



## The role of transcatheter arterial chemoinfusion (TACI) in unresectable adenocarcinoma colorectal: a case report

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### ABSTRACT

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Colorectal cancer (CRC) is the fourth most common cancer in worldwide. In the last 10 years, the mortality rate of CRC decreased by more than 20% and 5-year survival remains approximately 60% due to the rising developments in diagnostic techniques and optimization of surgical, neoadjuvant and palliative therapies. We reported a case of 80-year-old woman with diarrhea, blood in the stool and weight loss for a year. The patient was diagnosed with colonic polyp eight years ago. In double-contrast barium enema (DCBE) showed filling defects in sigmoid with pedunculated form. Optical colonoscopy demonstrated tumor in sigmoid. Computed tomography (CT) abdomen showed circumferential thickening and luminal narrowing of sigmoid colon with stranding of the serosa and mesenteric fat as well as enlarge pericolic nodes without distant metastasis. Based on American Joint Committee on Cancer criteria the stage was T3N1M0. From histopathological diagnosis, the tumor was well differentiated adenocarcinoma. We concluded as unresectable adenocarcinoma colorectal. Patient received transcatheter arterial chemoinfusion (TACI) with oxaliplatin and bevacizunab in three courses every 2 months. After first TACI, symptoms and patient's performance status improved without systemic side effects. Arteriography imaging showed decrease in tumor staining after third TACI. CT evaluation showed a significant decrease of tumor size, without nodal and distant metastasis. In this case, TACI treatment with oxaliplatin and bevacizumab in unresectable adenocarcinoma colorectal demonstrated improvement of patient's performance status, partial response, decrease stage and symptoms, without systemic side effects. It is proven that TACI treatment may be an effective palliative therapy for unresectable colorectal cancer. Further studies should be performed to verify these findings. We reported a case of a woman with unresectable adenocarcinoma colorectal showed good results after received TACI treatment.

### ABSTRAK

Kanker kolorektal (KKR) adalah kanker paling banyak keempat di seluruh dunia. Dalam 10 tahun terakhir, angka kematian KKR menurun lebih dari 20% dan harapan hidup 5 tahun tetap sekitar 60% karena meningkatnya perkembangan teknik diagnostik dan optimalisasi teknik bedah, terapi neoadjuvant dan paliatif. Kami melaporkan kasus wanita berusia 80 tahun dengan keluhan diare, darah dalam tinja dan penurunan berat badan selama setahun. Pasien didiagnosis polip kolon delapan tahun lalu. Pada *double-contrast barium enema* (DCBE) tampak *filling defect* pada sigmoid dengan bentuk *pedunculated*. *Colonoscopy* menunjukkan tumor di sigmoid. *Computed tomography* (CT) abdomen tampak penebalan sirkumferensial dan penyempitan lumen pada sigmoid, dengan *fat stranding* pada lapisan serosa dan mesenterika serta pembesaran limfonodi perikolon tanpa metastasis jauh. Menurut kriteria *American Joint Committee on Cancer* stadium nya adalah T3N1M0. Diagnosis histopatologi menunjukkan *adenocarcinoma* diferensiasi baik. Kami simpulkan sebagai *unresectable adenocarcinoma colorectal*. Pasien menjalani terapi *transcatheter arteri chemoinfusion* (TACI)

### Keywords:

imaging  
adenocarcinoma  
colorectal,  
transcatheter arterial  
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unresectable  
adenocarcinoma  
colorectal,  
oxaliplatin,  
bevacizunab,

