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## Concise Version

# Diagnostics, Treatment and Surveillance of Low-Grade Appendiceal Mucinous Neoplasms (LAMN)

S2k-Guideline

by

Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV)

In cooperation with:

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Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e. V. (DGGG)

Deutsche Gesellschaft für Pathologie (DGP)

Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und  
Stoffwechselkrankheiten (DGVS)

Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)

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GESELLSCHAFT FÜR  
PÄDIATRISCHE ONKOLOGIE  
UND HÄMATOLOGIE



# 1. Pathological classification and differentiation to other appendiceal neoplasms

Recommendation 1	
Mucinous neoplasms of the appendix <b>should</b> be classified according to the current WHO classification.	↑↑
Strong consensus: 100 %	

Table 1 histological criteria of mucinous neoplasms of the appendix (LAMN, HAMN and mucinous adenocarcinoma)

LAMN	HAMN	Mucinous adenocarcinoma
<ul style="list-style-type: none"> <li>- Filiform or villous mucinous epithelium with tall cytoplasmic mucin vacuoles and compressed bland nuclei or epithelial undulations/ scalloping with columnar cells with nuclear pseudostratification</li> <li>- Broad pushing margin</li> <li>- Various degrees of extracellular mucin</li> <li>- Fibrosis, hyalinization and calcification of the appendiceal wall</li> </ul>	<ul style="list-style-type: none"> <li>- Features similar to LAMN with:</li> <li>- Enlarged hyperchromatic and pleomorphic nuclei</li> <li>- Numerous atypical mitotic features</li> <li>- Single-cell necrosis</li> <li>- Sloughed necrotic epithelial cells in the appendix lumen</li> </ul>	<ul style="list-style-type: none"> <li>- Irregular or jagged glands infiltrating the wall of the appendix</li> <li>- Extracellular mucin composing &gt;50% of the tumour</li> <li>- Mucin pools containing floating strips of glands or clusters of mucinous epithelial cells</li> </ul>

Table 2 3-tier classification of mucinous neoplasms of the appendix and their peritoneal metastases

Grade	Appendiceal primary	Peritoneal metastases
1	LAMN: low-grade cytology with pushing margins	Hypocellular mucin deposits Neoplastic epithelial elements with low-grade cytology No infiltrative-type invasion
2	HAMN: high-grade cytology with pushing margins Mucinous adenocarcinoma without signet-ring cells	High-grade cytological features Infiltrative-type invasion characterized by jagged or angulated glands in desmoplastic stroma or small mucin pool pattern with mucin pools containing clusters of tumour cells
3	Signet-ring cell adenocarcinoma with signet-ring cells or infiltrating tissue	Mucinous tumour deposits with signet-ring cells

Recommendation 2	
Low-grade appendiceal mucinous neoplasms <b>should</b> be classified according to the current TNM-classification.	↑↑
Strong consensus: 100 %	

Table 3 TNM-classification of LAMN and consecutive pseudomyxoma peritonei

	Definition
<b>Tis:</b>	Tumour confined to the appendix with acellular mucin or mucinous epithelium confined to the muscularis propria
<b>T1</b>	<b>Not applicable in LAMN</b>
<b>T2</b>	<b>Not applicable in LAMN</b>
<b>T3</b>	Tumour or acellular mucin extends onto the subserosal soft tissue
<b>T4</b>	Tumour extends to the serosa of the appendix or mesoappendix including perforation of cellular or acellular mucin
- <b>T4a:</b>	Tumour perforation including cellular or acellular mucin within the right lower quadrant
- <b>T4b:</b>	Tumour invades other organs or structures
<b>N-Status</b>	n/a
<b>M0</b>	No metastatic disease
<b>M1</b>	Metastatic disease
<b>M1a:</b>	Intraperitoneal acellular mucin
<b>M1b:</b>	Intraperitoneal cellular mucin
<b>M1c:</b>	Metastases beyond the abdominal cavity

Table 4 Tumour stages of LAMN/ pseudomyxoma peritonei according to UICC

Stage	T-category	N-category	M-category
<b>0</b>	Tis	N0	M0
<b>IIA</b>	T3	N0	M0
<b>IIB</b>	T4a	N0	M0
<b>IIC</b>	T4b	N0	M0
<b>IVA</b>	Every T	N0	M1a
<b>IVA</b>	Every T	N0	M1b G1
<b>IVB</b>	Every T	Every N	M1b G2, G3,Gx
<b>IVC</b>	Every T	Every N	M1c, every G

Recommendation 3	
Histological specimens of low-grade appendiceal mucinous neoplasms <b>should</b> be representative and the appendiceal wall <b>should</b> be captured orthograde.	↑↑
Strong consensus: 100 %	

