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Peritoneal mesothelioma and Pseudomyxoma peritonei

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Peritoneal mesothelioma and Pseudomyxoma peritonei

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1 Summary

Peritoneal mesothelioma (MPM) and Pseudomyxoma peritonei (PMP) are the most common primary malignant peritoneal tumors with an overall very low incidence. Pseudomyxoma peritonei occupies a special position in this regard, as its origin is usually not clear and it does not follow a distinct metastatic pattern. It is associated with the formation of biliary ascites, the site of origin is in most cases a mucinous neoplasia of the appendix.

Treatment of primary malignant tumors of the peritoneum should be multidisciplinary and attributed to specialized centers, because the diseases are rare, the treatment is complex, and the available evidence is limited.

Therapeutically, the focus is on cytoreductive surgery, often in combination with hyperthermic intraperitoneal chemotherapy (HIPEC). In systemic therapy, due to the lack of evidence, the treatment of peritoneal mesothelioma is usually analogous to that of pleural mesothelioma. Pseudomyxoma peritonei usually shows a very low growth tendency and proliferation activity.

2 Basics

Primary malignant tumors of the peritoneum are rare tumor entities. A distinction is made between

- Mesothelioma:
  - Highly differentiated papillary mesothelial tumor (WDPMT).
  - Peritoneal mesothelioma (MPM)
  - Inclusion cysts (former name: multicystic mesothelioma)
- Pseudomyxoma peritonei
  - Low grade pseudomyxoma
  - High grade pseudomyxoma

Other forms not addressed in this guideline include:

- Adenomatoid tumor
- Primary "low-grade" serous tumors of the peritoneum
  - Serous borderline tumor
  - Atypical proliferative serous tumor
  - Eventually with implants: epithelial type, desmoplastic type

    - Serous borderline tumor, micropapillary variant/noninvasive micropapillary serous carcinoma
    - Invasive "low-grade" serous carcinoma (LGSC)
- Primary "high-grade" serous carcinoma (HGSC)
- Primary malignant mixed Müllerian tumor (MMMT)
- Primary adenosarcoma of the peritoneum
- Primary teratoma of the peritoneum
- Intraabdominal cystic lymphangioma
- Primary effusion lymphoma of the peritoneum

2.1 Definition and basic data

Peritoneal tumors are rare and are often diagnosed at advanced stages with mostly nonspecific abdominal symptoms. Prognosis varies widely, depending on the stage and underlying histology. The differential diagnostic assignment to the various primary malignancies of the peritoneum as well as the differentiation from secondary malignancies in case of peritoneal metastasis is important.

2.1.1 Peritoneal mesothelioma

Diffuse mesothelioma is a tumor originating from the mesothelial or submesothelial cells of the pleura, peritoneum, or very rarely the pericardium. Under 20% of mesotheliomas originate in the peritoneum. Advanced peritoneal mesotheliomas show a wide variation in prognosis with a median overall survival of 5-30 months [1, 2].

The highly differentiated papillary mesothelial tumor (WDPMT) represents a special clinical and prognostic disease. It occurs predominantly in women of childbearing age and is usually diagnosed as an incidental finding during surgery for another reason. There is not always a connection to asbestos exposure. After complete resection, patients mostly have a good prognosis [3, 4].

2.1.2 Pseudomyxoma peritonei

Pseudomyxoma peritonei is a clinical diagnosis characterized by disseminated abdominal mucinous deposits. The most common site of origin is a mucinous neoplasm of the appendix (low grade appendiceal mucinous neoplasm, LAMN). In perforated LAMN, approximately 65% of patients develop Pseudomyxoma peritonei. If non-perforated LAMN is present, PMP develops in approximately 17% of patients within 50 months [5].

2.2 Epidemiology

2.2.1 Peritoneal mesothelioma

The incidence rate for peritoneal mesothelioma in industrialized countries is reported to be 0.5 to 3 per 1,000,000 in men and 0.2 to 2 per 1,000,000 cases in women [1]. In the United States, the reported incidence is approximately 200 peritoneal mesotheliomas for a total of 2000 mesotheliomas per year.

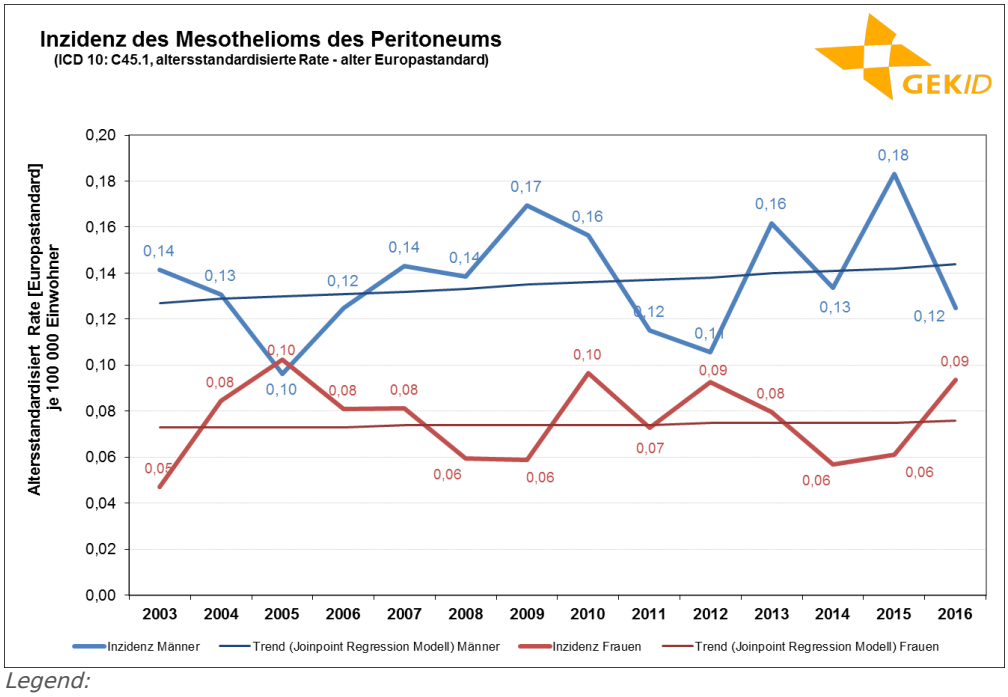
Currently, about 150 cases of the disease are diagnosed in Germany each year. Men are diagnosed about twice as often as women. In both sexes, mesothelioma of the peritoneum accounts for less than 0.5 per thousand of all cancers.

