Radiologic staging of peritoneal and retroperitoneal disease

Peritoneum und Retroperitoneum: Seltenes aber Wichtiges beim Staging

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ABSTRACT

Peritoneal and retroperitoneal tumors consist of a heterogenous group of benign and malignant lesions of different origin. Due to often complex multidisciplinary treatment concepts in patients with peritoneal surface malignancies radiological imaging plays a pivotal role regarding the therapeutic options. Moreover, tumor entity, abdominal tumor distribution and common as well as rare differential diagnoses have to be taken into account. Using different radiological modalities non-invasive pretherapeutic diagnostics might be significantly improved.

Key Points:

- Diagnostic CT is a valuable part of the initial diagnostic approach to peritoneal surface malignancies.
- Sensitivity might be increased by the additional use of dwMRI and PET/CT considering tumor entity and individual diagnostic issues.
- The Peritoneal Cancer Index (PCI) should be determined independent of radiologic modality.

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ZUSAMMENFASSUNG

Tumoren des Peritoneums und des Retroperitoneums bilden eine heterogene Gruppe von Raumforderungen unterschiedlicher Ätiologie und Dignität. Bei Patient*innen mit primären peritonealen Malignomen oder peritonealer Metastasierung spielt die Schnittbildgebung aufgrund oftmals komplexer multimodaler Therapiekonzepte eine entscheidende Rolle für die Festlegung der therapeutischen Optionen. Zudem müssen beim Staging die Tumorentität, das Befallsmuster und die oft seltenen Differenzialdiagnosen besonders beachtet werden. Durch den adäquaten Einsatz verschiedener radiologischer Modalitäten kann die nicht invasive prätherapeutische Diagnostik erheblich verbessert werden.

ABBREVIATIONS

CC	Completeness of cytoreduction score
CT-PCI	Computed tomography peritoneal cancer index
DMPM	Diffuse malignant peritoneal mesothelioma
FDG-PET	^{18}Fluorodeoxyglucose positron emission tomography
HIPEC	Hyperthermic intraperitoneal chemotherapy
IMS	Inframesocolic space
lapPCI	Laparoscopic peritoneal cancer index
LS	Lesion score
LAMN	Low-grade appendiceal mucinous neoplasm
MRI-PCI	Magnetic resonance imaging peritoneal cancer index
PCI	Peritoneal cancer index
pmCRC	Peritoneal metastasis of colorectal cancer
PMP	Pseudomyxoma peritonei
SMS	Supramesocolic space
CRS	Cytoreductive surgery

Background

In addition to histological diagnosis, preoperative imaging diagnosis plays a critical role in the treatment of peritoneal malignancies as well as other peritoneal and retroperitoneal diseases. Multimodality therapy concepts such as cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for primary peritoneal malignancies and peritoneal metastasis require consistent preoperative patient selection and thus place high demands on accurate staging [1].

The indications for surgical intervention as well as interdisciplinary therapy concepts diverge greatly depending on the tumor entity and the peritoneal disease pattern [2–4]. At the same time, radiological diagnosis of peritoneal tumor involvement is particularly challenging, not least because of frequent small-nodule tumor manifestations and numerous differential diagnoses. This is especially true for limited peritoneal tumor involvement without associated symptoms such as ascites or stenosis with congestive ureters, cholestasis or ileus. Continuously improving radiological techniques and the combination of different diagnostic modalities can help to further optimize the accuracy of noninvasive pretherapeutic diagnostics.

