

REVIEW

The Accuracy of Computed Tomography in the Pretreatment T and N Staging of Colorectal Cancer

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ABBREVIATIONS

CT = computed tomography

CTC = computed tomography colonoscopy

ERUS – endorectal ultrasound

MDCT = multidetector computed tomography

MP = muscularis propria

MPR = multiplanar reconstruction (reformations)

MRI = magnetic resonance imaging

PET = positron emission tomography

TNM = Tumor Node Metastasis

WE-CT = CT with water enema

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ABSTRACT

Computed tomography (CT) is a widely used detection and staging modality for colorectal cancer patients in clinical practice. The role of CT in assessing patients with colorectal cancer has been well established, but the accuracy of evaluating and staging the colorectal cancer by CT varies in different reports. With the development of CT techniques, some reformations such as multi-detector CT, CT with water enema or air insufflations, and multiple planner reconstruction help to give us higher resolution images in shorter time. CT is playing an increasingly important role in pretreatment staging of colorectal cancer, although magnetic resonance imaging and endorectal ultrasound (also called transrectal ultrasound) may provide more precise images and evaluation of local T and N staging of rectal cancer. Finally, positron emission tomography (PET) or PET/CT have not shown any significant improvement after completion of standard pretreatment evaluation.

INTRODUCTION

Colorectal cancer is the third most common malignant tumor and the third leading cause of cancer-related death in Western countries.¹ According to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute long-term reports (beginning in 1973), the mortality of colorectal cancer from 2005 to 2009 was 20.2 in males and 14.1 in females per 100,000, and the incidence was 54.0 (males) and 40.3 (females) per 100,000.² It is gratifying that there was a decline of colorectal cancer incidence rates over the last 5 years, and this should be largely attributed to early screening, which could allow early diagnosis and removal of precancerous polyps.³⁻⁵ With the development of multimodality therapies including surgery, chemotherapy, radiotherapy and targeted therapy, the 1-year and 5-year relative survival rates of colorectal cancer are 83.2% and 64.3%, respectively.⁶ For colorectal cancers detected at a localized stage, the 5-year relative survival rate is 90.1%. If cancer has spread regionally to involve adjacent organs or lymph nodes, the 5-year survival rate decreases to 69.2%. What appears to be worse, if the disease has spread to distant

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organs, is the 5-year survival rate which is only 11.7%.⁶ So an early and accurate detection of colorectal cancer is very important, and a precise tumor staging can help physicians to predict the patients' mean residual life on which the clinical decision is based.

The purpose of this review is to summarize the pretreatment T and N staging accuracy of CT relative to pathological examination, and compare the diverse results of different CT equipment with various parameters and preparations, and thus determine the value of CT for pretreatment colorectal cancer staging and recommend the best CT parameters and preparations in clinical practice. By stating the deficiencies of CT staging and comparing CT with magnetic resonance imaging (MRI), endorectal ultrasound (ERUS) and positron emission tomography (PET)/CT, we could give a recommendation for the pretreatment imaging modality choice.

THE ADVANTAGES OF CT STAGING

The American College of Radiology recommends enhanced CT as the first choice for the pretreatment staging of colonic or rectal cancers. Indeed, compared with MRI or other imaging modalities, CT has its own irreplaceable advantages.

First of all, CT is a non-invasive modality to obtain a rapid overall assessment, not only of regional lesions, but also of distant metastases. For example, with a CT scan of the abdomen, we could obtain images of not only the bowel lesion, but also of some other main organs including liver, pancreas, gall bladder, lymph nodes and so on. Though PET could provide whole body images, PET alone could not offer images clear enough for evaluation.

Secondly, CT could acquire all the images in less than one minute, while MRI could only acquire part of the abdominal images in several minutes, sometimes more than ten minutes. Thus, cancer patients in some busy hospitals would prefer CT as the pretreatment evaluation rather than MRI which would require patients to wait for several days to have it scheduled.

Thirdly, fast scan of CT would reduce the image artifacts caused by breath and bowel peristalsis. The image artifact is really a problem with MRI, because even though patients can hold their breath for a long time, the bowels are still moving, which would influence the accuracy of the scan. This is the reason why the colon is rarely evaluated with MRI.