dengan oxaliplatin dan bevacizunab dalam tiga prosedur setiap dua bulan. Setelah TACI pertama, gejala dan status kinerja pasien membaik tanpa efek samping sistemik. Pencitraan arteriografi menunjukkan penurunan *tumor staining* setelah TACI ketiga. Hasil evaluasi CT menunjukkan penurunan yang signifikan pada ukuran tumor, tidak ada nodal metastasis maupun dan metastasis jauh. Pada kasus ini, terapi TACI dengan oxaliplatin dan bevacizunab pada *unresectable adenocarcinoma colorectal* menunjukkan peningkatan status kinerja pasien, *partial response*, penurunan gejala dan stadium kanker, tanpa efek samping sistemik. Ini membuktikan bahwa terapi TACI mungkin dapat menjadi terapi paliatif yang efektif untuk *unresectable adenocarcinoma colorectal*. Studi lebih lanjut harus dilakukan untuk memverifikasi temuan ini. Kami melaporkan kasus seorang wanita dengan *unresectable adenocarcinoma colorectal* yang menunjukkan hasil yang baik setelah menerima terapi TACI.

## INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant diagnosis and the fourth most common cause of cancer deaths in the world, accounting for about 1.4 million new cases and nearly 693,900 deaths by 2012.<sup>1</sup> Recently, the CRC became a public health problem in Indonesia due to it ranked third most of all cancers diagnosed with an incidence rate of 19.1 in men and 15.6 in women per 100,000 inhabitants.<sup>2</sup> The mortality rate among Indonesian CRC was 18,958 in 2012. This high incidence and mortality are due to the lack of early detection and public awareness against CRC.<sup>3</sup>

In the past 10 years the mortality rate of CRC has declined by more than 20% due to the increasing development of diagnostic techniques and optimization of surgical techniques, neoadjuvant and palliative therapy.<sup>4</sup> The imaging modalities used in current CRC management are varied and heterogeneous in many countries and health institutions.<sup>4</sup> The recommendation of CRC therapy depends on several factors such as cancer stage, histopathology, possible side effects, patient condition and patient preference.<sup>5</sup> Chemotherapy can be performed with the minimally invasive procedure of transcatheter arterial chemoinfusion (TACI), by infusion of chemotherapy drug in arterial feeding that supplies blood to the tumor, which aims to maximize the concentration and uptake of drugs in

the target organ and minimize systemic toxicity.<sup>6</sup>

In the last decade, the life expectancy of CRC patients has increased worldwide.<sup>7</sup> In Asia the life expectancy of 5 years is about 60%.<sup>7</sup> It is related to the increased early detection and progress on the handling of the CRC.<sup>7</sup> In this case report, we reported the case of a woman with unresectable adenocarcinoma colorectal who underwent TACI therapy.

## CASE REPORT

An 80-year-old woman came with bowel complaints of bloody, fresh red, slimy and smelly with bowel habit disorders since approximately one year. Patient experienced weight loss in the past year. Patient had a habit of eating fatty foods but lacking fiber-feeding foods. Patient had no smoking or drinking habits. Patient had a history of non-specific chronic proctitis with colon polyp eight years ago. In the family there was no one suffered the CRC.

On the DBCE examination, we found a filling defect on the sigmoid with a form of pedunculated (valve phenomenon) (FIGURE 1). Further recommendations for the examination are colonoscopy and anatomical pathology biopsy of the tumor. The colonoscopy examination result was a tumor in sigmoid pars proximal with diverticulitis (FIGURE 2a), and the result of biopsy was a well differentiated adenocarcinoma (FIGURE 2b).