Diseases of the Peritoneum and Retroperitoneum

Masses of the peritoneum and retroperitoneum are a heterogeneous group of partly solid, partly cystic tumors of different etiology and dignity (▶ **Table 1**) [5, 6]. Peritoneal metastases of diverse primary tumors are the most common malignant peritoneal tumors. These include in particular ovarian, gastric and colorectal carcinoma, but also many other gastrointestinal, pancreatobiliary and urogenital tumors. There are also rare diseases such as pseudomyxoma peritonei (PMP) and primary tumors of the peritoneum such as serous-papillary adenocarcinoma of the peritoneum and diffuse malignant peritoneal mesothelioma (DMPM). Typical radiological signs of peritoneal metastasis include the presence of ascites, tumor infiltration of the greater omentum ("omental cake"), invasion of the mesentery with thickening and contrast enhancement, and evidence of peritoneal tumor nodules with contrast enhancement. These can be mimicked by other malignant as well as benign diseases of the peritoneum. These include lymphoma, posttraumatic or postoperative splenosis, peritoneal tuberculosis, or peritoneal leiomyomatosis [7]. This further complicates accurate radiological staging. A typical therapy-relevant misinterpretation is, for example, the diagnosis of a putative subcapsular hepatic metastasis in a peritoneal tumor involvement of the right upper abdomen with or without infiltration of the liver capsule (▶ **Fig. 1**) [8].

▶ **Fig. 2** summarizes the diagnostic procedure for peritoneal masses in an algorithm. Differentiation from retroperitoneal lymph node metastases is particularly important in the staging of peritoneal malignancies. More detailed diagnostics of retroperitoneal tumors, their particularities and differential diagnoses will not be further discussed here. Various diagnostic algorithms have been published for this purpose [9, 10].

Anatomy of the Peritoneum

The anatomy of the peritoneum and the peritoneal and extraperitoneal spaces and boundary structures is crucial for peritoneal metastasis as well as for its diagnosis and possible surgical therapy. The peritoneum consists of the parietal peritoneum, which covers the abdominal cavity in the region of the diaphragm and abdominal wall and in the lesser pelvis up to the peritoneal infold from the inside, and the visceral peritoneum, which covers most of the abdominal organs and the intestinal mesentery. The omental bursa is also covered by the peritoneum. The retroperitoneal space adjoins dorsally. Extraperitoneal organs include kidneys, adrenal glands, ureters and urinary bladder, vagina and prostate, mid and lower rectum, as well as the aorta and vena cava. The intraperitoneal space can be divided into 3 compartments: (1) the supramesocolic space (SMS) with the right SMS including the bursa omentalis and the left SMS, (2) the inframesocolic space (IMS) with the right and left paracolic gutters and the right and left IMS, and (3) the pelvis with the paravesical and the rectovesical or rectouterine space (Douglas pouch). The greater omentum, frequently affected in the course of peritoneal metastasis, is assigned to the supramesocolic space [11].

Peritoneal Metastasis

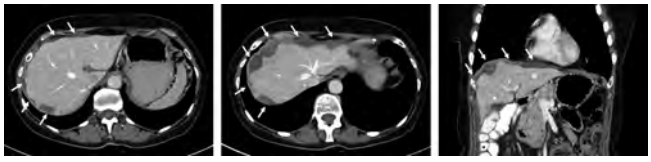
Primary peritoneal malignancies such as diffuse malignant peritoneal mesothelioma (DMPM) or primary serous adenocarcinoma of the peritoneum account for a very small proportion of peritoneal tumor involvement. Low-grade pseudomyxoma peritonei (PMP), which is also rare, usually results from perforation of a low-grade appendiceal mucinous neoplasm (LAMN) and often leads to massive intraperitoneal accumulation of mucin. This tumor entity should be distinguished from mucinous adenocarcinoma with infiltrative invasion of the peritoneum [12]. However, the most

▶ **Table 1** Common and rare peritoneal and retroperitoneal tumors [5, 6].