Given such small numbers of cases and the associated annual fluctuations, it is difficult to assess changes over time. The age-standardized incidence rates (Figure 1) in the joinpoint regression model show a slight slope (0.9% per year since 2003) in men and virtually constant disease rates in women (model 0.3% per year since 2003). Both values are not statistically significant.

To a similar extent as the disease rates, the number of cases naturally also shows strong fluctuations (Figure 2). In men, the numbers vary between 52 and 120 cases, in women between 23 and 59 cases. The joinpoint regression model [6] shows a larger increase in the number of cases than in the number of cases (+2.8% in men, +2.3% in women per year since 2003). Again, both values are not statistically significant.

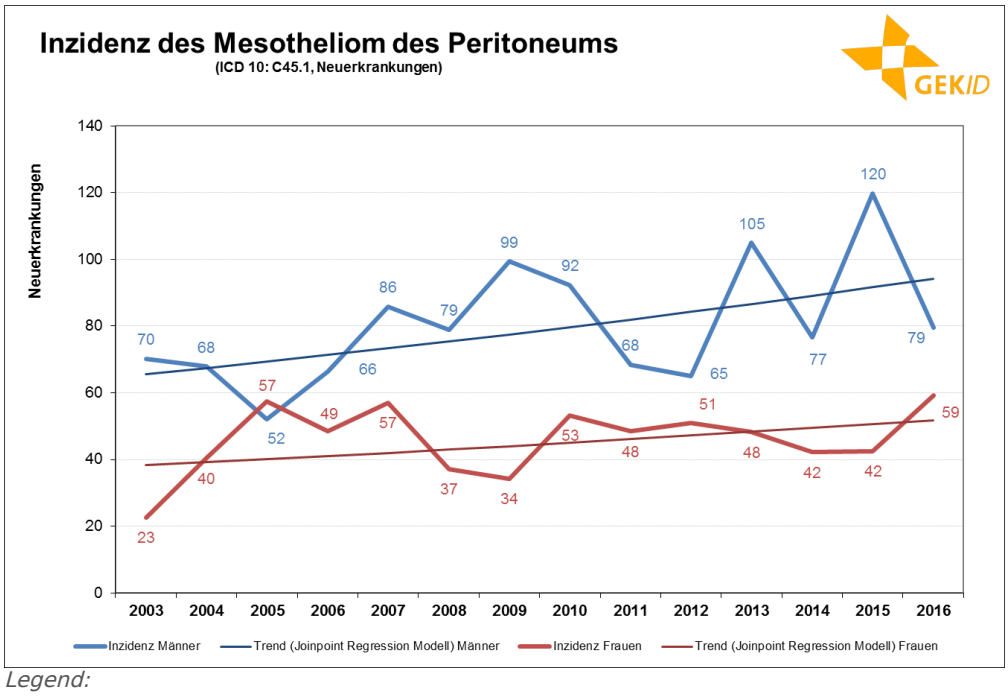
Given the low number of cases, mortality is also low. The official causes-of-death statistics show an average of 28 deaths in men and 19 deaths in women per year for the period 2003-2016. A presentation in diagrams has been omitted here.

Figure 1: Estimated incidence of peritoneal mesothelioma (ICD 10: C45.1) in Germany - Age-standardized rates (old European standard)



Legend:
Source: Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V., special evaluation.

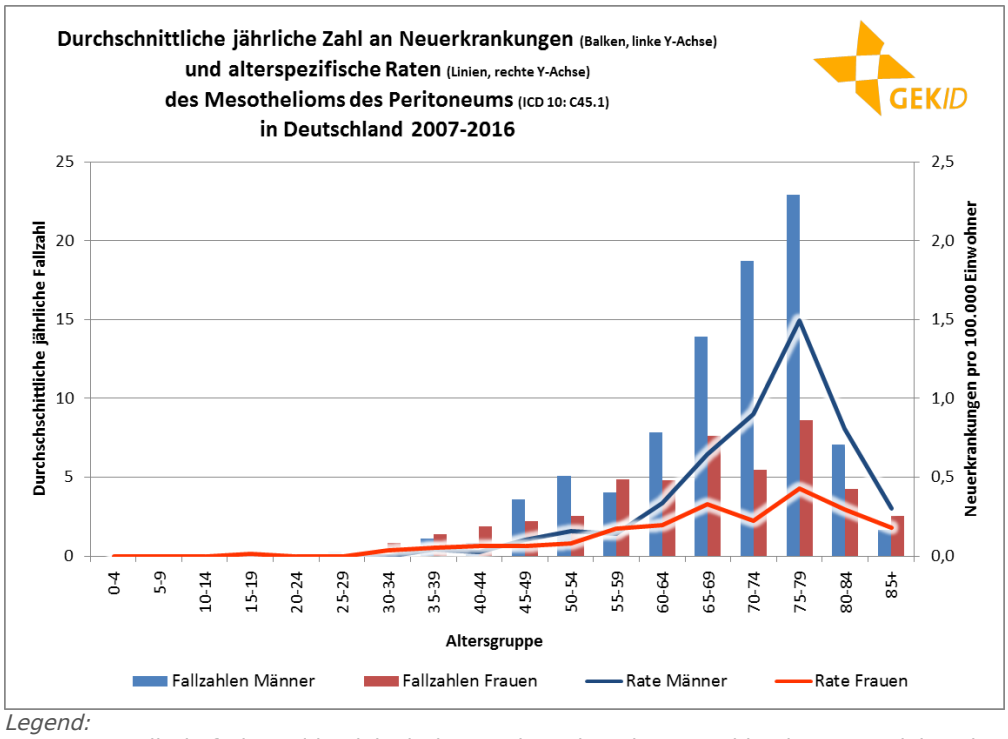
Figure 2: Estimated incidence of mesothelioma of the peritoneum (ICD 10: C45.1) in Germany - number of cases



Legend:
Source: Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V., special evaluation.

With a median age of onset of 72 years (men) and 70 years (women), peritoneal mesothelioma is a disease of older age. The median age of onset is two years and one year higher than the median age of onset of cancer overall. Most cases occur in both sexes in the age group 75 to 79 years Figure 3 (bars). This age group also shows the highest disease rates, i.e., the number of cases relative to the underlying population Figure 3 (lines). Up to the age of 60, the risk of disease is almost equal in both sexes. It starts at about age 30 and increases steadily until age 60. Thereafter, the risk in women continues to rise steadily until the age of 80, while in men the probability of disease increases significantly from the age of 60. From the age of 80, the rates decrease again in both sexes.

Figure 3: Age distribution of incidence of peritoneal mesothelioma (ICD 10: C45.1) - Age-specific case numbers and rates



Legend:
Source: Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V., special evaluation.

