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Imaging the Adverse and Late Effects in the Treatment of Colorectal Cancer

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Side effects are common in the clinical practice and its diagnosis and radiologic manifestations are not always evident or known. Adverse effects may cause medical complications of a disease or a procedure and negatively affect its prognosis. Several typical patterns can be recognized on imaging and making a correct diagnosis has relevant clinical and therapeutic implications.
In this article we present a part of our preliminary results of the retro- and prospective study started in 2009 in the National Institute of Oncology. The aim of the study is to evaluate the imaging diagnostic examinations (US, CT, MR, PET/CT) of patients who have been diagnosed, treated and operated in the Hungarian National Institute of Oncology from 01 January, 2008. In this part we analyze the post-therapeutic consequence symptoms, side- and late effects during the treatment of colorectal cancer patients.

Keywords: side effects, late effects, colorectal cancer, imaging

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Introduction

Nearly one million patients are diagnosed with colorectal cancers (CRC) annually worlwide. The incidence of CRC is the highest in the western world, where it is the second most common cause of cancer death and fourth most common cause of death from cancer around the world. In the western world there is a lifetime risk of CRC of 5%. The management of rectal cancer has evolved over the past years.

Rectal cancer treatment

Three types of standard treatment are used: surgery, radiation therapy and chemotherapy. Surgery is the most common treatment for all stages of rectal cancer. Nowadays monoclonal antibody therapy is being studied in the treatment of rectal cancer.

Colorectal cancer surgical techniques and survival after surgery have improved over the past 15 years. Surgery can cure about 90% of the colorectal cancers, when they are detected early.

Researchers began testing drug combinations with 5-FU as early as the 1980s, and in the mid-1990s the combination of 5-FU and leucovorin became the standard adjuvant treatment for patients with stage III colon cancer. The addition of oxaliplatin to 5-FU and leucovorin was later found to improve survival in comparison with 5-FU and leucovorin alone. A newer drug called capecitabine, is an alternative to 5-FU and leucovorin. Capecitabine is sometimes combined with oxaliplatin as well. Capecitabine is taken by mouth, whereas 5-FU must be given intravenously. For some patients whose cancer has metastatized, the drug irinotecan may also be part of the chemotherapy. Patients with stage II or stage III rectal cancer receive radiation plus chemotherapy before surgery, so called neoadjuvant therapy, in addition to post-surgical adjuvant chemotherapy. If a patient does not receive neoadjuvant radiation therapy, he or she may be treated with adjuvant radiation therapy plus chemotherapy. The rectum is less radiosensitive than the small intestine. At levels of 10–20 Gy, the initial reaction of hypermotility rapidly disappears. The tolerance dose (TD) is higher, 50–55 Gy.

The targeted therapy bevacizumab, a monoclonal antibody against vascular endothelial growth factor, blocks the growth of new blood vessels in tumors. Studies have shown that bevacizumab can help extend survival for some patients with metastatic colorectal cancer.

Therapy is dependent of the stage of CRC.

Stage 0 (carcinoma in situ): treatment of stage 0 may include simple polypectomy, local excision or resection (when the tumor is too large to be removed by local excision) and radiotherapy.

Stage I rectal cancer: treatment of stage I rectal cancer may include local excision or resection, and resection with radiation therapy and chemotherapy before or after surgery.

Stage II rectal cancer: treatment of stage II rectal cancer may include resection plus a combination of chemotherapy and radiation therapy before or after surgery as well as resection with or without chemotherapy after surgery.

Stage III rectal cancer: treatment of stage III rectal cancer may include resection plus a combination of chemotherapy and radiation therapy before or after surgery, as well as resection with or without chemotherapy after surgery.

Stage IV and recurrent rectal cancer: treatment of stage IV and recurrent rectal cancer may include resection with or without a combination of radiation therapy and chemotherapy before surgery.

Resection or pelvic exenteration, and/or radiation therapy, chemotherapy, as well as a combination of both can be performed as palliative therapy to relieve symptoms and improve the quality of life.

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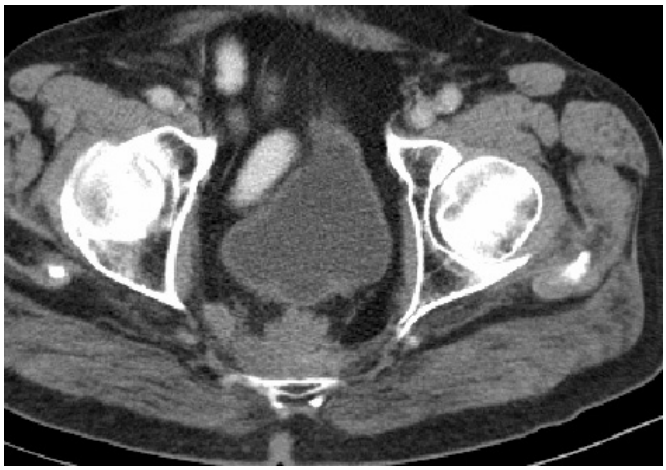

Fig. 1. Large presacral mass after APR mimicing recurrent tumor

Placement of a stent helps to keep the rectum open if it is partly blocked by the tumor, as palliative therapy to reduce symptoms and improve the quality of life.