Origin	Malignant	Benign
Mesothelial	Malignant mesothelioma (epitheloid, sarcomatoid, desmoplastic, biphasic)	Adenomatoid tumors Well differentiated papillary mesothelioma Benign multicystic peritoneal mesothelioma
Epithelial	Primary peritoneal serous carcinoma	Serous borderline tumors Atypic proliferating serous tumors
Sarcomatoid	Liposarcoma (well differentiated, dedifferentiated, pleomorphic, myxoid) Dermatofibrosarcoma protuberans Solitary fibrous tumor (SFT) (myxoid) fibrosarcoma Malignant tenosynovial giant cell tumor Leiomyosarcoma Malignant glomus tumor Rhabdomyosarcoma (embryonal, alveolar, pleomorphic, spindle cell type) Epitheloid Hemangioendothelioma Angiosarcoma Extraskeletal osteosarcoma Malignant GIST Malignant peripheral nerve sheath tumor (MPNT) Ectomesenchymoma Synovial sarcoma Epitheloid sarcoma Alveolar soft tissue sarcoma Clear cell sarcoma (CCS) Extraskeletal myxoid chondrosarcoma Extraskeletal Ewing sarcoma Desmoplastic small and round cell tumor (DSRCT) Extrarenal rhabdoid tumor Perivaskular epitheloid cell tumor Dedifferentiated sarcoma (pleomorphic, epitheloid, spindle cell, round cell)	Leiomyomatosis peritonealis disseminata
Neuroendocrine	Malignant paraganglioma Malignant pheochromocytoma	Paraganglioma Pheochromocytoma Neurofibroma Schwannoma Ganglioneuroma Ganglioneuroblastoma
Secondary	Peritoneal metastasis (PM) Lymph node metastasis Metastases from other organ tumors Pseudomyxoma peritonei (high-grade, low-grade PMP) Lymphoma	
Others, tumor-like		Lipoma Fibroma Lymphangioma Myxoma Hemangioma Solitary fibrous tumor Pelvic fibromatosis Calcific fibrous tumor Desmoid-like fibromatosis Mesothelial hyperplasia Peritoneal cyst Transitional cell metaplasia Cartilaginous, osseous metaplasia Endometriosis Endosalpingiosis Benign histiocytic tumors Ectopic deciduosis Splenosis

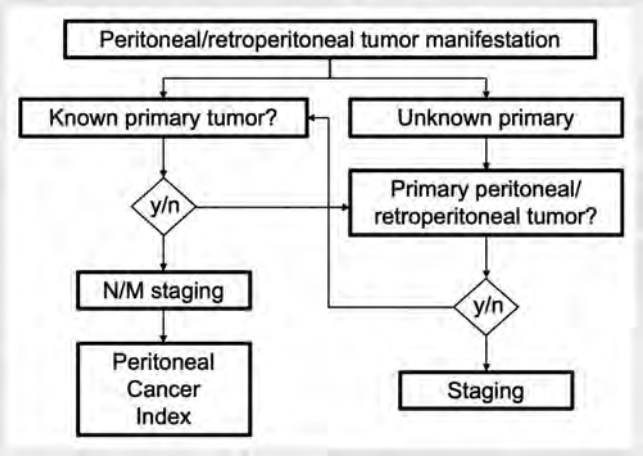
▶ **Table 1** (Continuation)

Origin	Malignant	Benign
Inflammatory		Inflammatory myofibroblastic tumor Sclerosing mesenteritis/peritonitis Retroperitoneal fibrosis (M. Ormond) Abscess Tuberculosis
Cystic		Cystic Lymphangioma Dermoid cyst Pseudocyst Echinococcosis



▶ **Fig. 1** Computed tomography of colorectal peritoneal metastasis in the right upper quadrant with impression ("scalloping") of the liver surface.

