

Geriatric Nutrition Risk Index as a Predictive Marker of Tolerability and Vulnerability to Chemotherapy in Patients With Colorectal Cancer

Kota Sasaki (✉ h17gm107@hirosaki-u.ac.jp)

Hirosaki University School of Medicine Graduate School of Medicine: Hirosaki Daigaku Igakubu
Daigakuin Igaku Kenkyuka <https://orcid.org/0000-0002-0746-4487>

Kengo Hasui

Hirosaki University School of Medicine Graduate School of Medicine: Hirosaki Daigaku Igakubu
Daigakuin Igaku Kenkyuka

Yu Chen

Hirosaki University School of Medicine Graduate School of Medicine: Hirosaki Daigaku Igakubu
Daigakuin Igaku Kenkyuka

Kensuke Saito

Hirosaki University School of Medicine Graduate School of Medicine: Hirosaki Daigaku Igakubu
Daigakuin Igaku Kenkyuka

Takenori Takahata

Hirosaki University School of Medicine Graduate School of Medicine: Hirosaki Daigaku Igakubu
Daigakuin Igaku Kenkyuka

Atsushi Sato

Hirosaki University School of Medicine Graduate School of Medicine: Hirosaki Daigaku Igakubu
Daigakuin Igaku Kenkyuka

Research Article

Keywords: Geriatric Nutrition Risk Index, colorectal cancer, adverse event rates, tolerability, nutrition support

Posted Date: March 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-236105/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose: Malnutrition increases chemotherapy toxicity and impairs quality of life. Previous studies have shown an association between nutrition assessment tools, such as the Geriatric Nutrition Risk Index (GNRI), and adverse events of chemotherapy. However, none are specific to colorectal cancer (CRC). Therefore, we evaluated this association by investigating adverse events needing treatment (AENT) in patients with CRC.

Methods: We retrospectively classified 147 patients with CRC into the risk group (GNRI<98, 85 patients) and the no-risk group (GNRI≥98, 62 patients). We defined AENT as infection requiring antibiotics administration, grade ≥2 leukocytopenia, feasible neutropenia, anemia and thrombocytopenia requiring transfusion, grade≥3 diarrhea, and acute organ failure.

Results: We compared the two groups regarding AENT, antibiotic use, admission treatment for AENT, and mortality. Fifty-two (61.2%) and twenty-eight (45.1%) patients in the risk group and no-risk group, respectively, experienced AENT (odds ratio [OR], 0.948; [95% confidence interval, 0.919–0.978]; area under the curve of the receiver-operating characteristic curve, 0.694; [0.608–0.780]). Those in the risk group had increased antibiotic use (OR, 0.945; [0.912–0.979]) and mortality (OR, 0.845; [0.765–0.932]). AENT and performance status were not associated, while GNRI score and chemotherapy toxicity were inversely associated.

Conclusion: GNRI can predict a patient's tolerability for cytotoxic chemotherapy. Prospective studies should validate GNRI and nutrition support benefits.

Introduction

Malnutrition is common among patients with unresectable cancer [1, 2]. About 40–65% of patients with colorectal cancer (CRC) are diagnosed with malnutrition [3]. Moreover, malnutrition increases infection, hospitalization, and medical expenses and is associated with poor prognosis in patients with cancer [4, 5]. If cancer treatment is ineffective, the disease progression worsens the patient's nutrition status, and cancer-related inflammation and metabolic changes increase their risk of infection and mortality [6, 7]. However, cytotoxic chemotherapy may be overtreatment for malnourished patients due to the severe adverse events arising as a result of chemotherapy. If cytotoxic chemotherapy is excessive, adverse events worsen nutrition status and impair quality of life in patients with cancer [8, 9]. Therefore, we considered the adverse events associated with cytotoxic chemotherapy to indicate malnutrition and tolerance to chemotherapy [6, 10–12]. Thus, in patients with cancer, nutrition assessment and support are essential [1].

Previous reports have validated several nutrition assessment tools associated with adverse events due to chemotherapy and prognosis, such as the Patient-Generated Subjective Global Assessment (PG-SGA) [3, 13, 14], Mini-Nutrition Assessment-Short Form (MNA-SF) [9, 10, 15–17], Nutrition Risk Index (NRI) [18], and Geriatric Nutrition Risk Index (GNRI) [10, 11, 19]. Malnutrition scores from PG-SGA and MNA-SF were

associated with adverse events due to chemotherapy and less tolerability to chemotherapy [15, 20, 21]. However, these nutrition assessment tools based on extensive questionnaires are primarily subjective and have the risk of memory bias [22, 23]. Therefore, PG-SGA and MNA-SF are difficult for geriatric patients and uncooperative patients. The NRI comprises objective calculations based on basal body weight, height, and serum albumin levels. However, basal body weight is uncertain, which may cause memory bias, and most patients with cancer experience weight loss before diagnosis [24]. Furthermore, NRI calculation is impossible without records of the patient's weight. A previous study reported the association between NRI and chemotherapy toxicity [24]. In contrast, other studies reported that NRI might not predict chemotherapy-induced adverse events [3, 25]. Thus, the association between NRI and chemotherapy toxicity remains controversial. Among the four validated nutrition assessment tools, GNRI is the only accurate and objective tool.