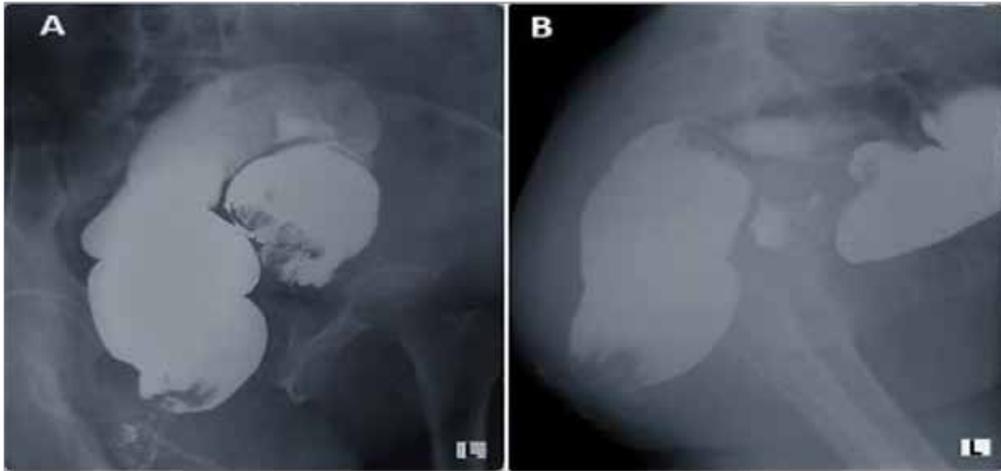


FIGURE 1. DBCE shows a filling defect on a sigmoid with a pedunculated form (valve phenomenon). A) left oblique projection; B) lateral projection.

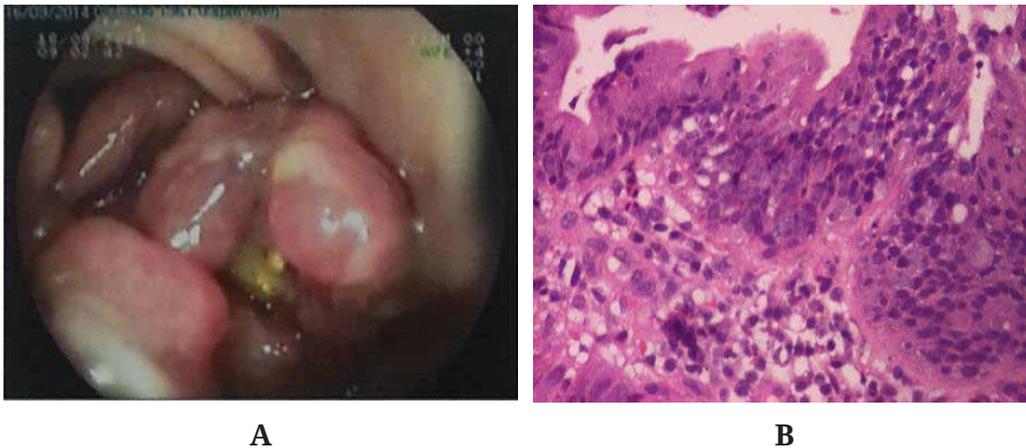


FIGURE 2. A) Colonoscopy: tumors in the proximal pars sigmoid with diverticulitis; B) pathology anatomy: adenocarcinoma well differentiation.

Furthermore, CT scan abdomen was performed for tumor staging enforcement which resulted in circumferential thickening and luminal narrowing of the sigmoid colon of 9.1 x 8.3 x 7.4 cm, with fat stranding of serous and mesenteric lining and pericolone lymph node enlargement without

distant metastasis (FIGURE 3). From these results it was concluded that this patient was in T3N1M0 stage IIIB based on AJCC. The patient refused to be treated with surgery and the tumor was considered as a case of unresectable adenocarcinoma colorectal, therefore it was decided to be treated with TACI procedure.