Based on the current incidence of the disease and the 14th coordinated population projection of the Federal Statistical Office (G2L2W2, moderate development), an increase in the number of cases to 170 new cases (2040) can be expected in the next 25 years, solely due to the shift in age structures in the population.

2.2.2 Pseudomyxoma peritonei

The actual incidence rate is not known because no uniform classification systems are available. Thus, in Germany, it may be recorded under ICD 10 C48.1, C48.2, and C48.8, but these also include other diseases. The estimated incidence is approximately 2 per 1,000,000 inhabitants per year [7].

Data from the Netherlands [8] show an incidence of mucinous neoplasia of the appendix of 0.3%, of which again 20% progress to PMP.

2.3 Pathogenesis

2.3.1 Peritoneal mesothelioma

Mesotheliomas arise from mesothelial cells. Less than 20% of mesotheliomas are of peritoneal origin; the majority arise in the pleura. Peritoneal mesotheliomas, like pleural mesotheliomas, may be associated with past exposure to asbestos. Despite the ban on asbestos use, the incidence of asbestos-related disease continues to rise. This can be explained by the long latency period after asbestos exposure of 15 to 60 years [9]. Therefore, the main age of manifestation is in the 6th decade of life [10].

Simian virus 40 (SV40) infection is considered another risk factor.

In non-asbestos-associated cases of peritoneal mesothelioma, rearrangements in the anaplastic lymphoma kinase (ALK) gene have been described as the underlying pathomechanism [11].

Germline mutation of BAP1 is a rare predisposing factor for peritoneal mesothelioma [12, 13].

2.3.2 Pseudomyxoma peritonei

PMP are characterized by mucinous biliary ascites, usually following perforation of a mucinous neoplasm of the appendix, leading to the appearance of a so-called "biliary abdomen/carcinoma". This term is a purely macroscopic, i.e., clinical, description. Here, a mucinous neoplasia of the appendix is the most frequent site of origin; in principle, an origin in the entire gastrointestinal tract or also in the area of the ovary is possible. A typical pathomechanism is the occurrence of a "redistribution phenomenon" in which the pseudomyxoma cells distribute and proliferate freely in the peritoneal fluid to predilection sites in the abdominal cavity. Typical predilection sites include the omentum majus and minus and the underside of the diaphragm, especially on the right side [7] or the paracolic gutters, the omentum majus, the right subdiaphragmatic and subhepatic spaces, and the lesser pelvis [14].

2.4 Risk factors

2.4.1 Peritoneal mesothelioma

Exposure to asbestos is considered a recognized risk factor for the development of peritoneal mesothelioma. Thus, peritoneal mesothelioma caused by asbestos is accepted as an occupational disease under section 4105 of the Occupational Diseases Ordinance.

2.4.2 Pseudomyxoma peritonei

Specific risk factors are not known.

3 Prevention and early detection

3.1 Peritoneal mesothelioma

The recommendations for the prevention of peritoneal mesothelioma refer to the avoidance of asbestos exposure. After exposure to asbestos, appropriate screening (G 1.2) or follow-up screening (GVS) is recommended. For early detection measures with regard to peritoneal mesothelioma, recommendations currently exist only in the context of studies for high-risk patients (S2K AWMF Guideline for the Diagnosis and Assessment of Asbestos-Related Occupational Diseases Chpt. 5.9.3).

No screening measures have been established for the general population in Germany.

3.2 Pseudomyxoma peritonei

Specific measures for prevention and early detection have not been established.

However, after perforated LAMN, there is an increased risk of developing pseudomyxoma peritonei (PMP) later on. Therefore, MRI of the abdomen and pelvis is recommended every 6-12 months as a follow-up.

4 Clinical characteristics

4.1 Symptoms

4.1.1 Peritoneal mesothelioma

Peritoneal mesothelioma (MPM) has no pathognomonic symptoms, so diagnosis may be difficult.

Clinically, 3 subgroups can be distinguished

- Patients with abdominal circumferential proliferation: massive ascites formation and large tumor nodules, weight loss, and abdominal pain
- Patients with acute problems who require emergency surgical therapy
- Patients with unclear fever, weight loss, and a picture of inflammatory bowel disease

In early stages, there may be non-specific general symptoms such as fatigue, loss of appetite, weight loss, and unexplained fever (B symptoms).

Malignant ascites is present in up to 90% of advanced MPM. In advanced stages of disease, there may be constriction or infiltration of the bowel, resulting in obstruction with ileus. Dyspnea, abdominal pain, nausea, vomiting, diarrhea, and increasing abdominal circumference with a feeling of tightness (ascites) indicate an already advanced stage, as do non-specific tumor signs such as anemia, thrombocytosis, or eosinophilia [15].

Spread of tumor cells into subcutaneous adipose tissue along incisions is common, so the resection of incision or puncture sites should be part of the surgical treatment.

Approximately 10% of patients are diagnosed with MPM during umbilical hernia repair.

4.1.2 Pseudomyxoma peritonei

The diagnosis is often made as an incidental finding in the case of an unclear tumorous mass in the region of the ovary, in connection with an inguinal hernia, appendicitis or an etiologically unclear ileus, as well as in the context of an extended diagnosis in the case of unclear abdominal complaints.

In 30-50% of cases, there is an increase in abdominal circumference (so-called "jelly belly"). Less common symptoms are abdominal pain, weight loss, micturition problems, constipation, vomiting and dyspnea [7].

5 Diagnosis

5.2 Diagnostics

Peritoneal mesothelioma and Pseudomyxoma peritonei are often associated with nonspecific symptoms. Diagnosis can also be difficult using laboratory chemistry and imaging techniques; therefore, histology is the essential basis for diagnosis.

When performing a diagnostic laparoscopy as part of the spread diagnosis, it is important to place the trocar positions in the midline so that the trocar sites can be excised during subsequent surgery.

In peritoneal mesothelioma, tumor biopsies should be extended to the subperitoneal tissue, as tumor cell invasion is important in making the diagnosis. It is recommended that the biopsies should not be taken in the diaphragmatic region.

An overview of the diagnostic procedures is given in Table 1.