Fourthly, CT images could be well retained for comparison of pretreatment and post-treatment tumor size, as well as the lymph node size or other benign and malignant nodules.

Finally, with advances in CT technology and computing software, such as CT angiography, the post-processing computed reconstruction techniques including multiplanar reconstruction (MPR), volume rendering technique, CT colonoscopy (CTC) and so on, make CT more helpful to precise diagnosis of lesions.^{8,9} CT colonoscopy is especially beneficial

after incomplete colonoscopy to evaluate the remainder of the colon and is currently being advocated in some countries as a screening tool.¹⁰ For avoidance of uncomfortable colonoscopy experience, more than 95% of patients prefer CTC to routine colonoscopy.¹¹ Also, 64-slice, 128-slice, or even 320-slice CT scanners provide us with higher resolution images in shorter time associated with less radiation exposure.¹²

DIAGNOSTIC ACCURACY OF CT IN T STAGING

Nowadays, the Tumor Node Metastasis (TNM) classification is used worldwide for the staging of colorectal cancer.¹³ In some early studies, Dukes' classification was more often used.^{14,15} Here we firstly focus on the T staging of TNM classification.

As with different kinds of CT scanners, experience of operators, parameters of CT and so on, the T staging accuracy of CT varies in different studies.

The most important reason why CT staging may not so correctly correspond to the histopathological T staging may be the difficulty to differentiate bowel wall layers. Without the improved spatial resolution of multi detector CT (MDCT) scanning, it is really a tough problem to differentiate the mucosa, submucosa, muscularis propria, serosa and visceral peritoneum with conventional single row CT. The commonly used criteria modified by Smith et al and Burton et al for tumor staging of MDCT recommended intraluminal projection of a colonic lesion without any visible distortion of the wall layers as T1 stage,¹⁶ and T2 stage was recommended as asymmetrical thickening projecting intraluminally and smooth preservation of muscle coat and clear adjacent pericolic fat, but the inability to distinguish between T1 and T2 lesions was still a known limitation for CT.¹⁷⁻²⁰

In a recent study,²¹ even though the section thickness was as thin as 0.5 mm, the MDCT only correctly staged 45 local tumors of 73 in total, compared with the histopathological examination, with the best accuracy of 74% in T2 stage. The sensitivity for T4 is 0 in 6, which means all 6 tumors were understaged. Also, a similar trend of results was shown in another study which acquired images with a collimation of 5 mm and 7 mm;²⁰ the accuracy of T2, T3, T4 gradually decreased from 60% to 25% in 99 tumors, and 75% of T4 tumors were understaged. T4-stage tumors could be easily understaged to T3, for some microscopic invasions penetrating the bowel wall and infiltrating adjacent tissues which could only be confirmed on pathological examination were tough to recognize on CT images. On the other hand, the T3 stage tumors which appeared to be an involvement of the adjacent bowel could be easily overstaged to T4 stage.

Additionally, it is always difficult to differentiate inflammatory or desmoplastic reaction from true transmural spread.

Small strands of tumor tissue in pericolic fat on CT images may give clues in differentiating T2 from T3 stage. These strands may indicate tumoral involvement in the pericolic fat or serosa. Fibrosis, inflammation or congestive changes may also result in these strand images. So the peritumoral reaction consisting of fibrosis and inflammation is an important cause of overstaging.

Therefore, how can we make tumor depth of invading the bowel wall layers easier to be recognized by the radiologists? How can we have the thickened intestinal wall get caught by the radiologists' first sight?

1. THE CHOICE OF MDCT AND THE SECTION THICKNESS OF CT

The choice of MDCT and the section thickness of CT are important for the evaluation of T staging. Some early studies demonstrated a sensitivity of 55-61% for tumor invasion beyond muscularis propria (MP),^{14,22,23} which was equivalent to T3 or T4 stage according to the TNM classification, and specificity of 67-81%, compared with the histopathological findings. Such a low sensitivity, in other words such a high false negative rate, should be attributed to use of conventional CT scanners instead of spiral or MDCT and with a section thickness of 10 mm. The poor image quality combined with 10 mm section thickness may be the most likely reason of failure to detect the small amount of tumor lesions or the microscopic invasion beyond the MP.

