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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) is the most common primary malignant tumor of the peritoneum. Pseudomyxoma peritonei (PMP) is the most common tumor that originates from the appendix but usually affects the peritoneum exclusively. Both have a very low incidence. Pseudomyxoma peritonei occupies a special position here, as it has a unique pattern of spread and metastasizes exclusively intraperitoneally. It is associated with the formation of gelatinous ascites; in most cases, the site of origin is a mucinous neoplasm of the appendix.

The treatment of primary malignant tumors of the peritoneum should be multi-disciplinary and carried out at specialized centers, as the diseases are rare, the treatment is complex and the available evidence is limited. Treatment at expert centers can reduce the complication rate and increase the proportion of complete cytoreduction.

The main therapeutic approach is cytoreductive surgery, often in combination with hyperthermic intraperitoneal chemotherapy (HIPEC). In systemic therapy, peritoneal mesothelioma is usually treated in the same way as pleural mesothelioma due to a lack of solid evidence. Pseudomyxoma peritonei generally has very low proliferative activity and is therefore difficult to treat with systemic therapies.

2 Basics

Tumors of the peritoneum are rare tumor entities. A distinction is made between

- Mesothelioma - primary tumor of the peritoneum
  - Highly differentiated papillary mesothelial tumor (WDPMT)
  - Peritoneal mesothelioma (MPM) with subtypes (see below)
  - Inclusion cysts (previous name: multicystic mesothelioma)
- Pseudomyxoma peritonei: usually originating from the appendix - peritoneum as the primary site of metastasis
  - Low-grade pseudomyxoma
  - High-grade pseudomyxoma

Other forms not addressed in this guideline:

- Adenomatoid tumor
- Primary "low-grade" serous tumors of the peritoneum
  - Serous borderline tumor

    - Atypical proliferative serous tumor
    - Occasionally with implants: epithelial type, desmoplastic type
    - Serous borderline tumor, micropapillary variant/non-invasive 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
- Intra-abdominal cystic lymphangioma
- Primary effusion lymphoma of the peritoneum

2.1 Definition and basic information

Peritoneal tumors are rare and are often only diagnosed at an advanced stage with mostly unspecific abdominal symptoms. The prognosis varies greatly depending on the stage and the underlying histology. It is important to make a differential diagnosis with the various primary malignancies of the peritoneum and to distinguish them from other malignancies with peritoneal metastasis.

2.1.1 Peritoneal mesothelioma

Diffuse mesothelioma is a tumor that originates from the mesothelial or submesothelial cells of the pleura, the peritoneum or, very rarely, the pericardium. Less than 20% of mesotheliomas originate in the peritoneum. Among advanced peritoneal mesotheliomas, there are substantial differences in terms of prognosis, while median overall survival is 5-30 months [1, 2].

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

2.1.2 Pseudomyxoma peritonei

Pseudomyxoma peritonei (PMP) is a clinical diagnosis characterized by disseminated abdominal mucus deposits. The most common origin of PMP is a mucinous neoplasm of the appendix (low-grade appendiceal mucinous neoplasm - LAMN). In the case of non-perforated LAMN, the probability of developing PMP after appendectomy is very low, whereas this risk is significantly higher in the case of perforated LAMN [5- 8].

2.2 Epidemiology

2.2.1 Peritoneal mesothelioma

Mesothelioma of the peritoneum (ICD-10: C45.1) is diagnosed in around 140 individuals in Germany every year. The incidence has recently been stable at around 0.1/100,000 inhabitants (age-standardized according to the age of the European population). Compared to pleural mesothelioma, which is 9 times more common, proportionally more women are affected. Those

affected are younger on average, and younger patients at least have a better chance of survival (Table 1).

Table 1: Epidemiologic figures for mesothelioma of the peritoneum and pleura in Germany

	Pleura	Peritoneum
Annual new cases	1220	138
Median age at onset	78 years	69 years
Proportion of women	18%	40%
Current trend (incidence since 2010)	declining	constant
Relative 5-year survival	10.0%	27.7%
Median survival (patients < 70 yrs.)	18 Mon.	31 Mon.
Median survival (patients ≥ 70 yrs)	11 Mon.	9 Mon.
Data refer to the period 2020 - 2022; the data on survival include cases from 2013 - 2022.		

2.2.2 Pseudomyxoma peritonei

The actual incidence rate is not known, as no standardized classification systems are available. In Germany, for example, it can be coded under ICD-10 C48.1, C48.2 and C48.8, but these also include other diseases. The estimated incidence is around 2 per 1,000,000 inhabitants per year [9].

Data from the Netherlands [10] show an incidence of mucinous neoplasia of the appendix of 0.3% of all appendectomies, of which 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 develop in the pleura. Peritoneal mesotheliomas - just like pleural mesotheliomas - can be associated with asbestos exposure. Despite the ban on the use of asbestos, the incidence of asbestos-related diseases continues to rise. This can be explained by the long latency period after asbestos exposure of 15 to 60 years [11]. Therefore, the main age of manifestation is in the 6th decade of life [12].

Another risk factor is an infection with Simian virus 40 (SV40) [13].