Table 1: Diagnostic procedures and staging

Investigation	Note
Physical examination	
Laboratory (blood)	To assess organ functions (blood count, liver and kidney function parameters, coagulation, TSH). Tumor markers: CEA, CA 19-9, CA 125
CT thorax, abdomen, pelvis with contrast medium (in case of contraindication to iodine-containing KM, alternatively MRI).	Diagnosis of intra-/extra-abdominal tumor manifestations. Before planned resection for accurate assessment of peritoneal tumor burden (PCI) and exclusion of extraperitoneal metastases. Sensitivity depends on lesion size. Vascular imaging before planned vessel resection
PET/CT (PET/MRT)	In individual cases for confirming the diagnosis and staging (especially recurrence) and in unclear cases in conventional imaging. Limited sensitivity in mucinous tumors
Histology	For inoperable tumors prior to initiation of therapy. For operable tumors with unclear findings: Cave intraabdominal tumor dissemination Immunohistochemistry: • Ki67 • Calretinin • WT1 (Wilms Tumor Antigen 1) • Cytokeratin 5/6 • D240 (Podoplanin) At least two positive and two negative markers
Laparoscopy	To assess the extent of the tumor (PCI, see chapter 5.3.2.1)
Gastroscopy, colonoscopy	A complete endoscopy is recommended due to the possibility of secondary tumors in the colon. If a mucinous-sealing ring cell tumor is present in the peritoneum, exclusion of gastric carcinoma is recommended

5.3 Classification

5.3.1 Subtypes

5.3.1.1 Peritoneal mesothelioma

According to the WHO, peritoneal mesothelioma (MPM) is classified into different histologic subtypes by analogy with pleural mesothelioma [16]:

- Epithelioid (75% of MPM with better prognosis): Cells resemble normal mesothelium, growth in tubulopapillary or trabecular patterns. A signet-ring cell component and concomitant desmoplastic reaction may complicate differential diagnosis to adenocarcinoma.
- Sarcomatoid (very rare; poor prognosis): tightly packed spindle cells, occasional evidence of osteoid, chondroid, or muscle fibers.
- Desmoplastic (very rare): irregularly arranged spindle cells in a dense hyaline stroma
- Biphasic/mixed (25%; worse prognosis than epithelioid subtype). At least 10% proportions with epithelioid or sarcomatoid growth.

Diagnosis based on the morphological growth pattern can be difficult, necessitating the use of immunohistochemical and possibly molecular pathological markers [17]. Here, an appropriate panel of markers is used. Mesotheliomas are typically positive for

- Total cytokeratin
- Calretinin
- WT1 (Wilms Tumor Antigen 1)
- EMA
- Cytokeratin 5/6
- D240 (Podoplanin)

and negative for

- CEA
- TTF1
- BerEP4
- B72.3
- MOC31
- BG8
- Claudin4

It is recommended to use two mesothelioma markers and two carcinoma markers.

Recent data identified mutations in the BAP1 gene as a potential prognostic and predictive biomarker in MPM. Here, BAP1 haploinsufficiency was associated with an inflammatory subtype [9, 18, 19].

5.3.1.2 Pseudomyxoma peritonei

Various classification systems are available:

The Ronnett classification [20] divides PMP into 3 categories

- Disseminated peritoneal adenomucinosis (DPAM)
- Peritoneal Mucinous Carcinomatosis (PMCA)
- Mixed type
- The PSOGI (Peritoneal Surface Oncology Group International) has issued a consensus statement [21] and divides PMP into
- low grade
- high grade
- high grade with signet ring cells

5.3.2 Classification according to disease extent

The main problem of all scores is that all mentioned classifications are semiquantitative and above all subjective. In addition, the scores can only be determined intraoperatively, whereas for optimal patient selection the precisely defined tumor burden should ideally already be known prior to laparotomy. This is not always possible, not even by staging laparoscopy.

TNM classification is currently available only for pleural mesotheliomas.

The most widely used score is the so-called peritoneal carcinomatosis index (PCI) according to Sugarbaker et al., see Chapter 5.3.2.1. and Figure 4.

5.3.2.1 Peritoneal carcinomatosis index according to Sugarbaker

The most widely used peritoneal carcinomatosis index (PCI) in clinical practice was described by Jacquet and Sugarbaker in 1996 [22]. The PCI is very detailed with regard to tumor localization, as it divides the abdomen into 13 regions: 9 regions in a grid of the abdomen, each on the right, middle, and left in three tiers - upper abdomen, middle abdomen, and lower abdomen/pelvis, as well as 4 regions of the small intestine (upper and lower jejunum and upper and lower ileum).

In addition, the tumor burden of the individual regions is described and documented in terms of a lesion size score (LSS) with 0-3 points (Table 2).

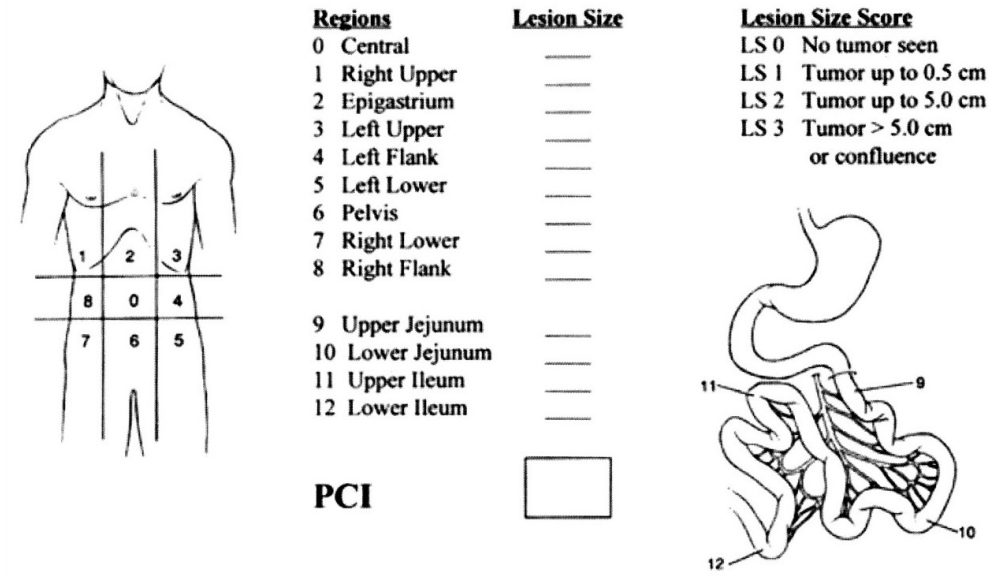
Table 2: Lesion Size Score

Tumor detection	Points
Absence of tumor detection	0
Tumor node up to 0.25 cm	1
Tumor node between 0.25 cm and 2.5 cm	2
Tumor node larger than 2.5 cm	3

The LSS is determined for each region, with the central region numbered 0 and all other regions described clockwise (starting with the upper right field). Each of the 13 regions can have a maximum LSS of 3, so that the maximum PCI is 39.

Several studies have shown that the extent of PCI in the respective tumor entities has a direct proportional impact on resectability and median survival [21].

Figure 4: PCI according to Sugarbaker et al 1996 [22]



5.4 Prognostic factors

Prognostic factors include mitotic activity and number of mitoses as well as nuclear size [23].

