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ORIGINAL ARTICLE

Correlation of preoperative magnetic resonance imaging of peritoneal carcinomatosis and clinical outcome after peritonectomy and HIPEC after 3 years of follow-up: preliminary results

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Abstract

Purpose: In patients with peritoneal carcinomatosis, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an evolving approach with curative intention. Previous studies indicate a correlation between preoperative magnetic resonance imaging (MRI) and surgical findings regarding the extent of peritoneal carcinomatosis. The aim of this study was to assess retrospectively whether preoperative MRI can predict the outcome and is therefore a suitable tool for patient selection. **Materials and methods**: Fifteen patients with laparoscopically proven peritoneal carcinomatosis were preoperatively examined using a 1.5-T whole-body MRI system. Results were correlated with surgical exploration. Follow-up was done by contrast-enhanced abdominal computed tomography and, if suspicious for recurring disease, laparoscopy or laparotomy. Survival time and interval to recurring disease were correlated with the preoperative peritoneal carcinomatosis index (PCI) on MRI (Spearman's rank correlation). **Results**: In five patients radical resection could not be achieved (PCI 34 ± 6.9); survival time was 78.2 ± 54.1 days. In seven patients recurring disease was found 430 ± 261.2 days after initial complete cytoreduction (PCI 11.6 ± 6.9); survival time was 765.9 ± 355 days. Two patients are still alive after 3 years. Two patients with initially complete cytoreduction are without recurring disease after 3 years (PCI 5 and 12). One patient was lost for follow-up. **Conclusions**: Results of the preoperative MRI correlate well with the surgical PCI, postoperative resection status, and survival time. MRI might be a suitable technique for patient selection when considering peritonectomy and HIPEC. In our patients the outcome seems to correlate well with the extent of peritoneal carcinomatosis found by the preoperative MRI.

Keywords: *Peritoneal carcinomatosis; cytoreductive surgery; magnetic resonance imaging; hyperthermic intraperitoneal chemotherapy.*

Introduction

Peritoneal carcinomatosis (PC) occurs in a variety of malignant diseases at a progressive stage of the underlying disease. In general, patient prognosis is poor when PC is diagnosed[1]. In recent years, peritonectomy with multivisceral resection of all involved viscera combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has been regarded as an approach with curative intention even at such a disease stage[2]. To achieve this goal, complete cytoreduction is mandatory[3–5].

When considering peritonectomy, tumor spread has to be assessed carefully preoperatively to enable optimal

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patient selection and to decide on the surgical approach[6]. A subsequent requirement is preoperative imaging, providing information on localization and extent of peritoneal tumor manifestations[7,8]. For this purpose several imaging modalities have gained acceptance, including computed tomography (CT)[9], magnetic resonance imaging (MRI)[10], hybrid positron emission tomography/computed tomography (PET/CT)[11], and, to a certain extent, ultrasound[12]. The most widespread technique is CT, providing high spatial resolution and availability[9]. Several studies have shown excellent results for MRI, in general attributed to its superior soft-tissue contrast and its capability to provide additional information about tissue characteristics by dynamic contrast-enhanced imaging, thus contributing to the differentiation between malignant and other tissue, i.e., postoperative scars[10,13–16]. Nevertheless, accurate assessment of the extent of PC remains challenging, especially because micronodular spread along the intestinum might escape detection, and the global extent of tumor spread may be underestimated by any imaging technique. To ensure optimal patient selection in regard of high morbidity and costs associated with peritonectomy and HIPEC, correlation between preoperative imaging and clinical outcome must be addressed[17–19].

The aim of our study was to find out whether preoperative abdominal MRI can predict the outcome after peritonectomy and HIPEC, and therefore is suitable for preoperative patient selection. We assessed retrospectively the clinical follow-up of patients after HIPEC over a period of 3 years regarding initial resection status, relapse-free period, time of relapse, and survival time in correlation with the preoperative peritoneal carcinomatosis index (PCI) as assessed by MRI.

Materials and methods

Patient group

Fifteen patients with PC previously proven by laparoscopy scheduled for peritonectomy and HIPEC were included. All patients were willing to participate in the study, and written informed consent was obtained from all of them. Because of the retrospective nature of the study using in-house patient data, no specific approval by the local ethics committee was necessary. Eleven patients were female and 4 were male. The mean age was 57.9 ± 8.8 years (range 43–75 years). PC was caused by ovarian cancer in 6 patients, appendix cancer in 4 patients, colorectal cancer in 3 patients, and tubarian cancer and malignant mesothelioma in 1 patient each.