In non-asbestos-associated cases of peritoneal mesothelioma, rearrangements in the *ALK gene* (anaplastic lymphoma kinase) have been described as the underlying molecular pathomechanism [14].

Germline mutation of *BAP1* is a rare predisposing factor for peritoneal mesothelioma [15, 16].

2.3.2 Pseudomyxoma peritonei

PMP is characterized by mucinous gelatinous ascites, usually after perforation of a mucinous neoplasm of the appendix, which leads to the appearance of a so-called "jelly belly". The term is a purely macroscopic, i.e., clinical description. A mucinous neoplasia of the appendix is the most common site of origin, although in principle it may originate in the entire gastrointestinal tract or in the ovarian area. A typical pathomechanism is the occurrence of a "redistribution

phenomenon", in which the pseudomyxoma cells spread and proliferate freely in the peritoneal fluid to predilection sites in the abdominal cavity. Typical predilection sites are the omentum major and minor, the right subdiaphragmatic and subhepatic space and the true pelvis [9, 17].

2.4 Risk factors

2.4.1 Peritoneal mesothelioma

Exposure to asbestos is a recognized risk factor for the development of peritoneal mesothelioma [11, 12]. This means that mesothelioma of the peritoneum caused by asbestos can be recognized as an occupational disease in accordance with §4105 of the German 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 relate to the avoidance of asbestos exposure. After an exposure to asbestos has taken place, appropriate surveillance or secondary screening are recommended. For early detection measures in relation to peritoneal mesothelioma, there are currently only recommendations in the context of studies for high-risk patients (German AWMF guideline on the diagnosis and assessment of asbestos-related occupational diseases chpt. 5.9.3) [18].

No early detection 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, there is an increased risk of developing a pseudomyxoma peritonei after perforated LAMN. It is therefore recommended that magnetic resonance imaging (MRI) of the abdomen and pelvis be arranged every 6 months as a follow-up; if MRI is contraindicated, a computed tomography (CT) scan should be ordered [19].

4 Clinical characteristics

4.1 Symptoms

4.1.1 Peritoneal mesothelioma

Peritoneal mesothelioma (MPM) has no pathognomonic symptoms, which can make the diagnosis difficult.

Clinically, 3 subgroups can be distinguished

- Patients with abdominal enlargement: pronounced ascites formation and large tumor nodules, weight loss and abdominal pain

- Patients with acute symptoms requiring emergency surgical treatment
- Patient with unclear fever, weight loss and symptoms of inflammatory bowel disease

In early stages, there may be non-characteristic constitutional symptoms such as fatigue, loss of appetite, weight loss and unclear fever.

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 [20].

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

Approximately 10% of patients are diagnosed with MPM during umbilical hernia repair [21, 22].

4.1.2 Pseudomyxoma peritonei

The diagnosis is often made incidentally during the diagnostic procedures for an unclear tumor in the ovarian area, in connection with an inguinal hernia, appendicitis or an etiologically unclear ileus as well as in the context of extended work-up of unclear abdominal complaints [6, 23].

In 30-50% of cases, there is an increase in abdominal circumference ("jelly belly"). Less common symptoms are abdominal pain, weight loss, micturition problems, constipation, vomiting and dyspnea [9].

5 Diagnosis

5.2 Diagnostic procedures

Peritoneal mesothelioma and pseudomyxoma peritonei often go along with non-specific symptoms. Diagnosis can be difficult using clinical chemistry and imaging procedures, so that histology is the essential basis for diagnosis. When planning a diagnostic laparoscopy as part of staging procedures, it is important to ensure that trocars are placed in the midline so that trocar sites can be resected during subsequent surgery.

In the case of peritoneal mesothelioma, tumor biopsies should be taken from the subperitoneal tissue, as tumor cell invasion is important for the diagnosis. It is recommended that biopsies are not taken in the diaphragm area.

Table 2 provides an overview of the diagnostic procedures.

Table 2: Diagnostics and staging

Procedures	Remarks
Physical examination	
Clinical chemistry (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 contrast media: 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 before initiating therapy. For operable tumors with unclear findings: Cave intra-abdominal tumor dissemination. Immunohistochemistry: • *Ki67* • Calretinin • *WT1* (Wilms tumor antigen 1) • Cytokeratin 5/6 • D2-40 (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-signet ring cell tumor is present in the peritoneum, exclusion of gastric cancer is recommended.

5.3 Classification

5.3.1 Subtypes

5.3.1.1 Peritoneal mesothelioma

According to the WHO, several histological subtypes are distinguished in peritoneal mesothelioma (MPM) by analogy to pleural mesothelioma [24]:

- Epithelioid (75% of MPM, better prognosis): cells resemble normal mesothelium, growth in tubulopapillary or trabecular patterns. A signet ring cell component and concomitant desmoplastic reaction may complicate the differential diagnosis versus adenocarcinoma.
- Sarcomatoid (very rare, poor prognosis): tightly packed spindle cells, occasional presence 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% with epithelioid or sarcomatoid growth.