A section thickness of 10 mm may produce more image artifacts than the thinner one, and the image artifacts may be the result of the partial volume effects, which can be defined as the loss of apparent activity in small objects or regions because of the limited resolution of the imaging system. Partial volume artifacts can be minimized by using a thin acquisition section width.²⁴ In recent years, with the utilization of spiral CT or MDCT and the section thickness of 5 mm or less, the sensitivity of detecting tumor invasion beyond MP increased to 80-100%, with a specificity of 75-91%.²⁵⁻²⁷

An excellent meta-analysis performed by Dighe et al provided a considerable pooled result and a serious subgroup analysis which concern many factors that may affect the pooled result.¹⁷ In the subgroup analysis of the total 19 studies with 907 patients, one of the best subgroup results for detection of tumor invasion beyond MP was obtained in studies that utilized CT section thicknesses of 5 mm or less (sensitivity of 95%, specificity of 84%, diagnostic odds ratio, DOR 95.3), compared to the pooled sensitivity, specificity, DOR (86%, 78%, 22.4) of the total 19 studies. The subgroup results obtained in studies utilizing MDCT (sensitivity of 93%, specificity of 86%, DOR 83.5) were also excellent, significantly higher than those on average. Thus, MDCT with thinner section thickness could help the radiologists achieve more accurate pretreatment tumor staging.

2. MULTIPLANAR REFORMATIONS

Multiphase reformations (MPR) are two-dimensional

reformatted images that are reconstructed secondarily in arbitrary planes from the stack of axial image data. MDCT with MPR allows improved visualization of the bowel in all directions. The evaluation of axial in combination with MPR could help to improve the staging accuracy.¹⁸ In a study evaluating the accuracy of contrast-enhanced MDCT for preoperative T staging,¹⁹ when transverse images were evaluated alone, the overall accuracy was 73% (30 of 41 patients), but the accuracy improved to 83% (34 of 41 patients) when transverse and MPR images were evaluated in combination. Similar results were obtained in another study,⁹ which were identified by two radiologists when differentiating $\leq T3$ from T4, whereby the specificity was significantly increased by using the combined axial and MPR data sets, compared with that of using axial data sets only. On the other hand, MPR images in the standard sagittal and coronal planes are readily generated with no additional radiation exposure for patients and with no additional labor or time required on the part of the radiologists. Thus, MPR may be an important technique that can improve the staging accuracy.

3. ADEQUATE BOWEL PREPARATION AND DISTENTION

Adequate bowel preparation and distention may also be of some help. The thickness of the normal bowel wall varies slightly depending on the degree of luminal distention. If the colon is well distended, the wall thickness should be measured to less than 3 mm, which is often imperceptible.²⁸ Frequently, because of fecal contents, fluid, or colonic redundancy, the true thickness is difficult to ascertain. In the pretreatment tumor staging, it is necessary to have a well distended bowel. The main ways are air insufflation of the colon or utilizing water enema, which means a bag of water or air would be gently infused into the rectum through a lubricated enema tube or by a special machine.

Air insufflation of the colon was first introduced by Megibow et al as an adjunct to CT of the pelvis in 1984,²⁹ then water enema was used in CT for imaging the colon cancers by Angelelli and Macarini in 1988.³⁰ Colonic preparation and distension with air or water contribute to the improvement of the obtained results, as exemplified by Balthazar et al.^{15,23} In the subgroup analysis of the meta-analysis performed by Dighe,¹⁷ the 95% sensitivity and the 86% specificity obtained in the subgroup of using rectal insufflation either with air or water was optimal, and the DOR (104.5) was the highest one among the subgroups. These results gave us a valid support that CT with water enema (WE-CT) or air insufflation was a helpful technique in pretreatment staging of colorectal cancer. Some early studies using Dukes' classification indicated that compared to the pathological staging, the colorectal cancer staging accuracy of WE-CT varies between 77% and 84%.^{25,31} These data need larger sample size studies to get confirmed because this technique has not been widely used in clinic so

far. Perhaps the major limitation of WE-CT was that water enema can be difficult and distressing in frail elderly patients and would have the risk of water incontinence.

CT imaging with pneumocolon, which means air insufflation of the colon, could clearly show the lumen and wall of the colon and colonic lesions, on which the thickness of the normal colonic wall ranged 1-2 mm.³² The staging accuracy could be 64% compared to Dukes' classification in an early study.³³ Combining with MDCT, the overall accuracy of the evaluation of local invasion could be 94.1%, and the accuracy of diagnosis for node was 80.5%.¹⁸ Nevertheless, this technique also has its limitations, requiring specific equipment for colon distension with carbon dioxide.

