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Peritoneal MRI In Patients Undergoing Cytoreductive Surgery and HIPEC: History, Clinical Applications, and Implementation

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ABSTRACT

MR imaging provides considerable advantages in the evaluation of patients with peritoneal metastases. A standardized peritoneal MRI protocol, including diffusion-weighted and gadolinium-enhanced sequences, allows an efficient exploration of small peritoneal tumors that are often missed on other imaging tests. In experienced hands, a dedicated reading allows producing a quantitative and qualitative evaluation of lesional localization to better assist surgeons in the selection of candidates for curative surgery by evaluating the possibility of complete resection, and to plan the surgical procedure. Based on a close collaboration between oncologic surgeon and radiologist, MRI provides a powerful tool for accurate preoperative imaging in patients being considered for curative surgery but also in their surveillance to detect an early recurrence.

KEYWORDS: Peritoneal metastases, peritoneal carcinomatosis, peritoneal cancer index, preoperative assessment; resectability, pseudomyxoma peritonei
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1. Introduction and Rationale for Peritoneal Imaging

Imaging of peritoneal metastases can play an essential role in diagnosis and management in patients with peritoneal malignancy being considered for surgical cytoreduction (CRS) and heated intra peritoneal chemotherapy (HIPEC). Abdominal and pelvic imaging could potentially contribute valuable information to initial diagnosis, preoperative staging, patient selection, detection of postoperative complications, and patient surveillance following successful treatment [1, 2].

Imaging peritoneal metastases provides unique challenges due to the complex peritoneal anatomy. Peritoneal metastases are often small with tumors that are a few millimeters in thickness or with even more subtle thin sheets of tumor cell coating the parietal and visceral peritoneum. The combination of complex peritoneal anatomy and the inherently small size of peritoneal metastases makes peritoneal tumor imaging arguably the most difficult challenge facing the abdominal imager.

Careful patient selection based on preoperative imaging may prevent unnecessary surgeries in patients whose tumors are too extensive and cannot be adequately cytoreduced. It also provides crucial information to the surgeon regarding the resections that will be required for complete cytoreductive surgery. This information facilitates planning of resources preoperatively and routing of patients to referral centers when needed. Following CRS and HIPEC surveillance imaging combined with serial tumor markers is routinely used to detect recurrent tumor.
2. Role of other Imaging Tools: CT and PET

Imaging options include computed tomography (CT), magnetic resonance imaging (MRI) and Positron Emission Tomography (PET). CT provides strictly cross-sectional anatomic imaging while MRI provides a combination of cross-sectional anatomic imaging and tumor functional imaging. PET imaging of peritoneal tumor provides functional imaging based upon an assessment of the tumor’s metabolism of glucose. Comparison of imaging modalities can be challenging. Performance of each modality may depend on the protocol used, the tumor type (mucinous/non mucinous and invasiveness), the type of exploration (initial staging or recurrence) and the level of experience of the radiologist.

a. Computed Tomography

At many centers CT is routinely used for malignant peritoneal disease, because of its availability and its fast image acquisition time. With multidetector CT, a spatial resolution of 1 mm can be achieved, thus allowing excellent multiplanar reformations. For peritoneal metastases CT can achieve a per patient sensitivity of 83% and specificity of 86%, however its shortcomings in accurately detecting peritoneal tumors at the region level is well documented [3].

The sensitivity of CT dramatically decreases with smaller peritoneal tumors. Koh et al [4] reported in patients with colorectal cancer a CT sensitivity of only 11% for lesions < 0.5 cm. Jacquet et al [5] in a similar analysis reported that CT
sensitivity for lesions <0.5 cm was 28%. Tumors 0.5 to 5 cm were depicted with a sensitivity of 72% and large tumors >5cm were depicted with a 90% sensitivity.

Even larger tumors can be missed on CT if they are large in size but thin plaque-like lesions or when lesions are located in regions with subtle contrast between the tumor and surrounding tissues. Indeed, the lack of contrast resolution of CT is a major weakness when evaluating pelvic regions and in the critical 4 small intestinal regions. Chua et al reported a 21% to 25% sensitivity in the small intestinal regions [6]. These shortcomings of CT result in a preoperative CT Peritoneal Cancer Index (PCI) that consistently underestimates the volume of peritoneal disease (Fig. 1) [1].