Diagnosis based on the morphological growth pattern can be difficult, necessitating the use of immunohistochemical and optionally also molecular pathological markers [25]. Here, an appropriate marker panel is used. Mesotheliomas are typically positive for

- Total cytokeratin
- Calretinin
- *WT1* (Wilms tumor antigen 1)

- EMA (epithelial membrane antigen)
- Cytokeratin 5/6
- D2-40 (Podoplanin)

and negative for

- CEA (carcino-embryonic antigen)
- TTF1
- BerEP4
- B72.3
- MOC31
- BG8 (Lewis^y Blood Antigen)
- 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. *BAP1* haploinsufficiency was associated with an inflammatory subtype [11, 26, 27].

5.3.1.2 Pseudomyxoma peritonei

Various classification systems are available:

The Ronnett classification [28] subdivides PMP into 3 categories:

- Disseminated peritoneal adenomucinosis (DPAM)
- Peritoneal mucinous carcinomatosis (PMCA)
- Mixed type

The PSOGI (Peritoneal Surface Oncology Group International) subdivides PMP into the following categories [29]:

- low grade
- high grade
- high grade with signet ring cells
- It should be noted that the classification and grading of appendiceal neoplasia and the corresponding PMP may differ. The classification of PMP is relevant here [30].

5.3.2 Classification according to disease extent

The main problem of currently existing scores is that all mentioned classifications are semi-quantitative 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.

A TNM classification is currently only available for pleural mesothelioma.

The most widely used score for quantifying the intraperitoneal tumor burden is the so-called peritoneal carcinomatosis index (PCI) according to Sugarbaker et al., see Chapter 5.3.2.1. and Figure 1.

5.3.2.1 Peritoneal carcinomatosis index according to Sugarbaker

The most commonly used peritoneal carcinomatosis index (PCI) in clinical practice was described by Jacquet and Sugarbaker in 1996 [31]. 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 as well as upper and lower ileum).

In addition, the tumor burden of the individual regions is described and documented as a Lesion Size Score (LSS) with 0-3 points (Table 3).

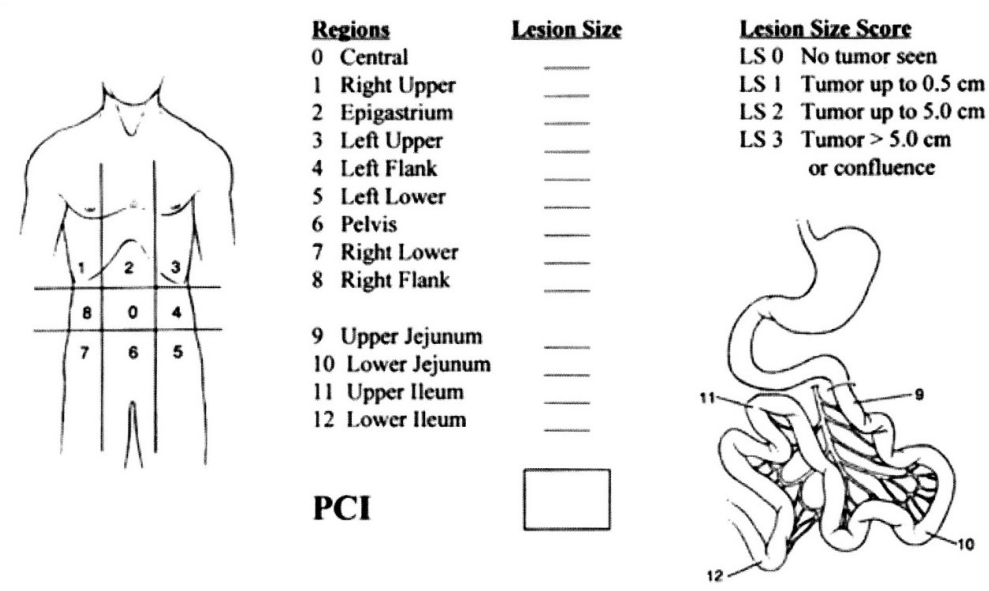
Table 3: Lesion Size Score

Lesion size	Points
Lack of tumor detection	0
Tumor nodules up to 0.25 cm	1
Tumor nodules between 0.25 cm and 2.5 cm	2
Tumor node >2.5 cm	3

The LSS is determined for each region, with the central region numbered 0 and all other regions are 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.

Various studies have shown that the extent of PCI in the respective tumor entities a direct proportional impact on resectability and median overall survival [29].

Figure 1: PCI according to Sugarbaker et al [31]



5.4 Prognostic factors

Prognostic factors are mitotic activity and number of mitoses as well as nuclear size [32].

The most important prognostic factor is the completeness of cytoreductive surgery in terms of complete macroscopic cytoreduction. The so-called "completeness of cytoreduction" (CCR) is documented here, see Table 4.

Table 4: CCR categories

Completeness of cytoreduction (CCR)	Residual tumor
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 >2.5 cm in size or confluent foci in the abdomen

A meta-analysis showed that a CCR-0/1 situation was achieved in 67% of MPM patients with a median PCI of 19 after CRS and HIPEC [33].

In PMP, KRAS mutation may have a prognostic impact [34- 36]. In addition, an increase biomarkers CEA, CA125 and CA19-9 three times above the upper limit of normal is associated with a poorer prognosis [37- 39].