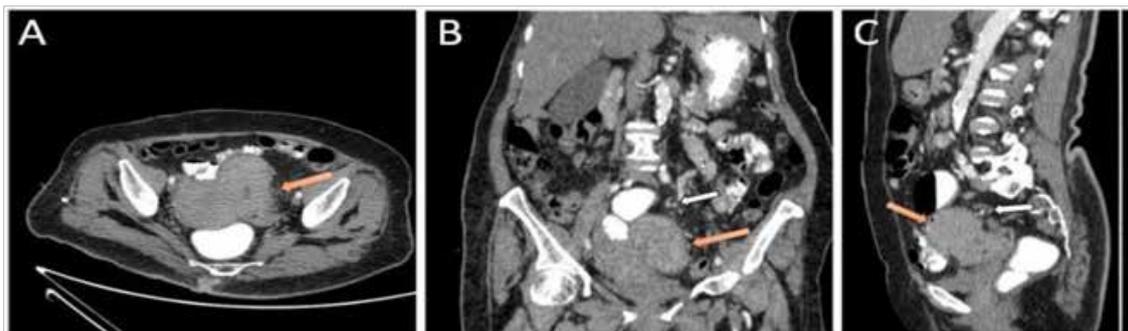


FIGURE 3. Abdominal CT scan shows circumferential thickening and luminal narrowing of the sigmoid colon of size 9.1 cm x 8.3 cm x 7.4 cm, with fat stranding on serous and mesenteric layers (red arrows) and pericoron lymph nodes (white arrows) without distant metastasis. A) axial projection; B) coronal projection; C) sagittal projection.

The patient received TACI treatment in three courses every two months. The TACI procedure was performed by introducing the Simons-2 5Fr catheter via the inferior mesenteric artery of the inferior arteriography, in which the inferior mesenteric artery appears inferior artery as an arterial feeding of a tumor characterized by a hypervascular staining tumor in the rectosigmoid region. Then infusion of oxaliplatin 50 mg and bevacizumab 100 mg were administered.

After the first TACI procedure, symptoms and patient performance

status improved without systemic side effects. Serial arteriography showed a decrease in staining tumor after the third TACI procedure (FIGURE 5). While in the CT scan evaluation showed a significant decrease in tumor size to 2.13 x 4.92 x 4.35 cm, without metastatic or metastatic nodal and distant metastasis, after re-staging the stage was declined to T3N0M0 stage IIA (FIGURE 5). From these results it was concluded that TACI treatment response in this case was a decline in stage and partial response according to RECIST criteria.

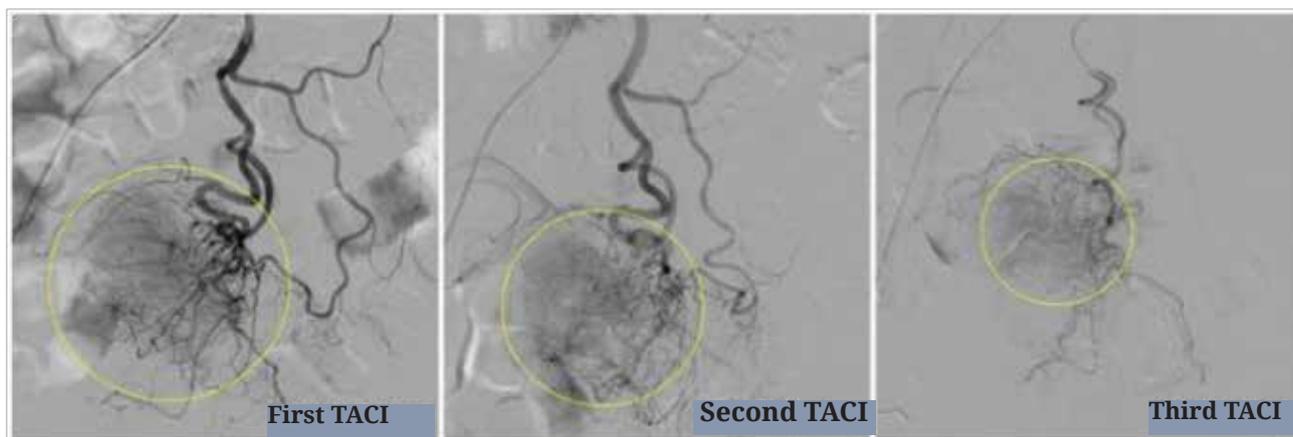


FIGURE 4. Arteriography shows decreased staining and vascularization tumors in feeding the tumor artery (yellow circle) from the first TACI to the third TACI.