The most important prognostic factor is the completeness of cytoreductive surgery in terms of complete macroscopic cytoreduction. Here, the so-called "completeness of cytoreduction" (CCR) is documented, see Table 3.

Table 3: CCR categories

Completeness of cytoreduction (CCR)	Remaining tumor nodes
CCR 0	No remaining tumor nodes
CCR 1	remaining lesions <2.5 mm
CCR 2	remaining lesions 2.5 mm to 2.5 cm
CCR 3	remaining lesions of a size >2.5 cm or confluent foci in the abdomen

In a meta-analysis, a CCR-0/1 situation was achieved in 67% of patients with peritoneal mesothelioma after CRS and HIPEC with a median PCI of 19 [24].

In Pseudomyxoma, mutation of KRAS may play a prognostic role [25]. In addition, elevation of tumor markers CEA and CA19-9 three times above the upper limit of normal range is associated with poorer prognosis [26, 27, 28].

5.4.1 Assessment of the response to therapy

5.4.1.1 Peritoneal Regression Grading Score (PRGS)

The Peritoneal Regression Grading Score (PRGS), a four-level score, is available to assess treatment response (see Table 4) [29]. However, it has not yet been validated.

Table 4: Peritoneal Regression Grading Score (PRGS)

Response of the primary tumor	Vital tumor cells present	Degree of fibrosis
PRGS 1 - complete tumor response	No vital tumor cells	Extensive fibrosis and/or acellular mucin and/or infarct-like necrosis
PRGS 2 - high tumor response	Some vital tumor cells (isolated, small clusters)	Fibrosis and/or acellular mucin and/or infarct-like necrosis predominant over tumor cell content
PRGS 3 - low tumor response	Dominant content of vital tumor cells	Tumor cells dominate over fibrosis and/ or acellular mucin and/or infarct-like necrosis
PRGS 4 - no tumor response	Well visible vital tumor cells, no regressive changes	

5.4.1.2 Degree of regression according to Dworak

The degree of regression after preoperative therapy can be ranked according to Dworak [30] (see Table 5), as has been used mainly for rectal carcinomas after neoadjuvant radiochemotherapy. For mesothelioma, no validated score exists to date.

Table 5: Degree of regression according to Dworak [30]

Degree	Residual status
0	No regression
1	Predominance of tumor cells over peritumoral fibrosis and radiation vasculopathy
2	Predominance of fibrosis over tumor-cell groups, but these are readily apparent in overview magnification
3	Fibrosis with few tumor-cell groups visible only in higher magnification
4	No detection of tumor cells

5.4.1.3 Degree of regression according to Becker

The regression score after preoperative therapy can be given according to Becker [31] (see Table 6), as used for gastric carcinomas after neoadjuvant chemotherapy. For mesothelioma, no validated score exists yet.

Table 6: Degree of regression according to Becker [31]

Degree of regression	Comment
Complete Response (CR) Grade 1a	No tumor cells detectable
Subtotal Response (SR) Grade 1b	In < 10% of the tumor bed, morphologically intact neoplastic cells
Partial response (PR) Grade 2	In 10 to 50% of the tumor bed, morphologically intact neoplastic cells
Low response (MR) Grade 3	In > 50% of the tumor bed, morphologically intact neoplastic cells
No response (NR)	No histological signs of regression

6 Therapy

6.1 Treatment structure

Because of the complex therapeutic options and the rarity of the diseases, recommendations should always be discussed and decided on a multidisciplinary basis.

The therapeutic decision is based on the extent of peritoneal involvement and other disease- and patient-related factors.

6.1.1 Peritoneal mesothelioma

A treatment algorithm for malignant peritoneal mesothelioma is shown in Figure 5.

Therapy of choice for resectable tumors is a combination of cytoreductive surgery (CRS) and intraperitoneal therapy, usually applied as hyperthermic intraperitoneal chemotherapy (HIPEC). Due to the complexity of the disease and the required interventions, patients should be treated in specialized and certified (see also DGAV homepage) high-volume centers. Therapeutic decisions must be made in a multidisciplinary board.

Surgical treatment aims to achieve a complete peritonectomy if possible. This may not be feasible in cases of multiple small bowel involvement. In these cases, serial debulking may also be useful.

Adnexa in young patients are a special problem. In general, bilateral adnectomy is usually also recommended with hysterectomy for peritoneal tumors, due to frequent involvement to achieve complete cytoreduction, and must be discussed individually.

Splenectomy is often necessary in case of extensive tumors. It may therefore be useful to perform vaccinations preoperatively, when imaging or laparoscopy show extensive involvement of the left upper quadrant.

The value of neoadjuvant and/or adjuvant systemic treatment has not been clarified. The proliferation index (determined with the immunohistochemical marker Ki67) allows the identification of high-risk patients and can be used for further differential therapeutic considerations. Data from retrospective evaluations indicate a potential benefit of adjuvant chemotherapy with an improvement in 5-year overall survival (OS) to 67% from 56% without systemic therapy [32].

Patients with rapidly proliferating tumors (Ki67 > 9%), increased PCI (> 17), and a biphasic/sarcomatoid histologic subtype (compared with an epithelioid) were identified as a high-risk population in a retrospective evaluation of 117 patients, with a median OS after surgery and HIPEC of 10.3 months. In these patients, primary preoperative/neoadjuvant systemic chemotherapy with a platinum derivative plus pemetrexed may be considered [33]. Resectability should be re-evaluated after 2-3 cycles. However, other retrospective evaluations did not show a benefit from perioperative chemotherapy [34] or even described a disadvantage with neoadjuvant chemotherapy [32].

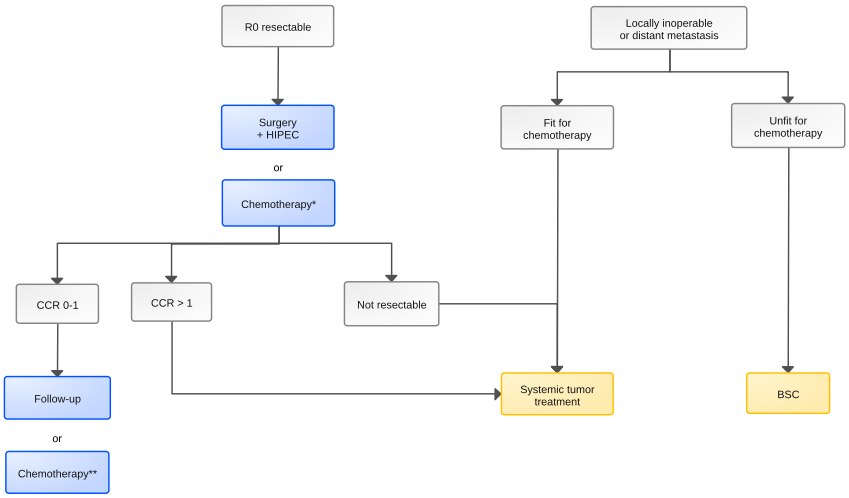
In locally advanced and/or metastatic tumors, systemic therapy with a combination of pemetrexed and a platinum derivative is standard, analogous to pleural mesothelioma. The value of an additional administration of bevacizumab [35] as well as that of a second-line therapy has not been conclusively explored.