5.4.1 Assessment of treatment response

5.4.1.1 Peritoneal Regression Grading Score (PRGS)

The Peritoneal Regression Grading Score (PRGS) is a four-level score for assessing treatment response (see Table 5) [40]. However, the score has not yet been validated.

Table 5: 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	Vital tumor cells predominant	Tumor cells dominate via fibrosis and/or acellular mucin and/or infarct-like necrosis
PRGS 4 - no tumor response	Clearly 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 [41] (see Table 6), which has so far been used primarily for rectal cancer after neoadjuvant radiochemotherapy. There is currently no validated score for mesothelioma.

Table 6: Degree of regression according to Dworak

Degree	Tumor residuals
0	No regression
1	Predominance of tumor cells over peritumoral fibrosis and radiation-associated vasculopathy
2	Predominance of fibrosis over the tumor cell nests, easily recognizable at low magnification
3	Fibrosis with few tumor cell nests visible only at higher magnification
4	No detection of tumor cells

5.4.1.3 Degree of regression according to Becker

The degree of regression after prior therapy can be specified according to Becker [42] (see Table 7), that was developed for gastric cancer after neoadjuvant chemotherapy. No validated score exists for mesothelioma to date.

Table 7: Degree of regression according to Becker

Degree of regression	Tumor residuals
Complete response (CR) Grade 1a	No tumor cells visible
Subtotal response (SR) Grade 1b	Morphologically intact neoplastic cells in < 10% of the tumor bed
Partial response (PR) Grade 2	Morphologically intact neoplastic cells in 10 to 50% of the tumor bed
Low response (MR) Grade 3	Morphologically intact neoplastic cells in > 50% of the tumor bed
No response (NR)	No histological signs of regression

6 Therapy

6.1 Treatment structure

Due to the complex treatment options and the rarity of the diseases, recommendations should always be discussed and decided on a multidisciplinary basis.

The treatment decision depends on the extent of the peritoneal involvement and other disease- and patient-associated factors.

6.1.1 Peritoneal Mesothelioma - Treatment structure

A treatment algorithm for malignant peritoneal mesothelioma is shown in Figure 2.

The treatment 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 high-volume centers (see also DGAV homepage) in order to keep morbidity and mortality as low as possible and to ensure the highest possible rate of complete cytoreduction [43- 45].

Surgical treatment aims at complete peritonectomy. This is not always feasible in the case of multiple small bowel manifestations. In these cases, "serial debulking" can also be useful.

The adnexa are a particular problem in young patients. Generally, bilateral adnexectomy with hysterectomy is also recommended due to the frequent involvement in peritoneal tumors, in order to achieve complete cytoreduction. This must be discussed individually.

Splenectomy is often required for extensive tumors. It may therefore be advisable to preoperatively ensure vaccinations recommended for asplenia by health care authorities in patients with involvement of the left upper quadrant suggested by imaging or laparoscopy.

The benefit from neoadjuvant and/or adjuvant systemic chemotherapy has not been clearly assessed. The proliferation index (determined using 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 possible benefit of adjuvant chemotherapy with an improvement in 5-year overall survival to 67% versus 56% without systemic therapy [46].

In a retrospective evaluation of 117 patients, those with rapidly proliferating tumors (Ki67 > 9%), a PCI > 17 and a biphasic/sarcomatoid histological subtype (compared to epithelioid) were identified as a high-risk group with a median OS after surgery and HIPEC of 10.3 months. In these patients, systemic preoperative/neoadjuvant systemic chemotherapy with platinum and pemetrexed can be primarily considered [47]. Resectability should be re-evaluated after 2-3 cycles. In other retrospective evaluations, however, no significant benefit was shown for perioperative chemotherapy [48] or even a negative prognostic impact of neoadjuvant chemotherapy was reported [46].

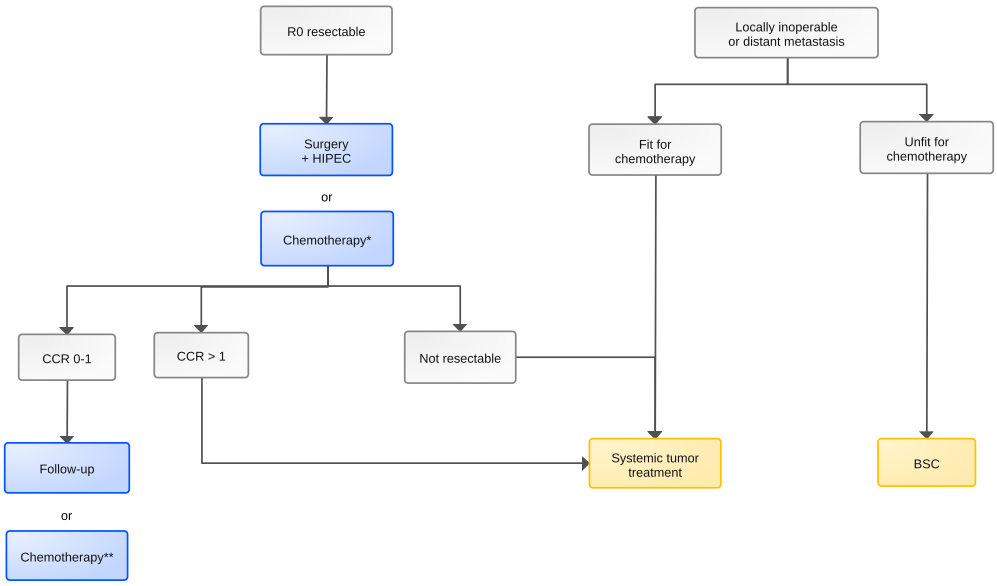
For locally advanced and/or metastatic tumors, systemic therapy with a combination of pemetrexed and a platinum derivative is standard, analogous to pleural mesothelioma. The value of additional administration of bevacizumab [49] and second-line therapy has not been conclusively clarified.