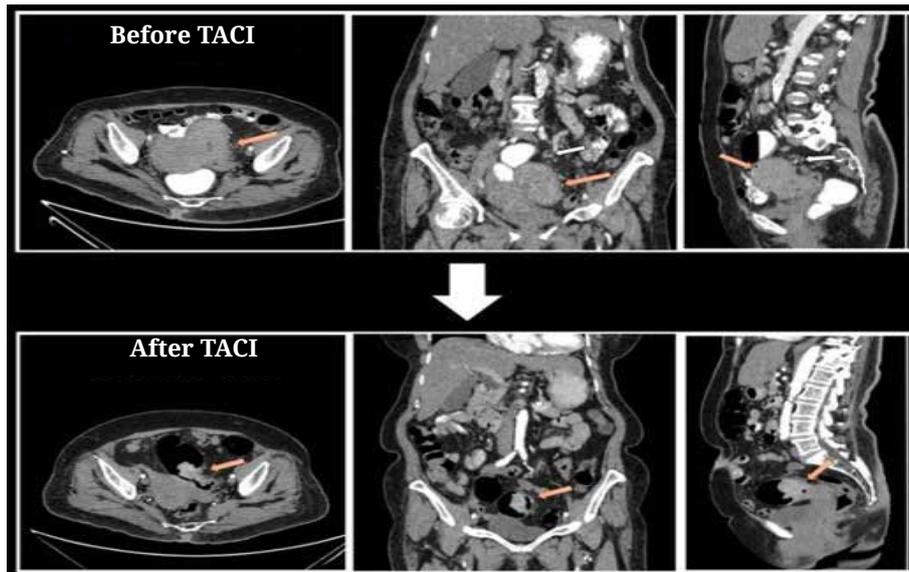


FIGURE 5. CT Scan Abdominal evaluation, before TACI size 9.1 cm x 8.3 cm x 7.4 cm (red arrow) accompanied by pericolon lymph nodes (white arrow), After third TACI procedures showed a significant reduction in tumor size to 2.13 cm x 4.92 cm x 4.35 cm, no metastatic or distant metastatic nodal.

## REVIEW OF COLORECTAL CANCER

### Risk factors

The risk factor of CRC is divided into two factors that unmodifiable and modifiable. Risk factors that unmodifiable are a history of cancer or colorectal adenoma polyps in individuals and/or families, a history of chronic inflammatory bowel disease, inherited genetic factors including familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) also called Lynch syndrome.<sup>8</sup> Risk factors that can be modified are the limitation of activity, obesity, high consumption of red meat, smoking and alcohol consumption habits.<sup>8</sup>

### Clinical symptoms

The characteristics of clinical symptoms of CRC may be the occurrence

of intestinal obstruction, hemorrhage (hematochezia, enterorrhagia), changes in bowel habits, and systemic effects such as significant weight loss.<sup>9</sup> Classical symptoms of CRC include constipation, blood in the stool, decreased caliber, appetite, weight loss, nausea and / or vomiting.<sup>10,11</sup>

### Pathogenesis

CRC occurs as a result of genetic defects and molecular abnormalities associated with the formation and progression of cell growth. The change from normal colonocytes to adenomatous tissue and eventually colorectal carcinoma induces a number of mutations that accelerate cell growth.<sup>12</sup> There are two mechanisms that give rise to genomic instability and lead to CRC: chromosome instability (chromosomal instability or CIN) and microsatellite instability (MIN).<sup>13-15</sup> The beginning of the process of colon cancer occurring involving somatic mutations

occurs in the adenomatous polyposis coli (APC) genes which subsequently develop into adenomas. The transition from adenoma to carcinoma is the result of a mutation of the p53 tumor suppressor gene that is the ultimate transformation to malignancy.<sup>13-15</sup>