b. Positron Emission Tomography

The functional information of PET is combined with CT to provide accurate anatomical information [7]. A sensitivity of 82% and 84% and specificity of 93% and 98% have recently been reported in meta-analysis [3,8]. However, these results were based on the patient, not on the peritoneal region. It remains unclear if PET CT has a clinical impact at the patient level regarding peritoneal cancer staging. In studies comparing imaging findings to surgical findings, there was no benefit of PET CT versus CT alone regarding the patient management [9,10, 11, 12]. Dromain et al [11] concluded that neither CT nor PET/CT examination was a reliable imaging method in the preoperative assessment of the extent of peritoneal involvement in colorectal cancer; in particular, to predict small bowel involvement.
Limitations of PET CT include false negative interpretations, due to small lesions that do not show FDG uptake, or that can be obscured by normal bladder or bowel activity. The lower cellularity of mucinous metastases is another source of false negative interpretations with PET. False positive interpretations with PET, decrease its specificity with a potential to over stage the disease. False positive PET findings may reflect inflammatory reaction of the peritoneum adjacent to large or multiple tumor implants, presence of foreign body or inflammatory reactions due to previous surgery or normal physiologic activity in bowel [13]. Nevertheless, PET-CT remains the best imaging modality to depict extraperitoneal metastases.

3. History of Peritoneal MRI

Peritoneal MR imaging had its origin 3 decades ago at Sharp Memorial Hospital - and Sharp and Children’s MRI Center- in San Diego, California. In many respects it was the chance confluence of multiple independent factors; novel MR software, a new contrast agent, and inquisitive attitudes, which created an environment of unrestrained discovery.

In 1990 a novel 2D gradient-echo MR pulse sequence – fast multiplanar SPGR - was so efficient that it allowed for breath-hold abdominal imaging for the first time. Previously, all abdominal MRI was performed with slow respiratory triggered spin-echo sequences that were time consuming and prone to respiratory artifact. While at Stanford University Medical Center, we optimized the FMSPSPGR research sequence for breath-hold abdominal imaging.

Gadolinium intravenous contrast material was still new and only routinely used for brain and spine imaging. Envisioning an opportunity to improve abdominal
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MRI signal we combined our optimized breath-hold FMSPGR with IV gadolinium. The resultant abdominal images with gadolinium and suspended respiration were stunning in anatomic detail, signal, and clarity. This was the beginning of contrast-enhanced breath-hold MRI that continues to this day with newer 3D gradient-echo sequences [14].

Upon my arrival at Sharp Hospital in San Diego in July, 1991 we implemented these new MRI techniques and began the practice of Body MRI in San Diego. The first depiction of enhancing peritoneal tumor was entirely fortuitous. In 1991 we observed perihepatic enhancement in a patient with metastatic endometrial cancer but did not realize its significance until her oncologist, informed me that his patient had known peritoneal metastases. We began to see enhancing peritoneal carcinomatosis in patients with many primary malignancies. This type of subtle peritoneal tumor had been previously invisible on all other imaging studies. We reported our initial finding describing gadolinium-enhanced MRI of peritoneal tumor in 1994 [15,16].

In 1992 fat suppression was implemented on our breath-hold, gadolinium-enhanced FMSPGR images. Eliminating the high signal intensity fat with fat suppression made enhancing peritoneal tumor much more conspicuous with only a slight increase in breath-hold scan time. We began administering water-soluble oral contrast to our patients in 1994. By distending the bowel lumen, peritoneal bowel serosal tumor was much more readily seen. We reported the use of intraluminal contrast for peritoneal tumor MRI in 1997 [17, 18]. Rectal tap water
was administered to distend the colon and rectum improving depiction of colonic and rectal serosal metastases.

In 1994 we began to utilize these MRI techniques to image Dr. Robert Barone’s patients with appendiceal cancer. It became apparent that gadolinium-enhanced MRI showed peritoneal tumor much more clearly. On CT limited soft tissue contrast, made it difficult to distinguish ascites, mucin, and tumor. On gadolinium-enhanced MRI only the tumor enhances allowing one to confidently assess the location, volume, and extent of tumor compared to the non-enhancing ascites and mucin. In 1995 Dr. Robert Barone began to perform CRS and HIPEC for his patients with peritoneal cancer. Dr. Barone very quickly adopted MRI as the preoperative imaging examination.

In 2004 Takahara et al [19] published a paper about DWI using a 3D projectional technique, which he called DWIBS. The DW images were dark with limited background signal, but the abnormalities were bright like light bulbs. It became apparent that we were seeing abnormalities, both benign and malignant, that had been previously overlooked. The contrast and resultant tumor conspicuity on these DW images was many times greater than on conventional MRI or CT.

In 2007 we described the first use of DWI for anatomic imaging in oncology patients [20]. Our experience using DWI for peritoneal tumor and appendiceal cancer was described in 2008 and 2009 [21, 22]. These articles represented the first description of DWI for peritoneal tumor imaging. We now had two distinct tools for peritoneal tumor MRI – delayed gadolinium-enhanced MRI, and DWI.
Now over 10 years later, these two contrast tools continue to represent the backbone of our peritoneal MRI examination.

