Discrepancy in Colorectal Cancer Staging: A Single Center Experience

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Abstract

Background: The TNM (Tumor Node Metastases) staging system developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is the most widely used classification system for colorectal cancer staging. Accurate predictions of the definitive pathological disease stage using pre-operative clinical-radiological staging techniques are crucial to facilitate timely oncological and surgical planning following diagnosis.

Aims: This study describes a cohort of patients treated for colorectal cancer in a general hospital. We aimed to assess the accuracy of pre-operative clinical-radiological staging in predicting pathological colorectal cancer stage at a non-specialist center.

Methods: A retrospective cohort study examined the records of 98 patients with histological confirmed colorectal carcinoma over a 6 year period from 2010 to 2015. Ninety eight patients were treated in St Luke's General Hospital, while 14 patients were managed and followed up in other hospitals. Data was collected by chart review and from prospectively maintained electronic histopathology and radiology databases.

Results: Ninety eight cases of colorectal cancer were identified. The mean age at presentation was 67.9 years; 50% patients were men; 26.5% had rectal tumors; and 85.7% underwent surgery following clinical staging. Clinical radiological stage and pathological stage differed in 27.4% (n=23) patients (p<0.0001). Of those 23 patients, eight were up staged (none of whom received neoadjuvant therapy), and 15 were down staged post operatively.

Conclusion: Discrepancy in staging colorectal cancer has critical effects on management, outcomes, and survival rates of patients. Appropriate and accurate clinical radiological staging enables multi disciplinary teams to plan optimal management approaches.

Keywords: Colorectal cancer; Cancer staging; Clinical radiological

Introduction

The TNM (Tumor Nodes Metastases) staging system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is the most widely used classification system for staging malignant tumors [1]. The importance of malignant tumor staging has increased significantly over the past 30 years owing to a trend towards individualized therapies often dependent on accurate knowledge of disease progression. Inaccurate staging may result in suboptimal management; under staging of disease may give rise to inadequate treatment approaches, whereas over staging can result in morbidity associated with excess treatment [2]. This is especially true for neoplasm's f the colon and rectum where there is a strong correlation between disease stage and prognosis [3,4]. This correlation has been established since the first colorectal cancer staging was developed by Cuthbert Dukes in 1929, when he classified rectal cancer based on its invasion into the bowel wall, through the bowel wall, or involving regional lymph nodes (Dukes A, B, and C, respectively) [5]. The AJCC TNM staging system provides a systematic method of colorectal cancer staging to aid with therapeutics planning. In the modern era of cancer management, neoadjuvant strategies are ubiquitous and close correlation between clinical-radiological and pathological staging is of great importance [6,7]. The goal of this study was the evaluation and comparison of clinical-radiological staging with pathological staging in a cohort of patients treated for colorectal cancer at a non-specialized general hospital. Clinical Radiological stage (rTNM) parameters are based on physical examination, imaging techniques, and biopsies of affected areas, whereas Pathological staging (pTNM) further incorporates intra operative findings and may only be elucidated following surgery to excise or explore the diseased colon [8].

Table 1: AJCC colon and rectum cancer: TNM definitions [1].

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor penetrates the surface of visceral peritoneum or invades other structures
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Tables 2: AJCC and modified Dukes colon and rectum cancer stages [1,10].

Anatomic Stage/Prognostic Groups				
Stage	**T**	**N**	**M**	**Dukes***
0	Tis	N0	M0	-
1	T1	N0	M0	A
1	T2	N0	M0	B
2	T3-4	N0	M0	B
3	T1-4	N1-2	M0	C
4	Any T	Any N	M1	D

*Dukes Criteria as Modified by Turnbull, 1967

Methods

This is a retrospective cohort study examined the records of 98 patients treated for colorectal cancer from 2010 to 2015 at St. Luke's Hospital, Kilkenny, patients are identified by interrogation of the Hospital In-Patient Enquiry (HIPE) database, which classifies disease based on the 10th revision of the International Statistical Classification of Diseases (ICD-10) developed by the World Health Organization (WHO) [9]. Patients with documented ICD-10 code diagnoses from C18 to C20 (malignant neoplasm of the colon, recto sigmoid and rectum) with histological confirmed colorectal carcinoma over a 6 year period from 2010 to 2015 were included. A data Performa sheet was used to record demographics and clinical pathological parameters, which were gathered via chart review and from prospectively maintained electronic histopathology and radiological databases. Data recorded included age, sex, presenting symptoms, mode of presentation, clinical radiological staging results and surgical management strategies. Ethical approval was obtained from the ethics committee in the hospital.