GNRI is a simple and objective tool requiring less time to perform and aids in undertaking patient nutrition risk assessment [1]. Physicians can calculate GNRI in clinical practice without changing the clinical routine because patient's body weight, height, and blood test parameters are routinely measured before cytotoxic chemotherapy. Bouillanne et al. developed GNRI as a tool to assess older patients' nutrition risk primarily [6, 22, 26]. However, recent studies showed that GNRI score can assist with the identification of nutrition risk and prediction of tolerability, vulnerability, and prognosis in patients with cancer [10, 11, 19, 23, 27], chronic diseases [28, 29], and who undergo hemodialysis [30]. Although GNRI is a well-established nutrition assessment tool for predicting adverse events associated with chemotherapy in various cancers, this tool's utility in patients with CRC remains unexplored.

This study aimed to assess the association between GNRI and tolerability, vulnerability to cytotoxic chemotherapy in patients with CRC by investigating the occurrence of chemotherapy-related adverse events.

Materials And Methods

Patients

We reviewed the medical records of patients with CRC visiting the Department of Medical Oncology at Hirosaki University Hospital from April 2008 to March 2020.

We found 214 medical records of patients with CRC. The eligibility criteria were as follows: chemotherapy undertaken at the Department of Medical Oncology, Hirosaki University Hospital; Eastern Cooperative Oncology Group Performance Status (PS) ≤ 2 ; stable condition without severe comorbidities; CRC diagnosed histologically; data available on height, weight, and serum albumin level at the first chemotherapy session; and follow-up data for 12 weeks after chemotherapy initiation. The exclusion criteria to reduce biases were the presence of grade ≥ 2 leukocytopenia, neutropenia, or receiving granulocyte colony-stimulating factor (G-CSF) in the first chemotherapy session at our hospital. Because, on the colorectal cancer chemotherapy, G-CSF administration is not routine generally. Moreover, G-CSF administration will modify the progress of bone marrow suppression. We thought that if the patient with

cancer has leukocytopenia or neutropenia in the first chemotherapy session, the medical oncologist will generally hesitate the cytotoxic chemotherapy. Besides, patients with cancer showing leukopenia or neutropenia before cytotoxic chemotherapy have a high risk of infection compared to not showing leukopenia or neutropenia. Sixty-seven patients were excluded based on these criteria. Finally, we enrolled 147 patients in this study (Figure1).

Procedures

We collected data regarding patients' age, sex, PS, height, body weight, serum albumin level, liver metastasis, chemotherapy protocol, dose-adjustment (dose reduction), use of antibiotics, admission treatment for adverse events, and mortality. We classified the chemotherapy protocol as oxaliplatin-based \pm Bevacizumab / Cetuximab / Panitumumab, irinotecan-based \pm Bevacizumab / Cetuximab / Panitumumab, FOLFOXIRI \pm Bevacizumab, or others. The oxaliplatin-based protocol included FOLFOX (Modified FOLFOX6; 5-fluorouracil: 5-FU, leucovorin, and oxaliplatin), CapeOX (capecitabine and oxaliplatin), and SOX (S-1; tegafur-gimeracil-oteracil potassium, and oxaliplatin). The irinotecan-based protocol included FOLFIRI (5-FU, leucovorin, and irinotecan), IRIS (irinotecan and S-1), and irinotecan alone. A combination of 5-FU, leucovorin, oxaliplatin, and irinotecan was FOLFOXIRI. Others were sLV5FU2 (5-FU, leucovorin), S-1, and Cetuximab / Panitumumab.

We assessed the nutritional risk in patients with CRC using GNRI at the first chemotherapy session for each patient. We calculated GNRI from body weight and serum albumin levels using the following equation: $GNRI = 1.489 \times \text{serum albumin (g/dL)} + 41.7 \times (\text{body weight/ideal body weight})$. Ideal body weight was defined as $\text{height (m)}^2 \times 22$; this formula was derived from the patient's height and a body mass index (BMI) of 22 kg/m². We classified patients into two groups according to previously published thresholds [22]: the no-risk group (GNRI \geq 98) and the risk group (GNRI <98). In the original GNRI equation, Bouillanne et al. calculated the ideal body weight using the Lorentz formula. However, we calculated ideal body weight from height and a BMI of 22 because a previous study validated the BMI formula [31]. A previous report showed that each formula's GNRI scores varied little from the calculated values [30]. We defined adverse events needing treatment (AENT) as infection used antibiotics; grade \geq 2 leukocytopenia or neutropenia leading to the postponement of chemotherapy; febrile neutropenia; anemia and thrombocytopenia requiring transfusion; grade \geq 3 diarrhea; acute liver failure; and acute kidney injury [3]. We considered AENT to indicate tolerability and vulnerability to chemotherapy [1, 10, 11, 19]. Therefore, we compared the two groups in terms of AENT, antibiotics use, admission treatment for adverse events, and mortality.