6.1.1.1 Immunotherapy and local palliative chemotherapy

Due to the low incidence of peritoneal mesothelioma compared to pleural mesothelioma, clinical trials of immunotherapy were conducted mostly in pleural mesothelioma. The randomized multicenter study CheckMate-743 showed that patients with inoperable pleural mesothelioma treated with nivolumab in combination with ipilimumab (n=303) achieved a longer overall survival compared to patients treated with platinum/pemetrexed chemotherapy (n=302) (median overall survival 18.1 vs 14.1 months (95% confidence intervals 16.8-21.4 and 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 transferred to peritoneal mesothelioma. However, a recommendation cannot yet be made [50].

In patients with diffuse disease not eligible for HIPEC, PIPAC (pressurized intraperitoneal aerosol chemotherapy) with cisplatin/doxorubicin is an option for improving ascites control and general condition, typically repeated initially at 6- to 8-week intervals and later at longer intervals [51].

Figure 2: Algorithm for the primary treatment of peritoneal mesothelioma



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

6.1.2 Pseudomyxoma peritonei - Treatment structure

A treatment algorithm for pseudomyxoma peritonei (PMP) is shown in Figure 3.

The treatment of choice is a combination of cytoreductive surgery (CRS) with intra-abdominal chemotherapy (IP). This can be given directly during surgery as HIPEC (hyperthermic intraperitoneal chemotherapy) or as postoperative EPIC (early postoperative intraperitoneal chemotherapy), aiming to improve both overall survival and progression-free survival [52]. The treatment goal is complete macroscopic cytoreduction/tumor resection, assessed and documented using the so-called Completeness of Cytoreduction Score (CCR), see Table 4. The CCR is a prognostically relevant factor.

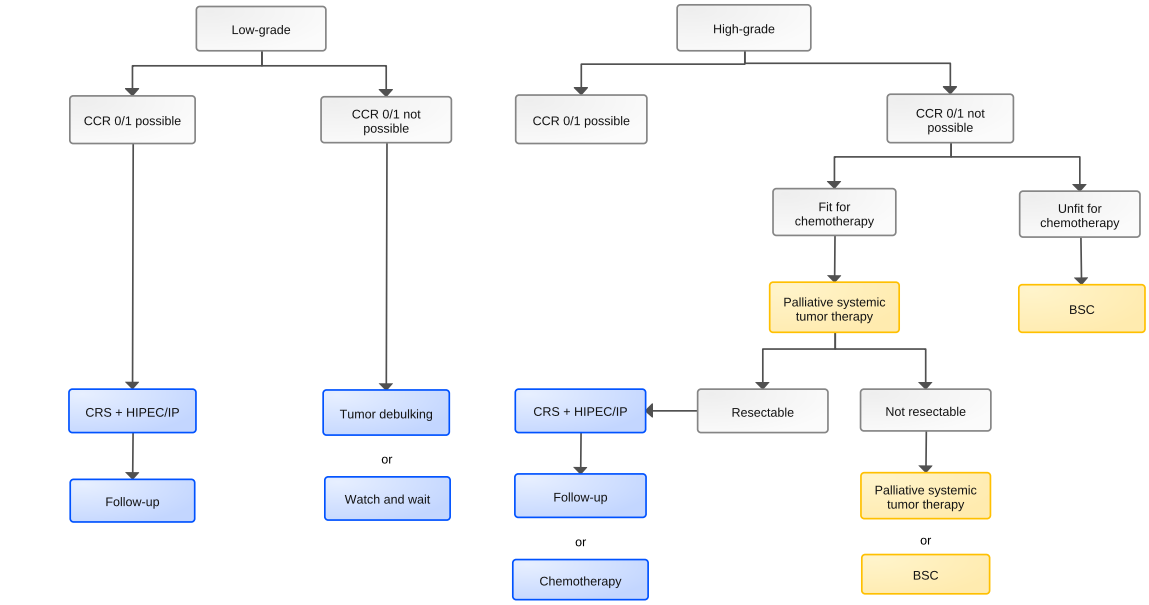
The procedures performed can be extremely complex and time-consuming, with average duration of operation around 9 hours [53].

In advanced PMP, tumor debulking can also alleviate symptoms and improve the prognosis [54].