4. Protocols and Techniques for Peritoneal MRI

   a. Patient Preparation

   All patients are asked to refrain from eating or drinking for the four hours prior to their MR appointment. Patients self-administer a Fleet’s enema prior to the examination, if rectal water is to be used.

   b. Intraluminal Contrast

   Distension of the stomach, small bowel, and colon is accomplished with water-soluble intraluminal contrast material. Collapsed bowel creates problems for image interpretation, since it can mask subtle peritoneal tumors or inflammation involving the bowel serosa, mesentery, or adjacent peritoneum. Alternatively, non-distended small bowel can be mistaken for an abdominal mass leading to false positive interpretations. Adequate bowel distention is an essential element in the peritoneal MR imaging protocol that improves the accuracy and confidence of image interpretation [17,18].

   Beginning 45 minutes before the start of the MR examination the patient drinks 1.0 – 1.5 liters of oral contrast material of sufficient volume to distend the small bowel and stomach. We currently use dilute barium sulfate suspension CT contrast material, which is 98% water. E-Z-EM Readi-CAT® (Bracco) to distend the small bowel for MR imaging. Other oral contrast agents including VoLumen®
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Barium Sulfate Suspension, 0.1% w/v, 0.1% w/w, 450 mL (Bracco). 1 Liter of rectal tap water can be administered through a balloon tipped barium enema catheter to distend the rectum and colon. The balloon should be filled with water and not air to decrease the susceptibility artifact that the air would create. While rectal water is not an absolute requirement it can improve the depiction of subtle serosal and peritoneal tumor involving the colon and rectum.

c. Intravenous Contrast Agents

Intravenous gadolinium is administered using a power injector at an injection rate of 2 cc per second. We currently use a single dose 0.1 mmol/kg of MultiHance® (gadobenate dimeglumine) (Bracco), which due to its higher relaxivity shows greater enhancement of peritoneal tumors.

d. Antiperistaltic Agents

Bowel peristalsis can degrade the image quality on the gadolinium-enhanced 3D FSPGR and 2D SGE images, which are sensitive to bowel motion. Image quality is improved by administering an antiperistaltic drug. Available agents include Glucagon for injection (Eli Lilly and Company, Indianapolis, IN) 1 mg administered intravenously at the time of gadolinium injection, Buscopan®(hyoscine-N-butylbromide), and Levsin® (Hyoscyamine sulfate Injection) 0.25 mg administered intravenously at the start of the examination.

e. MR Hardware - MR Scanner and Coils
1.5T or 3T high field strength MR scanner should be used for imaging peritoneal tumors. High performance gradients (50mT / m, 200 mT /m/sec) are advantageous for high quality DW imaging but are not absolutely essential. In practice peritoneal imaging on 3.0-T MR scanners may be limited by dielectric artifact caused by the presence of ascites. For this reason, we prefer peritoneal MR imaging on our 1.5T scanner. An external phased array surface coil providing simultaneous coverage of the abdomen and pelvic should be used to improve signal and image quality.

**f. MRI Peritoneal Protocol - General Principles**

We have optimized our peritoneal MRI protocol for depicting small peritoneal tumors. All images are obtained during breath-holding to minimize breathing artifact that can obscure subtle peritoneal tumors. Other key elements that improve tumor depiction are fat suppression and high spatial resolution. We currently utilized fat suppression on T2-weighted imaging; diffusion weighted imaging and all gadolinium-enhanced images. Peritoneal tumors become much more conspicuous after suppressing the adjacent high signal intensity fat. Some sites prefer to use non-fat suppressed T2-weighted imaging to better visualize normal anatomic landmarks.

Table 1 lists the specific imaging parameters for our current peritoneal MRI protocol. In summary the examination includes axial T1 SGE images, fat suppressed T2-weighted Single shot FSE imaging, and breath hold DWI using an intermediate b-value of 800 s/mm2. Following injection of 10 mmol/kg intravenous gadolinium we obtain fat suppressed 3D FSPGR images in the axial plane twice
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thru the abdomen and pelvis. Coronal and sagittal 3D FSPGR imaging is performed. The final set of images is the axial fat suppressed 2D SGE acquisition. The 2D images are less sensitive to motion artifact, which is common at the end of the study as fatigued patients may not suspend respiration completely. The fat suppressed 2D SGE images are obtained about 5 minutes after the injection of gadolinium, when slowly enhancing peritoneal tumors are most conspicuous.

5. MR Image Interpretation and Reporting

The following five steps to successful image interpretation and reporting of peritoneal have been proposed at the 10th Peritoneal Surface Oncology Group International (PSOGI) congress 2016 [23].

a. First step: Establish the Presence or Absence of Peritoneal Metastases

Peritoneal tumors can be very subtle requiring a thorough and systematic approach to image evaluation. Following the normal clockwise peritoneal circulation, one should pay careful attention to known sites of preferential tumor deposition in areas of stasis. Signs of peritoneal metastases include the presence of peritoneal nodules, thickening, or fat stranding. With multiparametric MRI one can detect peritoneal tumors on T1- and T2-weighted, gadolinium-enhanced, and diffusion-weighted images. The final interpretation should combine the information from the multiple different sequences for optimal tumor detection.
**T1- and T2-weighted images**

The T1- and T2-weighted sequences provide anatomic details to precisely localize the larger peritoneal tumors and nodules, but are relatively insensitive for depicting small peritoneal tumors and subtle fat stranding. T2-weighted images are particularly useful for depicting mucinous lesions and cystic mesothelioma due to the conspicuity of high signal intensity mucin and fluid within these tumors.