The AJCC cancer staging manual 7th edition (AJCC) guidelines for TNM staging were used to determine staging parameters based on clinical examination and imaging findings (Table 1 and 2) [10]. The radiologist and pathologist recorded rTNM and pTNM designations, respectively, and adhered to AJCC 7th edition TNM staging standards for colorectal cancers. Computed Tomography (CT) of the thorax, abdomen, and pelvis was routinely used to assess local and distant tumor spread for all patients with colorectal cancer. In selected cases, mostly for rectal cancers, Magnetic Resonance Imaging (MRI) of the pelvis and/or abdomen in addition to ultrasound scanning and colonoscopy examination was also utilized.

Pathological staging parameters were determined post operatively by a colorectal specialist pathologist based in the University Hospital Waterford (UHW), which is a designated cancer center under the Irish National Cancer Control Program (NCCP). Tumor local invasion, lymph node involvement, and resection margin status were routinely reported by the pathologist. All pathology reports specifically documented pTNM stage values. All cases were discussed at multi disciplinary gastro-intestinal oncology team meetings.

Overall disease staging was compared with the pre operative clinical radiological stage. Changes in individual pTNM parameters, including local tumor size and extent (T), lymph node involvement (N), and distant metastases (M) were individually examined. Statistical analysis was performed using SPSS v20 and Pearson's *chi square* test was utilized for comparing frequencies of categorical variables.

Results

We identified 98 patients with colorectal cancer for evaluation. The mean age at presentation was 67.9 years (+/- SD 12.1); 50% (n=49/98) were men; 26.5% (n=26/98) had rectal tumors, and 73.5% (n=72/98) had colon cancer. At presentation, 87% (n=85/98) of our patients had T3/T4 tumors. Following clinical-radiological staging, 85.7% (n=84/98) received surgery. Of patients with rectal tumors, 96% (n=25/26) received surgery with curative intent, 17 of whom received neoadjuvant therapy. Of patients with colon cancer, 81.9% (n=59/72) received surgery, one of whom received neoadjuvant treatment for a rectosigmoid lesion.

All patients had a contrast-enhanced Computed Tomography (CT) scan of the thorax, abdomen, and pelvis. Additionally, baseline serum Carcinoembryonic Antigen (CEA) levels were measured as part of clinical staging. Colonoscopy was performed in all patients to obtain tumor biopsies and to assess for synchronous colonic lesions.

Table 3: Breakdown of clinical presentations.

n (%)	Colonic Disease Only (n=72)	Rectal Disease Only (n=26)	All patients (n=98)
Rectal Bleeding	35 (48.6%)	19 (73.1%)	54 (55.1%)
Weight Loss	22 (30.6%)	7 (26.9%)	29 (29.6%)
Abdominal Pain	24 (33.3%)	4 (15.4%)	28 (28.6%)
Altered Bowel Habit	15 (20.8%)	11 (42.3%)	26 (26.5%
Anemia*	20 (27.8%)	1 (3.8%)	21 (21.4%)
Bowel Obstruction	6 (8.3%)	3 (11.5%)	9 (9.2%
Bowel Perforation	4 (4.1%)	0 (0%)	4 (4.1%)

*Anemia defined as <13 g/dL for men, <12 g/dL for women

Table 4: Variation in post-operative pathological disease staging compared to clinical-radiological staging.

	Overall Stage		
	Up-staged	Down-staged	Same stage
Colonic (n=59)	8 (8.5%)	6 (10.2%)	45 (76.3%)
Rectal, Neoadjuvant (n=17)	0 (0%)	8 (47.1%)	9 (52.9%)
Rectal, No Neoadjuvant (n=8)	0 (0%)	1 (5.6%)	7 (94.4%)

Rigid sigmoidoscopy was performed in patients with rectal tumors. MRI of the pelvis was performed in 61.5% (n=16/26) of patients with cancers involving the rectum. Of the 10 patients who did not undergo MRI, seven were diagnosed with rectosigmoid tumors, and one did not proceed to surgery due to the extent of disease burden and comorbid conditions. The remaining two patients had contraindications to MRI.

