (IHC), MSI testing by polymerase chain reaction (PCR), and next generation sequencing (NGS) of the tumor tissue DNA. [4,5] IHC provides information about the MMR proteins expressed in the sample, MSI by PCR measures MMR function by detecting changes in DNA that results when major MMR function is lost, and NGS detects mutations within microsatellite sequences of tumor samples.[6] The application of immunohistochemistry (IHC) testing for mismatch repair proteins (MMR) and BRAF mutation followed by genetic consultation as indicated play a crucial role in guiding clinical decision-making and improving patient outcomes in CRC. Among the available methods, IHC testing that uses an antibody to detect absent MMR proteins and BRAF (V600E) mutant protein in CRC tumor tissue has become the most widely utilized practice in most tertiary cancer centers.

Historically, MMR deficiency testing was not uniformly recommended for all patients with CRC, but rather for individuals at higher risk for MMR deficiency based on personal or family history. The Amsterdam criteria and the Bethesda guidelines were developed to help identify patients at high risk for Lynch syndrome according to age, personal cancer history, and family history. Universal MMR deficiency testing was proposed by Hampel et al in 2008 but was not incorporated into the National Comprehensive Cancer Network guidelines until 2014. Currently, most national consortiums recommend universal screening for MSI tumors in all patients with newly diagnosed CRC. However, significant underuse of universal testing may occur.

In the current study, we retrospectively analyzed utilization of universal molecular testing for all CRC patients along with genetic consultation referral pattern for the diagnostic evaluation and management of CRC patients in a rural community hospital-based cancer center in central Nebraska.

METHODS

Between January 2018 and December 2023, two hundred seventy two patients with pathologically confirmed colorectal cancer diagnosed at Mary Lanning Healthcare Morrison Cancer Center in rural central Nebraska were evaluated for age, gender, tumor location, stage, year of diagnosis, receipt of MMR deficiency testing from initial diagnosis through the first course of treatment, and BRAF (V600E) mutation analysis and genetic consultation referral rates as indicated. We categorized tumor location as right (cecum to transverse colon), left (splenic flexure to sigmoid colon), and rectosigmoid or rectal. Treatment characteristics evaluated included receipt of definitive surgical resection, type of resection, number of regional lymph nodes examined (<12 vs ≥12) in patients who underwent colectomy, and receipt of chemotherapy. Pathology reports, laboratory reports (internal or external), admission notes, or consultation notes (internal or external) were utilized to identify whether MMR deficiency testing was performed and if followed by BRAF testing in MMR deficient cases.

The independent sample t-test, and Fisher's exact tests were used to look at the association of patient characteristics with the MMR status.

RESULTS

A total of 272 patients, 137 female, 135 male, median age 71 (range:38-96) were evaluated. Among 272 patients 215 (79%) were non-metastatic while twenty one percent (57/272) were metastatic CRC. Seventy five percent (205/272) of patients were documented as undergoing MMR deficiency testing with thirty two percent (86/272) also having had BRAF V600E mutation testing. Among 272 patients 67 (25%) did not have MMR testing done. Overall, fifteen percent (42/272) of patients had dMMR and 163/272 (60%) had pMMR.

Metastatic CRC patients were more likely to have dMMR status than non-metastatic patients [4/47 (8.5%) vs 38/158 (2.4%)], p=0.023. More pts with dMMR status than pMMR status had BRAF mutation [22/28 (78%) vs 6/28 (21%)], p=0.0001. Genetic consultation referrals and Lynch syndrome were more likely in dMMR CRC group, p=0.0009, and p=0.002. There was an increasing trend for more patients with right sided tumors to have dMMR. An increasing trend in the proportion of patients tested for both MMR and BRAF mutation was observed over the five year period.(**Figure 1 and 2**).

Thirty-nine percent (107/272) of patients were referred for genetic consultation. Twelve percent (33/272) complied and followed through with genetic counseling appointments. Lynch Syndrome was diagnosed in four patients (4/272, 1.4%). dMMR was more common in metastatic colorectal cancer patients (4/47 (8.5%) versus non-metastatic patients 38/158

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(2.4%), p=0.023. More patients with dMMR status had BRAF mutations [22/28 (78%) than pMMR status [6/28 (21%)], p=0.0001. Genetic consultation referrals and Lynch syndrome were more likely in dMMR CRC group, p=0.0009, and p=0.002. (**Table 1**)

Figure 1.