**Gadolinium-enhanced MRI images**

Peritoneal tumors enhance with intravenous gadolinium increasing their conspicuity so that very small tumors are depicted easily. Peritoneal tumors enhance slowly so that they may not be visible on early arterial phase images but are best depicted on the final set of images obtained at about 5 minutes following gadolinium (Fig. 2) [24].

Normal peritoneal tissues are relatively thin measuring <3mm in thickness and typically show only mild enhancement that is less than or equal to that of the liver parenchyma. Moderate to marked peritoneal enhancement and associated thickening is abnormal and is the hallmark of peritonitis or peritoneal carcinomatosis. It should be noted that the distinction between peritoneal inflammation and peritoneal tumor is based upon the clinical presentation since the MR imaging findings can be identical. Peritoneal thickening from tumors may be thin and regular, nodular, or mass-like. Peritonitis usually presents as smooth and regular peritoneal thickening and enhancement.
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Bowel serosal tumor may be depicted as focal or diffuse bowel wall thickening and enhancement of the visceral peritoneum with associated restricted diffusion (Fig. 3 and Fig.4).

The coronal post contrast images are optimal to depict lesions in the mesentery, the paracolic gutter, and the undersurface of the hemidiaphragm. Distinguishing mesenteric lymph nodes from mesenteric peritoneal metastases is also challenging. Schematically, lymph nodes are close to the vessels within the fat, mostly oval or round and well defined, while mesenteric peritoneal nodules are between vessels with a sheet-like configuration on the bowel serosa.

**Diffusion-weighted MRI imaging of peritoneal metastases**

Oncologic applications of DW imaging take advantage of restricted diffusion shown by most tumors. The higher cellularity of solid tumors and their increase in cell membranes per unit volume results in restriction of water movement and corresponding high signal intensity on DW images. DW images are also very useful for depicting peritoneal tumors shown as high signal intensity masses, nodules, and peritoneal thickening [22]. On DW images ascites and bowel contents are suppressed while peritoneal and serosal tumors show restricted diffusion and are depicted as areas of high signal intensity. We have found that the most accurate examination for detecting peritoneal tumors is the combination of DWI and delayed gadolinium-enhanced MRI [25].

The DW images are more easily interpreted when viewed in conjunction with the conventional MR images, which provided better depiction of anatomic landmarks. Mesenteric tumors, bowel serosa tumors, and tumors involving the
peritoneal reflections around the liver and pancreas are usually better seen on the DW images due to the high contrast of peritoneal tumors on these images (Fig. 4). The combination of morphological sequences with diffusion demonstrated an increase in the sensitivity of MRI detection of lesions by 20% [22]. Diffusion-weighted imaging will also detect tumors not shown on CT because the tumor nodules are isodense to the surrounding structures. Finally, extraperitoneal tumors involving lymph nodes, liver and osseous structures are often best seen on DW images.

Limitations of DW imaging include T2-shine through of cystic lesions on magnitude DW images. Generating an apparent diffusion coefficient (ADC) map, which only demonstrates true restricted diffusion, can eliminate this T2 signal. The radiologists should become familiar with normal structures showing restricted diffusion including benign lymph nodes, bowel mucosa and spleen. Restricted diffusion is not specific for malignancy and can be seen in inflammation and ischemia.

b. Second step: Qualitative Analysis of Peritoneal Metastases

Three types of peritoneal tumors require qualitative description, i) Unresectable tumors, ii) Tumors requiring special surgical expertise, and iii) Potentially occult tumors.

i. Detection of unresectable lesions through identification of concerning radiologic features
The concept of unresectability is complex, depending on patient age and status, the primary cancer (invasive versus non-invasive histopathology), and the tumoral distribution and volume [26]. Extensive tumor at particular anatomic sites may preclude surgery and accurate MRI description aims to avoid an open and close procedure. The three more frequent sites for unresectable lesions are small bowel and its mesentery, the porta hepatis, and pelvis.

**Small Bowel and Mesentery**

Diffuse involvement of the root of the mesentery is nonresectable. Thin sheets of mesenteric tumor are invisible on CT and PET. MRI shows diffuse abnormal mesenteric enhancement and restricted diffusion.