Most patients (72.4%; n=71/98) were diagnosed following presentation in an elective setting, following general practitioner or emergency department referral to the surgical outpatient department, referral from another hospital department, or during endoscopic surveillance. The remaining 27.6% (n=27/98) were admitted through the Emergency Department with acute presentations. The most common presenting symptoms among colorectal cancer patients were per rectal bleeding, unexplained weight loss, and abdominal pain. As expected, more patients with rectal tumors presented with rectal bleeding than with colon lesions (73.1% *vs.* 48.6%; Table 3).
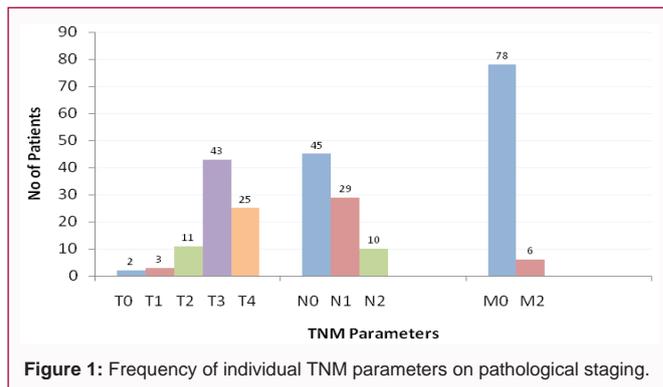
Of 84 patients who received resectional surgery, 94.0% (n=79) had an R0 complete resection reported on histopathology; 4.8% (n=4/84) had an R1 resection (microscopic residual cancer), and 1.2% (n=1/84) had an R2 resection (macroscopic residual cancer). The most frequently performed operation was a sigmoid colectomy (26.2%, n=22/84), followed by anterior resection and right hemicolectomy, each at 23.8% (n=20). The next most frequent procedures were extended right hemicolectomy (13.1%, n=11/84), abdominoperineal resection 10.7%, n=9/84), subtotal colectomy (2.4%, n=2/84), and left hemicolectomy (1.2%, n=1/84).

Overall disease staging

Of patients who underwent surgery, 27.4% (n=23/84) demonstrated discordance between the clinical-radiological and the pathological colorectal disease stage (p<0.0001), as defined by the AJCC cancer staging manual (7th edition) guidelines (Table 4). The pathological stage differed from clinical-radiological staging in 22.7% (n=15/66) of the cases where pre operative neoadjuvant treatment was not given (p<0.0001). Of the 23 patients with variations in post-operative disease staging (Table 4), eight patients were up-staged (none of whom received did not receive Neoadjuvant therapy), whereas 15 patients were down staged (seven of none of whom receive neoadjuvant therapy). In two cases, there were variations in TNM staging parameters without a resulting change in the overall

Figure 1: Frequency of individual TNM parameters on pathological staging.

disease stage.

Primary tumor staging (T)

Variation in Tumor (T) staging was noted in 13.1% (n=11/84) of patients at pathological staging compared to pre-operative clinical-radiological staging (Table 5). Four of these patients had an increase in T stage, none of whom had Neoadjuvant treatment. At histopathology, primary tumor stage pT3 occurred most frequently (in 51.2% of patients; n=43/84; Figure 1). Two patients had an increase in stage from rT3 to pT4, one from rT2 to pT3, and the remaining patient had a pT1 tumor that was not detected on imaging, and pre-operatively staged as rT0 [11].

Regional lymph node staging (N)

The greatest discrepancy in individual TNM staging parameters was found in nodal disease (N) staging, where 17.9% (n=15/84) of cases differed between pathological staging and clinical radiological staging (Table 5). Nodal disease burden was detected in 46.4% (n=39/84) of pathology specimens, whereas node positivity was radiographically evident in 54.8% (n=46/84).