### **Radiology imaging**

Imaging on the CRC is divided into imaging for diagnosis, tumor stage and therapeutic evaluation. American College of Radiology recommends modalities used for diagnosis with DCBE modalities, flexible sigmoidoscopy, colonoscopy and CT colonography.<sup>5</sup> Staging is recommended with modalities of CT scan and magnetic resonance imaging (MRI).<sup>4,6,18</sup> While evaluation of therapy and metastasis detection using CT scan, MRI and positron emission tomography - computed tomography (PET-CT) modalities.<sup>4,6,18</sup>

The morphology of CRC images in DCBE examination can be seen as a description of filling defect in the form of sessile or pedunculated, exophytic, circumferential (apple core), ulceration or desmoplastic.<sup>19</sup> Flexible sigmoidoscopy is safer, faster, more tolerable and does not require sedation, but requires follow-up colonoscopy because it cannot detect lesions in the proximal colon.<sup>20</sup> Colonoscopy has been considered as a gold standard for early detection of CRC, because its sensitivity is 96.7% and its specificity is 98% for detecting colon polyps as well as possible for polypectomy actions which are then sent for histopathological examination.<sup>19,20</sup> CT colonography or non-invasive virtual colonoscopy that produces a two-dimensional image to identify lesions in the colon and a three-dimensional reconstruction image that produces a prospective image of endoluminal colon and rectum.<sup>4,16,20-25</sup> Compared with colonoscopy, CT colonography is safer, more precise at and cheaper with the

effectiveness of similar results, while the shortage does not allow biopsy or removal of polyps.<sup>4,23-25</sup>

CT scans are widely used to assess preoperative tumor stage, extension of tumor to surrounding tissue, metastasis, vascular abnormalities and possible complications of surgery or tumor complications.<sup>19,26</sup> In CT, the CRC is usually seen as soft tissue mass constricting the colon lumen and may also manifest as focal thickening of the colon walls and narrowing of the lumen.<sup>26</sup> A meta-analysis study showed that the sensitivity and specificity differentiating between T1/T2 versus T3/T4 were 86% and 78% respectively.<sup>27</sup> MRI was the most accurate modality for CRC staging, its accuracy ranged between 84% - 90% .<sup>4,19</sup> MRI is recommended as a standard modality for preoperative staging.<sup>28,29</sup>

Assessment of the evaluation of the CRC treatment response was based on the criteria for response evaluation criteria in solid tumors (RECIST) based on tumor size reduction as measured by anatomical imaging modalities such as CT scan or MRI (TABLE 1).<sup>30,31</sup> Dynamic contrast enhanced CT (DCE-CT) becomes a valid technique for assessing tumor angiogenesis and monitoring disease control after local-regional therapy.<sup>30</sup> Dynamic contrast-enhanced MRI (DCE-MRI) and DWI are useful for evaluation of post-chemotherapy responses which show biological effects and functional treatment, as an early sign of therapeutic response because cell apoptosis, anti-angiogenesis can be detected before tumor size changes from 2 weeks post-therapy.<sup>4,28-30</sup> PET-CT becomes a valuable modality for assessing neoadjuvant post-chemoradiotherapy response, with metabolic responses early on FDG PET allows for a change in therapeutic management.<sup>32</sup> PET-CT FDG has been shown to be superior in accuracy in metastatic nodal assessment, hepatic metastasis detection and extracellular metastases.<sup>32</sup>

TABLE 1. RECIST response criteria, version 1.1<sup>31</sup>

Level of Response	Criteria of Response
Complete response	Loss of all target lesions. All pathologic lymph nodes (target or non-targeted) should have a short axis reduction of <10 mm
Partial response	Decrease $\geq 30\%$ of the target diameter of the target lesion, using the longest diameter as the reference base.
Progressive disease	Increased $\geq 20\%$ of the target diameter of the lesion, the presence of one or more new lesions is also considered progressive disease
Stable disease	Depreciation that is not eligible for partial response or an increase that is not eligible for progressive disease