6.1.1.1 Immunotherapy

Due to the low incidence of peritoneal compared to pleural mesothelioma, clinical trials of immunotherapy have predominantly been performed in pleural mesothelioma. The randomized multicenter CheckMate-743 trial demonstrated that patients with pleural inoperable mesothelioma achieved significantly longer survival with nivolumab in combination with ipilimumab (n=303 patients) compared with patients receiving chemotherapy alone (n=302 patients) (median overall survival 18.1 months (95% CI 16.8-21.4 vs 14.1 months (12.4-16.2); hazard ratio 0.74 (96.6% CI 0.60-0.91); p=0.0020). It is highly likely that these data can also be applied to peritoneal mesothelioma. However, a recommendation cannot yet be made [36].

In patients with diffuse disease who are not eligible for CRS/HIPEC, pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin/doxorubicin is an option to improve the general condition, especially for ascites control, which can be repeated initially at 6- to 8-week intervals and later at longer intervals [37].

Figure 5: Algorithm for primary treatment of peritoneal mesothelioma



Legend:
curative therapy, palliative therapy;
**Ki67 > 10% and PCI > 17 are associated with a high risk of recurrence and argue for initial chemotherapy. This also applies to comorbidities that do not allow primary resection*
***Ki67 > 10% gives reason for postoperative chemotherapy*
HIPEC = hyperthermic intraperitoneal chemotherapy; CCR = completeness of cytoreduction; BSC = best supportive care.

6.1.2 Pseudomyxoma peritonei

A treatment algorithm for pseudomyxoma peritonei (PMP) is shown in Figure 6.

Therapy of choice is a combination of cytoreductive surgery (CRS) with aspiration of mucinous ascites in combination with intraabdominal chemotherapy (IP). This can be given directly during surgery as HIPEC (hyperthermic intraperitoneal chemotherapy) or as postoperative EPIC (early postoperative intraperitoneal chemotherapy), which aims to improve both overall survival and progression-free survival.

The goal here is to achieve complete macroscopic cytoreduction/tumor removal, which is assessed and documented using the Completeness of Cytoreduction (CCR), see Table 2. CCR is a prognostically relevant factor.

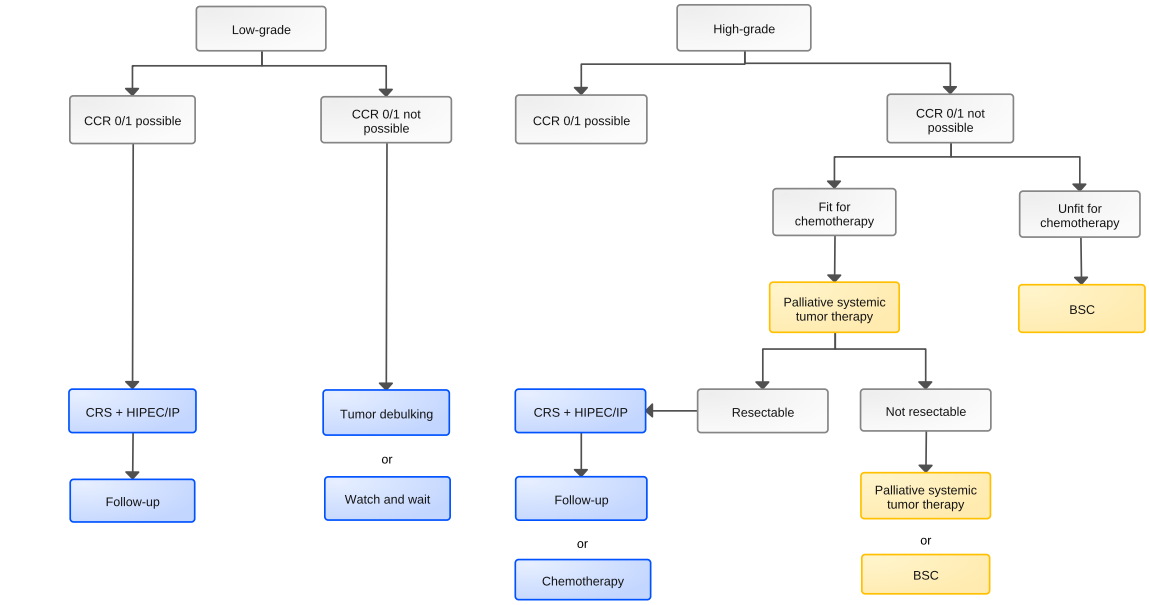
The procedures performed can be extremely complex and time consuming, with median operation times of approximately 9 hours [38].

In locally advanced PMP, tumor debulking may also improve prognosis [39].

Postoperative systemic therapy may help to improve prognosis in high-grade PMP or may be used in unresectable tumors [40]. However, the available data are sparse. Here, most data are available for combination therapies in analogy to systemic treatment for metastatic colorectal carcinoma.

The adnexa are a special problem in young patients. Due to the usually high tumor burden in the minor pelvis, a complete resection can only be achieved by including the ovaries, the uterus and the rectum up to the fold as an extraperitoneal anterior rectum resection en bloc with hysterectomy and salpingoovarectomy. In low-grade PMP with low tumor burden, leaving the left adnexa in place may be considered in individual cases.

Figure 6: Algorithm for primary treatment of Pseudomyxoma peritonei



Legend:
curative therapy, palliative therapy;
CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy; IP = intraabdominal chemotherapy; CCR = completeness of cytoreduction; BSC = best supportive care.

6.2 Treatment modalities

6.2.1 Surgery

Cytoreductive surgery (CRS) is an essential component of multimodal therapy and is recognized as the standard surgical procedure for peritoneal mesothelioma. The most important goal is to remove all tumor nodules as completely as possible. Due to the frequent distribution of tumor nodules over a large area and due to the origin of the primary in the area of the peritoneum itself, a complete peritonectomy should therefore be aimed for.

The largely extraperitoneal dissection and tumor distribution across all quadrants of the abdomen requires special visceral surgical expertise for the operation. Cytoreductive surgery is usually a time-consuming procedure associated with large wound areas. In addition to peritonectomy, which is usually (sub)total, multivisceral resection may be necessary.