Recommendation 4	
If pseudomyxoma peritonei is present, representative embedding <b>should</b> be performed. The following can be used as a guide: 1 block/cm of altered tissue.	↑↑
Strong consensus: 100 %	

Recommendation 5	
<b>Statement:</b> Currently, mutation analysis has no role in prognostic assessment and prediction of low-grade appendiceal mucinous neoplasms and pseudomyxoma peritonei.	
Mutation analysis <b>can</b> be used for the differential diagnosis of reactive to low-grade findings and in selected patients with unresectable pseudomyxoma peritonei, for the evaluation of individual tumour therapy in accordance with the recommendations of a molecular multidisciplinary meeting.	↔
Strong consensus: 100 %	

## 2. Diagnostics

Recommendation 6	
If a low-grade appendiceal mucinous neoplasms/ pseudomyxoma peritonei is suspected preoperatively, e.g. by ultrasound findings, contrast-enhanced MRI abdomen-pelvis with diffusion-weighted imaging (especially in children and adolescents) or alternatively contrast-enhanced CT abdomen-pelvis <b>should</b> be performed.	↑↑
Strong consensus: 100 %	



In children and adolescents contrast-enhanced MRI abdomen-pelvis **should** always be performed and CT-studies should be avoided.

Recommendation 7	
<p><b>Statement:</b> If a low-grade appendiceal mucinous neoplasm without evidence of pseudomyxoma peritonei is diagnosed postoperatively and adequate treatment has already been provided by surgery (see chapter on Therapy), no immediate staging including radiological imaging is indicated; this is performed later as part of surveillance (see chapter on Surveillance).</p>	
<p>To provide better comparability during further surveillance, immediate radiological imaging <b>can</b> be performed.</p>	↔
<p>Strong consensus: 100 %</p>	

Recommendation 8	
<p>If a low-grade appendiceal mucinous neoplasm/ pseudomyxoma peritonei is suspected preoperatively, the tumour markers CEA, CA19-9 and CA 125 <b>ought</b> to be determined in the preoperative work-up to differentiate from other neoplasms.</p>	↑
<p>Strong consensus: 100%</p>	

Recommendation 9	
<p>Screening colonoscopy to rule out synchronous colorectal neoplasms <b>should</b> be performed according the recommendations of the S3 guideline "colorectal carcinoma" in patients with low-grade appendiceal mucinous neoplasms and pseudomyxoma peritonei.</p>	↑↑
<p>Strong consensus: 100 %</p>	



Occurrence of LAMN in children is very rare and is mainly described in case reports. In these, no synchronous cases of colorectal cancer are reported, therefore a colonoscopy should not be performed in children.

Recommendation 10	
<p>Instead of a surgical biopsy for histological confirmation of low-grade appendiceal mucinous neoplasms/ pseudomyxoma peritonei, treatment <b>should</b> be performed in the first instance (see chapter on Therapy).</p>	↑
<p>Strong consensus: 100 %</p>	

### 3. Therapy

#### 3.1. Perioperative phase

Recommendation 11	
All patients diagnosed with low-grade appendiceal mucinous neoplasms/ pseudomyxoma peritonei <b>should</b> be discussed in a multidisciplinary team meeting, who are experienced in the management of these conditions. When imaging suggests low-grade appendiceal mucinous neoplasms/ pseudomyxoma, multidisciplinary discussion <b>should</b> be done prior to any treatment.	↑↑
Strong consensus: 100 %	



The diagnosis of LAMN/ PMP in childhood/ adolescence is very rare. To ensure appropriate evidence-based therapy, these children should be discussed in paediatric multidisciplinary team meetings and treatment should be based on these recommendations. These paediatric multidisciplinary team meetings should include: paediatric haematology/ oncology, paediatric surgery, pathology, paediatric radiology, and radiation oncology. Furthermore, it is recommended to include these patients in the registry for rare diseases in children (STEP-registry) by the Society for Paediatric Oncology/ Haematology (GPOH). Website:

[https://www.gpoh.de/acl\\_users/login/index\\_html?came\\_from=/meldungen/archiv/e80/umzug\\_des\\_registers\\_seltene\\_tumorerkrankungen\\_in\\_derpaediatric/](https://www.gpoh.de/acl_users/login/index_html?came_from=/meldungen/archiv/e80/umzug_des_registers_seltene_tumorerkrankungen_in_derpaediatric/)

Given the rare occurrence of LAMN/ PMP in children, additional discussion of these cases in an adult multidisciplinary team meeting can be considered.