Statistical analysis

We examined the association of GNRI, AENT, antibiotics use, admission treatment for adverse events, and mortality. We used multivariable logistic regression analysis to control for potentially confounding factors such as age, sex, PS, liver metastasis, chemotherapy protocol, and dose-adjustment (dose reduction). We performed all statistical analyses using EZR (Saitama Medical Center, Jichi Medical University, Saitama,

Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [32]. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Characteristics

The median GNRI was 95.05 (range, 66.26 - 139.01). Of the 147 patients, we classified 85 and 62 patients in the risk and no-risk groups, respectively. Table 1 shows patients' characteristics from the GNRI Classification. In the risk group, more patients had liver metastasis than in the no-risk group. Age, sex, primary cancer site, PS, chemotherapy protocol, chemotherapy line, dose-adjustment (dose reduction), height, weight, and albumin were not significantly different between the two groups. Patients in the risk group had more AENT and antibiotic use, as well as increased mortality than patients in the no-risk group.

AENT and GNRI

The risk group patients tended to have more AENT than the no-risk group patients. In the risk group, 52 patients had AENT (61.2%), while in the no-risk group, 28 patients had AENT (45.1%). After applying logistic regression analysis, we observed a significant association between GNRI and AENT (odds ratio [OR], 0.948; 95% CI, 0.919–0.978; and the area under the curve of the receiver-operating characteristic curve (AUC of ROC) was 0.694; 95% CI, 0.608–0.78). (Table 2.).

Infection and Antibiotics

In the risk group, 29 patients used antibiotics (34.1%), while in the no-risk group, 11 patients used antibiotics (17.7%). In the multivariable logistic regression analysis, we observed a significant association between GNRI and antibiotics use (OR, 0.945; 95% CI, 0.912–0.979; AUC of ROC, 0.675; 95% CI, 0.576–0.773).

Admission treatment

In the risk group, 20 patients received admission treatment (23.5%), while in the no-risk group, eight patients received admission treatment (12.9 %). However, we did not observe a significant association between GNRI and admission treatment (OR, 0.978; 95% CI, 0.936–1.02; $p=0.319$) in the multivariable logistic regression analysis.

Mortality

Seven patients died during the study period. Four patients died due to infection (cholangitis, pneumonia, and sepsis), one due to cancer-associated thrombosis, and two due to primary cancer. In the multivariable logistic regression analysis, we observed a significant association between GNRI and mortality (OR, 0.845; 95% CI, 0.765–0.932; AUC of ROC, 0.881; 95% CI, 0.77–0.994). Additionally, we observed a two-

factor model PS 2 and Low GNRI were significantly associated with mortality (AUC of ROC, 0.966; 95% CI, 0.916–1]).

Discussion

Malnutrition increases the toxicity of chemotherapy and impairs quality of life of patients with cancer [33]. Our current findings suggest an association between nutrition risk classified by GNRI, and AENT in the early period, antibiotics use, and mortality in patients with unresectable CRC receiving cytotoxic chemotherapy. We calculated GNRI using three factors: height, body weight, and serum albumin levels. Therefore, GNRI is an accurate, objective, and time-saving tool for nutrition assessment [1, 10]. More patients in the risk group (GNRI <98) had AENT than in the no-risk group (GNRI ≥98). Furthermore, AENT may increase due to infection and malnutrition, which results in higher treatment costs for the patients in the risk group because of the need for antibiotic treatment and other supportive care forms.

Previous reports validated the association between malnutrition and the patient's tolerability and vulnerability to cytotoxic chemotherapy due to severe chemotherapy-associated adverse events [1, 8]. However, in patients with CRC, the effect of body weight, BMI, or hypoalbuminemia alone on tolerability and vulnerability has remained controversial [25, 33-35]. The body weight of patients with CRC changes easily due to decreased food intake, ascites, pleural effusion, and dehydration [36]. Similarly, serum albumin levels are easily influenced by inflammation and dehydration [37]. Therefore, the association between BMI or albumin alone and the nutrition risk of patients with cancer may be controversial [4, 34].

In the GNRI calculation, body weight and serum albumin levels are inversely proportional. In other words, if the patient's body weight increases due to ascites or pleural effusion, the patient's serum albumin levels decrease by increasing body fluid volume unless intra-vascular dehydration occurs. Conversely, if the amount of body fluid decreases, the patient's body weight decreases, but the patient's serum albumin levels increase due to high blood concentration. However, our findings showed no correlation between body weight and albumin. Thus, GNRI calculation may reflect nutrition status and risk complementarity, although BMI, body weight, or albumin alone cannot reflect nutrition status and risk comprehensively because of unknown risk factors.

NRI is composed of basal weight and serum albumin levels. NRI seems useful for identifying malnutrition and nutrition risk. However, baseline body weight is uncertain because malnutrition occurs before cancer diagnosis. In addition, it is difficult to exclude the patient's memory bias. Therefore, NRI may not comprehensively reflect nutrition status and risk [3]. In contrast, the body weight used in GNRI is obtained at just one point in time. Thus, GNRI may help identify nutrition status and risk before chemotherapy, enabling prediction concerning the tolerability to chemotherapy.

Malnutrition increases the risk of infection and hospitalization in patients with cancer [4]. Moderate or severe infection disease is critical in some cases. Prediction of patients' immunocompromised status through a novel method can help patients exercise preventive measures, e.g., avoiding crowds, following hand wash practices, wearing a mask on the mouth, following a diet avoiding fresh vegetables and

fermented food. Furthermore, we need to assess for the presence of comorbidities that lead to severe infection, such as diabetes mellitus, chronic obstructive pulmonary disease, and asthma. Therefore, nutrition risk assessment is essential in patients with cancer.