Postoperative systemic therapy can contribute to an improvement in the prognosis of high-grade PMP or be used for inoperable tumors [55]. However, the available data are sparse and available mostly for combination therapies analogous to systemic treatment of metastatic colorectal carcinoma.

The adnexa are a particular problem in young patients. Due to the usually high tumor burden in the true pelvis, only a complete resection including ovaries, uterus and rectum up to the fold can be achieved as an extraperitoneal anterior rectal resection en bloc with hysterectomy and salpingoovarectomy. In low-grade PMP with low tumor burden, leaving the left adnexa intact can be considered in individual cases. It is essential that patients are informed preoperatively about the procedures that may be required, so that fertility-protecting measures such as cryopreservation of ovarian tissue can be arranged preoperatively [56].

Figure 3: Algorithm for the primary treatment of pseudomyxoma peritonei



Legend:
curative intended therapy, palliative intended therapy;
CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy; IP = intra-abdominal chemotherapy; CCR = completeness of cytoreduction; BSC = best supportive therapy

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 nodes as completely as possible. Due to the frequently widespread distribution of tumor nodules and the origin of the primary tumor in the peritoneum itself, a complete peritonectomy should be aimed for.

The largely extraperitoneal preparation and the tumor dissemination across all abdominal quadrants makes special visceral surgical expertise mandatory. Cytoreductive surgery is a time-consuming procedure going along with large wound areas. In addition to peritonectomy, which is usually performed as a (sub-) total procedure, a multivisceral resection may be required.

Free tumor cells are distributed in the peritoneal fluid throughout the abdominal cavity and lead to peritoneal carcinomatosis (complete redistribution phenomenon, CRP), predominantly at typical predilection sites, so that a complete parietal peritonectomy usually is indicated [57].

Basic therapy procedures depend on the localization

- Peritonectomy in the upper abdomen
- Peritonectomy in the lower abdomen
- Peritonectomy inter-enteric

6.2.1.1 Perioperative management

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

metabolic changes or hypalbuminemia [58]. Targeted coagulation management plays an important role here, particularly in the HIPEC phase. Anticipatory temperature management is essential in every phase of the procedure.

In terms of anesthesia management, combined anesthesia should be used if possible: for example, total intravenous anesthesia (TIVA) combined with thoracic epidural anesthesia (PDA). The use of PDA, carefully respecting contraindications, offers many advantages here. Optimized perioperative pain management with prevention of chronic pain development as well as the (proven) reduction of pulmonary complications, myocardial ischemia and protracted ileus are thus possible.

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 in general complications during the generally complex surgeries and appear to be an important prerequisite for 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 indicate advantages in the postoperative course. However, there is currently a lack of high-quality studies with a high level of evidence - not least due to the strong heterogeneity of patients included [59, 60].

6.2.1.2 Preparation devices

Cytoreductive surgery generally requires blunt dissection. If the peritoneum cannot be removed bluntly, dissecting instruments are used to separate the layers - for example the peritoneum from fascia, muscle or fatty tissue.

Vessel-sealing instruments can be used to minimize blood loss, the duration of the procedure and adhesion formation. These include high-frequency surgical devices such as monopolar or bipolar coagulation and 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 by drug treatment. In patients with peritoneal mesothelioma, postoperative irradiation of the trocar sites and puncture sites may be considered.

Pseudomyxoma peritonei is hardly sensitive to radiation.

6.2.3 Systemic tumor therapy

6.2.3.1 Intraperitoneal chemotherapy

Intraperitoneal administration of chemotherapeutic agents can achieve a higher local concentration of cytotoxic drugs in the tumor. A lower expected systemic distribution of cytostatic drugs also results in lower systemic toxicity. A relevant factor here is the first-pass metabolism

of the liver, whereby drugs with a high first-pass effect (e.g., fluorouracil [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 for HIPEC of colorectal carcinoma, is associated with increased morbidity (in terms of intraoperative bleeding) and should not be used at the reported dosage [61].

The pharmacokinetic advantage of intraperitoneal administration is all the greater, the slower a drug is absorbed from the abdominal 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 [62].

An overview of cytostatic drugs that can be used for intraperitoneal application is given in Table 8 [62].

Table 8: Cytostatic agents for intraperitoneal administration

Drug	Dose	Exposure time	Penetration depth	Thermal reinforcement
Cisplatin	20-250 mg/m²	20 min to 20 h	1-5 mm	+
Carboplatin	200-800 mg/m²	30 min to 20 h	0.5-9 mm	+
Oxaliplatin	360-460 mg/m²	30 min to 20 h	1-2 mm	+
Mitomycin C	13-35 mg/m²	90-150 min	2 mm	+
Doxorubicin	15-75 mg/m²	90 min	4-6 cell layers	+
5-FU	650 mg/m² over 5 days	23 h (EPIC)	0.2 mm	(+)
Gemcitabine	50-1000 mg/m²	1-24 h	n/a	n/a
Pemetrexed	500 mg/m²	24 h	n/a	n/a

The most common procedure, which is now routinely used 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, only sparse structured data are available as yet.