If we compare MDCT with water enema and MDCT with air, which would acquire higher accuracy? Stabile et al did this head-to-head comparison study with 70 patients who were divided into two groups;³⁴ the results reported that the overall diagnostic accuracy of MDCT with water and with air were 68.6%, 62.8%, respectively. Regarding the T staging, the accuracies were 88.6% for water and 80% for air colonography. With regards to the N staging, the accuracies were 77.1% and 74.3% for water and air MDCT colonography, respectively.³⁴ This may somehow support the water enema as a better bowel distension method.

DIAGNOSTIC ACCURACY OF CT IN N STAGING

The evaluation of lymph node status is essential before making treatment plan, especially for rectal cancer patients. Those with evidence of lymph node metastasis will require adjuvant therapy to reduce the possibility of local recurrence.

According to the TNM classification, the criteria of N staging modified by Burton et al are as follows,¹⁶ N0: No lymph node >1 cm and no abnormal clustering. N1: 1-3 lymph nodes >1 cm, or abnormal clustering of 3 or more normal-sized lymph nodes. N2: More than 3 lymph nodes >1 cm.

The accuracy of CT in N staging was not as good as that of T staging. In the early studies in 1980's,^{22,23} the low sensitivity (from 26% to 73%) and the low specificity (from 58% to 96%) came from the conventional CT with 10 mm section thickness, while the sensitivity (from 86% to 89%) and the specificity (from 75% to 82%) of the studies in 2000's with MDCT of 1-3 mm section thickness demonstrate some improvement,^{19,35} though the results were not statistically significant, compared with the results in 1980's. The factors which may improve the accuracy of T staging in CT were also important in the evaluation of N staging, including the section thickness of CT, the use of MDCT, the technique of multiplanar reformations.^{9,17,26,35} However, CT with water enema or air insufflation did not make significant improvement in pretreatment N staging of colorectal cancer.^{15,17,25,30,31,34}

Modern MDCT has been used to identify lymph nodes of more than 5 mm in diameter.³⁶ Most studies of colorectal cancer pretreatment staging use lymph node size as the criterion for predicting nodal involvement.³⁷⁻³⁹ Unfortunately, there is evidence to demonstrate that nodal size is poor at differentiating benign from metastatic lesions.⁴⁰⁻⁴⁴ Also there is little agreement on the critical cut-off diameter to determine whether lymph nodes are involved. A specific threshold value was difficult to establish to distinguish benign from malignant nodes, as a low size threshold could gain a higher sensitivity with low specificity, and a higher size threshold lowered the sensitivity but improved the specificity. On the other hand, microscopic tumor involvement can be present in non-enlarged lymph nodes and benign reactive nodes can sometimes be enlarged. Dworak et al examined 12,759 nodes histologically following resection. They found that the mean diameter of benign lymph nodes was 3.34 mm compared with 3.84 mm for the metastatic nodes.⁴⁵ Thus, the nodal size would be a poor discriminator of colorectal metastatic nodal status.

Although CT could not provide an ideal accuracy of N staging, this was not a significant clinical problem for colon cancer, because regional enlarged lymph node would not be a contraindication to surgery, and lymph node sampling is routinely performed at surgery. But for rectal cancer, if we can precisely detect the involved lymph nodes, we can make a better selection among surgery, chemotherapy or radiotherapy. Thus, the role of pretreatment staging is relatively more important, luckily MRI and ERUS could help increase the accuracy of N staging, which will be discussed below.

COMPARISON WITH OTHER IMAGING MODALITIES

1. PET IS NOT MORE ACCURATE THAN CT

PET/CT has been allowed for better staging in a number of tumors, and resulted in clinical management variations in clinical practice.⁴⁶⁻⁴⁹ Currently, about colorectal cancer, PET/CT is recommended only in pretreatment staging prior to metastasectomy and in the assessment of suspected recurrence.

In T staging of colorectal cancer, PET/CT was inappropriate to determine the exact depth of the primary tumor invasion because of its limited resolution.⁵⁰ Thus, the accuracy of T staging of colorectal cancer by PET/CT was almost totally reliant on CT and PET could hardly be helpful for T staging.