We consider that nutrition risk assessment can be used similarly to Geriatric Assessment (GA) to discover (diagnose) a missing problem, predict adverse events of treatment and disease prognosis, and determine treatment strategy [38]. Importantly, the diagnosis of unrecognized problems underlying malnutrition has benefits[39]. Patients with nutritional risk have metabolic, cardiovascular, and respiratory comorbidities and potential psychosocial and economic problems [40-42]. Thus, supportive care for physical comorbidities and psychosocial and economic difficulties is important in patients with cancer. GNRI is useful for assessing nutrition risk in patients with cancer, and the GNRI assessment enables the discovery of problems associated with malnutrition. Recognizing comorbidities and malnutrition-associated problems in patients with cancer will enhance supportive care [2]. Supportive care enhancement will reduce antibiotics use, admission treatment for adverse events, and mortality-associated excessive chemotherapy. Therefore, enhanced supportive care can reduce medical expenses [13, 43].

Another aspect of essential supportive care for patients with cancer involves identifying the patients requiring supportive care and what type of care they may benefit from. Our findings support the utilization of GNRI in predicting AENT. Recent studies reported that nutrition support might reduce adverse events associated with toxic chemotherapy [44]. Support for comorbidities that causes malnutrition is also important. However, nutrition intervention for all patients with cancer may not be practical and increase medical expenses [26, 41]. Therefore, before chemotherapy initiation, the GNRI nutrition risk assessment will help physicians identify patients who may benefit from nutrition support and comorbidity screening. If the patient with cancer has a GNRI lower than 98, we should introduce nutrition support and intervention practically as a part of the cancer treatment strategy. Nutrition support and intervention comprise nutrition education and counseling, exercise with rehabilitation therapists, and life support from medical social workers and care workers. However, the effect of nutrition support based on GNRI remains unexplored on patients with CRC of tolerance and vulnerability to chemotherapy. Thus, a prospective study is needed to validate the benefit of nutrition support for chemotherapy in patients with CRC.

We did not observe any association between GNRI and admission. Admission treatment is complicated. When the patients determine whether to be admitted for treatment, disease severity is not the only determinant. Many patients and families may have many other determinants, such as financial conditions, family situations, and insurance issues. Therefore, nutrition risk assessment alone may not reflect all essential issues. To expand upon the current findings, we intend to delve into issues concerning admission treatment.

The present study has some limitations. First, the present study enrolled only patients covered by a single center. Thus, it is undeniable there was bias regarding diet and exercise habits as regional culture, climate, and economy influence patients' lifestyle. Second, most of the patient's chemotherapy protocol was an oxaliplatin-based protocol. Japanese clinical physicians more commonly use an oxaliplatin-

based protocol than an irinotecan-based protocol for the first-line chemotherapy [45]. Thus, we might have some selection bias. Finally, regarding treatment strategy, the chemotherapy protocol was determined by internal meetings within the department. We determined the treatment strategy based on the Japanese Society for Cancer of the Colon and Rectum guidelines and considering the patient's age, PS, organ dysfunction status, and patient's wishes. Although our strategy included more than one physician's opinion, the inherent aspects of single-center studies may cause a degree of selection bias in the treatment strategy. Thus, a multi-center study is needed to resolve the biases.

In conclusion, in patients with CRC receiving chemotherapy, our study results indicate an association between nutrition risk classification by GNRI and AENT, antibiotic use, and mortality. GNRI may be a useful screening tool predicting tolerability and vulnerability to chemotherapy. Further prospective research is needed to validate nutrition support based on nutrition status and risk classification by GNRI in patients with CRC.

Declarations

Acknowledgments

The authors would like to thank M. Matsuzaka for advice on study design. We gratefully acknowledge the work of past

members of our department. We thank Taylor & Francis Editing Services for their assistance in editing and proofreading

the manuscript in English.

Authors' Contributions

Kota Sasaki conceived and designed the study, analyzed and interpreted the data, wrote the paper, reviewed the content of the article, and approved the final version of the article. Atsushi Sato, Kengo Hasui, and Yu Chen assisted in designing the study, reviewed the content of the article, and approved the final version of the article. Kensuke Saitou and Takenori Takahata reviewed the content of the article and approved the final version of the article.

Funding No funding was received to assist with the preparation of this manuscript

Data availability statement

One author, Kota Sasaki, who is independent of the commercial funder, had full access to all the data and takes responsibility for the integrity of the data and analyses.

The data that support the findings of this study are available from the corresponding author, Kota S, upon reasonable request.

Compliance with ethical standards

Conflict of interest

Atsushi Sato, co-authors, received research donations from Chugai Pharmaceutical CO., LTD, TAHIO Pharmaceutical CO., LTD, Eli Lilly and Company, ONO Pharmaceutical CO., LTD, DAIICHI SANKYO Company, LIMITED. Their donations were no relationship to this work.

Any other authors have no conflicts of interest to disclose.