6.2.3.1.1 HIPEC

The heating of the applied fluid leads to increased cell membrane permeability and can thus improve the uptake of cytostatic drugs into tumor tissue. In addition, hyperthermia leads to direct cytotoxic effects by impairing DNA repair, protein degradation and induction of heat-shock proteins (HSP), which further enhance the proapoptotic effects of chemotherapy. Isotonic saline and dextrose-based dialysis solutions are most commonly used.

Cis- or carboplatin are used alone or in combination with doxorubicin, pemetrexed, ifosfamide or mitomycin as chemotherapeutic agents. Other treatment regimens have been tested as well [63]. The duration of HIPEC varies between 30 and 120 minutes in the established treatment protocols. HIPEC can be carried out as an open or closed approach. Advantages of open HIPEC include the additional manual management of remaining lesions and the intra-abdominal distribution of chemotherapy. The closed approach 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 by which chemotherapeutic agents are administered directly intraperitoneally in aerosolized form. Aerosolization and a laparoscopic pressure of 10-12 mmHg optimize the distribution and depth effect of cytotoxic agents. Currently, this procedure is mainly used for patients with advanced tumors that cannot be radically resected. A combination of cisplatin and doxorubicin is often used, with a significantly reduced dose as compared to HIPEC.

6.2.3.2 Systemic therapy

6.2.3.2.1 Peritoneal mesothelioma - Systemic therapy

No data from randomized studies are available on the benefit of adjuvant chemotherapy. In analogy to pleural mesothelioma, pemetrexed can be used in combination with cisplatin or carboplatin. The indication for adjuvant chemotherapy should be decided individually in a multidisciplinary tumor board. For 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 additional administration of bevacizumab for peritoneal mesothelioma has not been clarified with certainty. However, data from the MAPS study have shown an advantage 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 in small, retrospectively analyzed patient cohorts [49, 64]. In clinical practice, at best a temporary disease stabilization can be achieved.

In non-resectable pleural mesothelioma, the combination of nivolumab and ipilimumab showed superiority over platinum and pemetrexed chemotherapy in terms of overall survival in a randomized phase III trial, which led to the approval of nivolumab in combination with ipilimumab for this indication. In subgroup analyses, this advantage was particularly evident in non-epithelioid histology [50]. It can therefore also be assumed that immunotherapy will also be effective in peritoneal mesothelioma. In this regard, initial promising data from small case series are available for second-line therapy using the combination of tremelimumab and durvalumab [65] or bevacizumab and atezolizumab [66].

If standard therapies are obviously exhausted, patients in good general condition (ECOG 0-1) should undergo next-generation sequencing (NGS)-based molecular diagnostics and the findings be discussed in a molecular tumor board with regard to further potential treatment options.

6.2.3.2.2 Pseudomyxoma peritonei - Systemic therapy

The data on systemic therapy for PMP are extremely limited. An analysis of SEER data shows no benefit of systemic treatment in patients with low-grade tumors [67]. 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 settings

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

LAMN is diagnosed as an incidental finding in approx. 1% of appendectomy specimens, of which approx. 9% develop a Pseudomyxoma peritonei within 2 years [10].

In acutely perforated LAMN or small amounts of extra-appendicular mucin, the cellularity of the mucus is of prognostic importance [68]. With acellular mucus, the risk of developing PMP is low (<5%). In such cases, some centers perform a planned re-laparoscopy after 9-12 months.

In general, a "watch and wait" strategy is indicated for incidental findings of LAMN and, in principle, appendectomy is the appropriate treatment. In order to detect and treat PMP as early as possible, regular monitoring including cross-sectional imaging (MRI abdomen/pelvis, CT abdomen/pelvis in case of contraindications) and the test for of tumor markers (CEA, CA19-9 and CA 125) at approx. 6-month intervals is recommended [19].

7 Rehabilitation

Malignant peritoneal tumors by themselves, but also their treatment with frequently extensive surgery and chemotherapy often lead to considerable somatic sequelae including weight loss or 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 level of psychological stress and a corresponding need for psycho-oncological care. Targeted rehabilitative measures are therefore required. These should be started as soon as possible after completion of primary therapy as part of rehabilitation. When selecting the rehabilitation facility, the approval of the facility for carcinoma patients by health insurance provider (pension insurance, health insurance) is mandatory; in addition, patient right to choose should be taken into account. During rehabilitation, in addition to the general therapy options (sports/physio/occupational therapy), comprehensive nutritional advice should be provided, patients should be included in a training kitchen and there should be the possibility of administering all scientifically recognized diets - from normal whole foods to complete parenteral nutrition. All patients should be offered psycho-oncological care. Rehabilitation facilities should be able to continue systemic tumor therapies if indicated. Patients who have not yet reached the statutory retirement age should be informed about benefits for participation in working life as part of medical-occupational rehabilitation (German MBOR). Further socio-medical questions and any necessary care for the patient should be clarified during rehabilitation.

8 Surveillance and follow-up

Imaging morphological follow-up procedures, preferably using MRI or CT, are regularly indicated in order to early detect an unfavorable course of the disease and to avoid exposing patients to ineffective therapies for an unnecessarily long time, and to provide the option of more effective therapies. During ongoing chemotherapy, the patients' general condition and vital body functions should be checked once a week.