## Stadium

Stage CRC can be conducted by using two systems. The traditional system according to Dukes that has been largely superseded by the TNM system published by the American Joint

Committee on Cancer (AJCC) (TABLE 2), but is still frequently used clinically. This staging system is related to the prognosis and 5-year life expectancy of the patient. Recommended using a TNM staging system with a modified Aston-Coller Dukes system (TABLE 3).<sup>16,17</sup>

TABLE 2. TNM classification system for colorectal cancer stage according to AJCC edition<sup>7,17</sup>

Classification	Definition of TNM classification
T - Primary tumor	
Tx	Primary tumor can not be assessed
T0	There is no primary tumor
Tis	In situ carcinoma, invasion of lamina propria or intraepithelial
T1	Invasion of tumors in the sub-mucous layer
T2	Invasion of tumors in the muscle layer of propria
T3	The invasion of the tumor passes through the propria muscle to the subserosa or into the peritoneal pericardial pericardial tissue
T4a	Penetration of the tumor to the surface of the visceral peritoneum
T4b	Invasion of the tumor directly or following against the organ or the surrounding structure
N-Regional lymph nodes	
Nx	Regional lymph nodes can not be assessed
N0	No regional lymph nodes were obtained
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in a regional lymph node
N1b	Metastasis in 2 - 3 regional lymph nodes
N1c	Tumor deposits on the subserosa, mesentery, or pericoly or perirectal tissue that are not coated peritoneum without regional lymph node metastases
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4 to 6 regional lymph nodes
N2b	Metastasis in 4 or more regional lymph nodes
M - Remote metastases	

M0	There is no distant metastasis
M1	There is a distant metastasis
M1a	Metastasis is limited to one organ or place (eg, liver,pulmo, ovary, non-regional lymph nodes)
M1b	Metastasis in more than one organ or place or peritonium

TABLE3. Colorectal cancer stage based on TNM system with Dukes system modified by Astler-Coller<sup>33</sup>

Stadium	T	N	M	Dukes	MAC
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Ant T	Any N	M1a	-	-
IVB	Ant T	Any N	M1b	-	-

MAC is an Astler-Coller modification classification

### Management

The management of the CRC is multidisciplinary involving several specializations/subspecialties including gastroenterology, gastroenterology surgery, medical oncology, and radiotherapy. Surgical therapy is a major modality for early stages with curative goals. Chemotherapy is the first choice of advanced cancer with palliative goals.<sup>9,10</sup> The standard chemotherapy regimen of either adjuvant or palliative is FOLFOX consisting of 5-fluorouracil, leucovorin and oxaliplatin. Targeted therapy has

grown rapidly and can be given in a variety of clinical situations, either as a single drug or a combination with other therapeutic modalities. Targeted therapy commonly used for CRC is bevacizumab, which is an alternative regimen for adjuvant therapy for stage III CRC and palliative therapy at stage IV, in combination with FOLFOX.<sup>5,18</sup>

### REVIEW OF TACI

TACI is a minimally invasive technique in the field of interventional

radiology in conducting locally-guided fluoroscopy therapy for treatment in patients with primary tumors and metastases.<sup>6</sup> The purpose of this therapy is to kill tumor cells by infusion of chemotherapy via arterial catheter selectively on arterial feeding which supplies blood to the tumor, resulting in maximum concentration and uptake of the drug in the target organ and increased therapeutic response with minimal systemic side effects.<sup>6,33,34</sup>

The TACI technique has been shown to kill tumor cells more strongly than conventional chemotherapy techniques, and shows an increase in life expectancy in some studies.<sup>6</sup> With the digital subtraction angiographic (DSA) technique in TACI it is possible to evaluate the therapeutic response by measuring staining and vascularization tumors in arterial feeding.<sup>6</sup> An imaging evaluation is usually performed 4-6 weeks after therapy, and the maximum therapeutic response is usually seen 3-4 months after therapy.<sup>6</sup> This unique TACI therapy characterization provides an attractive therapeutic option in patients who previously had several alternative treatment options.<sup>6</sup>

## DISCUSSION

The development of diagnostic and therapeutic techniques in the current CRC management is highly variable and heterogeneous. The options and recommendations of CRC therapy depend on the stadium, histopathology, possible side effects, patient condition and patient preferences, allowing multiple alternative options to the patient.