Ethics approval

The Hirosaki University Hospital ethics committee approved the study of our hospital approved this study protocol (No. 2020-152). We obtained informed consent in the form of opt-out on the website of the Hirosaki University Hospital.

References

1. Lidoriki I, Schizas D, Frountzas M, Machairas N, Prodromidou A, Kapelouzou A, Karavokyros I, Pikoulis E, Kales SN, Liakakos T (2020) GNRI as a Prognostic Factor for Outcomes in Cancer Patients: A Systematic Review of the Literature. *Nutr Cancer*: 1-13
2. Spiro A, Baldwin C, Patterson A, Thomas J, Andreyev HJ (2006) The views and practice of oncologists towards nutritional support in patients receiving chemotherapy. *Br J Cancer* 95: 431-434
3. Gallois C, Artru P, Lievre A, Auclin E, Lecomte T, Locher C, Marthey L, Zaimi Y, Faroux R, Pernot S, Barret M, Taieb J (2019) Evaluation of two nutritional scores' association with systemic treatment toxicity and survival in metastatic colorectal cancer: an AGEO prospective multicentre study. *Eur J Cancer* 119: 35-43
4. Hebuterne X, Lemarie E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F (2014) Prevalence of malnutrition and current use of nutrition support in patients with cancer. *Jpen-Parenter Enter* 38: 196-204
5. Alwarawrah Y, Kiernan K, MacIver NJ (2018) Changes in Nutritional Status Impact Immune Cell Metabolism and Function. *Front Immunol* 9: 1055
6. Aaldriks AA, van der Geest LG, Giltay EJ, le Cessie S, Portielje JE, Tanis BC, Nortier JW, Maartense E (2013) Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. *J Geriatr Oncol* 4: 218-226
7. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, Lichtman SM, Gajra A, Bhatia S, Katheria V, Klapper S, Hansen K, Ramani R, Lachs M, Wong FL, Tew WP (2011) Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 29: 3457-3465
8. Ryan AM, Power DG, Daly L, Cushen SJ, Bhuachalla EN, Prado CM (2016) Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proceedings of the Nutrition Society* 75: 199-211

9. Caillet P, Liuu E, Raynaud Simon A, Bonnefoy M, Guerin O, Berrut G, Lesourd B, Jeandel C, Ferry M, Rolland Y, Paillaud E (2017) Association between cachexia, chemotherapy and outcomes in older cancer patients: A systematic review. *Clin Nutr* 36: 1473-1482
10. Gu W, Zhang G, Sun L, Ma Q, Cheng Y, Zhang H, Shi G, Zhu Y, Ye D (2015) Nutritional screening is strongly associated with overall survival in patients treated with targeted agents for metastatic renal cell carcinoma. *J Cachexia Sarcopenia Muscle* 6: 222-230
11. Lee GW, Go SI, Kim DW, Kim HG, Kim JH, An HJ, Jang JS, Kim BS, Hahn S, Heo DS (2020) Geriatric Nutritional Risk Index as a prognostic marker in patients with extensive-stage disease small cell lung cancer: Results from a randomized controlled trial. *Thorac Cancer* 11: 62-71
12. Laviano A, Di Lazzaro L, Koverech A (2018) Nutrition support and clinical outcome in advanced cancer patients. *Proc Nutr Soc* 77: 388-393
13. Gallagher-Allred CR, Voss AC, Finn SC, McCamish MA (1996) Malnutrition and clinical outcomes: the case for medical nutrition therapy. *J Am Diet Assoc* 96: 361-369
14. Abe Vicente M, Barao K, Silva TD, Forones NM (2013) What are the most effective methods for assessment of nutritional status in outpatients with gastric and colorectal cancer? *Nutr Hosp* 28: 585-591
15. Soubeyran P, Fonck M, Blanc-Bisson C, Blanc JF, Ceccaldi J, Mertens C, Imbert Y, Cany L, Vogt L, Dauba J, Andriamampionona F, Houede N, Floquet A, Chomy F, Brouste V, Ravaud A, Bellera C, Rainfray M (2012) Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol* 30: 1829-1834
16. Phillips MB, Foley AL, Barnard R, Isenring EA, Miller MD (2010) Nutritional screening in community-dwelling older adults: a systematic literature review. *Asia Pac J Clin Nutr* 19: 440-449
17. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, Albarede JL (1999) The mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* 15: 116-122
18. Veterans Affairs Total Parenteral Nutrition Cooperative Study G (1991) Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 325: 525-532
19. Kubo N, Sakurai K, Tamura T, Toyokawa T, Tanaka H, Muguruma K, Yashiro M, Ohira M (2019) The impact of geriatric nutritional risk index on surgical outcomes after esophagectomy in patients with esophageal cancer. *Esophagus* 16: 147-154
20. Aaldriks AA, Maartense E, le Cessie S, Giltay EJ, Verlaan HA, van der Geest LG, Kloosterman-Boele WM, Peters-Dijkshoorn MT, Blansjaar BA, van Schaick HW, Nortier JW (2011) Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. *Crit Rev Oncol Hematol* 79: 205-212
21. Phippen NT, Lowery WJ, Barnett JC, Hall LA, Landt C, Leath CA, 3rd (2011) Evaluation of the Patient-Generated Subjective Global Assessment (PG-SGA) as a predictor of febrile neutropenia in gynecologic cancer patients receiving combination chemotherapy: a pilot study. *Gynecol Oncol* 123: 360-364

22. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, Benazeth S, Cynober L, Aussel C (2005) Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. *American Journal of Clinical Nutrition* 82: 777-783
23. Kanemasa Y, Shimoyama T, Sasaki Y, Hishima T, Omuro Y (2018) Geriatric nutritional risk index as a prognostic factor in patients with diffuse large B cell lymphoma. *Ann Hematol* 97: 999-1007
24. Mantzorou M, Koutelidakis A, Theocharis S, Giaginis C (2017) Clinical Value of Nutritional Status in Cancer: What is its Impact and how it Affects Disease Progression and Prognosis? *Nutrition and Cancer* 69: 1151-1176
25. Seo SH, Kim SE, Kang YK, Ryoo BY, Ryu MH, Jeong JH, Kang SS, Yang M, Lee JE, Sung MK (2016) Association of nutritional status-related indices and chemotherapy-induced adverse events in gastric cancer patients. *BMC Cancer* 16: 900
26. Cereda E, Pedrolli C, Zagami A, Vanotti A, Piffer S, Opizzi A, Rondanelli M, Caccialanza R (2011) Nutritional screening and mortality in newly institutionalised elderly: a comparison between the geriatric nutritional risk index and the mini nutritional assessment. *Clin Nutr* 30: 793-798
27. Konishi T, Doki N, Kishida Y, Nagata A, Yamada Y, Kaito S, Kurosawa S, Yoshifuji K, Shirane S, Uchida T, Inamoto K, Toya T, Igarashi A, Najima Y, Kobayashi T, Kakihana K, Sakamaki H, Ohashi K (2019) Geriatric nutritional risk index (GNRI) just before allogeneic hematopoietic stem cell transplantation predicts transplant outcomes in patients older than 50 years with acute myeloid leukemia in complete remission. *Ann Hematol* 98: 1799-1801
28. Kinugasa Y, Kato M, Sugihara S, Hirai M, Yamada K, Yanagihara K, Yamamoto K (2013) Geriatric nutritional risk index predicts functional dependency and mortality in patients with heart failure with preserved ejection fraction. *Circ J* 77: 705-711
29. Matsumura T, Mitani Y, Oki Y, Fujimoto Y, Ohira M, Kaneko H, Kawashima T, Nishio M, Ishikawa A (2015) Comparison of Geriatric Nutritional Risk Index scores on physical performance among elderly patients with chronic obstructive pulmonary disease. *Heart Lung* 44: 534-538
30. Yamada K, Furuya R, Takita T, Maruyama Y, Yamaguchi Y, Ohkawa S, Kumagai H (2008) Simplified nutritional screening tools for patients on maintenance hemodialysis. *Am J Clin Nutr* 87: 106-113
31. Cereda E, Pedrolli C (2009) The Geriatric Nutritional Risk Index. *Curr Opin Clin Nutr Metab Care* 12: 1-7
32. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* 48: 452-458
33. Arrieta O, Michel Ortega RM, Villanueva-Rodriguez G, Serna-Thome MG, Flores-Estrada D, Diaz-Romero C, Rodriguez CM, Martinez L, Sanchez-Lara K (2010) Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. *BMC Cancer* 10: 50
34. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, Strasser F, Thoresen L, Jagoe RT, Chasen M, Lundholm K, Bosaeus I, Fearon KH, Baracos VE (2015) Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol* 33: 90-99

35. Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, Feng T, Smith D, Sun CL, De Glas N, Cohen HJ, Katheria V, Doan C, Zavala L, Levi A, Akiba C, Tew WP (2016) Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. *J Clin Oncol* 34: 2366-2371
36. Barao K, Abe Vicente Cavagnari M, Silva Fucuta P, Manoukian Forones N (2017) Association Between Nutrition Status and Survival in Elderly Patients With Colorectal Cancer. *Nutr Clin Pract* 32: 658-663
37. Beck AM, Holst M, Rasmussen HH (2008) Efficacy of the Mini Nutritional Assessment to predict the risk of developing malnutrition or adverse health outcomes for old people. *E Spen Eur E J Clin Nutr Metab* 3: e102-e107
38. Caillet P, Laurent M, Bastuji-Garin S, Liuu E, Culine S, Lagrange JL, Canoui-Poitrine F, Paillaud E (2014) Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. *Clin Interv Aging* 9: 1645-1660
39. Maas HA, Janssen-Heijnen ML, Olde Rikkert MG, Machteld Wymenga AN (2007) Comprehensive geriatric assessment and its clinical impact in oncology. *Eur J Cancer* 43: 2161-2169
40. Freijer K, Tan SS, Koopmanschap MA, Meijers JMM, Halfens RJG, Nuijten MJC (2013) The economic costs of disease related malnutrition. *Clinical Nutrition* 32: 136-141
41. Pirlich M, Schütz T, Kemps M, Luhman N, Minko N, Lübke HJ, Rossnagel K, Willich SN, Lochs H (2005) Social risk factors for hospital malnutrition. *Nutrition* 21: 295-300
42. Elia M, Zellipour L, Stratton RJ (2005) To screen or not to screen for adult malnutrition? *Clin Nutr* 24: 867-884
43. Van Cutsem E, Arends J (2005) The causes and consequences of cancer-associated malnutrition. *European Journal of Oncology Nursing* 9: S51-S63
44. Bauer JD, Capra S (2005) Nutrition intervention improves outcomes in patients with cancer cachexia receiving chemotherapy—a pilot study. *Support Care Cancer* 13: 270-274
45. Yamada Y, Denda T, Gamoh M, Iwanaga I, Yuki S, Shimodaira H, Nakamura M, Yamaguchi T, Ohori H, Kobayashi K, Tsuda M, Kobayashi Y, Miyamoto Y, Kotake M, Shimada K, Sato A, Morita S, Takahashi S, Komatsu Y, Ishioka C (2018) S-1 and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer (TRICOLORE): a randomized, open-label, phase III, noninferiority trial. *Ann Oncol* 29: 624-631