Clinical radiological staging of lymph node metastases was concordant more often in patients with rectal disease (87.5%, n=7/8) than in those with colon tumors (84.7%, n=50/59). In one patient with rectal disease, N stage increased from rN1 to pN2, despite Neoadjuvant therapy. Out of 67 patients who did not receive Neoadjuvant therapy, 15.2% (n=10) had a change in N-stage; in three, the stage increased from rN0 to pN1 and in one, from rN1 to pN2. Down-staging occurred in six patients: in four, the stage decreased from rN1 to pN0; in one from rN2 to pN1; and in one from rN2 to pN0.

Distant metastasis staging (M)

In patients with colorectal cancer, 22.6% (n=19/84) had metastases identified radiologically; three were patients with rectal disease and 16 had primary colonic disease. Fourteen of these patients did not proceed to surgery. Of the five who proceeded to surgery, two were patients with rectal tumors who both received Neoadjuvant

Table 5: Post-operative pathological TNM variations, as compared to clinical-radiological TNM parameters.

	T Stage			N Stage			M Stage		
	up-staged	down-staged	same -stage	up-staged	down-staged	same -stage	up-staged	down-staged	same -stage
Colonic (n=59)	3 (5.1%)	2 (3.4%)	54 (91.5%)	4 (6.8%)	5 (8.5%)	50 (84.7%)	3 (5.1%)	1 (1.7%)	55 (93.2%)
Rectal, Neoadjuvant (n=17)	0 (0%)	5 (29.4%)	12 (70.6%)	1 (5.9%)	4 (23.5%)	12 (70.6%)	0 (0%)	1 (5.9%)	16 (94.1%)
Rectal, No Neoadjuvant (n=8)	1 (12.5%)	0 (0%)	7 (87.5%)	0 (0%)	1 (12.5%)	7 (87.5%)	0 (0%)	0 (0%)	8 (100%)

therapy. One remained in Stage 4, while the second was down staged to stage 3 following treatment. The remaining three patients had colonic tumors, and proceeded to surgery with the stage in one being restaged as pM0 following surgery. Metastatic disease was found in six patients at surgery; in three, metastases were not detected by preoperative investigations.

Discussion

Although surgery remains the mainstay of colorectal cancer management in the modern era, overall treatment strategies increasingly include both adjuvant and Neoadjuvant radiotherapy and chemotherapeutic modalities [5,12]. Treatment strategies are formulated following multi disciplinary team discussion, as in this study. Provision of personalized treatment regimens gives rise to increasing permutations and combinations of management approaches. Arriving at the optimal management plan for any given patient necessitates a complex decision making process, which relies heavily on clinical-radiological staging. Neoadjuvant therapy is now a frequently utilized modality for many advanced gastrointestinal solid tumors, including rectal, esophageal, and gastric cancers [13,14]. Pre operative chemotherapy has not yet been adequately proven for colonic tumors, although it is being investigated because earlier treatment may be more effective at eradicating micro metastatic disease when compared to systemic treatment months after surgery. Thus, recurrence rates may be reduced and rates of curative resection potentially increased. Recently, the FOxTROT randomized control trial group reported a study of the feasibility, safety, and efficacy of neoadjuvant treatment for advanced colon cancers [14].

The profile of clinical radiological presentations in our cohort compared to published presentations.

In this cohort, Pre-operative clinical-radiological evaluation and diagnostics were inaccurate for nearly a quarter of all patients who did not receive Neoadjuvant treatment for colorectal cancer. Eight patients were up-staged and seven down staged following pathological staging. Incorrect over-staging may have significant impact on morbidity and mortality secondary to over-treatment. Conversely, insufficient treatment of inaccurately under staged patients may cause increased rates of metastatic and recurrent disease. Best practice guidelines recommend CT of the thorax, abdomen, and pelvis for staging of all colorectal tumors. MRI of the pelvis or endoanal ultrasound is recommended for patients with rectal disease. Full colonoscopy is also a minimum requirement, usually performed pre operatively, but may be performed post-operatively in patients who present with primary tumors not navigable endoscopically or in emergency presentations [12,15].