Systemic chemotherapy with or without monoclonal antibody therapy, such as bevacizumab can be also applied.

Normal findings after CRC treatment

The modified anatomical changes can be seen as the result of the surgery. Following the anterior resection (AR) and abdominoperineal resection (APR), with or without radiation therapy, postsurgical changes can range from only minimal praesacral fibrosis to scar tissue formation. This fibrotic tissue sometimes may be a huge mass and can mimic rectal tumor recurrence (Figure 1). It is essential therefore to perfom imaging in the first 3 months after surgery, in order to obtain baseline images of the expected anatomical changes. The key to detection of local recurrence is the demonstation of an increase in soft tissue mass in subsequent studies.

Gastrointerstinal radiation changes are bowel wall thickening, ulceration on mucosal injury. Later the mucosal changes might decrease because of the rapid renewal system of the gastrointerstinal tract.

Acute complications of RC treatment

Acute complications of the treatment in CRC patients typically appear within days or weeks of initiation of therapy, but may be seen up to the third month, next subacute or early delayed complications occur. However, there is variation in susceptibility among individuals and there may be some overlap between the acute and early delayed effects in the first weeks up to two months following the treatment. Radiological manifestations are often non-specific and thus the clinical context and temporal relationship in induction of therapy are important considerations.

Complications of chemoterapy include disordered motility, malabsorption, inflammation and ischemia. Most are predictable and do not require imaging.

Most common complications after gastointerstinal surgery are as follows: anastomosis insufficiency, abscess, ileus,

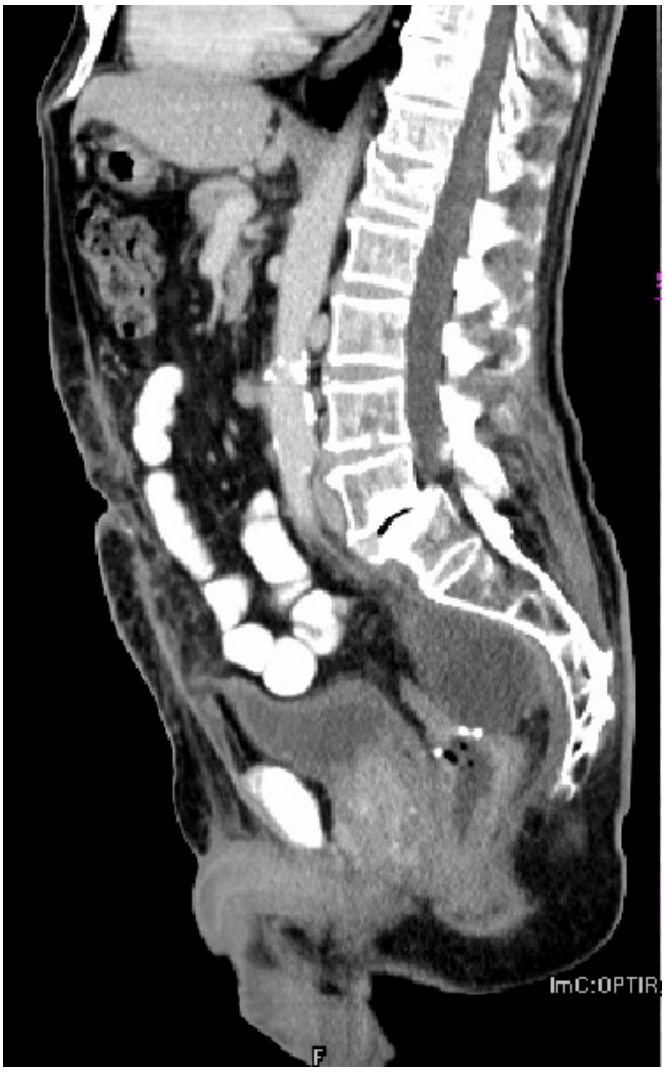

Fig. 2. Presacral abscess after rectum resection

haemorrhage, infections, thromboembolic complications, necrosis with perforation and fistulas (Figure 2).