Tables

Table 1. Patient characteristics				
	Total	The Risk group	No-Risk group	<i>p</i> -Value
		GNRI<98	98 ≤ GNRI	
	<i>n</i> = 147	<i>n</i> = 85 (%)	<i>n</i> = 62 (%)	
Age	Mean ± SD	62.4 ± 11.4	61.65± 11.2	0.690
	25-44 years	5 (5.9%)	4 (6.5%)	0.878
	45-54	9 (10.6%)	7 (11.3%)	
	55-64	35 (41.2%)	29 (46.8%)	
	65-74	26 (30.6%)	14 (22.6%)	
	75~	10 (11.8%)	8 (12.9%)	
Sex	Male	48 (56.5%)	40 (64.5%)	0.395
	Female	37 (43.5%)	22 (35.5%)	
Liver Metastasis		62 (72.9%)	30 (48.4%)	0.003 [†]
Primary site	Colon	55 (64.7%)	30 (48.4%)	0.091
	Right side	26 (30.6%)	16 (25.8%)	
	Left side	29 (34.1%)	15 (24.2%)	
	Rectum	30 (35.3%)	31 (50.0%)	
Chemotherapy Protocol				0.833
	Oxaliplatin Based	67 (78.8%)	46 (74.2%)	
	FOLFOX(mFOLFOX) ± Bevacizumab	43 (50.6%)	25 (40.3%)	
	± Cetuximab/Panitumumab	8 (9.4%)	1 (1.6%)	
	S-OX ± Bevacizumab	3 (3.5%)	4 (6.5%)	
	± Cetuximab/Panitumumab	1 (1.2%)	0 (0.0%)	
	CapeOX ± Bevacizumab	12 (14.1%)	16 (25.8%)	
	Irinotecan Based	11 (12.9%)	9 (14.5%)	
	FOLFIRI ± Bevacizumab	0 (0.0%)	1 (1.6%)	
	± Cetuximab/Panitumumab	2 (2.4%)	2 (3.2%)	
	IRIS ± Bevacizumab	7 (8.2%)	6 (9.7%)	
	± Cetuximab/Panitumumab	1 (1.2%)	0 (0.0%)	

Irinotecan		1 (1.2%)	0 (0.0%)	
FOLFOXIRI ± Bevacizumab		2 (2.4%)	3 (4.8%)	
Others		4 (4.7%)	3 (4.8%)	
Performance Status (PS)	0	64 (75.3%)	55 (88.7%)	
	1	8 (9.4%)	6 (9.7%)	
	2	13 (15.3%)	1 (1.6%)	0.017 [†]
Chemotherapy Line	First 1 st	81 (95.3%)	59 (95.2%)	1.00
	Second 2 nd	2 (2.4%)	2 (3.2%)	
	Third 3 rd	2 (2.4%)	1 (1.6%)	
Dose Reduction (Dose Adjustment)		8 (9.4%)	3 (4.8%)	0.357

GNRI: Geriatric Nutrition Risk Index

SD: standard deviation

FOLFOX: modified FOLFOX(mFOLFOX)

†A significant difference was observed for “Liver Metastasis” and “Performance Status 2” between the risk group and the no-risk groups.

All p-values were obtained from the Fisher exact test.

Table 2. GNRI and Results.				
		Risk group	No-Risk group	<i>p</i> -Value
		GNRI<98	98≤GNRI	
		<i>n</i> = 85 (%)	<i>n</i> = 62 (%)	
Height (cm)	Mean ± SD (Median)	160.8 ±9.09 (160.3)	162.1 ±9.08 (162.1)	0.387 (0.357)
Pretreatment body weight (kg)		57.87 ± 12.2 (56.4)	58.52 ± 11.8 (58.9)	0.749 (0.646)
Albumin (g/dL)		3.72 ± 0.52 (3.70)	3.50 ± 0.62 (3.58)	0.140 (0.167)
Geriatric Nutrition Risk Index (GNRI)	Mean ± SD (Median)	88.40 ± 6.61 (90.23)	108.3 ± 7.59 (106.97)	<0.01 [†]
Adverse Event Needing Treatment		52 (61.2%)	28 (45.1%)	< 0.01*
	Infection	18 (21.2%)	5 (8.1%)	0.038 [†]
	Leukopenia/Neutropenia ≥ Grade 2	19 (22.4%)	14 (22.6%)	
	Anemia	2 (2.4%)	1 (1.6%)	
	Thrombocytopenia	1 (1.2%)	1 (1.6%)	
	Diarrhea ≥ Grade 3	2 (2.4%)	4 (6.5%)	
	Others	10 (11.8%)	3 (4.8%)	0.239
Treatment with Antibiotics		29 (34.1%)	11 (17.7%)	0.044 [†]
Admission treatment for Adverse Event		20 (23.5%)	8 (12.9%)	0.319*
Death		8 (9.4%)	0 (0.0%)	0.021 [†]