common peritoneal malignancies are peritoneal metastases of various gastrointestinal, gynecological and urogenital tumors. The individual stages of classical peritoneal metastasis have been well studied for colorectal carcinoma and other tumors. Initially, there is spontaneous or therapy-associated detachment of individual tumor cells from the primary tumor and their release into the intraperitoneal space. Subsequently, the tumor cells are transported with the physiologically circulating peritoneal fluid first into the lesser pelvis and further via the right paracolic gutter into the subdiaphragmatic space. Through direct and indirect cell-cell interactions, adherence of a subpopulation of circulating tumor cells to mesothelial or endothelial cells occurs initially and eventually leads to invasion of the peritoneal stroma. In principle, lymphatic and hematogenous metastasis may also occur, particularly in the diaphragmatic region, due to infiltration of subperitoneal lymphoid lacunae. These drain predominantly into the mediastinal substernal, parasternal and para-aortic lymph nodes, as well as the lymph nodes at the renal hilus [13]. Both the direction of circulation of peritoneal fluid dictated by gravity, excursion of the diaphragm and anatomy as well as possible atypical lymphatic (and hematogenous) metastasis via the peritoneum should be given special consideration in the diagnostic evaluation of cross-sectional imaging. Peritoneal metastases tend to occur in the lesser pelvis, along the right paracolic groove, subdiaphragmally and perisplenically. The greater omentum is likewise frequently affected. However, the metastasis pattern can vary widely among different tumor entities, but also independently of the primary tumor. It ranges from large singular or confluent tumor nodules, such as are typical for ovarian carcinoma, up to a diffuse small nodular or even sugar icing-like peritoneal tumor infestation, which occurs more frequently in gastric carcinomas and is often



▶ **Fig. 2** Diagnostic algorithm for peritoneal/retroperitoneal tumors.

not detectable on imaging. In addition, typical metastases such as a Krukenberg tumor as an ovarian drop metastasis of gastric carcinoma occasionally occur. In principle, however, the metastatic pattern alone does not allow a valid statement on tumor entity in the absence of evidence of a primary tumor, irrespective of the imaging modality used.

Classification Systems

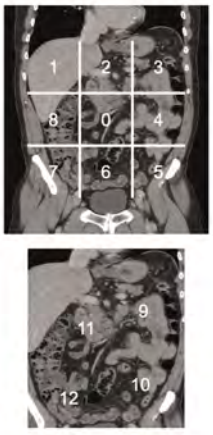
Various classification systems record and quantify peritoneal tumor involvement. The most common application internationally for peritoneal metastasis and primary peritoneal malignancies is the peritoneal cancer index (PCI) developed by Paul Sugarbaker, which is determined intraoperatively after laparotomy or, with methodological limitations, also by laparoscopy (lapPCI). The abdomen is divided into a total of 13 regions (0–12), which include four small bowel regions. Each region is assigned a value between 0 and 3 (lesion score, LS) depending on the size of the visible tumor nodules, resulting in a PCI between 0 and a maximum of 39 depending on the involvement pattern (▶ **Fig. 3**) [14]. The peritoneal cancer index can also be determined preoperatively as CT-PCI using cross-sectional imaging [15]. Koh et al. showed

agreement of CT-PCI with intraoperatively determined PCI in 60 % of cases. Peritoneal tumor involvement on CT was underestimated in 33 % of cases and overestimated in 7 % [16]. For tumor nodules < 1 cm, sensitivity ranged from 9.1 % to 50 %; for tumor nodules < 0.5 cm, sensitivity was only 11 % [15, 16]. Comparable results were found in a study of 52 patients from 16 centers published by Esquivel et al. with also 33 % underestimation of peritoneal tumor involvement. Misclassifications were most common in the right upper quadrant, followed by the left lower quadrant, right lower quadrant, distal jejunum, and distal ileum. However, only 6 patients (12 %) showed clinical relevance with a change in treatment regimen [17]. The correlation of imaging with intraoperative PCI can be increased by using contrast-enhanced and diffusion-weighted MRI compared with CT. Low et al. published an accuracy of MRI-PCI of 84 % or, in a comparative analysis, 88 % compared with 63 % for CT-PCI [18, 19]. Comparable results were also shown for FDG-PET with diagnostic contrast CT [20].