Recommendation 12	
Patients diagnosed with low-grade appendiceal mucinous neoplasms/pseudomyxoma peritonei <b>ought</b> to be referred to/ treated in hospitals with expertise in the treatment of same.	↑
<b>Statement:</b> The following criteria appear reasonable to prove expertise: multidisciplinary discussion of at least 50 patients with malignant diseases of the peritoneum per year, and frequent cytoreductive surgeries and HIPEC procedures (25/year).	
Expertise <b>can</b> be demonstrated through publicly accredited certification.	↔
Strong consensus: 100 %	



Currently there is no certification/ qualification for paediatric peritoneal malignancy centres in Germany. If cytoreductive surgery, peritonectomy and HIPEC is necessary for a paediatric patient, they should be referred to hospitals that can provide experience in both paediatric surgery and visceral surgery.

Recommendation 13	
Patients with low-grade appendiceal mucinous neoplasms/pseudomyxoma peritonei <b>should</b> be offered psycho-oncological care.	↑↑
Strong consensus: 100 %	



The occurrence of LAMN has also been described in children and adolescents. We refer to the S3 guideline "Psychosocial care in paediatric oncology and haematology" for psycho-oncological support for this patient cohort.

Recommendation 14	
If low-grade appendiceal mucinous neoplasm/ pseudomyxoma peritonei is suspected on imaging, surgical exploration and resection <b>should</b> be performed at a hospital with sufficient expertise (see Recommendation 12) after preoperative diagnostics.	↑↑
In individual cases, postponing the surgery <b>can</b> be considered for specific circumstances.	↔
Strong consensus: 100 %	

### 3.2. Treatment of locally confined LAMN

Recommendation 15	
<p><b>Statement:</b> Patients with low-grade appendiceal mucinous neoplasms with pTis or pT3 tumours, without evidence of extra-appendicular mucin (M0), corresponding to a maximum UICC stage IIa and complete resection with an appendicectomy (R0 status), are fully treated with an appendicectomy.</p>	
Strong consensus: 100 %	

Recommendation 16	
<p><b>Statement:</b> Patients with low-grade appendiceal mucinous neoplasms pT4a und pT4b without evidence of extra-appendicular mucin beyond the right lower quadrant, and complete resection (R0 status) do not require a right hemicolectomy, omentectomy, parietal peritonectomy, or systemic treatment.</p>	
These patients <b>should</b> undergo surveillance.	↑↑
If mucin is present on the appendiceal surface or in the right lower quadrant (cellular mucin or cellularity not determined), HIPEC and local cytoreductive surgery <b>can</b> be considered. The treatment decision is individual and needs to be discussed with the patient.	↔
Strong consensus: 100 %	

Recommendation 17	
If a low-grade appendiceal mucinous neoplasm is suspected intraoperatively while performed an exploratory laparoscopy (i.e. for suspected appendicitis or ovarian pathology), the main goal <b>should</b> be to prevent intra-abdominal perforation of the neoplasm.	↑↑
If appendicectomy cannot be performed laparoscopically in a safe manner, conversion to open surgery <b>should</b> be performed.	↑↑
Furthermore, the whole abdominal cavity <b>should</b> be inspected.	↑↑
Strong consensus: 100 %	



### 3.3. Treatment of pseudomyxoma peritonei

Recommendation 18	
In patients with pseudomyxoma peritonei due to low-grade appendiceal mucinous neoplasms, complete cytoreductive surgery and HIPEC <b>should</b> be performed in hospitals with expertise in the treatment of these patients (see Recommendation 12).	↑↑
If cytoreduction without HIPEC was performed without prior knowledge of the diagnosis of pseudomyxoma peritonei secondary to low-grade appendiceal mucinous neoplasm, patients <b>should</b> be referred to a hospital with expertise (see Recommendation 12) for individual evaluation of HIPEC.	↑↑
Strong consensus: 100 %	



Current literature reports individual cases of children with LAMN but no cases of children with PMP. For other tumours (neuroblastoma, rhabdomyosarcoma, Wilms-tumours, desmoplastic small-round-cell tumour and others) reports of peritoneal spread with cytoreductive surgery and HIPEC is described. There is no literature reporting that children with PMP should be treated the same as adults, conversely there is no evidence that they should be treated in an alternative way.

Recommendation 19	
In the case of M1a-situation and completely resected mucin, as well as R0-resection at the appendix base, cytoreductive surgery and HIPEC <b>can</b> be renounced.	↔
Strong consensus: 100 %	

Recommendation 20	
If mucin is present intraoperatively, a representative sample for histopathological evaluation <b>should</b> be taken.	↑↑
Strong consensus: 100 %	

Recommendation 21	
In symptomatic patients with irresectable pseudomyxoma peritonei (obstructive symptoms), tumour debulking <b>can</b> be considered.	↔
<b>Statement:</b> In these cases of irresectable disease, HIPEC has not been proven to prolong overall survival or symptom-free survival in the literature.	
Strong consensus: 100 %	

Recommendation 22	
In patients with pseudomyxoma peritonei, the Sugarbaker peritoneal carcinomatosis index (PCI) <b>should</b> be calculated as well as the completeness of cytoreduction score (CC-score) after resection.	↑↑
Strong consensus: 100 %	