SD: standard deviation

Anemia: Anemia needing transfusion; ≥ Grade 3

Thrombocytopenia: Thrombocytopenia needing transfusion; Grade 4

Others: Febrile neutropenia, liver failure, acute kidney injury

All adverse events were diagnosed on a grade scale of Common Terminology Criteria for Adverse Events Ver.4.0

A significant difference was observed for adverse events needing treatment, antibiotic treatment, and death.

† χ^2 -values were obtained from the Fisher exact test, *p-values were obtained from logistic regression analysis

Figures

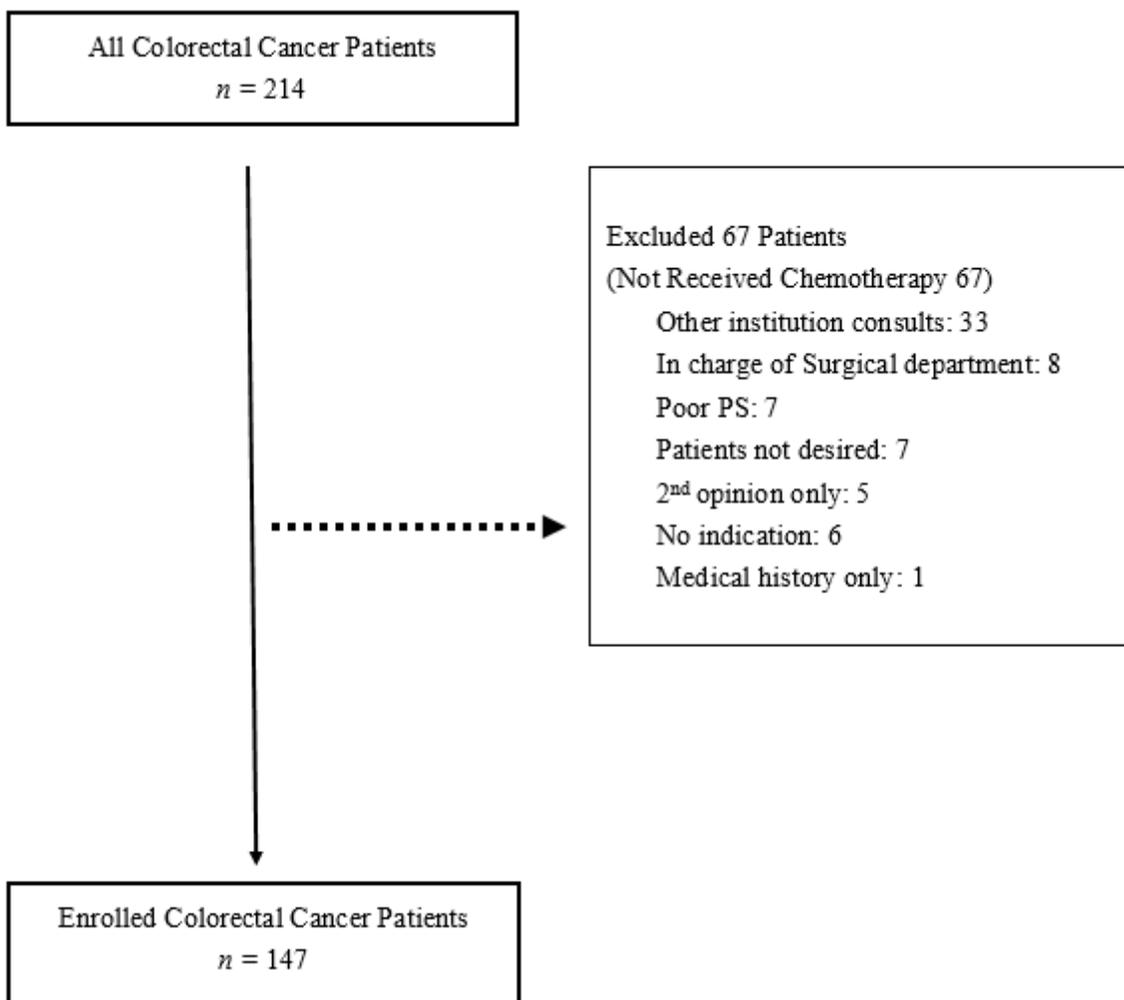


Figure 1

Flow Chart of Patients Enrollment Other institution consults: difficult geographic conditions or the patient and family live far away In charge of Surgical department: patient with malignant colon strictures, or

bowel obstruction, or resectable cancer Poor PS: patient with poor PS (3–4) No indication: early-stage colorectal cancer, or no recurrence. or patients with multi comorbidities, such as severe cardiovascular, respiratory, renal, and liver dysfunctions