PCI serves not only as a standardized descriptor of the extent of peritoneal tumor involvement, but also plays an important role in treatment decisions, particularly with regard to cytoreductive surgery (CRS) and intraperitoneal hyperthermic chemotherapy (HIPEC). For example, while patients with pseudomyxoma peritonei benefit from CRS and HIPEC even in the presence of very high PCI [3], the multimodal therapy concept should be considered, for example, in gastric carcinoma at most in the case of very limited local peritoneal tumor involvement (PCI < 6). Since, in addition to the tumor entity, many other criteria such as the peritoneal distribution pattern, presence of ureteral stenosis, ascites and small bowel involvement, but also histology, etc. are included in the indication, the specification of tumor-specific cut-off values is only possible to a very limited extent. In 2015, Goeré et al. published a cut-off PCI of 17 for peritoneal metastatic colorectal cancer (pmCRC) [21]. In a recent prospective randomized trial of CRS and HIPEC in pmCRC, only patients with PCI between 11 and 15 benefited in the subgroup analysis [22]. Independently of this, a correlation between the peritoneal cancer index and overall survival has been demonstrated for pmCRC as well as for various other tumor entities [23].

Due to the particular importance of small bowel involvement with regard to treatment options for patients with peritoneal tumor disease, Yan et al. published a CT-based classification system (▶ **Table 2**). This classifies tumor involvement of the small intestine and mesentery into 4 classes (0 to III) based on radiological criteria and thus supports noninvasive preoperative patient selection [24].

Sugarbaker et al. also defined 15 radiologic constellations of findings on CT that make achieving complete macroscopic cytoreduction (CC-0/1) [25] less likely. These include infiltration of the small intestine and mesentery, retroperitoneal tumor manifestations and lymph node filiae, infiltration of the pelvic wall, tumor involvement in the hepatic hilus with possible bile duct obstruction and in the area of the lesser omentum with consecutive gastric outlet stenosis, and various forms of ascites [26]. These can be applied to other diagnostic modalities, as can the PCI and the classification of Yan et al.



13 Regions	Lesion size	Score
0 Central abdomen	No lesion	0
1 Right upper quadrant	Tumor ≤ 0.5 cm	1
2 Epigastrium	Tumor ≤ 5.0 cm	2
3 Left upper quadrant	Tumor < 5.0 cm or	3
4 Left flank	confluent tumors	
5 Left lower quadrant		
6 Small pelvis		
7 Right lower quandrant		
8 Right flank		
9 Upper jejunum		
10 Lower jejunum		
11 Upper ileum		
12 Lower ileum		
PCI = sum of scores over all regions (0-39)		

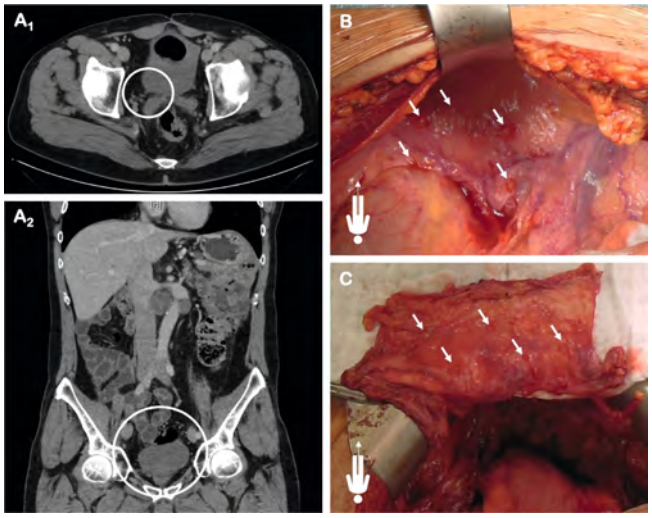
▶ **Fig. 3** Peritoneal Cancer Index (CT PCI).