Examination protocol

To assess the extent of PC, all patients were examined on a 1.5-T whole-body MRI system using 2 phased-array surface coils (Magnetom Avanto; Siemens Health Care, Erlangen, Germany). All sequences were acquired using the breath-hold technique. The examination protocol included dynamic contrast-enhanced high-resolution three-dimensional (3D) T_1-weighted gradient-echo (GRE), T_2-weighted turbo spin-echo, T_2-weighted 3D true-fast imaging, T_2-weighted half-Fourier acquisition turbo spin-echo, and contrast-enhanced T_1-weighted two-dimensional GRE sequences[10]. Prior to contrast injection and 35 s, 70 s, and 105 s after injection of 0.15 mmol gadolinium chelate per kilogram body weight (flow: 2 ml/s), contrast-enhanced T_1-weighted GRE sequences were acquired. Sequence parameters are given in Table 1. Patient preparation included 40 mg butylscopalamine intravenously to reduce intestinal motion artifacts, and oral administration of 2000 ml mannitol solution (2.5%) for intestinal distention.

Peritonectomy

In all patients, the complete peritoneal cavity was explored surgically. Depending on the results, complete cytoreduction was carried out, followed by HIPEC. The extent of PC was assessed according to the PCI, as described by Jacquet et al.[20]. To confirm results, samples of each segment were examined histopathologically. Patients with CC 0 and CC 1 were classified as complete cytoreduction according to the Sugarbaker completeness of cytoreduction classification, and CC 2 and CC 3 as incomplete cytoreduction (CC 0: no residual tumor; CC 1: residual tumor tissue <0.25 cm; CC 2: residual

Table 1 **Examination protocol and sequence parameters used in the study**

	T_2 HASTE	T_2 TSE	T_2 Trufi 3D	T_1 GRE 3D	T_1 GRE 2D
TR (ms)	1100	2200	3.8	2.9	243
TE (ms)	118	95	1.7	1.1	4.1
Flip angle	120°	150°	65°	18°	70°
Slice (mm)	6	6	2	1.8	6
Matrix	256	320	256	256	320
BW (Hz/pixel)	488	300	610	560	140
Acceleration factor	0	2	3	3	2
Voxels (mm)	$2.1 \times 1.6 \times 6$	$1.5 \times 1.2 \times 6$	$2 \times 2 \times 2$	$2 \times 2 \times 1.8$	$1.5 \times 1 \times 6$
Fat saturation	No	No	No	Yes	Yes

T_2, T_2-weighted; T_1, T_1-weighted; 2D, two-dimensional; 3D, three-dimensional; HASTE, half-Fourier acquisition turbo spin-echo; TSE, turbo spin-echo; Trufi, true-fast imaging; GRE, gradient-echo; TR, repetition time; TE, echo time; BW, bandwidth.

Table 2 **Patients' characteristics including baseline PCI, overall survival (OS) as far as monitored, time to relapse (TTR), and initial status of cytoreduction (complete: CC 0, CC 1; incomplete: CC 2, CC 3)**

Patient no.	PCI MRI	Cytoreduction	TTR (months)	OS (months)
1	39	Incomplete	n.a.	5
2	36	Incomplete	n.a.	0
3	4	Complete	18	20
4	5	Complete	n.a.	36
5	3	Complete	11	23
6	38	Incomplete	n.a.	3
7	12	Complete	n.a.	36
8	35	Incomplete	n.a.	3
9	11	Complete	n.a.	n.a.
10	6	Complete	25	36
11	18	Complete	3	12
12	18	Complete	24	36
13	17	Complete	5	12
14	15	Complete	14	36
15	22	Incomplete	n.a.	2

Completeness of cytoreduction (CC): CC 0, no residual tumor; CC 1 residual tumor <0.25 cm; CC 2, residual tumor 0.25–2.5 cm; CC 3, residual tumor >2.5 cm.
In patients with incomplete cytoreduction the time to relapse is indicated as not applicable (n.a.). This is also the case in patients without proof of relapse in the follow-up period. Patient 9 was lost for follow-up. Patients with survival time of 36 months were still alive after 3 years of follow-up.