Side and late effects

During the neoadjuvant therapy, the irradiation of rectosigmoid region frequently results colitis. This postirradiation inflammation is radiologically indistinguishable from early ulcerative colitis. The radiologic appearance of the colitis includes thickened folds, ulceration and mucosal abnormalities such as srictures and fibrosis, which lead to a rigid bowel with a relatively loss in its function. Smooth and tapered strictures in midsigmoid colon or rectum are the most common post irradiation changes. Not uncommonly, radiation injury of the colon leads to fistulas (recto/colo-vaginal-, recto-vesical-, recto-cutan fistula).

Chemotherapy induced changes of the colon and the rectum are nonspecific and therefore it is a huge challenge to evaluate them radiologically. The critical postirradiation lesion as a late effect in the alimentary tract is the progressive endarteritis, resulting either ulceration and infarction necrosis or a progressive slow fibrosis and stricture of bowel.

Chemotherapy alone does not seem to produce significant late gastrointestinal complications despite the acute

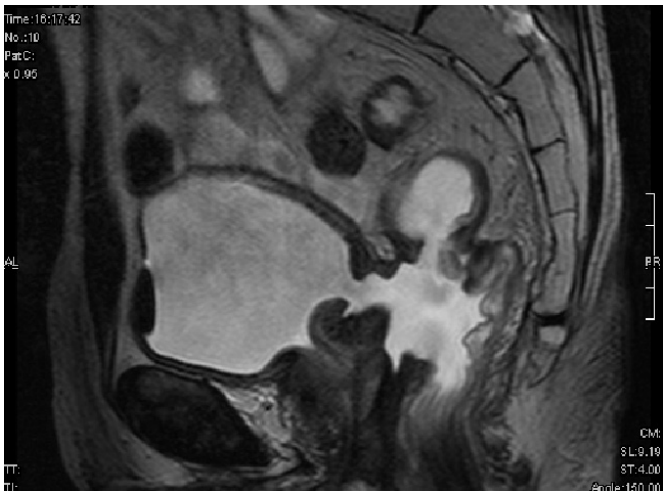

Fig. 3. Rectovesical fistula after chemotherapy as a result of tumorlysis

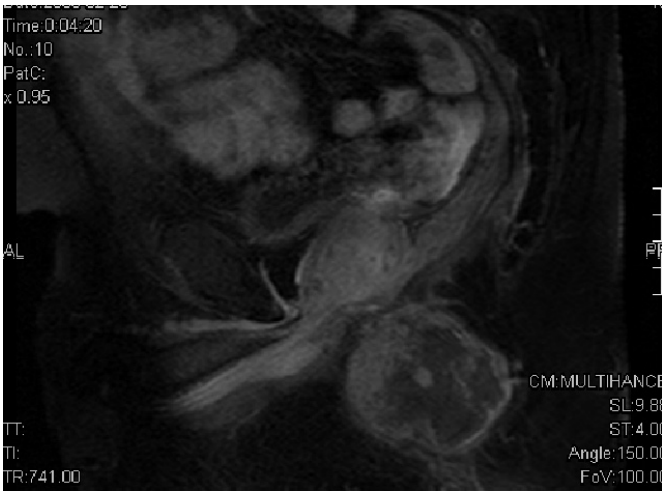

Fig. 4. Local recurrence 28 months after surgery

toxicity caused by 5-flourouracyl (5-FU), the basic drug of the colorectal cancer treatment, which induce enteritis. More severe late effects such as gastrointestinal bleeding, delayed stricture and fistulatization are seen only in combination with irradiation in 20–40% of the patients. Tumorlysis within bowel may result perforation or fistulatization (Figure 3).

Recent therapeutical combinations in metastatic colorectal cancer consist of molecular targeted agents, namely bevacizumab and 5-FU, as well as leucovorin. Classic chemoterapy agents predominantly attack rapidly all proliferating cells, but molecular targeted therapies target specific key membranes and intracellular molecules. Bevacizumab decreases the neoangiogenesis of the tumor. Recently, GI perforations have been reported in conjunction with bevacizumab in 1.5 to 2% of patients treated with metastatic colorectal cancer.

The pathogenesis of bowel perforation is unknown, but suggested mechanisms include ischemia with thrombosis of intestinal mesenteric vessels.

The most common late effects are fibrosis, adhesion, stricture of the anastomosis and other strictures.

Imaging modalities

Plain film, barium examinations, ultrasound (US), computed tomograpy (CT) and magnetic resonance imaging (MRI) are useful for detecting and evaluating different complications and side effects of CRC therapy.

CT is the most useful tool in the acute and early delayed complications. It is quickly able to detect perforation or an abcess, as well as abdominal fluid collection. CT is also the best tool for guided punction or drainage.

