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Hepatic Resection for Colorectal Liver Metastases and the Role of Positron Emission Tomography Imaging

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Abstract

Colorectal cancer remains the third most prevalent cancer worldwide, contributing to over 600,000 deaths per year. In North America, colorectal cancer is the fourth most common newly diagnosed cancer each year. Colorectal cancer often metastasizes to the liver, which is best treated with a combination of surgical hepatic resection and chemotherapy. Unfortunately, only 20% of patients are candidates for surgical resection at presentation. Accurately determining resectability of hepatic metastatic disease is important prior to proceeding to surgery. The optimal imaging modality remains to be determined. Computed tomography (CT) and magnetic resonance imaging (MRI) have been the primary imaging modalities used to date to identify intrahepatic metastatic disease. Positron emission tomography (PET) imaging has been shown to increase sensitivity and specificity for detecting extrahepatic metastases. However, PET imaging is limited by the inability to accurately localize these lesions. Combined PET/CT imaging has been proposed as method to improve accuracy in detecting intra and extra-hepatic metastases. Current evidence is limited and further prospective studies are needed to clarify the role of PET/CT imaging in metastatic colorectal disease.

Keywords: Colorectal, Cancer, Hepatic resection, Positron emission tomography, Metastasis

Introduction

Worldwide, colorectal cancer (CRC) is the 3rd most prevalent cancer with an estimated incidence of 0.02% [1]. This equates to approximately 1.2 million people worldwide diagnosed with (CRC) annually [1]. In 2008, colorectal cancer contributed to 609,051 deaths, which is an estimated 8.1% of all cancer-related deaths in the world [1]. In North America, CRC is the 4th most common diagnosed cancer each year and the 2nd leading cause of cancer-related death [2,3]. CRC may metastasize with the liver being the most common site of distant spread. When hepatic involvement is discovered, surgical resection of the liver metastases offers the only chance for long-term survival. However, prior to exploration of surgical treatment options, surgical resectability must be determined. Diagnostic imaging plays an important role in determining and defining resectability; however, the most effective diagnostic technique remains controversial in the literature. Positron emission tomography (PET) imaging is a novel diagnostic modality with potential diagnostic value in the setting of colorectal hepatic metastases. This review will explore the role of hepatic resection for colorectal metastases and the selective use of PET imaging as an investigational tool.

Liver Resection for Colorectal Metastases

Approximately 25% of patients with colorectal cancer have liver metastases at presentation [4] and 50-60% of patients will develop liver metastases at some point [5]. Without treatment, patients with liver metastases have an estimated overall survival of nine months [6]. Surgical resection of the hepatic metastases has been shown to improve survival [7,8], however, only 20% of patients with liver metastases are amenable to surgical resection at presentation [9-12].

A recent series of articles estimated the five-year survival to be between 29 - 43.1% following liver resection for colorectal metastases [10-12]. Other studies have demonstrated an improved 5-year survival rate of 58% in which complete resection of metastases is achieved [13,14]. This appears to constitute a significant improvement in survival compared to basic supportive treatment. However, variation in survival among series may reflect differences in patient selection, surgical approach and use of neoadjuvant and adjuvant chemotherapy. In a study by Tomlinson et al., patients who underwent surgical resection for colorectal liver metastases were followed for 10 years. They reported that 34% of the five-year survivors eventually died of cancer related deaths within the next five years and only 16.7% of their patients survived beyond 10 years [7]. Nevertheless, in appropriate surgical candidates, hepatic resection remains a vital treatment strategy.

Criteria for patient selection have evolved as accuracy of diagnostic imaging and surgical technique has improved. However, resectability is defined by each center differently. Some common selection criteria include: a residual liver volume greater than 30% after resection, limited and preferably no extrahepatic disease, clear resection margins, and satisfactory clinical condition of the patient [5,15]. According to the consensus statement by Charnsangavej et al., resectability was defined as (1) complete (R0) treatment of the disease; (2) preservation of atleast two adjacent liver segments; (3) preservation of vascular flow and biliary drainage; and (4) sufficient volume of the remnant liver [16]. These criteria suggest that surgical resection may be offered to patients in whom, complete resection of all intrahepatic disease and adjacent disease with negative margins is deemed feasible, with preservation of an adequate liver remnant.