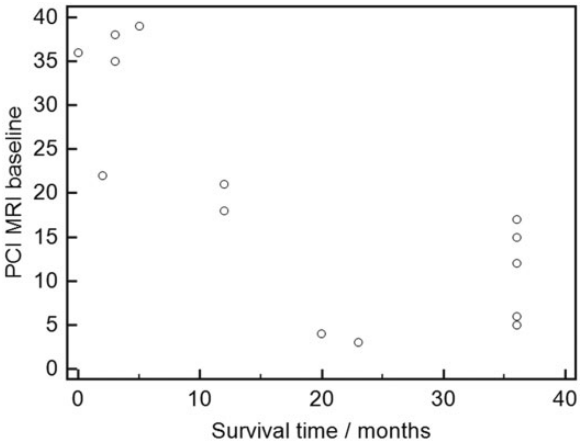

Figure 1 **Spearman's rank correlation of baseline peritoneal cancer index as assessed by MRI and patients' survival time after total peritonectomy and HIPEC reveals a significant negative correlation of PCI and survival (rho −0.748, $P = 0.0021$, 95% confidence interval for rho −0.915 to −0.360).**

tumor 0.25–2.5 cm; CC 3: residual tumor >2.5 cm). The interval between MRI and peritonectomy was 14 ± 24 days.

Image analysis

MR images were assessed by 2 experienced independent radiologists regarding localization and extent of PC in accordance with the PCI. Results were compared with the results of surgical exploration and histopathology.

Signs of PC included ascites, peritoneal thickening and contrast enhancement, peritoneal nodules, peritoneal masses, adhesions of parietal and visceral peritoneum, and pelvic masses indicating relapse of the underlying disease.

Follow-up

Patients were monitored after peritonectomy by regular contrast-enhanced abdominal CT. During the first year after peritonectomy CT was performed every 3 months, during the second year every 6 months, and in the third year after 12 months if no relapse was found during follow-up. Regular follow-up CT was performed 3, 6, 9, 12, 18, 24, and 36 months after peritonectomy. In patients with findings of uncertain status, PET/CT was also performed during the follow-up period. In patients with relapse of PC, examinations including CT, MRI, and PET/CT were performed, depending on therapy and course of the disease. If tissue formations suspicious of recurring PC were found, patients were admitted to laparoscopy with histopathologic assessment to confirm relapse of PC.

Statistics

In patients with histopathologically confirmed relapse of PC, the date of the CT was regarded as the time point of relapse. Consequently, the interval between the day of peritonectomy and HIPEC and the diagnosis of relapse was defined as the relapse-free period, given in days (time to relapse, TTR). The survival time of the patient was defined as the period between the day of peritonectomy and HIPEC, with the day of death also given in days (overall survival: OS). Patients without relapse during 3 years of follow-up were regarded as disease free (disease-free survival (DFS)). TTR, OS, and DFS were correlated with the preoperative PCI assessed by MRI using Spearman's rank correlation. As complete cytoreduction could not be achieved in all patients because of extensive spread of PC, the initial resection status also had to be correlated with the preoperative PCI assessed by MRI, also using Spearman's rank correlation. P values of less than 0.05 were regarded as significant correlation.

Results

MR imaging

Peritoneal carcinomatosis was reliably identified by preoperative MRI in all patients. The mean PCI was 18.6 ± 12.8 (range 3–39). A PCI score of 39 points defines involvement of all 13 segments with singular lesions or conglomerates exceeding 5 cm in size (Table 2).

Peritonectomy

Because of extensive spread of PC, complete cytoreduction could not be achieved in five patients. The resection status was classified CC 2 and CC 3, respectively, as macroscopic tumor manifestations remained. The preoperative PCI of these patients was 34 ± 6.9 (range 22–39). In 11 patients complete cytoreduction classified as CC 0 and CC 1 was achieved (Table 2).

