ASSESSMENT OF NUTRITIONAL STATUS TO DETERMINE THE PREVALENCE OF MALNUTRITION IN PATIENTS UNDERGOING SURGERY FOR COLORECTAL CARCINOMA USING INA SCORE

MUQEET A, HAIDER S, IBRAHIM F, HYDER A, SIRAJ MI, SAJID EU, RAJPUT IA, KHAN NA[*]

Dow University of Health And Sciences, Pakistan, Pakistan
*Correspondence author email address: noman_ahmed@iamafreebird.com

Abstract: *Colorectal cancer (CRC) is the third most commonly diagnosed malignancy worldwide. Malnutrition is a critical factor influencing postoperative morbidity and mortality in CRC patients. Surgical trauma exacerbates the metabolic response, increasing the risk of malnutrition-related complications such as cancer cachexia and reduced efficacy of postoperative chemotherapy or radiotherapy. This study aimed to assess the prevalence of malnutrition in patients undergoing surgery for colorectal carcinoma using the Instant Nutritional Assessment (INA) score.* **Objective:** *To determine the frequency and degree of malnutrition in patients undergoing resection surgery for colorectal carcinoma using the INA score.* **Methods:** *This cross-sectional study was conducted in the Department of Surgery at Dr. Ruth K. M. Pfau Civil Hospital Karachi over six months, from October 1, 2022, to March 31, 2023. A total of 93 patients undergoing elective resection for colorectal carcinoma were enrolled. Demographic and clinical data, including histological diagnoses, were recorded using a predesigned proforma. Nutritional status was assessed using the INA score, based on serum albumin levels and blood lymphocyte counts. Malnutrition was classified into four degrees according to operational definitions. Data analysis was performed using SPSS version 19.* **Results:** *The mean age of participants was 47.60 ± 12.87 years. Of the 93 patients, 56.99% were male, and 43.01% were female. The frequency of malnutrition was 27.96% (26/93), with malnutrition degrees distributed as follows: 8 patients (30.8%) with first-degree, 5 patients (19.23%) with second-degree, 9 patients (34.62%) with third-degree, and 4 patients (15.38%) with fourth-degree malnutrition.* **Conclusion:** *A significant proportion of patients undergoing surgery for colorectal carcinoma were found to be malnourished. These findings underscore the necessity for routine preoperative nutritional assessments and timely interventions to improve surgical outcomes and enhance the effectiveness of postoperative therapies. Incorporating nutritional support as a standard component of colorectal cancer care can mitigate the risk of cancer cachexia and associated complications.*

Keywords: Cholelithiasis; laparoscopic cholecystectomy; dexamethasone; post-operative nausea and vomiting.

Introduction

Globally, colorectal cancer (CRC) is the third most commonly diagnosed malignancies, approximately 6 percent of individuals will develop this malignancy in their lifetime. (1-3) In Pakistan, due to the lack of a national cancer registry, CRC data is scarce. (4) The single-centered data in

Pakistan reported CRC as the fourth most common cause of cancer in Pakistan. (5) The most common presenting symptoms of CRC include bleeding per rectum (PR), altered bowel habits, weight loss, tenesmus, and changes in the frequency and consistency of stools. (6) According to the study, cancer prevalence in Pakistan the prevalence of colorectal cancer ranged from 4 to 6%. (7) Rates of both incidence and mortality are substantially higher in males than in females. [8] Environmental and genetic factors can increase the likelihood of developing CRC. [9] These factors appear to be attributable to differences in dietary and environmental exposures, low socioeconomic status, and lower rates of CRC screening that are imposed upon a background of genetically

determined susceptibility. (8-10)
Malnutrition is a significant factor in postoperative morbidity and mortality rates and length of hospital stay. (11-13) In different studies, malnutrition in

colorectal cancer was assessed by numerous instruments and

prevalence of malnutrition in colorectal cases was 22.5% to 36.4% (11, 14, 15). As per a systematic review, the prevalence of hospital malnutrition ranged from 2.6% to 73.2%, published in 2017 (16). Increased rates of malnutrition were noted in patients who underwent gastrointestinal surgery on admission. Surgical trauma itself triggers a sequence of inflammatory events related to the metabolic response to trauma. (17) Several studies have shown worse clinical outcomes in malnourished