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The Role of Imaging Modalities

The goals of diagnostic imaging in CRC are to accurately identify and localize intrahepatic and extrahepatic metastatic disease. A number of diagnostic modalities are available to provide high-quality cross-sectional imaging to assess potential resectability in these patients. Contrast enhanced computed tomography (ceCT) and/or contrast enhanced magnetic resonance imaging (ceMRI) being the modalities most commonly applied. Depending on the resources and expertise available at each centre, either ceCT or ceMRI is used to define extent of intrahepatic metastatic disease in the segmental distributions for planning of resection. In addition, these techniques allow estimation of residual volume of the liver remnant. The sensitivity of intrahepatic lesion detection of new multidetector helical CT scanners is estimated to range from 70 to 95% [5,17]. The strength of ceCT imaging is excellent intrahepatic image resolution to provide segmental, lobar and vascular anatomical details for surgical planning. The limitation of ceCT is false negative rate in detecting lesions smaller than 1cm. In contrast, ceMRI is considered to have a higher sensitivity (83% to 98%) compared to ceCT when combined with a liver-specific contrast medium [4,18,19]. In a small series by Coenegrachts et al., ceMRI correctly identified all 24 patients with intrahepatic metastases (sensitivity 100%; CI 86-100%) [20]. Specifically, ceMRI has been suggested to be more accurate in identifying intrahepatic lesion less than 1cm than ceCT [21-23]. A meta-analysis by Niekel et al., reported MRI to have greater sensitivity (60.2%) compared to CT imaging (47.3) for intrahepatic lesion less than 1cm [21].

Accurate identification of extra-hepatic disease is an equally important aspect of diagnostic imaging in patients with CRC hepatic metastases. This includes localization of nodal, peritoneal and distant metastases. Hepatic resection in the presence of extra-hepatic metastatic disease is relatively contraindicated (except isolated pulmonary metastases), to avoid unnecessary surgery with minimal survival benefit. Currently, concern has been raised regarding the relatively lower sensitivity of CT and MRI to identify extrahepatic CRC metastases. A meta-analysis by Wiering et al., reported a sensitivity and specificity of 55% and 96% respectively, of CT for detecting extrahepatic metastases [24]. A prospective study on 35 patients by Rappeport et al., also reported a similar sensitivity (59%) for CT imaging [25]. The concern related to the decreased accuracy of CT and MRI in detecting extrahepatic CRC metastases compared to intrahepatic metastases have led to research into the potential role of PET and PET/CT.

FDG - Positron Emission Tomography

Recently, interest has arisen in assessing FDG-PET imaging in CRC metastases. FDG-PET imaging uses FDG-glucose molecules to identify regions of increased glucose metabolism. The radiolabeled glucose molecule is taken up by metabolically active cells and becomes trapped, which resultantly gives off a signal of increased intensity. It is proposed that neoplastic cells have an increased metabolic rate and will, therefore have greater FDG uptake.

The sensitivity of FDG-PET scans for detecting hepatic metastases has been reported to be greater than CT imaging by many early studies [5,26,27]. In a meta-analysis by Bipat et al., helical CT imaging was reported to have a per-patient sensitivity in identifying intrahepatic neoplastic disease of 64.7%, compared to a per-patient sensitivity of 94.6% for FDG-PET imaging [5]. However, a recent meta-analysis of 39 prospective studies, reported sensitivity of CT, MRI and FDG-PET on a per-lesion basis of 74.4 (CI 68.7-79.3), 80.2 (CI 74.6-85) and 81.4 (CI 66.5-90.6), respectively [21]. Thus, FDG-PET imaging is just as likely to miss a single lesion as other conventional imaging techniques. The same review also reported similar sensitivities for intrahepatic metastases between MRI and FDG-PET on a per-patient basis. These results suggest that all three of these imaging modalities may be comparable. However, one of the major disadvantages of FDG-PET imaging is determining the precise anatomic location of hepatic metastases. This is especially true for small (<2cm) lesions, limiting accurate localization to determine resectability [28]. Furthermore, there may be increased areas of FDG-glucose uptake related to inflammation or infection or decreased uptake by malignancies with low avidity for FDG. These confounding areas of increases and decreased FDG-glucose uptake may lead to false positive or negative results. Therefore the role of FDG-PET alone, without concordant cross-sectional imaging, remains limited.