Follow-up

Patients with resection status CC 2 and CC 3 all died within 6 months. The mean survival time (OS) was 78 ± 54.1 days (range 1–150 days). In seven patients with initially complete cytoreduction (resection status CC 0 and CC 1), a relapse of PC was diagnosed in the follow-up period within 430 ± 261.2 days (TTR) after peritonectomy. The preoperative PCI of these patients was 11.6 ± 6.9 (range 3–18), and the mean survival time (OS) was 765.9 ± 355 days. Two patients are still alive after 3 years. Two patients are still without relapse after 3 years (DFS). The preoperative PCI of these patients was 5 and 12. One patient was lost for follow-up. For the remaining 14 patients, the mean survival time (OS) was 565 ± 461 days after peritonectomy and HIPEC (Table 1). The survival time (OS) correlated well with the preoperative PCI score assessed by MRI, Spearman coefficient -0.75, $P < 0.05$, 95% confidence interval -0.915 to -0.360 (Fig. 1). In all patients with a PCI score of up to 18, complete cytoreduction (CC 0, CC 1) was achieved. However, according to our results, in patients with a PCI score exceeding 22, complete cytoreduction could not be achieved, reflected also by a significantly shorter survival time (OS) (Fig. 2). Nine patients found to have intestinal involvement (PCI 24.5 ± 12.4) survived 14.8 ± 16.3 months (OS, 2 alive after 3 years). Six patients without intestinal involvement (PCI 9.3 ± 6.3) survived 25.4 ± 10.5 months (OS, 2 alive after 3 years) (Table 2, Fig. 3).

Discussion

The primary goal of preoperative imaging is to select patients suitable for the intended surgical procedure[21–24], and the secondary target is the prediction of the clinical outcome after therapy[25]. In regard of PC this means to determine in which patients complete cytoreduction could be achieved by means of peritonectomy and HIPEC, and what could be expected regarding relapse of PC and survival time after peritonectomy[26–28]. As parts of the peritoneal cavity are also challenging for surgical assessment, which is

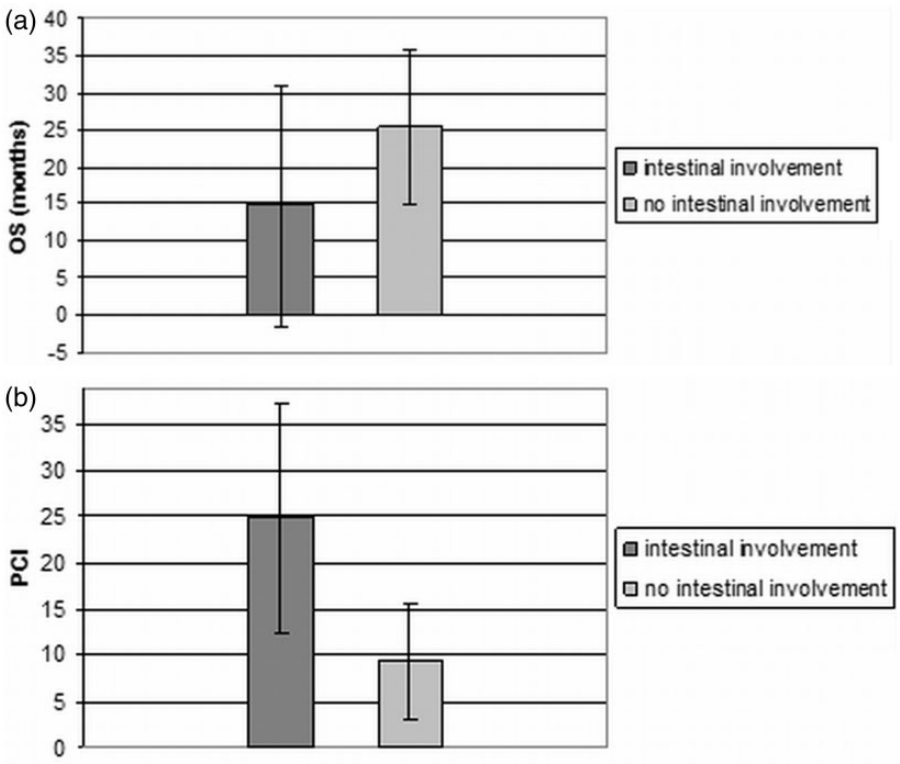

Figure 2 **Overall survival (OS) time given in months for patients with and without intestinal involvement of peritoneal carcinomatosis. The OS is markedly reduced in patients with intestinal involvement compared with those patients without intestinal involvement (a). The preoperative PCI depicted by MRI was significantly higher in patients with intestinal involvement compared with those without intestinal involvement (b).**