MRI, especially the new functional examinations such as diffusion MRI or dynamic contrast enhanced MRI, can differentiate better between scars and tumor recurrences.

Results

Between April 1, 2009 and March 31, 2011, 948 patients underwent CT and/or MRI examination and 141 patients were diagnosed, treated and operated in the Hungarian National Institute of Oncology with rectal cancer. During the neoadjuvant and adjuvant treatment and after the definitive operation, 57 patients underwent only CT, 16 patients only MRI and 42 of them both examinations.

Anastomosis insufficiency occured in 4 patients, 5 postoperative haemorrhage, 1 ileus and 3 abscesses were detected, respectively. CT controlled drainage was performed in 2 abscesses. Perforation was observed in 2 patients, one of them secondary to bevacizumab therapy, the other perforation was caused by tumor necrosis during chemotherapy and rectovesical fistula has developed. Neutropenic colitis and typhlitis were seen in 1 patient.

After the neoadjuvant therapy mild to severe bowel wall thickening was observed almost in every patient. In one case ileus developed during the chemotherapy. Within the observation period 16 local recurrences, confirmed histologically were found, 2 recto-cutan (recto-perineal) fistulas evolved in recurrent tumors (Tables I and II).

Table I. Imaging modalities during follow-up of 115 patients

Imaging modality	Patients (n=115)
CT	57 (50%)
MR	16 (14%)
CT/MR	42 (36%)

Table II. Complications occurring in the 115 patients

Complications	Patients (n=115)
Minor complication (haemorrhage in abdominal wall)	21 (15%)
Major complication	2.6%
Anastomosis insufficiency	4
Postoperative haemorrhage	5
Ileus	1
Abscess	3
Colitis	1
Perforation	2 (1 after Avastin)
Fistulization	2

Discussion

Adverse side and late effects are an important cause of morbidity and mortality in CRC treatment. Different studies have recorded adverse postirradiation and drug reactions related hospital admissions comprise up to 10% of the total number of the treated CRC patients.

Conventional radiological studies such as plain radiographs, barium studies can detect many of the more advanced posttherapeutic injuries.

X-ray examination is very useful to asses ileus and evaluate a bowel obstruction as well as to detect localized or generalized pneumoperitoneum. Barium examination can asses the late changes usually collerated with the clinical symptoms. The radiological signs are: fold and bowel wall thickening, impaired peristaltic, tapered strictures, thumbprinting and adhesions.

US shows bowel wall thickening, ascites or other fluid collections — but it is not valid for the to evaluation of the whole abdomen.

CT is the first modality of choice to detect and evaluate treatment complication in CRC. CT demonstrates the bowel wall, as well as its surrouding fat, the peritoneal cavity, mesenteric vascular pedicle and the solid organs, it can differentiate betweeen the air and calcification. Intravenous contrast help us to evaluate the bowel wall vascularity, this may be better shown without administration of oral contrast. When the clinical question is body wall or intestinal haemorrhage, preliminary unenhanced CT should be performed. The bowel wall thickening (> 4 mm) with low-density represents oedema and/or necrosis, or pericolic inflammation. Ascites, intestinal pneumatosis, presence of free air as sign of underlying mural necrosis and perforation can be also well detected by CT.

Additionally, CT is the best tool for the guided aspiration or drainage of fluid collections.

In case of inflammatory complications CT findings are: mucosal hyperaemia, wall thickening, and oedema („halo"sign), dilatation or luminar narrowing, perienteric stranding and mesenteric oedema, localised or free intraperitoneal fluid, para-enteric abscess, localised or free pneumoperitoneum.

MRI used as a problem solving modality in acute complications. It is the best modality to evaluate the late effects and local recurrence can be better distinct - thanks to its excellent contrast differentiation and the new funtional MRI technics (diffusion MRI, dynamic MRI).

It is essential to judge the revalence of the imaging findings with correlation of the clinical findings (Figure 4.)

Conclusion

The radiologist has an important role in the diagnosis of posttherapeutic complications in CRC. It is important to identify local recurrences as early as possible and differentiate from the non tumorous post-treatment complications because of the most effective therapy. Abdominal post-therapeutic effects have a wide spectrum of radiologic appearances. Most often posttherapeutic changes and recurrant/residual disease can be well differentiated by their morphologic features and temporal evolution. The radiologic features of these lesions can help us to ensure correct diagnosis and a proper management, but the differentiation is often not too easy. The new functional imaging tools, diffusion MRI, dynamic enchanced MRI can improve the differentiation.

To follow-up the patients with CT and/or MRI after APR is mandatory because imaging provides to detect recurrant tumor before its clinical presentation.

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