Diffuse small bowel involvement (mesentery and/or bowel serosa) is sometimes difficult to depict, but when present the radiologist has to estimate the extent of involvement as less or more than 50% of the bowel that may preclude complete cytoreduction [27]. Radiologist should also describe the number and the location of the stenoses of small bowel segments as well as colonic or gastric invasion to give a complete analysis of the entire digestive tract.

**Porta Hepatis and Hepatoduodenal Ligament**

Involvement of the hepatoduodenal ligament or the liver hilum may make a patient’s tumor non resectable. Tumor involvement can be challenging to detect unless it results in biliary or vascular stenoses. A concerning radiologic concerning is the partial or complete disappearance of the fatty tissue within the
hepatoduodenal ligament [27]. The tumor infiltration of the tissue of the portal triad results in replacement of the periportal fat with tumor that shows gadolinium enhancement and restricted diffusion.

**Pelvis – Diffuse tumor**

Unresectable pelvic tumor corresponds to the diffusely infiltrated or frozen pelvis. Involvement of the trigone also usually precludes cytoreductive surgery. Bladder and trigone involvement is best depicted on MRI with its high soft tissue contrast and multiplanar capabilities. In the absence of ureteral dilatation, this tumor will be very difficult to depict on CT or on PET-CT [28].

**ii. Detection of lesions of the anatomic site that require surgical subspecialty expertise**

Radiologist should carefully describe lesions requiring special surgical expertise for resection because they are at a difficult anatomic site resulting in higher morbidity and mortality. A single concerning radiologic feature will often add complexity to the cytoreductive surgery but does not preclude complete cytoreduction. Two or more concerning radiologic features usually indicates a suboptimal resection [26]. These surgically challenging tumors include:

- Diffuse involvement of liver capsule or diaphragm (Fig. 2).
- Peri-pancreatic lesions, pyloric or duodenal obstruction.

The pancreas is an organ that carries high surgical morbidity because the capsule is friable. A higher risk of leakage of pancreatic enzymes occurs
with any surgical trauma. Radiologist should describe lesser sac tumors and their relationships to the pancreas.

- Multifocal lesions of mesentery (Fig.4), small-bowel stenoses, and diffuse involvement of colon may require more extensive procedures with potential for anastomotic leakage. The location and number of lesions involving the mesentery, the small bowel, large bowel, and the stomach should be described.
- Encasement of one ureter and/or involvement of urinary bladder dome.
- Seminal vesicles.
- Pelvic wall and vascular spaces with involvement of external iliac vessels.
- Muscular involvement including the psoas muscle and abdominal wall.

iii. Detection of Occult Peritoneal Metastases

Lesions, which may be occult to the surgeon at exploration include those deeply embedded in the parenchyma of the spleen or liver, those within the sub peritoneal space, and retroperitoneal lesions. Other lesions may be occult at laparoscopy, which presents additional challenges for tumor depiction. For example, tumors in the lesser sac, Morison’s pouch or the posterior aspect of the liver can be invisible at laparoscopy and could require laparotomy for optimal access and surgical cytoreduction prior to HIPEC.

c. Third step: Quantitation of the Radiologic Peritoneal Cancer Index
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The third step in the written report for peritoneal metastases is a quantitative analysis. Determining the radiologic PCI can be very challenging with CT or MRI [4,12,29,30,31]. Even when the overall imaging PCI score and the surgical PCI are in agreement, one often finds regions that are overestimated with false positive, or underestimated with false negative findings. The radiological PCI can be more accurately determined using MRI or even by combining CT and MRI compared with CT alone [1, 32].

The most common cause of underestimation is the small or thin lesion. Thin sheets of peritoneal tumor a few millimeters in thickness are common in these patients and can be challenging to visualize.

Overestimation of tumor can occur with peritoneal thickening and fat stranding due to inflammation. Fat stranding can may be due to tumor infiltration, lymphatic blockage, or ascites. In our experience the presence of gadolinium enhancement and restricted diffusion will improved the specificity for tumor detection.

To improve the radiological PCI, a comprehensive and accurate radiological lexicon is needed to provide a score that strongly correlates the radiological and surgical findings. An internet application called PROMISE (PeRitOneal Malignancy Stage Evaluation), available at the Internet address, www.e-promise.org, may also facilitates tabulation and automatically calculates PCI [33].

Determining the imaging PCI; 1) standardizes radiological reading, 2) forces the radiologist to screen every region and lesion and, 3) provides an overall
estimate of tumor volume. The estimate of tumor distribution is perhaps more informative than the exact numerical value of the PCI.

The radiologist should at least provide a semi-quantitative assessment describing the peritoneal tumor as diffuse, multifocal or localized, and to report the total number of regions involved out of 13.

d.Fourth step: Description of Extraperitoneal Metastases

The fourth step in the written report for a patient with peritoneal metastases is to describe extraperitoneal metastases involving the liver, spleen, pleura, bones, or lymph nodes. Depending on the site and the number of lesions, the presence of extraperitoneal tumor can significantly change patient management.