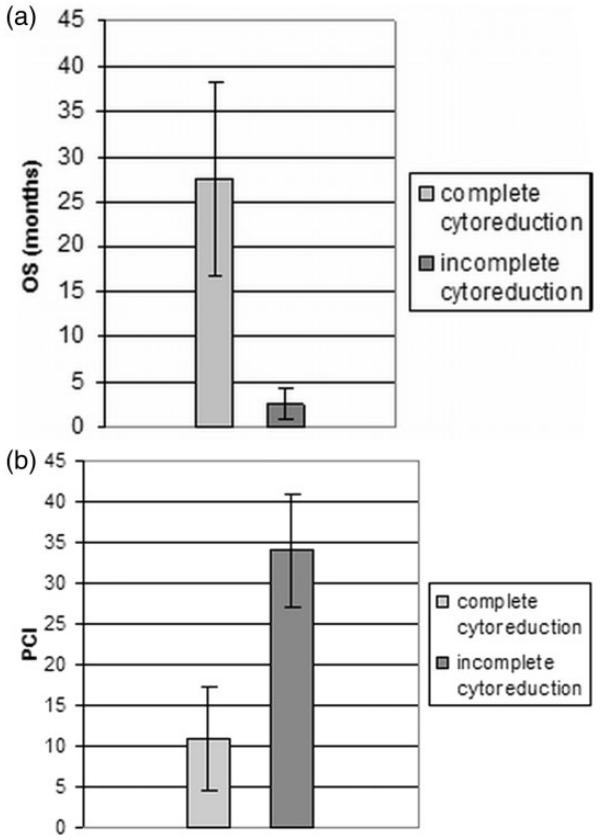

Figure 3 **Comparison of the OS time given in months (a) and the PCI on preoperative MRI (b) for patients with complete and incomplete cytoreduction. The OS and the preoperative PCI are correlated negatively in patients with complete and those with incomplete cytoreduction.**

regarded as the standard of reference, accurate preoperative imaging of PC and correlation with postoperative results is important. Therefore, the aim of our study was to correlate the clinical outcome after peritonectomy and HIPEC, with the extent of PC depicted by preoperative MRI.

Since, in general, the prognosis of patients with PC is poor, even intermediate survival times after peritonectomy might be regarded as a success[1]. The ultimate goal, i.e., cure, might only be achieved in a limited number of patients at such an advanced stage[29].

In five of our patients a complete cytoreduction could not be achieved (CC 2 and CC 3) at all, owing to excessive tumor load reflected by PCI scores 34 ± 6.9 (range 22–39). Consequently, survival time (OS) of these patients was significantly shorter (78 ± 54.1 days, range 1–150) compared with those with complete cytoreduction (CC 0 and CC 1) (765.9 ± 355). Moreover, excessive tissue resection necessitated by the attempt of complete cytoreduction is accompanied by increased perioperative morbidity and mortality, as one patient died shortly after surgery (PCI 39). In consequence, in patients exceeding a PCI of about 20 on preoperative MRI, complete cytoreduction seems difficult to achieve, reflected by limited survival time (OS). Therefore, these patients do not seem to derive an advantage from peritonectomy and HIPEC, but harbor the risk of perioperative morbidity and mortality, so might presumably fare better with systemic chemotherapy.

Patients with complete cytoreduction (CC 0 and CC 1) survived significantly longer than those with incomplete cytoreduction (CC 2 and CC 3). These patients had significantly lower PCI scores on preoperative MRI (11.6 ± 6.9, range 3–18). Consequently, these patients seem to benefit from peritonectomy and HIPEC, reflected by significantly longer survival time (OS), partially even relapse free (DSF), justifying the curative intention. In our patient group the highest PCI with complete cytoreduction was 18 and the lowest in the group with incomplete cytoreduction was 22, indicating that complete cytoreduction seems to be less probable in patients with extensive PC depicted by MRI. Nonetheless the preoperative MRI has to be analyzed individually, as resectability does not only depend on the total amount of tumor tissue represented by the PCI but also on tumor localization. Peritoneal carcinomatosis with limited PCI could also be nonresectable because of extensive intestinal involvement or infiltration of the liver hilum. This at least was not the case in our patients. Extensive intestinal involvement always was associated with higher PCI scores, owing to extensive tumor spread over the peritoneal cavity, although this could not be ascertained from our results because of the limited number of patients. Moreover, the correlation of preoperative PCI and postoperative survival time seems not to be linear, but to decrease significantly in patients with a PCI exceeding approximately 20.