Cross-sectional Imaging: CT, MRI and PET CT

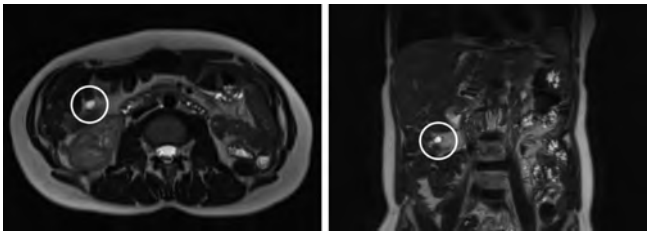
Contrast-enhanced computed tomography has long been considered the gold standard for staging diagnosis of peritoneal metastasis [27]. However, small-nodule tumor involvement is often difficult to detect, and CT findings may underestimate intraoperative PCI (▶ **Fig. 4**). In particular, small tumor recurrence after cytoreductive surgery can easily be missed or not adequately imaged during follow-up CT (▶ **Fig. 5**). Additional diagnostic options are now available as a result of advancements in MRI, particularly the use of diffusion-weighted sequences, and the combination of FDG-PET and diagnostic CT. ▶ **Fig. 6** exemplifies the visualization of metabolically active areas by additional focal enhancement on PET/CT in mucinous adenocarcinoma of the vermiform appendix compared with CT. In a recent meta-analysis, Van't Sant et al. evaluated 24 studies with a total of 2302 patients with peritoneal metastatic gastric, ovarian, colon, rectal and appendiceal carcinomas with regard to sensitivity and specificity of the different sectional imaging techniques. Of the 10 studies with FDG-PET, low-dose CT was used in four studies, contrast-enhanced diagnostic CT in four others and FDG-PET alone without CT in two studies. Of the seven MRI studies, 2 used contrast-enhanced MRI, two used diffusion-weighted MRI, and the remaining three used a combination of both methods. In summary, with regard to the detection of peritoneal metastases, there was a clear advantage of diffusion-weighted MRI with a sensitivity of 91 % (CI 84 %–96 %) versus 78 % for PET/CT and 68 % for CT. Specificity related to the regions was 85 % (CI 78 %–91 %) for MRI, 90 % (CI 80 %–96 %) for PET/CT and 88 % (CI 81 %–95 %) for CT. Based on patients, contrast-enhanced CT achieved a specificity of 94 % and a sensitivity of 70 % [28]. Michielsen et al. also published a sensitivity of diffusion-weighted MRI of 91 % with regard to peritoneal metastasis in patients with ovarian cancer. Sensitivity of 87 % was reported for the detection of retroperitoneal lymph nodes. Diffusion-weighted MRI was superior to PET/CT and CT for both issues [29]. A retrospective analysis published by van't Sant et al. obtained new findings were in 58/158 patients (43 %) with peritoneal metastatic colorectal carcinoma by complementary diagnosis using diffusion-weighted MRI. Therapy planning was modified for

▶ **Table 2** CT scan classification of small bowel involvement, Yan et al. 2005 [22].

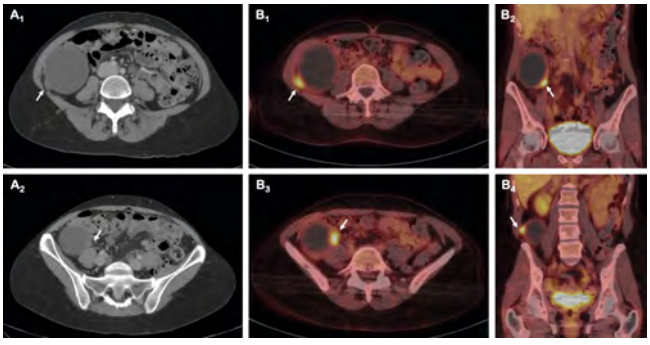
Class	Ascites	Small bowel and mesentery involvement	Loss of mesentery vessel clarity	CT scan interpretation
0	no	no	no	normal
I	yes	no	no	ascites only
II	yes	thickening, enhancing	no	solid tumor nodules
III	yes	nodular thickening, segmental obstruction	yes	loss of normal architecture



▶ **Fig. 4** Synchronous peritoneal metastasis arising from transverse colon carcinoma with small tumor nodules in the small pelvis. **A1**, **A2** computed tomography, **B** before cytoreductive surgery, **C** after complete pelvic peritonectomy. Arrows indicate small peritoneal tumor nodules.