Neoadjuvant chemo-radiotherapy is an increasingly utilized strategy for management of patients with rectal tumors, especially for those with locally advanced or node positive disease, and commonly includes options such as short course pre operative radiotherapy or chemo-radiotherapy [16,17]. MRI and endoanal ultrasound assist in identifying appropriate candidates for Neoadjuvant management options. These investigations evaluate both T and N stage, and examine mesorectal nodal burden and mesorectal fascia involvement [16-18], which is essential for surgical planning. MRI aids in measuring the distance from the anal verge, thereby aiding the surgeon's decision on the optimal surgical strategy: Abdomino-perineal resection or sphincter saving ultra-low anterior resection, which is permissible to a distance of 1 cm from the anal verge in contemporary guidelines

[15]. The identification of nodal disease is important for decisions regarding Neoadjuvant therapy in rectal disease. This has proven a difficult diagnostic task for radiologists and is often based on lymph node shape and size identified on MRI, with nodes >8 mm deemed positive on imaging for clinical staging [15].

CT is the most frequently utilized modality for colorectal cancer staging, with a reported accuracy ranging from 45% to 77% for the assessment of nodal metastases [16,18,19]. MRI has a reported staging accuracy of 73% with a sensitivity of 40% for lymph node metastases detection. The addition of MRI to CT further improves the overall accuracy of staging rectal cancer [16-18]. Access to clinical and radiological staging resources played a role in the accuracy of colorectal cancer staging in our cohort. CT is undertaken on site at our institution, whereas MRI, although accessible via other institutions, is not readily available on site. Lack of direct access to PET/CT and endoanal ultrasound scanning may also have a negative impact on optimal staging. Although PET/CT is not routinely recommended for initial staging of colorectal cancer, it is frequently used to clarify equivocal findings on traditional modalities such as CT and MRI, especially in the setting of potential metastatic disease and synchronous lesions where colonoscopy cannot be completed due to obstructing tumors. For staging of rectal cancer, MRI was typically used to augment CT in our cohort, with no use of endoanal ultrasound. Although there is limited conclusive evidence to demonstrate superiority of one modality over the other, endoanal ultrasound is generally beneficial in rectal T staging, especially for early disease, whereas MRI improves visualization of mesorectum and circumferential resection margin involvement for more advanced tumors [16-18]. Access to MRI and PET/CT modalities and the availability of endoanal ultrasound may have improved the accuracy of clinical radiological staging in our cohort.

Variability in staging may also alter the management approach in colonic lesions. Pre operative CT can identify loco-regional tumor extent, lymphatic and distant metastases, and disease complications such as perforation or fistula formation. Differentiation between T3 and T4 tumors aids in planning the surgical approach, when tumor extension into surrounding structures may necessitate more extensive resection, possibly with surgical interdisciplinary cooperation required at surgery. Especially for our center, T4 tumors typically necessitate referral to centers where urologic and gynecologic oncology input is available for multi disciplinary procedures. In addition, accurate assessment for liver metastases, initially with CT and then MRI or ultrasound scanning pre-operatively, allows for optimal surgical planning for metastatic tumors [20]. PET/CT is valuable in selected cases for localizing synchronous colorectal cancers proximal to obstructing lesions, and for evaluating extra colonic and hepatic disease. However, there is no robust evidence to support the routine use of PET/CT for staging [20]. There are increasingly improved outcomes for patients following curative resection of liver metastases. Five year survival (58%) and overall recurrence rates (52%) have been reported post liver resection [21]. Many surgeons opt for resection of liver metastases in an index procedure followed by primary tumor resection. The early identification of metastases facilitates a timely transfer to the tertiary referral center for metastasectomy.

Colorectal cancer is a disease entity responsive to screening given that it has a defined pathological progression and is highly treatable if diagnosed early [13]. In cases of symptomatic patients, timely diagnostics and prompt management result in improved

outcomes [14]. Clarke et al. report an increase in late stage colorectal disease presentations (Stage 3 to Stage 4) from 42% (n=1,752) to 50% (n=2,298) following their interrogation of Ireland's National Cancer Registry for the period 1995 to 2010 [21]. In 2016, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) published their national bowel cancer audit annual report, which examines demographics and clinical pathological parameters of over 30,000 patients in England and Wales with colorectal cancer diagnosed between April 1, 2014 and March 31, 2015 [13]. This ACPGBI audit indicated an incidence of locally advanced T3/T4 tumors of 57% (n=17,220/30,122) at clinical radiological staging, which is less than the 87% (n=85/98) of our patients who had T3/T4 tumors at presentation. Our cohort exhibited node positivity in 54.8% of patients at clinical-radiological staging, which is more frequent than the 41% (n=12,420/30,122) reported by the ACPGBI [20]. The metastatic disease incidence was 22.6% (n=19/84) in our cohort at clinical radiological staging, whereas the ACPGBI reported 18.2% (n=5,471/30,122). Thus, our rates of advanced disease at clinical radiological staging appear higher than those reported in the national bowel cancer audit. This increased rate of late presentations of cancer at our hospital requires spending the least possible time from presentation to clinical radiological workup.