Regarding the time to relapse (TTR) of PC, there was a tendency that patients with higher PCI are more likely to have a relapse, but we did not find a significant correlation between preoperative PCI and TTR (Figs. 4 and 5). This result might arise from the small patient group. However, the probability and time of relapse might also be influenced by factors other than the preoperative PCI, such as tissue biology of the underlying malignancy, localization of tumor manifestations, and the surgical resection itself. Those patients without hint for relapse (DFS) after 3 years of follow-up had a preoperative comparably low PCI score, although not the lowest within the study group, also indicating no linear correlation between preoperative PCI score and clinical outcome.

Compared with [^{18}F]fluorodeoxyglucose (FDG)-PET/CT, MRI provides slightly inferior results in the primary staging of PC, although the difference is not significant[30]. Both methods can be regarded as suitable in the preoperative assessment of PC when considering cytoreductive surgery and HIPEC. Yet there are differences attributable to specific advantages and limitations of both imaging modalities. FDG-PET/CT is more robust and covers the

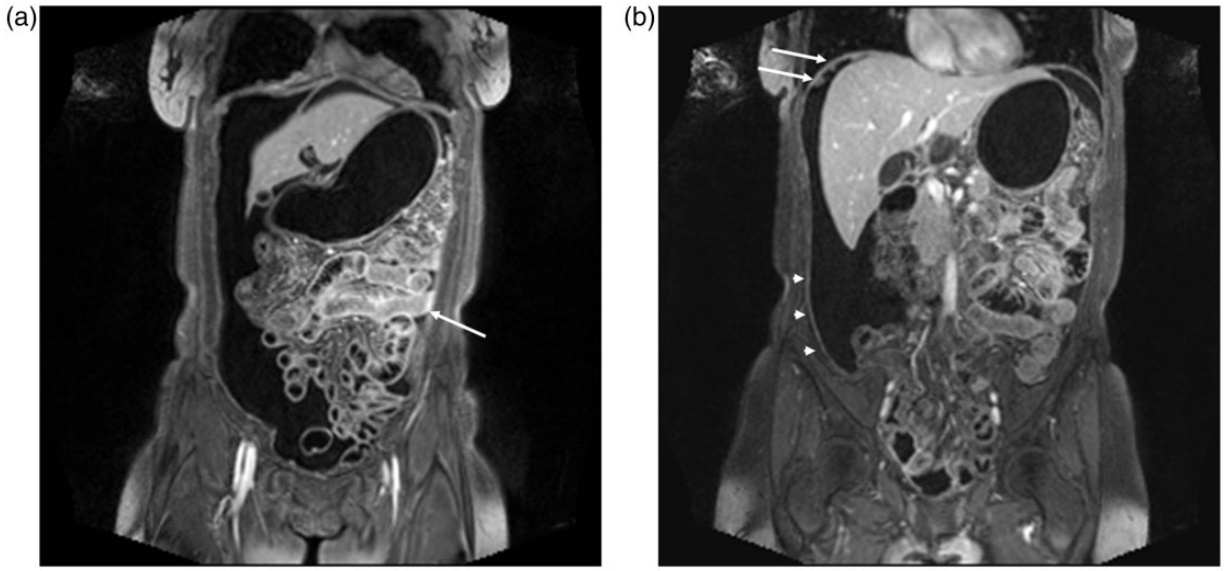

Figure 4 **MR images of a 55-year-old female patient with peritoneal carcinomatosis from ovarian cancer depict segmental thickening and increased contrast enhancement of the small bowel (a, arrow) as sign of intestinal involvement. Macronodular manifestations can be identified below the right diaphragm (b, arrows). Regional increased contrast enhancement of the parietal peritoneum also indicates micronodular spread (b, arrowheads). The baseline PCI was 17 points. After initially complete cytoreduction, relapse of peritoneal carcinomatosis was detected 5 months later, and the patient survived for 12 months.**