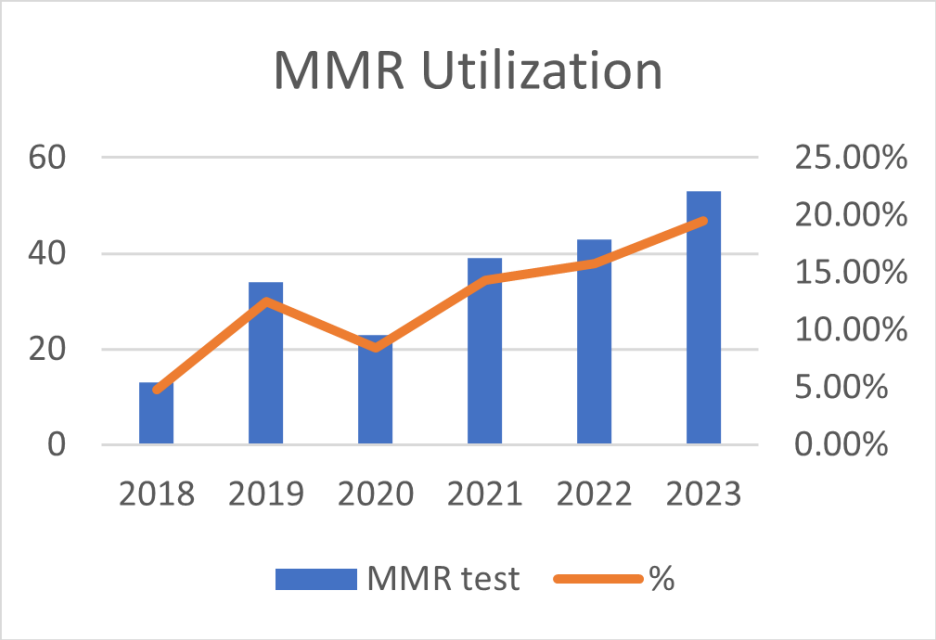
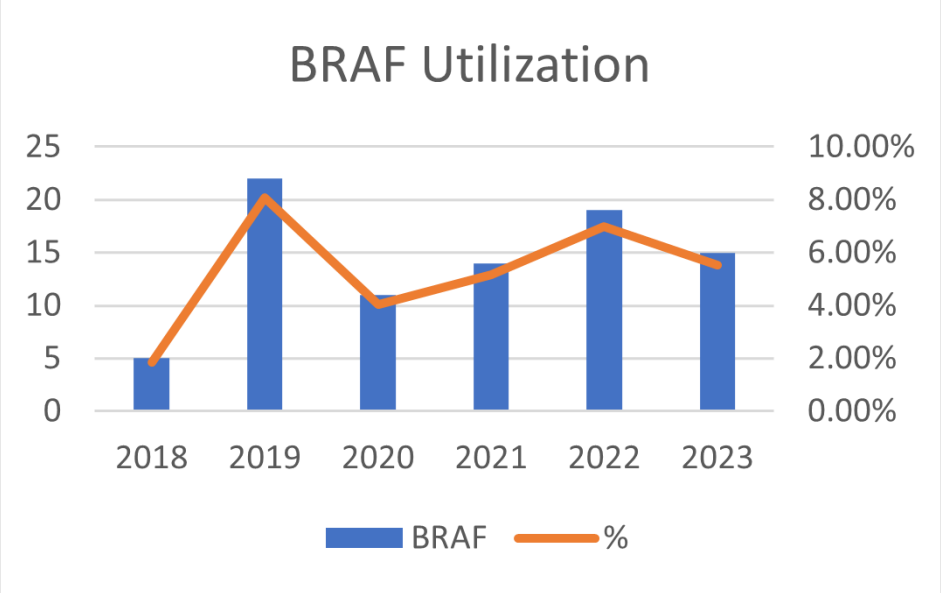


Figure 2.