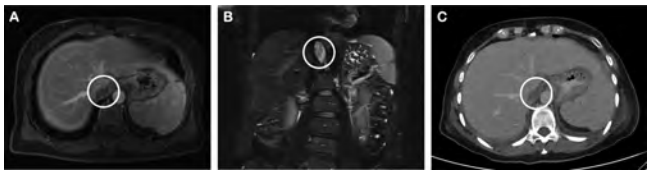
▶ **Fig. 5** MRI of local recurrence of benign multicystic mesothelioma (diameter 8 mm).



▶ **Fig. 6** Mucinous appendiceal adenocarcinoma with intraluminal mucus. **A1–2** contrast enhanced CT, **B1–4** PET/CT.

29 patients (18 %). Three patients were excluded from cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) planned on the basis of contrast-enhanced CT [30]. A multicenter prospective randomized study in the Netherlands is currently investigating whether in the future diffusion-weighted MRI can replace surgical staging in patients with peritoneal metastatic colorectal cancer [31].

A meta-analysis published by Kim et al. showed that FDG-PET with diagnostic CT (PET/CT) had a sensitivity of 87 % and a specificity of 92 % for the detection of peritoneal metastases [32]. Limitations arise in particular in mucinous tumors, which often do not show significant enhancement in FDG-PET [33]. ▶ **Fig. 7** illustrates the improved visualization of mucinous tumor formations on MRI compared with CT using the example of an interaortocaval tumor recurrence in a patient with low-grade pseudomyxoma peritonei (PMP). Superiority of PET/CT in the staging of peritoneal metastasis could only be demonstrated compared with MRI without diffusion weighting [34]. However, based on the data published by Lumpp et al, depending on the primary tumor, PET/CT may have an advantage in detecting peritoneal tumor recurrence after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), possibly due to postoperative changes that are often difficult to classify radiologically [35]. FDG-PET alone without diagnostic CT is no longer important in the diagnosis of peritoneal tumors [36]. A still new examination technique is the combination of FDG-PET with MRI (PET/MRI). Initial published data indicate a higher correlation between radiological and intraoperative PCI in patients with peritoneal metastatic ovarian and endometrial cancer without prior systemic chemotherapy compared with diffusion-weighted MRI [37]. Future studies will need to show whether this benefit is clinically relevant and potentially justifies the costly examination for certain subgroups of patient with peritoneal malignancies. In addition, there is currently only very limited availability of the method, further limiting its diagnostic application.



▶ **Fig. 7** Imaging of recurrent retrohepatic low-grade pseudomyxoma peritonei between abdominal aorta and inferior vena cava. T1- (**A**) and fat-suppressed T2-weighted MRI (**B**) **C** computed tomography.

Conclusions

CT of the thorax/abdomen/pelvis with intravenous, oral and rectal contrast is also the basic diagnostic modality in the staging of primary peritoneal malignancies and in peritoneal metastasis with regard to possible hematogenous metastasis. This modality is also recommended by the Peritoneal Surface Oncology Group International (PSOGI) as an initial diagnostic test for patients with pseudomyxoma peritonei (PMP) and peritoneal mesothelioma [3, 4].

If the findings are ambiguous with regard to peritoneal tumor involvement, diffusion-weighted MRI can be added to the diagnostic workup if the therapeutic consequence is appropriate. FDG-PET with diagnostic CT should be reserved for targeted issues in the context of both initial staging and follow-up, regardless of tumor entity.

Diffusion-weighted MRI should be preferred for patients with disease confined to the peritoneum, such as low-grade pseudomyxoma peritonei (PMP), especially in the context of follow-up, which is often long-term and initially high-frequency, due to its higher sensitivity and against the background of lower radiation exposure.

The imaging peritoneal cancer index (CT-PCI, MRI-PCI) should be determined for better comparability of findings and to determine therapeutic options.

For follow-up after cytoreductive surgery (CRS) or restaging during and after systemic chemotherapy, immunotherapy, or radiotherapy, uniform imaging should generally be established and performed based on the above criteria.

Conflict of Interest

The authors declare that they have no conflict of interest.

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