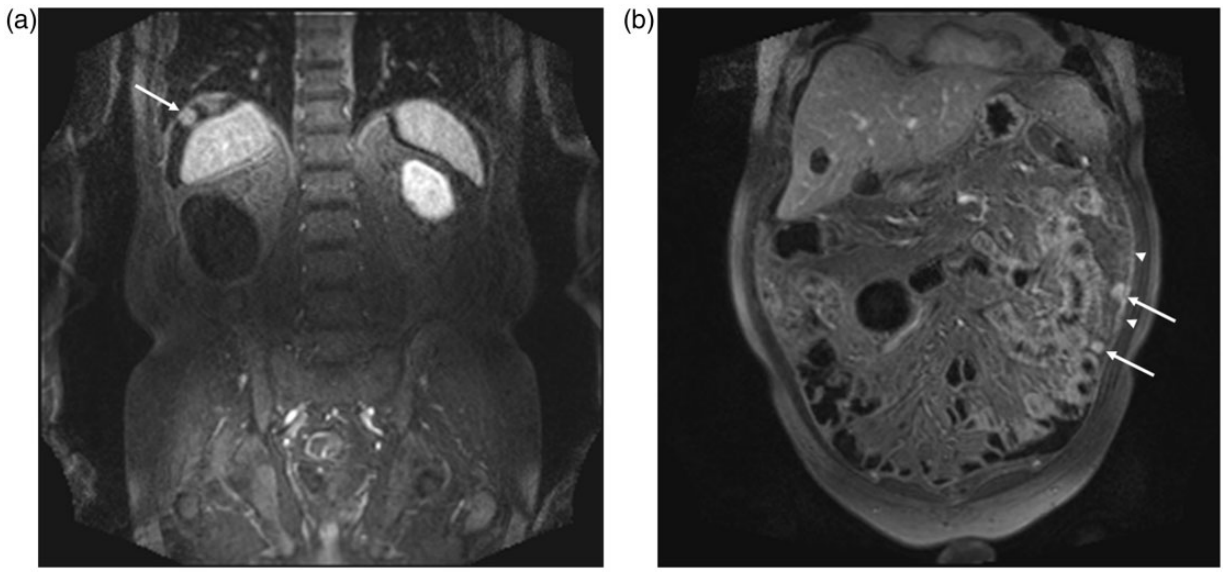

Figure 5 **MR images of a 63-year-old male patient with peritoneal carcinomatosis arising from rectal cancer and a baseline PCI of 18 points depict macronodular manifestations along the right hemidiaphragm (a, arrow) as well as in the left flank (b, arrows). There is also a regionally increased contrast enhancement along the parietal peritoneum of the left flank indicating diffuse tumor spread. Thickening of the intestinal wall and increased contrast enhancement in parts of the left abdomen are suspicious of small bowel involvement. Despite complete cytoreduction, a relapse of peritoneal carcinomatosis was already detected after 3 months, and was lethal after 12 months.**

whole body in identifying extra-abdominal tumor manifestations, whereas MRI offers high sensitivity for liver metastasis and small perihepatic peritoneal implants, owing to its superior soft-tissue contrast[30].

In the follow-up after cytoreductive surgery and HIPEC, imaging becomes more challenging. Extensive post-therapeutic tissue alterations caused by inflammatory reaction and scar tissue might mimic or conceal the relapse of PC for imaging techniques relying on morphologic assessment[8]. Therefore, additional tissue characterization is desirable regarding perfusion that might be provided by MRI or glucose metabolism provided by FDG-PET/CT. In our study, however, regular CT was used in the follow-up, which might have delayed the identification of recurring PC. After peritonectomy and resection of the greater omentum, typical manifestations of PC can no longer be found, a relapse infiltrating along the small bowel instead of the surface of the visceral peritoneum becomes far more difficult to identify when relying on pure morphologic assessment. Thus, PET/CT or PET/MRI might be the method of choice in the follow-up after peritonectomy and HIPEC.

Limitations of our study are that for statistical purposes we defined the period from peritonectomy to diagnosis of relapse as the relapse-free interval, knowing that the relapse of PC had to have occurred somewhat earlier, although the real date of relapse could not be confirmed by any means. Besides this, the TTR might be prolonged using regular CT during the follow-up period. PET/CT was only performed if findings were suspicious for relapse or equivocal. Otherwise the disease-free interval might have been shortened, as PET/CT could have detected relapse at an earlier stage because of its higher sensitivity for PC compared with other imaging modalities[30]. Moreover, our patient group was inhomogeneous regarding different primary histologies resulting in PC, which might influence postoperative outcome, as the probability and time point of relapse might depend on tumor biology[31–33].

Conclusions

Preoperative dynamic contrast-enhanced MRI might contribute to the selection of patients who benefit from cytoreductive surgery and HIPEC, as the extent of PC depicted by MRI correlates with survival time and resection status after cytoreductive surgery and HIPEC. However, there is no clear correlation between preoperative PCI on MRI and the time point of recurrence of PC, as this might probably depend on more factors than the preoperative PCI alone.

Conflict of interest

The authors declare that they have no conflicts of interest.

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