Free tumor cells spread in the peritoneal fluid across the abdomen and lead to peritoneal carcinomatosis (complete redistribution phenomenon, CRP) predominantly at the typical predilection sites, so that a complete parietal peritonectomy usually has to be performed [41].

The selection of the surgical approach depends on the localization:

- Upper abdominal peritonectomy
- Lower abdominal peritonectomy
- Interenteric peritonectomy

6.2.1.1 Perioperative management

The extent of cytoreductive surgery and, if necessary, the application of hyperthermic chemotherapy can sometimes lead to considerable fluid, blood, and protein shifts or losses. Extensive hemodynamic monitoring according to the principle of "early goal directed therapy" (EGDT) should be implemented. This includes optimized fluid management and antici-

pation of metabolic changes or hypoalbuminemia [42]. Especially in the HIPEC phase, goal-directed coagulation management plays an important role. Anticipatory temperature management in every phase of the procedure is essential.

With regard to anesthetic management, combined anesthesia should be used if possible: for example, as total intravenous anesthesia (TIVA) combined with thoracic peridural anesthesia (PDA). The use of PDA, carefully respecting contraindications, offers many advantages in this regard. Optimized perioperative pain management with prevention of chronic pain development and (proven) reduction of pulmonary complications, myocardial ischemia or protracted ileus are thereby achievable.

Fast-track concepts or Enhanced Recovery After Surgery (ERAS) programs are intended to lead to a faster regaining of autonomy, a better quality of life and a reduction of perioperative complications during the usually complex surgeries and are regarded as important basic requirements for an optimal postoperative care. The concepts are based on the following key points:

- Optimal analgesia and antiemetic therapy
- Rapid resumption of enteral nutrition
- Avoidance (or fastest possible removal) of drains, tubes and catheters
- Early postoperative mobilization.

The data available to date on ERAS concepts in CRS/HIPEC suggest an improvement of the postoperative course. However, high-quality studies with a high level of evidence are still lacking - not least due to the strong heterogeneity of patients included [43].

6.2.1.2 Preparation Devices

In the context of cytoreductive surgery, blunt dissection is usually used. If the peritoneum cannot be bluntly detached, dissecting instruments are used to separate the layers - for example, the peritoneum from fascia, muscle or fatty tissue.

To minimize blood loss, duration of the procedure and adhesion formation, vessel-sealing instruments can be used. These include high-frequency surgical instruments such as mono- or bipolar coagulation as well as ultrasound-based instruments.

6.2.2 Radiotherapy

For both entities, no conclusive data on radiotherapy are available. Possible indications for palliative radiotherapy are (rare) bone metastases or local complications that cannot be treated surgically and/or with medication.

In patients with peritoneal mesothelioma, irradiation of the trocar sites and puncture sites may be considered postoperatively.

Pseudomyxoma peritonei is hardly sensitive to radiation.

6.2.3 Drug treatment

6.2.3.1 Intraperitoneal chemotherapy

Intraperitoneal administration of chemotherapeutic agents may result in a higher local concentration of cytotoxic drugs in the tumor. A lower expected concentration of cytostatic drugs in the systemic circulation also results in a lower systemic toxicity. The relevant factor here is the first-pass metabolism of the liver, whereby drugs with a high first-pass effect (e.g., 5-FU) lead to fewer systemic side effects than drugs with a low first-pass effect (e.g., platinum derivatives).

High-dose oxaliplatin, as used in the PRODIGE 7- study in HIPEC of colorectal carcinoma, is associated with increased morbidity (in terms of intraoperative bleeding) and should not be used at the indicated dosage [44].

The pharmacokinetic advantage of intraperitoneal administration is greater the slower a drug is absorbed from the peritoneal cavity and the higher the plasma clearance is. Clearance can also be influenced by the choice of the carrier solution, however, a hypotonic solution appears to be associated with an increased complication rate [45].

An overview of cytostatic drugs that can be used for intraperitoneal application is given in Table 7 [43].

Table 7: Cytostatic drugs for intraperitoneal administration

Drug	Dose	Exposure time	Penetration depth	Thermal reinforcement
Cisplatin	20-250 mg/m²	20min to 20h	1-5 mm	+
Carboplatin	200-800 mg/m²	30min to 20h	0,5-9 mm	+
Oxaliplatin	360-460 mg/m²	30min to 20h	1-2 mm	+
Mitomycin C	13-35 mg/m²	90-150min	2 mm	+
Doxorubicin	15-75 mg/m²	90min	4-6 cell layers	+
5-FU	650 mg/m² over 5 days	23h (EPIC)	0.2 mm	(+)
Gemcitabine	50-1000 mg/m²	1-24h	n.a.	n.a.
Pemextrexed	500 mg/m²	24h	n.a.	n.a.

The most common and now routinely used procedure in the respective centers is hyperthermic intraperitoneal chemotherapy (HIPEC, see chapter 6.2.3.1.1.). Early postoperative intraperitoneal chemotherapy (EPIC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC) are currently under development. For both methods, sparse structured data is available yet.

6.2.3.1.1 HIPEC

Heating of the applied fluid leads to increase of cell membrane permeability and can thus enhance the uptake of cytostatic drugs by the tumor tissue. In addition, hyperthermia leads to direct cytotoxic effects through impairment of DNA repair, denaturation of proteins and the induction of heat-shock proteins (HSP), which further enhance the cytotoxic activity of chemotherapy.

Isotonic saline and dextrose-based dialysis solutions are most commonly used.

For HIPEC, cis- or carboplatin is used alone or in combination with doxorubicin, pemetrexed, ifosfamide, or mitomycin.

The duration of HIPEC varies between 30-120 minutes in the different therapeutic protocols. HIPEC itself can be performed open or closed. Advantages of open HIPEC include additional manual manipulation of remaining lesions and intra-abdominal distribution of chemotherapy. The closed version offers higher intra-abdominal pressure and more safety for all actors in the operating room.

6.2.3.1.2 PIPAC

PIPAC (pressurized intraperitoneal aerosol chemotherapy) is a laparoscopic and repetitively applicable procedure in which chemotherapeutic agents are applied directly intraperitoneally in an aerosolized form. Aerosolization and laparoscopic pressure (10-12 mmHg) improve the distribution and depth effect of the substances. The procedure is currently used mainly in patients with advanced and not completely resectable tumors. A combination of cisplatin and doxorubicin is often used, with a significantly reduced dose compared to HIPEC.