patients who underwent surgical procedures (18-20). There are a variety of instruments for assessing nutritional status, but there is no gold standard method. The nutritional status assessment can be approached by simultaneous use of clinical, anthropometric, and biochemical markers that are necessary to make a comprehensive diagnosis. The INA (INSTANT NUTRITIONAL ASSESSMENT) score is also used for nutritional assessment by using serum albumin and blood lymphocyte counts (21-23). This study aims to assess the prevalence of malnutrition status in patients undergoing surgery for colorectal carcinoma to offer timely nutritional support and thus avert the risk of cancer cachexia and the ineffectiveness of post-surgical treatment with chemotherapy or radiotherapy. Thus the objective of the study was to determine the frequency of malnutrition in patients undergoing surgery for colorectal carcinoma using the INA score.
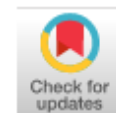
Methodology

This cross-sectional study was conducted in the Department of Surgery at Dr. Ruth K. M. Pfau Civil Hospital Karachi over a six-month period, from October 1, 2022, to March 31, 2023. The study aimed to determine the frequency of malnutrition among patients undergoing resection surgery for colorectal carcinoma using the Instant Nutritional Assessment (INA) score. The sample size was calculated based on previous studies that reported malnutrition prevalence rates between 22.5% and 36.4%. Using an average prevalence of 40%, with a 10% margin of error and a 95% confidence interval, a minimum sample size of 81 was determined. However, 93 eligible patients were included during the study period.

Patients aged 18 to 70 years undergoing elective resection surgery for colorectal cancer were included in the study. Those with other cancers, conditions causing chronic malnutrition (such as chronic renal failure or liver cirrhosis), cognitive impairments, or those receiving artificial nutritional support were excluded. Informed consent was obtained from all participants prior to enrollment. Ethical approval was secured from the College of Physicians and Surgeons Pakistan and the Ethics Committee of Dow University of Health Sciences. A non-probability consecutive sampling method was used to include all eligible patients during the study period.

Data were collected by the principal investigator using a structured proforma. Information on demographic variables, including age, gender, education, occupation, and ethnicity, as well as clinical characteristics such as histological diagnosis, tumor size, lymph node involvement, presence of metastases, and type of surgery, was recorded. Nutritional status was assessed using the INA score, which evaluates serum albumin levels and blood lymphocyte counts. Patients were categorized as malnourished based on predefined criteria, with malnutrition classified into four degrees according to the INA score.

Serum albumin levels and blood lymphocyte counts were analyzed in the hospital laboratory. Continuous variables, including age, tumor size, serum albumin levels, and blood lymphocyte counts, were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed variables were presented as means and standard deviations, while non-normally distributed variables were reported as medians and interquartile ranges. Categorical variables, such as gender, education, comorbidities, tumor site, disease stage, and nutritional assessment, were summarized as frequencies and percentages.

Stratification was performed to control for confounding variables such as age, gender, education, occupation, ethnicity, and type of surgery. Post-stratification analysis was conducted using chi-square or Fisher's exact test where appropriate, with a p-value ≤ 0.05 considered statistically significant. This rigorous methodology ensured a comprehensive assessment of malnutrition and its prevalence among patients undergoing colorectal cancer surgery.

Results

A total of 93 patients undergoing resection surgery for colorectal cancer were included in the study. The mean age of the participants was 47.60 ± 12.87 years, with a median age of 48 years (IQR: 21 years). The gender distribution showed a predominance of males (56.99%) compared to females (43.01%) (Table 1). Among the patients, 50% were diabetic, and 80% were hypertensive. The mean tumor size was 10.42 ± 4.22 mm, with a median size of 9 mm (IQR: 3 mm). Serum albumin levels averaged 2.946 ± 0.63 g/dL, and the mean blood lymphocyte count was $1.308 \pm 0.18 \times 10^9$/L (Table 1).