Lymph nodes involvement should also be described in the mesentery, celiac region, the retroperitoneum (infra or suprarenal para-aortic and pelvic lymphadenopathy) and inguinal regions, as well as in cardiophrenic angles, although the tumour character is difficult to ascertain even when enlarged [34].

e.Fifth step: Search for the Primary Cancer

As a final step in the written report for patients with peritoneal metastases, the radiologist must search for a primary cancer. In the absence of a known primary malignancy, the radiologist should perform a thorough analysis of all extra peritoneal organs in an attempt to identify the primary cancer.

6.Clinical Applications of Peritoneal MRI

a. Preoperative Imaging and Staging
Preoperative imaging of the abdomen and pelvis plays an integral role in determining the extent of peritoneal and visceral disease in patients being considered for CRS and HIPEC for appendiceal, ovarian, colorectal, primary peritoneal, gastric, mesothelioma and other rare types of gastrointestinal disease involving the peritoneum. In the preoperative imaging assessment determining resectability is critical to avoid unnecessary surgeries. However, CT with its limited soft tissue contrast consistently underestimates the volume of peritoneal tumor [1, 35]. Rivard et al [35] found that the results of CT do not predict resectability of peritoneal tumor. In our experience MRI provides a much more accurate imaging examination for preoperative evaluation of patients being assessed for CRS and HIPEC.

Preoperative MRI can estimate the PCI with good accuracy compared to surgical findings. In 33 patients being considered for CRS and HIPEC there was no significant difference between the preoperative MRI PCI and surgical PCI MRI correctly categorized the tumor volume found at surgery in 29 (88%) of 33 patients [25]. MRI accurately categorized the tumor volume as small volume (PCI 0-9) in 89% of patients, moderate volume (PCI 10-20) in 75% of patients, and large volume (PCI >20) in 90% of patients [25].

In a comparison of preoperative CT and MRI compared to the surgical PCI we found that the median surgical PCI 33 was in good agreement with the MRI PCI of 36, while the median CT PCI of 15 underestimated tumor volume ion 19 of the 22 patients [1]. The median percentage difference between the surgical PCI and the CT PCI was 50% compared to 6% for the MRI PCI versus the surgical
PCI. Compared to the surgical PCI, MRI PCI correctly categorized tumor volume in 91% of the patients as opposed to only 50% with CT scanning. Notably in the small bowel areas (sites 9-12) MRI had an accuracy of 92% versus 48% for CT. Overall, surgery confirmed 222 sites of tumor. MRI demonstrated per site sensitivity of 0.95, specificity 0.70 and accuracy 0.88. CT showed a corresponding per site sensitivity 0.55, specificity 0.86, and accuracy 0.63 (Fig. 3).

A recent study of 49 patients with colorectal cancer (36 non-mucinous adenocarcinoma) also showed that MRI PCI had a stronger correlation with surgical PCI, and accurately predicted resectable patients with a PCI<21 with an excellent intraclass correlation [36].

b. Surveillance MRI following HIPEC

Despite successful treatment local intraperitoneal recurrence of tumor occurs in 28% - 44% of patients and remains a significant problem that reduces overall survival [37, 38]. MRI is very useful in the surveillance setting following CRS and HIPEC. Unlike CT serial MR examinations can be performed without concern for cumulative radiation exposure. MRI can detect recurrence, even sometimes earlier than serial tumor markers [2]. In a longitudinal study of 50 patients with appendiceal neoplasm following CRS and HIPEC, tumor recurrence was documented in 30 patients with median time to recurrence of 13 months. MRI detected recurrent tumor in 28 patients including 11 patients with normal laboratory values (sensitivity 0.93, specificity 0.95, accuracy 0.94, PPV 0.97, and NPV 0.90).
Serial laboratory values showed tumor recurrence in 14 patients (sensitivity 0.48, specificity 1.00, accuracy 0.69, PPV 1.0, and NPV 0.57) [2].

Obtaining a baseline postoperative MRI is mandatory to establish the normal post-surgical appearance. Otherwise changes caused by prior surgical interventions can be very misleading. On subsequent surveillance MRI examinations the radiologist has to report if these changes are stable, resolved, or progressing, which indicates tumor recurrence.