There are no prospective data providing the basis for recommending a specific agenda for follow-up. The schedules listed below are frequently used in studies.

8.1 Peritoneal mesothelioma - follow-up

In past and current studies, the schedule shown in Table 9 has been used:

Table 9: Structured surveillance and follow-up after surgery for peritoneal mesothelioma

Procedure	Months post surgery										
	6	12	18	24	30	36	42	48	54	60	
Physical examination	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	
Imaging CT thorax/abdomen/pelvis or MRI abdomen/pelvis	X	X	X	X	X	X	X	X	X	X	

Imaging follow-up should be continued for 5 years, as late recurrences can occur and can potentially be treated curatively. In young patients, an MRI should be ordered instead of a CT scan.

8.2 Pseudomyxoma peritonei - follow-up

No standardized recommendation is available; follow-up visits should be performed every 6-12 months (Table 10 and Table 11).

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

Procedure	Months post-surgery of high-grade PMP										
	6	12	18	24	30	36	42	48	54	60+	
Physical examination	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry CA 19-9, CEA, CA125	X	X	X	X	X	X	X	X	X	X	
Imaging CT thorax MRI abdomen/pelvis or CT abdomen/ pelvis	X	X	X	X	X	X	X	X	X	X	

Table 11: Structured surveillance and follow-up after surgery for low-grade Pseudomyxoma peritonei

Procedure	Months post-surgery of low-grade PMP										
	6	12	18	24	30	36	42	48	54	60+	
Physical examination	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry CA 19-9, CEA, CA 125	X	X	X	X	X	X	X	X	X	X	
Imaging: MRI abdomen/pelvis or CT abdomen/pelvis	x	X	x	X		x		X		X	

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10 Active studies

Table 12: Current studies on peritoneal mesothelioma and/or pseudomyxoma peritonei according to the Clinical Trials Registry

Study ID	Title of the study	Institution
NCT06513065	Study to Evaluate the Non-inferiority of Low-dose HIPEC Versus High-dose HIPEC in the Treatment of PMP (HIPEC-PMP) (HIPEC-PMP)	Basingstoke, Hampshire, United Kingdom
NCT02387203	Antibiotic Treatment and Long-term Outcomes of Patients with Pseudomyxoma Peritonei of Appendiceal Origin	Baltimore, Maryland, United States
NCT01617382	Register With Patients in Which Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) was Performed	Leuven, Flemish Brabant, Belgium
NCT06617897	Phase 3 Study of Fibrinogen Concentrate (CSL511) in Subjects With Pseudomyxoma Peritonei Undergoing Cytoreductive Surgery	Basingstoke, Hampshire, United Kingdom
NCT02073500	Peritoneal Surface Malignancies - Characterization, Models and Treatment Strategies (PSM)	Oslo University Hospital
NCT06084780	Intestinal & Multivisceral Transplantation for Unresectable Mucinous Carcinoma Peritonei (Transcape)	Cleveland, Ohio, United States
NCT03503071	Quality of Life After Cytoreductive Surgery and Intraperitoneal Chemotherapy	Daegu, Korea
NCT05939193	Effect of Urine-guided Hydration on Acute Kidney Injury After CRS-HIPEC	Beijing, China
NCT04779554	Flat Dose Vs. Weight-based IP Chemotherapy for CRS/HIPEC	Lexington, Kentucky, United States
NCT06057935	A Study of Additional Chemotherapy After Surgery for People With Malignant Peritoneal Mesothelioma	Multi-Center, United States
NCT05449366	Intraperitoneal Paclitaxel for Patients with Primary Malignant Peritoneal Mesothelioma (INTERACT MESO)	Rotterdam, Netherlands
NCT03875144	Treatment of Malignant Peritoneal Mesothelioma (MESOTIP)	Montpellier, France
NCT05001880	Chemotherapy With or Without Immunotherapy for Peritoneal Mesothelioma	Multi-Center, United States
NCT06543069	Sintilimab, Bevacizumab, Pemetrexed, and Cisplatin for Unresectable MPeM	Beijing, China
NCT06581549	Immune Microenvironment and Gene Expression Profiling in Mesothelioma	Multi-Center, Italy
NCT04847063	Individualized Response Assessment to Heated Intraperitoneal Chemotherapy (HIPEC) for the Treatment of Peritoneal Carcinomatosis From Ovarian, Colorectal, Appendiceal, or Peritoneal Mesothelioma Histologies	Bethesda, Maryland, United States

Further information and updates on current clinical trials are available on the website:

https://clinicaltrials.gov/

15 Links

German AWMF guideline "Diagnosis, treatment and follow-up of low-grade mucinous neoplasia of the appendix (LAMN)

Website: https://register.awmf.org/de/leitlinien/detail/088-012

German AWMF guideline "Diagnosis and assessment of asbestos-related occupational diseases"

Website: https://register.awmf.org/de/leitlinien/detail/002-038

German AWMF guideline "Fertility preservation in oncological diseases"

Website: https://register.awmf.org/de/leitlinien/detail/015-082

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17 Disclosures

according to the rules of the responsible Medical Societies.