Conclusion

High quality, accurate clinical-radiological staging enables multi-disciplinary teams to plan optimal management strategies for patients with colorectal neoplasms. All patients presenting with red flag symptoms should be promptly investigated and staged according to international standards followed by discussion in a multi disciplinary setting prior to treatment. There is a disparity between clinical-radiological staging and pathological staging in our cohort, which may be improved with education for high risk patients and their families, priority access to endoscopy, and optimal radiological staging modalities such as CT, MRI, PET/CT, and endoanal ultrasound.

References

1. Edge SB, Compton CC. The American joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.

2. Hermanek P, Sobin LH, Wittekind C. How to improve the present TNM staging system. Cancer. 1999;86(11):2189-91.

3. Compton CC, Greene FL. The staging of colorectal cancer: 2004 and beyond. CA Cancer J Clin. 2004;54(6):295-308.

4. Lindblom A. Improved tumor staging in colorectal cancer. New England J Med. 1998;339(4):264-5.

5. Dukes CE. The classification of cancer of the rectum. J Pathol Bacteriol. 1932;35(3):323-32.

6. Harisi R, Schaff Z, Flautner L, Winternitz T, Jaray B, Nemeth Z, et al. Evaluation and comparison of the clinical, surgical and pathological TNM staging of colorectal cancer. Hepatogastroenterology. 2008;55(81):66-72.

7. Harisi R, Schaff Z, Winternitz T, Nemeth Z, Harsanyi L, Morvay K, et al. TNM staging at colorectal cancer. Zeitschrift für Gastroenterologie. 2005;43(05):40.

8. American Joint Commitee on Cancer (AJCC). What is Cancer Staging? 2017[24 June 2017].

9. Organization WH. International statistical classification of diseases and related health problems: World Health Organization; 2004.

10. Turnbull RB, Jr KK, Watson FR, Spratt R. Cancer of the colon: The influence of the no-touch isolation technic on survival rates. Ann Surg. 1967;166(3):420-7.

11. Moreno CC, Mittal PK, Sullivan PS, Rutherford R, Staley CA, Cardona K, et al. Colorectal cancer initial diagnosis: Screening colonoscopy, diagnostic colonoscopy, or emergent surgery, and tumor stage and size at initial presentation. Clin Colorectal Cancer. 2016;15(1):67-73.

12. National Institute for Health and Care Excellence. Colorectal cancer: diagnosis and management. Clinical Guideline 131. London: NICE; 2014.

13. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) N, RCS. National Bowel Cancer Audit - Annual Report 2016. London: 2016.

14. Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: The pilot phase of a randomised controlled trial. Lancet Oncol. 2012;13(11):1152-60.

15. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol. 2012;23(10):2479-516.

16. McPhee SJ, Papadakis MA, Tierney LM. Current medical diagnosis and treatment 2010. New York: McGraw-Hill Medical; 2010.

17. Dahnert W. Radiology Review Manual. Baltimore MD, USA: Lippincott Williams & Wilkins; 2003.

18. Horton KM, Abrams RA, Fishman EK. Spiral CT of colon cancer: Imaging features and role in management. Radiographics. 2000;20(2):419-30.

19. Choi AH, Nelson RA, Schoellhammer HF, Cho W, Ko M, Arrington A, et al. Accuracy of computed tomography in nodal staging of colon cancer patients. World J Gastrointest Surg. 2015;7(7):116-22.

20. Kijima S, Sasaki T, Nagata K, Utano K, Lefor AT, Sugimoto H. Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT. World J Gastroenterol. 2014;20(45):16964-75.

21. Clarke N, McDevitt J, Kearney PM, Sharp L. Increasing late stage colorectal cancer and rectal cancer mortality demonstrates the need for screening: a population based study in Ireland, 1994-2010. BMC Gastroenterology. 2014;14(1):92.