Table 1: Baseline Characteristics of Patients

Variable	Mean ± SD	Median	IQR
Age (years)	47.60 ± 12.87	48	21
Tumor size (mm)	10.42 ± 4.22	9	3
Serum albumin (g/dL)	2.946 ± 0.63	3.2	1.1
Blood lymphocyte count (×10⁹/L)	1.308 ± 0.18	1.3	0.3

The education, occupation, and ethnicity statuses of the participants were analyzed. Most participants had completed matriculation or intermediate education (41.9%), while a smaller proportion (7.5%) were illiterate. Regarding occupation, 45 patients (48.4%) were engaged in indoor jobs, while 8 (8.6%) were housewives. Ethnically, the majority were Urdu-speaking (43%), followed by Punjabi (22.6%), Sindhi (26.9%), and others (7.5%).

The tumor characteristics and staging showed that the majority of tumors were located in the colon (58.06%), followed by the sigmoid (23.66%) and rectum (18.28%). Preoperative staging revealed that 45.2% of patients were in Stage I, 40.9% in Stage II, and 14% in Stage III. Adenocarcinoma was the predominant histological type, observed in 72% of cases, while 28% were squamous cell carcinoma. Lymph node involvement was observed in 11.8% of patients, and 16.1% had metastases (Table 2).

Table 2: Tumor Characteristics and Staging

Variable	Count (n)	Percentage (%)
Tumor site		
Colon	54	58.06
Sigmoid	22	23.66
Rectum	17	18.28
Preoperative stage		
Stage I	42	45.2
Stage II	38	40.9

[Citation: Muqeet, A., Haider, S., Ibrahim, F., Hyder, A., Siraj, M.I., Sajid, E.U., Rajput, I.A., Khan, N.A., (2024). Assessment of nutritional status to determine the prevalence of malnutrition in patients undergoing surgery for colorectal carcinoma using ina score. *Biol. Clin. Sci. Res. J.,* **2024***: 1273*. doi: https://doi.org/10.54112/bcsrj.v2024i1.1273]

Stage III	13	14.0
Stage IV	0	0.0
Histological type		
Adenocarcinoma	67	72.0
Squamous cell carcinoma	26	28.0
Lymph node involvement		
Yes	11	11.8
No	82	88.2
Presence of metastases		
Yes	15	16.1
No	78	83.9

Nutritional assessment revealed that 27.96% of patients (26/93) were malnourished based on the INA score. Among the malnourished patients, 8 (30.8%) had first-degree malnutrition, 5 (19.23%) had second-degree, 9 (34.62%) had third-degree, and 4 (15.38%) had fourth-degree malnutrition. Additionally, 63.4% of patients reported absent appetite, and 45.2% had inadequate food intake. Weight loss was reported in 49.5% of patients (Table 3).

Table 3: Nutritional Assessment and Gastrointestinal Characteristics

Variable	Count (n)	Percentage (%)
Appetite		
Presence	34	36.6
Absence	59	63.4
Food intake		
Adequate	51	54.8
Inadequate	42	45.2
Recent dietary changes		
Yes	58	62.4
No	35	37.6
Weight loss		
Yes	46	49.5
No	47	50.5

Table 4: Degrees of Malnutrition Among Patients

Malnutrition Degree	Count (n)	Percentage (%)
First degree	8	30.8
Second degree	5	19.23
Third degree	9	34.62
Fourth degree	4	15.38

Stratification analysis showed significant associations between malnutrition and variables such as food intake (p=0.004), recent dietary changes (p=0.022), and weight loss (p=0.0005). However, no significant associations were found between malnutrition and comorbidities such as diabetes (p=0.056) and hypertension (p=0.185).

Discussion

Previous studies have demonstrated that low albumin values, as well as low absolute lymphocyte counts are predictive of a more dismal prognosis in patients with colorectal malignancies, with albumin being indicative of patients' general nutritional status, while lymphocyte counts correspond to the host's anticancer immunity capabilities (24). Concerning decreased albumin levels in cancer patients, one of the main proposed mechanisms for hypoalbuminemia is the increased production of pro-inflammatory cytokines, such as IL-6 and TNF-a by hepatocytes (25-27).