In N staging of colorectal cancer, PET/CT could not improve the accuracy of colorectal cancer pretreatment N staging compared with conventional CT scan, but may bring some false-negative information. Like the result of a study performed by Cipe G et al,⁵⁰ after comparing with the histopathological results, the accuracy of MDCT in N staging was higher than PET/CT. The sensitivity of PET/CT was as low as 52.38%, which meant that it missed many metastatic lymph

nodes and underestimated N stage in many patients. Several other studies reported comparable results of PET/CT, showing low sensitivity (29–37%) and high specificity (83–96%).^{51,52} Thus, for the N staging of colorectal cancer, PET/CT could not offer much help, though the accuracy of MDCT is still not so ideal for N staging.

Some recent studies demonstrated that routine use of PET/CT for preoperative staging did not impact disease management for most of the colorectal cancer patients after completion of standard work-up, including physical examination, ERUS, CT of the abdomen and pelvis, and chest CT or chest X-ray.^{50,53} With the rapid development of CT, MRI and ERUS, and considering the cost-effectiveness, PET/CT is not recommended routinely for pretreatment staging for most of the colorectal patients after the completion of standard work-up.

2. CT IN LOCAL STAGING OF RECTAL CANCER IS NOT SO GOOD AS MRI OR ERUS

In the American College of Radiology appropriateness criteria,⁷ ERUS was recommended as the first choice for assessment of rectal wall involvement level of small or superficial rectal cancer, and for large or advanced rectal cancer, CT and MRI were recommended in the first place.

A meta-analysis comparing ERUS, CT, and MRI pretreatment staging accuracy for rectal cancer,⁵¹ showed that for T2, T3 staging, ERUS achieved significantly higher accuracy than MRI and CT. While evaluating T4 or N stage, the results were comparable. Results from other studies were similar, also showing that ERUS was better than CT for preoperative assessment of depth of invasion.^{36,54,55}

However, ERUS also has its own limitations. One is that it depends greatly on the operators' experience, being associated with a steep learning curve.⁵⁶⁻⁵⁸ Tumors exceeding 50 mm in length could not be reliably measured by ERUS due to the limit in the length of each recording. Another problem may be stenotic lesions, which would limit access of the ultrasound probe. Almost all the deficiencies of ERUS could be overcome by CT.

With the help of diffusion-weighted magnetic resonance imaging (DWI), gadolinium-based contrast agents and tumor or nodal morphology with higher resolution, MRI images were more distinct than CT images on local staging of rectal cancer after comparing with histopathological results.^{42,51,59,60}

MRI either with phased array coil or with endorectal coil can distinguish various layers of the rectal wall. As the apparent limitations, such as high cost, limited field of examination, discomfort of insertion and insertion failure rate, which could be up to 40%, MRI with endorectal coil was not commonly used. Thus, MRI with phased array coil may be more acceptable than MRI with endorectal coil. Although the accuracy of local assessment for rectal cancer is better than CT, the time-consuming and limited scan area defects of MRI make it not so commonly used as CT.

In summary, for rectal cancer, MRI and ERUS could be used under different conditions, and both of them are better than CT for the pretreatment local staging. However, CT could be less time-consuming and more suitable than MRI for claustrophobic patients or elder patients who cannot hold their breath for long time.

CONCLUSION

Many modalities are available for the pretreatment staging of colorectal cancer. CT is the most practical and convenient method, and CT is the most common choice in clinical practice for pretreatment evaluation of colorectal cancer except that in the local staging of rectal cancer one may select MRI or ERUS as the modality of choice. With the rapid development of CT technique, MDCT with thinner section thickness and multiplanar reformations could provide higher resolution images and make more accurate pretreatment staging. When combining MDCT with the water enema or air insufflation, we may achieve higher sensitivity and specificity for T staging, but not for N staging. For N staging, the accuracy of CT was not as good as that in T staging. Considering the cost-effectiveness, PET/CT is not recommended for pretreatment staging for most of the colorectal cancer patients after the completion of standard work-up, and PET/CT may even bring some false-negative information in N staging. Finally, more large scale trials are needed on tumor staging accuracy with MDCT and/or with other new imaging techniques.

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