6.2.3.2 Systemic therapy

6.2.3.2.1 Peritoneal mesothelioma

No data from randomized trials are available for the benefit of adjuvant chemotherapy. In analogy to pleural mesothelioma, pemetrexed in combination with cisplatin or alternatively with carboplatin may be used. The indication for adjuvant chemotherapy should be made individually in a multidisciplinary tumor board.

For patients with inoperable tumors, systemic therapy with pemetrexed and a platinum derivative is the first choice. In this case, co-medication with folic acid and vitamin B12 should be initiated seven days before the start of therapy, as this significantly reduces the toxicity of pemetrexed.

The value of supplemental administration of bevacizumab has not been established with certainty for peritoneal mesothelioma. However, data from the MAPS trial [35] for pleural mesothelioma have shown a benefit in PFS and OS. Similarly, the value of second-line therapy has not been conclusively established. In pleural mesothelioma, gemcitabine and/or vinorelbine have been used here in small, retrospectively evaluated collectives [46]. A response is practically not achieved, at best a disease stabilization.

In non-resectable pleural mesothelioma, the combination of nivolumab and ipilimumab showed superiority over platinum and pemetrexed chemotherapy in a randomized phase III trial in terms of overall survival and 3-year survival rates, which led to the approval of nivolumab in combination with ipilimumab in this indication [36]. In peritoneal mesothelioma, the efficacy of immunotherapy can thus also be assumed. In this regard, promising initial data from small case series are available for second-line therapy for the combination of tremelimumab and durvalumab [47] as well as bevacizumab and atezolimab [48].

6.2.3.2.2 Pseudomyxoma peritonei

Data on systemic therapy are extremely limited. An analysis of SEER data shows no benefit of systemic treatment in patients with low-grade tumors [49]. For high-grade tumors, chemotherapy may be administered in analogy to colorectal carcinoma/appendix carcinoma. Combinations of oxaliplatin and a fluoropyrimidine are most commonly used.

6.2.4 Special treatment situations

6.2.4.1 Incidental finding of low-grade mucinous neoplasia of the appendix (LAMN).

Approximately 1% of appendectomized patients are diagnosed with LAMN as an incidental finding, and of these, approximately 9% develop Pseudomyxoma peritonei within 2 years [8].

In freshly perforated LAMN or low levels of extra-appendicular mucin, the cellularity of the mucus plays a prognostic role [50]. In acellular mucus, the risk of developing PMP is small (<5%). Some centers perform re-laparoscopy after 9-12 months in such cases, including imaging follow-up by MR.

In general, a "watch and wait" strategy is indicated for incidental findings of LAMN. Regular monitoring by means of cross-sectional imaging (usually CT) and test for tumor markers (CEA) at approximately 6-month intervals is recommended.

7 Rehabilitation

Malignant peritoneal tumors themselves, but also their treatment with sometimes very extensive surgery and chemotherapy, often lead to significant somatic sequelae such as weight loss up to tumor cachexia, postoperative maldigestion, chemotherapy-induced polyneuropathy and general weakness up to a (chronic) fatigue syndrome.

As a result of these side effects and the oncological diagnosis itself, there is also often a high psychological burden and a corresponding need for psycho-oncological co-treatment.

Targeted rehabilitative measures are therefore necessary. These should take place as soon as possible after completion of the primary therapy within the framework of follow-up rehabilitation.

When selecting the rehabilitation facility, the approval of the facility for carcinoma patients by the funding agencies (pension insurance, health insurance) is a mandatory requirement; in addition, the patient's right of wish and choice according to §9 SGB IX should be taken into account.

During rehabilitation, in addition to general therapy services (sports/physio/occupational therapy), comprehensive nutritional counseling should be provided, patients should be included in a teaching kitchen, and it should be possible to administer all scientifically approved diets, from normal whole foods to complete parenteral nutrition.

Every patient should be offered psycho-oncological care.

Rehabilitation facilities should be able to continue systemic tumor therapies, if necessary.

Patients who have not yet reached the statutory retirement age should be informed about benefits for participation in working life within the framework of medical-occupational rehabilitation

(MBOR). Further socio-medical questions as well as the possibly required legal care of the patients should be clarified during the rehabilitation.

8 Follow-up

Imaging follow-up examinations, preferably using CT or MRI scans, are regularly indicated in order to early detect an unfavorable disease course and not to expose patients to ineffective therapies for an inappropriate time, and to open up the chance of switching to a more effective therapy. During ongoing chemotherapy, the patient's general condition and vital bodily functions should usually be checked once a week.

There are no prospective data on the basis of which a specific regimen for follow-up or follow-up can be recommended.

8.1 Peritoneal mesothelioma

In past and ongoing studies, the scheme in Table 8 has proven effective:

Table 8: Structured follow-up and follow-up after surgery for peritoneal mesothelioma

Diagnostic procedure	**Peritoneal mesothelioma After surgery (months)**									
	6	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Physical examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Lab:	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Imaging: CT thorax/abdomen/pelvis Or MRI abdomen	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Imaging follow-up should be continued through the 5-year interval, as late recurrences may occur and can be treated curatively. In young patients, MRI may be preferred instead of CT.

8.2 Pseudomyxoma peritonei

No standardized recommendation is available; follow-up visits should be performed every 6-12 months (Table 9 and Table 10).

Table 9: Structured follow-up and follow-up after surgery for high-grade Pseudomyxoma peritonei

Diagnostic procedure	**High grade PMP After surgery (months)**									
	6	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Physical examination	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Lab: CA 19-9, CEA	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Imaging: CT thorax/abdomen/pelvis	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Table 10: Structured follow-up and follow-up after surgery for low-grade Pseudomyxoma peritonei

Diagnostic procedure	Low-grade PMP After surgery (months)									
	6	12	18	24	30	36	42	48	54	60
Physical examination	X	X	X	X	X	X	X	X	X	X
Lab: CA 19-9, CEA	X	X	X	X	X	X	X	X	X	X
Imaging: CT abdomen/pelvis or MRI abdomen	x	X	x	X		x		X		X

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10 Active studies

currently none

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License [4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Bachleitner-Hoffmann, Thomas	Medizinische Universität Wien	**No**	**No**	**No**	**No**	**No**	**No**	**No**
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Legend:

[1] - Current employer, relevant previous employers in the last 3 years (institution/location).

[2] - Activity as a consultant or expert or paid participation in a scientific advisory board of a company in the health care industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract research organization, or an insurance company.

[3] - Ownership of business shares, stocks, funds with participation of companies of the health care industry.

[4] - Relates to drugs and medical devices.

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[6] - Financial support (third-party funds) for research projects or direct financing of employees of the institution by a company in the health care industry, a commercially oriented contract institute or an insurance company.

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[8] - Personal relationship with an authorized representative(s) of a healthcare company.