Further studies have demonstrated an inverse association between the circulating levels of these cytokines and the aggressive biological behavior of gastrointestinal tumors, including colorectal cancer (28, 29). In addition, lymphocytes comprise a mixed cellular population, regarded as the cornerstone of cellular immunity against malignant cells (29). Under this notion, the presence of lymphocytopenia is considered as a negative prognostic factor in patients with colorectal cancer (30). Combining these two laboratory parameters in a unifying scoring system, Onodera and coworkers proposed and validated PNI, a cost-effective and globally accessible score for assessing malnutrition (31). In this study The average age of the patients was 47.60±12.87 years, indicating a middle-aged population predominantly affected by colorectal carcinoma. The gender distribution showed a slightly higher prevalence in males (56.99%) compared to females (43.01%). In Seretis et al study (11) males were 55.4% and females were 44.6%, with a mean age of 69.46 years.

In present study 58.06% tumor were colon, 23.66% sigmoid and 18.28% in rectum. Preoperative stage disease, 45.2% stage I, 40.9% stage II and 14% were in stage III. 72% were adenocarcinoma and 28% squamous cell. Lymph node was observed in 11.8% and 16.1% were metastases. Malnutrition is a significant factor in postoperative morbidity and mortality rates and length of hospital stay. (11-13) In different studies,

malnutrition in colorectal cancer was assessed by numerous instruments and the prevalence of malnutrition in colorectal cases was 22.5% to 36.4% (11-15). As per a systematic review, the prevalence of hospital malnutrition ranged from 2.6% to 73.2%, published in 2017 (16). Increased rates of malnutrition was noted in patients who underwent gastrointestinal surgery on admission. Surgical trauma itself triggers a sequence of inflammatory events related to the metabolic response to trauma. (17) Several studies have shown worse clinical outcomes in malnourished patients who underwent surgical procedures (18-20). In this study found that the frequency of malnutrition in patients undergoing surgery for colorectal carcinoma, assessed using the INA score, was 27.96%. Malnutrition is a significant concern as it can adversely affect surgical outcomes and recovery. First degree 30.8%, second degree

19.23%, third degree 34.62% and fourth degree 15.38%. This breakdown indicates that while a substantial portion of patients experienced mild (first-degree) and moderate (second-degree) malnutrition, a significant number also suffered from severe (third and fourth-degree) malnutrition. Addressing nutritional deficiencies preoperatively is essential to enhance recovery and reduce

postoperative complications. The INA score is also used for nutritional assessment by using serum albumin and blood lymphocyte counts (21-23). Although limited studies are clarifying that NRI is an effective predictor of postoperative outcome in patients with colorectal cancer, a study by Sungurtekin and colleagues (24) of 100 patients who had undergone major intra-abdominal surgery showed that NRI, when compared with SGA, was also predictive of malnutrition and

postoperative complications in these populations. (24) When evaluated against the PG-SGA, which served as the gold standard, the NRI had a lower sensitivity (66%) and specificity (60%).16 Additionally, although the NRI itself is a quick and simple technique, it requires blood biochemical parameter tests (25, 26) That being said, its objectivity and potential predictive value allow it to be useful in screening for malnutrition in patients with colorectal cancer.

Maeda and colleagues in 2014 (32) demonstrated that a low PNI score was an independent negative prognostic factor of overall survival, using a cut-off value of 44.5. However, they did not demonstrate the presence of any differences in terms of progression-free survival between their study groups. Using the same cut-off value for PNI, Ikeya and colleagues (33) suggested that a PNI score greater than 44.5 was associated with longer overall survival in a study of 80 patients with unresectable colorectal metastases. In keeping with these findings, Nozoe et al. (34) found that along with an advanced tumor stage and the presence of vascular invasion, a PNI score below 40 was an independent negative prognostic factor of survival in 219 patients undergoing colorectal cancer surgery with curative intent. In agreement with our findings, they also demonstrated an inverse association between PNI and tumor stage.