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Table1.

	dMMR 42/272	pMMR 163/272	P
Age (Median)	76	70	
Gender			
Female	22 (52%)	79 (49%)	0.7
Male	20 (48%)	84 (51%)	
Tumor Site			
Right Colon	28 (67%)	83 (51%)	
Left Colon	11 (26%)	46 (28%)	0.07
Rectum	3 (7%)	34 (21%)	
Tumor Stage			
Metastatic	4 (10%)	43 (26%)	0.02
Non-metastatic	38 (91%)	120 (74%)	
BRAF mutation			
BRAF (-)	11 (33%)	47 (89%)	0.0001
BRAF (+)	22 (67%)	6 (11%)	
Genetic Consultation			
Referral	16 (49%)	17 (17%)	0.0009
No referral	17 (52%)	81 (83%)	
Lynch syndrome			
Yes	4 (16%)	0 (0%)	0.0020
No	21 (84%)	87 (100%)	

DISCUSSION

Although hereditary CRC syndromes constitute only 3% to 5% of all CRCs, approximately 20% to 30% of CRCs are potentially linked to genetic factors. (7) Systematic screening for Lynch syndrome for all colorectal tumors has been recommended since 2009, but implementation of universal screening has been variable.(8) The 2013 National Comprehensive Cancer Network guidelines and United States Multi-Society Task Force on colorectal cancer have recommended tumor screening for Lynch Syndrome for all CRC patients or for CRC patients diagnosed before age 70 and those 70 years and above who meet Bethesda guidelines and for all endometrial cancer patients up to age 50. (9,10)

Due to advances in our understanding of MSI and discovery of effective immunotherapy options for CRC patients with MSI, in 2018, NCCN has updated its recommendations by endorsing molecular testing for MMR/MSI or analysis for deficient MMR protein expression in all patients with newly diagnosed CRC. (11) Despite all these guideline based recommendations, compliance with utilization of universal MMR deficiency testing for all CRC patients has been poor with significant underuse of testing among adult CRC patients.

In a National Cancer Data Base study involving 152,993 adult CRC patients, while the proportion of patients tested for MMR deficiency showed some increase between 2010 and 2012 (22.3% vs 33.1%; P<.001), overall, only 43,143 patients (28.2%) underwent testing. Among 17,218 younger adult patients with CRC, overall, 7422 (43.1%) underwent MMR deficiency testing and the proportion of patients tested in this younger group also increased between 2010 and 2012 (36.1% to 48.0%;P < .001). Irrespective of age higher educational level, later diagnosis year, early stage disease, and number of regional lymph nodes examined (≥12) were independently associated with the use of MMR deficiency testing, whereas older age, Medicare, Medicaid, or uninsured status, nonacademic vs academic/research facility type, rectosigmoid or rectal tumor location, unknown grade, and nonreceipt of definitive surgery were associated with underuse of MMR deficiency testing. (12)

In a survey of 151 US physicians (91 oncologists, 15 surgeons and 45 pathologists), universal testing of all CRC patients for MMR/MSI testing was reported by 68.9% (104/151) of surveyed physicians, while 29.8% (45/151) of surveyed physicians stated selectively ordering the test for some CRC patients. Key barriers for testing included insufficient tissue sample (48.3%, 73/151), declination of the test (35.8%, 54/151) and insurance cost concerns for patients (31.1%, 47/151), while 27.2% (41/151) of surveyed physicians reported no barriers.(13) In a survey of US cancer centers (39 National Cancer Institute-designated Comprehensive Cancer Centers, 50 randomly selected American College of Surgeons-accredited Community Hospital Comprehensive Cancer Programs, and 50 Community Hospital Cancer Programs),

the use of reflex IHC and/or MSI screening after diagnosis of CRC was 71% for NCI comprehensive cancer centers, 36% for American Colleague of Surgeons-accredited community hospital comprehensive cancer centers, and only 15% for community hospital centers. (14) In another study, when asked how does the family history of patients with stage II CRC influence selection of genetic and molecular testing, both related and unrelated to Lynch syndrome, 0ncologists' self-reported ordering of Lynch syndrome–related tests was strongly associated with the strength of CRC family history, but even so, not all oncologists would order germline testing for mismatch repair (MMR) genes, much less screen for Lynch syndrome by ordering microsatellite instability and/or immunohistochemistry for MMR proteins, in a patient scenario with the strongest family history of CRC. (15)