In this case the patient is an 80-year-old woman with a history of colon polyps with clinical symptoms of bloody, red, slimy and smelly bowel movements accompanied by defecating habits, weight loss and having a habit of eating fatty foods but lacking fiber foods. From age, risk factors, and clinical symptoms

that strongly lead to the diagnosis of CRC.

The diagnosis of this case used DCBE and colonoscopy modalities, where in DCBE a filling defect of pedunculated form was found and in colonoscopy the tumor was detected in the sigmoid pars proximal colon. The DCBE was chosen because it is non-invasive while the colonoscopy is chosen because it is a gold standard and biopsy for anatomical pathology is examined.<sup>19,20</sup> The location of the tumor is in the sigmoid, which is the second largest site after the rectum.<sup>35</sup>

In this case, histopathologic examination results were concluded as a good adenocarcinoma differentiation. 95% CRC is an adenocarcinoma derived from colonic polyps that develop into cancer, where in general the prognosis is quite good.<sup>36</sup>

Determination of staging in this case by CT scan examination to assess tumor extension to neighboring tissues, metastases, vascular abnormalities and tumor complications.<sup>26</sup> CT scan results show a proximal sigmoid tumor 9.1 x 8.3 x 7.4 cm accompanied by severe lumen colon narrowing, with invasion of the subserosa and mesenterial fat with a fat stranding image but no infiltration to the surrounding tissue, but metastatic nodules on the pericolon, invisible metastases of the liver. It was concluded that this patient was included in T3N1M0 stage IIIB based on AJCC.

The choice of CRC therapy at stage IIIB according to the ESMO Consensus Guidelines is wide surgical resection with anastomosis followed by adjuvant chemotherapy after surgery.<sup>5</sup> In this case because the patient refuses to undergo surgery it is considered as unresectable adenocarcinoma colorectal, so it is decided to take chemotherapy treatment with TACI procedure for therapy palliative with a combination of Oxaliplatin and Bevacizumab in three procedures every 2 months. Selection of TACI therapy due to the unique characteristics of therapy proven capable of lethal tumor

cells is stronger than conventional chemotherapy techniques, and shows an increase in life expectancy.<sup>6</sup> In addition, TACI allows for simultaneous evaluation of treatment.<sup>33</sup>

In the evaluation of therapy with screening of arteriography, there was a decrease in tumor staining and vascularization on arterial feeding from the first TACI to the third TACI. While the CT scan evaluated the size of the tumor shrank to 2.13 cm x 4.92 cm x 4.35 cm and there was no infiltration to the surrounding tissue or metastatic nodules and distant metastases on heparset after the third TACI action, based on RECIST categorized partial response and at the re-staging assessment has decreased the stage to T3N0M0 stage IIA.

This proves that the management of CRC in this case, TACI therapy using Oxaliplatin and Bevacizumab infusions in three procedures is quite effective as palliative therapy. However further studies should be undertaken to verify these findings.

## CONCLUSION

Choosing the right radiological imaging modalities in diagnosis, staging and treatment evaluation is crucial in CRC management that can assist in the choice of therapy, treatment success and survival rate of CRC patients. We reported the case of a woman with unresectable adenocarcinoma colorectal who showed good results after receiving TACI therapy in the form of partial response, decreased stage, disappearance of clinical symptoms and improvement of quality of life without systemic side effects.

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