Conclusion

The study highlights a significant prevalence of malnutrition among patients undergoing surgery for colorectal carcinoma, with 27.96% of the patients classified as malnourished according to the INA score. These findings emphasize the critical need for routine nutritional assessments and interventions as part of preoperative care in colorectal carcinoma patients to potentially improve surgical outcomes and overall recovery. Addressing malnutrition proactively can help mitigate its adverse effects on patient health and enhance the effectiveness of surgical treatments.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department Concerned. (IRBEC-TCHLL-048/23)
Consent for publication
Approved
Funding
Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

Authors Contribution

ABDUL MUQEET
Data Analysis
SIRAJ HAIDER
Revisiting Critically
FAISAL IBRAHIM & ABSAR HYDER
Concept & Design of Study
MUHAMMAD IMRAN SIRAJ & EMAD UDDIN SAJID
Drafting
IQRA ANEES RAJPUT & NOMAN AHMED KHAN
Final Approval of version

References

1. Islami F, Ward EM, Sung H, Cronin KA, Tangka FK, Sherman RL, et al. Annual report to the nation on the status of cancer, part 1: national cancer statistics. JNCI: Journal of the National Cancer Institute. 2021;113(12):1648-69.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: a cancer journal for clinicians. 2018;68(1):7-30.
3. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA oncology. 2017;3(4):524-48.
4. Anwar B, Uzair S, MERIT A. Pakistan Clinical Research Landscape Report 2022. A collaborative project of APPNA MERIT and BMY HEALTH Version.1.
5. Mahmood S, Faraz R, Yousaf A, Quader A, Asif H, Atif A, et al. Collective Cancer Registry Report from December 1994 to December 2019, of the Shaukat Khanum Memorial Cancer Hospital & Research Center, Pakistan [Internet]. Pakistan [Internet]. 2020.

6.   Macrae FA, Bendell J, Tanabe K, Savarese D, Grover S. Clinical presentation, diagnosis, and staging of colorectal cancer. UpToDate Retrieved from (https://www uptodate com/contents/clinical-presentation-diagnosis-and-stagingof-colorectal-cancer) Accessed on. 2016;2:2016.

7.   Idrees R, Fatima S, Abdul-Ghafar J, Raheem A, Ahmad Z. Cancer prevalence in Pakistan: meta-analysis of various published studies to determine variation in cancer figures resulting from marked population heterogeneity in different parts of the country. World journal of surgical oncology. 2018;16:1-11.

8.   Doubeni CA, Laiyemo AO, Major JM, Schootman M, Lian M, Park Y, et al. Socioeconomic status and the risk of colorectal cancer: an analysis of more than a half million adults in the National Institutes of Health-AARP Diet and Health Study. Cancer. 2012;118(14):3636-44.

9.   Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010;138(6):2029-43. e10.

10.   Doubeni CA, Major JM, Laiyemo AO, Schootman M, Zauber AG, Hollenbeck AR, et al. Contribution of behavioral risk factors and obesity to socioeconomic differences in colorectal cancer incidence. Journal of the National Cancer Institute. 2012;104(18):1353-62.

11.   Seretis C, Kaisari P, Wanigasooriya K, Shariff U, Youssef H. Malnutrition is associated with adverse postoperative outcome in patients undergoing elective colorectal cancer resections. J buon. 2018;23(1):36-41.

12.   van Stijn MF, Korkic-Halilovic I, Bakker MS, van der Ploeg T, van Leeuwen PA, Houdijk AP. Preoperative nutrition status and postoperative outcome in elderly general surgery patients: a systematic review. Journal of parenteral and enteral nutrition. 2013;37(1):37-43.

13.   Kwag S-J, Kim J-G, Kang W-K, Lee J-K, Oh S-T. The nutritional risk is a independent factor for postoperative morbidity in surgery for colorectal cancer. Annals of surgical treatment and research. 2014;86(4):206-11.

14.   Daniele A, Divella R, Abbate I, Casamassima A, Garrisi VM, Savino E, et al. Assessment of nutritional and inflammatory status to determine the prevalence of malnutrition in patients undergoing surgery for colorectal carcinoma. Anticancer research. 2017;37(3):1281-7.

15.   Barbosa LRL, Lacerda-Filho A, Barbosa LCL. Immediate preoperative nutritional status of patients with colorectal cancer: a warning. Arquivos de gastroenterologia. 2014;51:331-6.