Little is known about how these molecular testing guidelines for CRC are translated into routine and real-life clinical practice in the rural community setting. Eighty-five percent of all cancer patients are treated in the community hospitals in the U.S. (16,17) For rural and underserved cancer patients and their families, there are significant advantages when they can receive high quality cancer treatment close to home.(18-21) However, there may be differences in the level of guideline-recommended care and outcomes provided in the community hospital based cancer centers compared to academic medical centers or National Cancer Institute (NCI)-Designated Cancer Centers. (17, 22-24) We assessed MMR/MSI and BRAF testing for CRC patients, as well as genetic consultation referrals in a rural community hospital based cancer program in Nebraska. Data collection covered a five-year period starting in 2018 when NCCN guidelines were updated to include molecular testing for MMR/MSI or analysis for deficient MMR protein expression for all patients with newly diagnosed CRC. (11)

In our study we found a high seventy-five percent (205/272) MMR/MSI testing rate along with thirty-two percent (86/272) BRAF V600E mutation testing rate in our American Colleague of Surgeons-accredited community hospital based cancer center. There was an increasing trend in these percentages over the five-year period. Our findings of seventy-five percent is well above the reported average 28.2 % in the National Cancer Data Base study, and above the 71% rate for NCI comprehensive cancer centers, 36% rate for American Colleague of Surgeons-accredited community hospital comprehensive cancer centers, and 15% rate for community hospital centers rates. (14) Possible explanations for this higher performance may include increased awareness of universal screening with the 2018 NCCN guidelines, availability of IHC MMR testing in community hospital based pathology departments, discovery and approval of immunotherapy options for dMMR CRC patients, and multidisciplinary tumor boards held by our for American Colleague of Surgeons-accredited community hospital comprehensive cancer center. Among 272 patients 67 (25%) did not have MMR testing done due to varying reasons similar to previously reported barriers including insufficient tissue sample, declination of the test, and insurance cost concerns. We also evaluated BRAF testing which was ordered as a reflex test for dMMR patients along with genetic consultation referrals. Genetic consultation referrals were more likely in dMMR CRC group in addition to family history.

Our findings may provide some insights into the differences of cancer care delivery in a geographically and demographically diverse population, shedding light on approaches to genetic consultation services and immunohistochemistry testing. The findings of this study not only contribute to our understanding of rural cancer care but also emphasize the need for tailored interventions and support systems to address the distinct needs of rural communities in the provision of high-quality cancer care. While our molecular and genetic screening rates for all CRC patients are above the reported national levels and genetic consultation services are available in our rural community-based cancer center, their utilization remains suboptimal. This is likely due to various barriers including limited access to genetic counselors, lack of awareness among healthcare providers, patient non-compliance, and financial constraints.

CONCLUSIONS

Little is known about the uptake and application of national guidelines into routine and real-life clinical practice in the community setting. Our data provides a glimpse of universal molecular testing for all CRC patients since its firm national guideline recommendation, along with BRAF testing and genetic consultation referrals in a rural community-based cancer center over the five-year period. Efforts to enhance the accessibility and integration of universal molecular testing for all CRC patients and genetic counseling services into routine cancer care pathways are necessary to ensure equitable access for all patients, regardless of geographic location.

REFERENCES

1. Siegel RL, Giaquinto AN, Jemal DVM A. Cancer Statistics 2024. CA Cancer J Clin.2024;74:12–49.

2. Gutierrez C, Ogino S, Meyerhardt JA et al. JCO Precision Oncology 2023;7: https://doi.org/10. 1200/ PO .22.0017

3. Vilar, E., Gruber, S. Microsatellite instability in colorectal cancer—the stable evidence. Nat Rev Clin Oncol 7, 153–162 (2010).

4. Sargent, D.J.,Marsoni, S., Monges, S.N., et al. Defective

mismatch repair as a predictive marker for lack of efficacy of fluorouracil based adjuvant therapying colon cancer . J Clin Oncol 2010 ;28:3219-3226.