7. Implementation of MRI into Surgical Planning and Post HIPEC Management: A Surgeon’s View

MR imaging in experienced hands can provide as much, if not more, information as to the extent of disease than laparoscopy with significantly less cost. Using MRI we have not had an open and closed case at our institution in over 15 years.

a. Early Evaluations of MRI

Prior to 1994, CT was the primary imaging modality used to stage patients being considered for cytoreductive surgery. In 1995 studies on cytoreduction and early postoperative intraperitoneal chemotherapy and subsequently heated intraperitoneal chemotherapy were initiated at our institution. Patients with ovarian, primary peritoneal, appendix, gastric, colorectal carcinomas and mesothelioma were eligible for entry into an Institutional Review Board sponsored study. Initially, both CT and MR imaging were utilized as preoperative assessment, since I wasn’t sure of the true value of MRI over CT at that time. Preoperatively the CT and MRI
studies were reviewed with Doctor Low. On numerous occasions he was present in the OR to assess the location and extent of disease. By doing so, he was able to correlate and compare what he saw at surgery and what was seen on the preoperative MRI. Even today, if there is a discrepancy between the MRI and the operative findings, we closely review the MRI to learn from the discrepancy.

**b. Patient Selection for CRS and HIPEC**

After years of this feedback, both of us were able to accurately predict the extent of peritoneal tumor present, especially the extent of small bowel, mesenteric and serosal bowel involvement. It didn’t take long for me to appreciate the superiority of MRI in visualizing tumors especially involving the sub diaphragmatic, peritoneum, hepatic capsule, mesentery and serosal surfaces of the small and large bowel. With time, combining both the MRI findings and physical findings, I could adequately determine which patients were and were not candidates for primary cytoreduction. This was especially useful in patients with aggressive histology (poorly differentiated, high grade serous, signet ring, and mesothelioma). Therefore, based on the MRI findings I felt confident in not recommending that patients undergo initial cytoreductive surgery when MRI revealed disease that could not be completely resected. These patients were referred to medical oncology for consideration of systemic chemotherapy. Suitable candidates were then evaluated after three to six courses for response. If there was a significant clinical response, with supporting MRI imaging, indicating a significant reduction in
tumor burden, the patients were reconsidered for cytoreductive surgery and intraperitoneal chemotherapy (Fig. 5). Therefore a significant number of patients have been spared unnecessary surgeries.

We have found that patients who are at high risk of peritoneal spread could be adequately followed with MRI. This includes patients, who at the time of appendectomy for acute appendicitis or appendiceal mass subsequently were found to have perforation or extraluminal intraperitoneal mucous with or without epithelial cells, from an appendiceal carcinoma or low-grade appendiceal mucinous neoplasm. Confirmatory development of peritoneal enhancement or restricted diffusion is highly indicative of disease recurrence. These patients should then undergo cytoreduction surgery and HIPEC.

c. Surveillance following HIPEC

We recommend that patients after CRS and HIPEC be followed every six months with MR imaging and tumor markers. To date only 20% of the patients who have been followed using this schema subsequently needed cytoreductive surgery and HIPEC.

Progressive disease after extensive cytoreductive surgery and HIPEC is usually manifested by increased peritoneal enhancement in 1 or multiple intraabdominal sites on MR imaging. This change may be seen before a rise in serum tumor markers. If this is identified a short interval repeat MRI is performed in 3-4 months to get a feel for the biologic behavior of the tumor. If there has been slow progression the patient is considered for second cytoreductive surgery and
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HIPEC. If there has been significant progression or significant involvement in the small bowel region (sites 9-12) second cytoreduction is not considered and the patients will receive systemic chemotherapy for 3-4 cycles and then restaged for possible surgery if they have had an excellent clinical response.

Patients with early extensive progressive disease (short disease-free interval of less than 1 year) who have peritoneal mucinous carcinomatosis, colorectal, ovarian, mesothelioma are referred for palliative systemic chemotherapy.

Patients with early progressive disease limited to 3-4 regions, low grade histology with minimal small bowel involvement or high-grade tumors with limited intraperitoneal spread are offered a second cytoreductive procedure with possibility of undergoing a second HIPEC depending on the volume and sites of disease recurrence.

Patients with late progressive disease (long disease-free survival) greater than 2 years with extensive intraabdominal disease without significant mesenteric or serosal small bowel disease are considered for a second or third cytoreductive surgery and HIPEC if they are in good health and a R0/1 resection can be accomplished without the need for extensive small bowel resections.

Patients with indolent disease, including appendiceal disseminated peritoneal adenomucinosis or low-grade peritoneal mucinous carcinomatosis, can be followed with serial MR imaging until signs of progression. Patients referred to us with minimal disease burden e.g. patients who have undergone an interval appendectomy and found to have a low grade appendiceal neoplasm, without
gross perforation, with or without limited acellular mucinous peritoneal deposits are also followed with MR scanning every 6 months and are only considered for cytoreductive surgery and HIPEC when the MRI detects progressive peritoneal spread.

8. Limitations of MRI

MRI has many advantages but also limitations. Some limitations are well known – the more limited availability, the higher cost, and the longer examination times, which are real considerations. The MR radiologist will require some additional time and substantial training to learn the subtleties of peritoneal MRI interpretation [39].

MR images are more susceptible to motion and breathing artifacts, which are more frequent in debilitated patients and at the end of the examination when the patient is fatigued. Artifacts related to bowel peristalsis, can reduce the quality of the image. Antiperistaltic agents such as buscopan can transiently reduce bowel peristalsis, improving image quality.