16.   Correia MIT, Perman MI, Waitzberg DL. Hospital malnutrition in Latin America: A systematic review. Clinical nutrition. 2017;36(4):958-67.

17.   Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clinical nutrition. 2017;36(3):623-50.

18.   Mosquera C, Koutlas NJ, Edwards KC, Strickland A, Vohra NA, Zervos EE, et al. Impact of malnutrition on gastrointestinal surgical patients. Journal of Surgical Research. 2016;205(1):95-101.

19.   Hu W-H, Cajas-Monson LC, Eisenstein S, Parry L, Cosman B, Ramamoorthy S. Preoperative malnutrition assessments as predictors of postoperative mortality and morbidity in colorectal cancer: an analysis of ACS-NSQIP. Nutrition journal. 2015;14:1-6.

20.   Leandro-Merhi VA, Aquino JLBd. Relationship between nutritional status and the clinical outcomes of patients with and without neoplasms according to multiple correspondence analysis. Arquivos de gastroenterologia. 2017;54(02):148-55.

21.   Seltzer MH, Bastidas JA, Cooper DM, Engler P, Slocum B, Fletcher HS. Instant nutritional assessment. Journal of Parenteral and Enteral Nutrition. 1979;3(3):157-9.

22.   Budzyński J, Tojek K, Czerniak B, Banaszkiewicz Z. Scores of nutritional risk and parameters of nutritional status assessment as predictors of in-hospital mortality and readmissions in the general hospital population. Clinical Nutrition. 2016;35(6):1464-71.

23.   Pablo A, Izaga MA, Alday LA. Assessment of nutritional status on hospital admission: nutritional scores. European journal of clinical nutrition. 2003;57(7):824-31.

24.   Sungurtekin Hl, Sungurtekin Uu, Balci C, Zencir M, Erdem En. The influence of nutritional status on complications after major intraabdominal surgery. Journal of the American College of Nutrition. 2004;23(3):227-32.

25.   Faramarzi E, Mahdavi R, Mohammad-Zadeh M, Nasirimotlagh B. Validation of nutritional risk index method against patient-generated subjective global assessment in screening malnutrition in colorectal cancer patients. Chinese journal of cancer research. 2013;25(5):544.

26.   Reilly H, Martineau J, Moran A, Kennedy H. Nutritional screening-evaluation and implementation of a simple nutrition risk score. Clinical nutrition. 1995;14(5):269-73.

27.   Yoneyama Y, Ito M, Sugitou M, Kobayashi A, Nishizawa Y, Saito N. Postoperative lymphocyte percentage influences the long-term disease-free survival following a resection for colorectal carcinoma. Japanese journal of clinical oncology. 2011;41(3):343-7.

28.   Chojkier M. Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. Journal of clinical gastroenterology. 2005;39(4):S143-S6.

29.   Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A. Cancer cachexia—pathophysiology and management. Journal of gastroenterology. 2013;48:574-94.

30.   Onate-Ocana LF, Aiello-Crocifoglio V, Gallardo-Rincon D, Herrera-Goepfert R, Brom-Valladares R, Carrillo JF, et al. Serum albumin as a significant prognostic factor for patients with gastric carcinoma. Annals of surgical oncology. 2007;14:381-9.

31.   Guthrie G, Roxburgh C, Richards C, Horgan P, McMillan D. Circulating IL-6 concentrations link tumour necrosis and systemic and local inflammatory responses in patients undergoing resection for colorectal cancer. British journal of cancer. 2013;109(1):131-7.

32.   Lee W-S, Baek J-H, You DH, Nam MJ. Prognostic value of circulating cytokines for stage III colon cancer. Journal of Surgical Research. 2013;182(1):49-54.

33.   Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon geka gakkai zasshi. 1984;85(9):1001-5.

34.   Kitayama J, Yasuda K, Kawai K, Sunami E, Nagawa H. Circulating lymphocyte is an important determinant of the effectiveness of preoperative radiotherapy in advanced rectal cancer. BMC cancer. 2011;11:1-6.