5. Le, D.T., Uram, J.N., Wang, H., et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015; 372:2509-2520.

6. Zhang, et al. (2008) Immunohistochemistry versus Microsatellite Instability Testing for Screening Colorectal Cancer Patients at Risk for Hereditary Nonpolyposis Colorectal Cancer Syndrome: Part II. The Utility of Microsatellite Instability Testing. J. Mol. Diagnostics. 10, 301–307.

7. Rustgi AK. The genetics of hereditary colon cancer. Genes Dev. 2007 Oct 15;21(20):2525-2538.

8. Rahm AK, Cragun D, Hunter JE, et al. Implementing universal Lynch syndrome screening (IMPULSS): protocol for a multi-site study to identify strategies to implement, adapt, and sustain genomic medicine programs in different organizational contexts. BMC Health Serv Res. 2018 Oct 30;18(1):824

9. Colorectal cancer screening.Version2.2013.

10. Giardiello FM, Allen JI, Axilbund JE, et al. Am J Gastroenterol 2014; 109:1159–1179

11. National Comprehensive Cancer Network. Genetic/ Familial High-Risk Assessment: Colorectal (Version 1 2018). Available online: https://www.nccn.org/ professionals/physician_ gls/pdf/genetics_colon.pdf

12. Shaikh T, Handorf EA, Meyer JE, Hall MJ, Esnaola NF. Mismatch Repair Deficiency Testing in Patients With Colorectal Cancer and Nonadherence to Testing Guidelines in Young Adults. JAMA Oncol. 2018 Feb 8;4(2):e173580.

13. Eriksson J, Amonkar M, Al-Jassar G, et al. Mismatch Repair/Microsatellite Instability Testing Practices among US Physicians Treating Patients with Advanced/ Metastatic Colorectal Cancer. J. Clin. Med. 2019, 8, 558.

14. Beamer, L.C.; Grant, M.L.; Espenschied, C.R.; Blazer, K.R.; Hampel, H.L.; Weitzel, J.N.; MacDonald, D.J. Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal results. J. Clin. Oncol. 2012, 30, 1058–1063.

15. Parikh, A.R.; Keating, N.L.; Liu, P.H.; Gray, S.W.; Klabunde, C.N.; Kahn, K.L.; Haggstrom, D.A.; Syngal, S.; Kim, B. Oncologists' selection of genetic and molecular testing in the evolving landscape of stage II colorectal cancer. J. Oncol. Pract. 2016, 12, 259–260, 308–319.

16. Petrelli NJ. A community cancer center program: getting to the next level. J Am Coll Surg. 2010;210(3):261–270.

17. Pfister DG, Rubin DM, Elkin EB. Risk Adjusting Survival Outcomes in Hospitals That Treat Patients With Cancer Without Information on Cancer Stage (vol 1, pg 1303, 2015). Jama Oncol. 2015;1(9):1323–1323.

18. Ambroggi M, Biasini C, Del Giovane C, Fornari F, Cavanna L. Distance as a Barrier to Cancer Diagnosis and Treatment: Review of the Literature. The oncologist. 2015;20(12):1378–1385.

19. Farrow DC, Hunt WC, Samet JM. Geographic variation in the treatment of localized breast cancer. The New England journal of medicine. 1992;326(17):1097–1101.

20. Bakker DA, DesRochers C, McChesney C, Fitch M, Bennett J. Community cancer clinics: patients' perspectives. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. 2001;9(4):234–240.

21. Joynt KE, Harris Y, Orav EJ, Jha AK. Quality of care and patient outcomes in critical access rural hospitals. Jama. 2011;306(1):45–52.

22. Friese CR, Earle CC, Silber JH, Aiken LH. Hospital characteristics, clinical severity, and outcomes for surgical oncology patients. Surgery. 2010;147(5):602–609.

23. Paulson EC, Mitra N, Sonnad S, et al. National Cancer Institute designation predicts improved outcomes in colorectal cancer surgery. Ann Surg. 2008;248(4):675–686.

24. Shulman LN, Palis BE, McCabe R, et al. Survival As a Quality Metric of Cancer Care: Use of the National Cancer Data Base to Assess Hospital Performance. Journal of Oncology Practice. 2018;14(1):e59-e72.