The role of FDG-PET imaging for extrahepatic CRC metastases is important as [29] FDG-PET scanning has been shown to have high sensitivity and specificity in detecting distant metastases. A meta-analysis by Wiering et al. reported a pooled sensitivity of 92% and specificity of 95% for FDG-PET imaging compared to pooled sensitivity and specificity of 60.9% and 91.1% for CT imaging, to identify extraheptaic disease in patients with colorectal cancer [24]. In addition, these authors suggested that identification of distant metastatic disease by FDG-PET imaging changed management in 25.0% (range, 20.0 –32.0%) of patients based on 5 of the 6 studies with high methodological quality [24,30]. However, the previously mentioned limitations of inappropriate FDG-uptake and lack of accurate localization make routine FDG-PET imaging controversial for identifying extrahepatic CRC metastases.

Combined FDG-PET and CT Imaging (PET/CT)

Currently, a combination of FDG-PET and CT imaging is used in most centers, and has generally replaced the use of isolated FDG-PET imaging. By overlapping the resultant images, PET/CT imaging offers the dual advantage of accurately localizing hepatic neoplastic disease while identifying FDG avid areas. Selzner et al. compared the sensitivity and specificity of ceCT imaging to PET/CT in 67 patients [31]. They reported similar sensitivity and specificity between the two imaging modalities in detection of intrahepatic metastases (sensitivity 95% vs. 91%, respectively). PET/CT missed extrahepatic disease in 11% (sensitivity 89%) of cases compared to 36% by CT imaging (sensitivity 64%). Rappeport et al. reported similar findings in 35 patients imaged with multiple imaging modalities prior to liver resection [25]. They reported lesion-by-lesion sensitivity for intrahepatic lesions of 83% for PET/CT compared to 77% for CT alone. For extrahepatic disease, the sensitivity was 83% for PET/CT compared to 58% for CT alone. In a retrospective review by Bellomi et al., all intrahepatic metastases were identified by both CT and PET/CT [32]. A systematic review by Patel et al., also concluded increased accuracy of PET/CT in detecting intrahepatic and extrahepatic colorectal metastatic disease compared to CT alone [27]. However, the authors of this report cautioned that there might be significant bias in the included studies, which may be related to their retrospective nature and small patient numbers. Furthermore, these authors suggest that further prospective trials are needed prior to adoption of PET/CT as a primary imaging modality for staging of colorectal metastases for possible hepatic resection. Interestingly, a retrospective analysis by Deleau et al. of 71 patients, reported a change in clinical management with PET/CT in 31 patients (40%) [33]. 15 of these patients avoided futile surgery following detection of extrahepatic metastases. However, the nuclear medicine physicians involved were aware of the relevant clinical data, results of CT imaging and PET/CT imaging was acquired based on clinical or radiologic suspicion. Kong et al. also retrospectively assessed 65 patients, and reported that PET/CT identified extrahepatic disease in 17% of patients leading to a change in clinical management [19]. These authors suggested that PET/CT was most useful in detecting small malignant mesenteric and peritoneal nodules. However, they also found false-positive PET/CT findings in 3% of patients. Kochhar et al. reported 3 false positives on PET/CT out of 157 patients who were retrospectively reviewed [34]. However, these authors caution that their low false positive rates may be related to a highly selected patient population. Based on limited literature on PET/CT, it cannot currently be estimated what the false positive rates truly are. Unknown false-positive rates of PET/CT are concerning since they may lead to delay or prevention of crucial surgical management. In adoption of any new imaging modality, an evidence-based approach is needed. A prospective randomized clinical trial is currently underway, which may clarify the role of PET/CT in this patient population. However, until further evidence is available, the selective use of PET/CT as a secondary imaging modality may be reasonable.

Conclusion

Colorectal cancer is a common disease with a tendency to metastasize to the liver. Accurate imaging of intrahepatic and extrahepatic metastatic disease is needed to determine resectability of liver disease. Both ceCT and ceMRI remain the most common and accurate cross-sectional imaging modalities for intrahepatic CRC metastases. PET/CT may have a role in detecting extrahepatic CRC metastases in the future. However, currently the evidence is limited on PET/CT and false positive rates are unknown. Further prospective research is needed to clarify the role of PET/CT imaging in this clinical setting.

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