In patients with large volume ascites the dielectric artifact or “black hole artifact” can significantly degrade image quality. The dielectric artifact is much more pronounced on 3.0-T scanners compared to 1.5-T scanners. It is more likely to occur on T2 images, which have a longer time of relaxation. Some centers recommend paracentesis in non-pseudomyxoma peritonei patients prior to imaging on 3.0T MR scanners to reduce artifact-producing ascites prior to MRI on
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3.0-T scanners. To eliminate this problem we perform all of our peritoneal MR examinations on a 1.5T MR scanner with high performance gradients.

9. Conclusion

MRI can be a powerful tool to assist the surgeon evaluating patients before and after CRS and HIPEC. With careful attention to the details of patient preparation, MR scanning protocols and techniques, and MRI interpretation, MRI can provide essential information regarding the volume and distribution of peritoneal tumor. Ongoing collaboration and communication between oncologic surgeon and radiologist will help to optimize patient selection for HIPEC and for surveillance following successful treatment.
Disclosures:

Conflict of interest statement

All authors have no financial conflicts of interest or financial ties to disclose.

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Ethical approval

Not applicable

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None
11. References


[20] Low RN, Gurney J. Diffusion Weighted MRI in the Oncology Patient:


## 12. Table

### Table 1: Peritoneal MR Imaging Protocol

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<th>Pulse Sequence</th>
<th>TR (msec)</th>
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<th>Gap (mm)</th>
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<td>4</td>
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<tr>
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<td>36</td>
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<td>2</td>
<td>36</td>
<td>90</td>
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</table>

- **Gadolinium Injection**
  - **3D FSPGR Dixon**
    - 7.06 2.39 320x288 1 4.4 -2.2 36 12
  - **2D SGE**
    - 125 minimum 192 1 8 2 36 80

<table>
<thead>
<tr>
<th>Pulse Sequence</th>
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<td>Axial and Coronal</td>
<td>Dixon Water</td>
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</table>

- **SGE** = spoiled gradient-echo
- **FRFSE** = fast recovery fast spin echo
- **LAVA** = Liver Acceleration Volume Acquisition
- **3D FSPGR Dixon** = 3D fast spoiled gradient-echo with Dixon water reconstruction (LAVA-FLEX, mDIXON, T1 Dixon)

Parallel Imaging is used on all sequences.
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12. Figure captions

**Figure 1**: Graph compares the preoperative CT PCI (yellow), MRI PCI (maroon), and surgical PCI (blue) in 22 patients undergoing CRS and HIPEC. MRI PCI and Surgical PCI were in good agreement while CT PCI consistently underestimated the amount of peritoneal tumor (from reference [1]).

**Figure 2**: 63-year-old man with pseudomyxoma from appendiceal mucocele. CT image (left) shows perihepatic and perisplenic low-density material that scallops the contour of the liver (arrow). On CT it is difficult to distinguish mucinous ascites from mucinous tissue. Delayed gadolinium MRI image (right) shows moderately thick and diffuse enhancing peritoneal tumor (arrows) in the upper abdomen, especially with regard to the liver capsule. Mucinous ascites does not enhance with gadolinium. The conspicuity of enhancing peritoneal tumor on MRI markedly improves tumor depiction compared to CT.

**Figures 3**: 56-year-old man with malignant mesothelioma. CT (top left) and PET-CT (top right) images do not show serosal or peritoneal tumor. Delayed gadolinium MRI image (bottom left) depicts an irregular tumoral thickening of the jejunal bowel serosa and its mesenteric border (arrows) which was confirmed at lapartomy (bottom right).

**Figure 4A**: 57-year-old woman with appendiceal cancer. Diffusion-weighted MRI b800 (top left) and delayed gadolinium (top right) MRI images show right and left subphrenic tumor (arrows).
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Diffusion-weighted MRI b800 (bottom left) and delayed gadolinium (bottom right) MRI images show right lower quadrant tumor involving the distal ileum and mesentery. No bulky mesenteric tumor was noted on MRI. 2 of 4 small bowel segments were involved with serosal tumor.

**Figure 5: 66-year-old woman with ovarian cancer status post multiple rounds of chemotherapy.**

Diffusion-weighted b800 (left) and delayed gadolinium-enhanced MRI (right) images show abnormal small bowel and mesentery and small bowel representing residual peritoneal tumor (arrows). At laparotomy, there was no gross tumor but a peritoneal thickening with no clear viable tumor. The histopathological evaluation of biopsies and surgical specimens confirmed small volume sheets of tumor coating the small bowel and mesentery shown on the MRI. Laparotomy and histopathological evaluation. The surgeon's operative assessment of tumor is much more challenging with preoperative chemotherapy, making the MRI results even more important.