Table 5 Lesion size score according to Sugarbaker

Score	Definition
0	no tumour visible
1	tumour up to 0.5cm
2	tumour up to 5.0cm
3	tumour > 5.0cm or confluent

Figure 1 Sugarbaker peritoneal carcinomatosis index, region 0 to 8

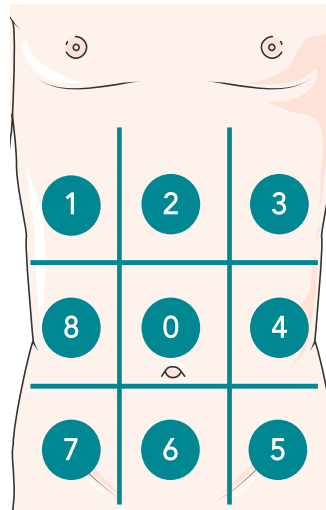


Table 5 Sugarbaker peritoneal carcinomatosis index, region 9-12

Region	Definition
9	proximal jejunum
10	distal jejunum
11	proximal ileum
12	distal ileum

Table 7 Completeness of Cytoreduction Score

Score	Definition
CC-0	no visible tumour
CC-1	residual tumour < 2.5mm
CC-2	residual tumour 2.5mm-2.5cm
CC-3	residual tumour >2.5cm

Recommendation 23	
Patients with pseudomyxoma peritonei with involvement of the uterus and/or adnexal regions should be treated in cooperation with gynaecology. Besides oncological goals, endocrine function including preservation of fertility <b>should</b> be considered.	↑↑
Strong consensus: 100 %	



LAMN and PMP are rare in children but the youngest patient in a German registry analysis was 11 years old at time of diagnosis. Detailed information regarding children with LAMN is only described through case reports. Even though the literature regarding children with LAMN/ PMP is rare, it demonstrates that LAMN/ PMP does occur in children. Treatment of same can lead to fertility impairment. Chapter 8 of the German guideline on “Fertility counselling in oncological patients” addresses paediatric fertility. When planning treatment in these patients, advice should be sought from specialists in paediatric fertility counselling.

Recommendation 24	
If HIPEC is planned in patients without disease of the reproductive organs (regardless of gender), they <b>should</b> be offered fertility counselling prior to performing this procedure.	↑↑
Strong consensus: 100 %	

## 4. Surveillance

Recommendation 25	
Surveillance of patients with low-grade appendiceal mucinous neoplasms or pseudomyxoma peritonei <b>ought</b> to include tumour markers CEA, CA 19-9 and CA 125.	↑
Strong consensus: 100 %	



Insertion of a cannula/ phlebotomy can induce stress or even be traumatic for children. Therefore during necessary cannula insertion for administering intravenous contrast prior to MRI, blood samples for tumour markers should be taken simultaneously. Additional phlebotomy should be prevented.

Recommendation 26	
Surveillance of patients with low-grade appendiceal mucinous neoplasms <b>ought</b> to include radiological imaging.	↑
If there is no contraindication, a contrast enhanced MRI of the abdomen and pelvis including diffusion-weighted imaging <b>ought</b> to be performed.	↑
Alternatively a contrast-enhanced CT of the abdomen and pelvis <b>can</b> be performed.	↔
Strong consensus: 100 %	



In paediatric patients, the modality of CT should not be used for surveillance of LAMN. If there are contraindications for MRI, an abdominal ultrasound should be performed by an experienced and certified sonographer.

Recommendation 27	
In the follow-up of patients with low-grade appendiceal mucinous neoplasms/ pseudomyxoma peritonei, the importance of screening colonoscopies for early detection of colorectal carcinoma <b>should</b> be highlighted.	↑↑
<b>Statement:</b> In asymptomatic patients who are followed up post low-grade appendiceal mucinous neoplasm/pseudomyxoma peritonei, there is no evidence to support screening colonoscopies before the age of 50.	
Strong consensus: 100 %	

Recommendation 28	
Surveillance for low-grade appendiceal mucinous neoplasms or pseudomyxoma peritonei <b>ought</b> to be performed for 5 years in six-monthly intervals.	↑
In individual cases, surveillance <b>can</b> be prolonged.	↔
Strong consensus: 100 %	

Table 6 Surveillance-Regimen

Months	6	12	18	24	30	36	42	48	54	60
Imaging*	X	X	X	X	X	X	X	X	X	X
Tumour markers**	X	X	X	X	X	X	X	X	X	X

\* MRI abdomen/pelvis, if contraindications for an MRI are present CT abdomen/pelvis should be used.

In paediatric patients with contraindications for MRI, ultrasound ought to be performed

\*\* CEA, CA 19-9, CA 125

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The symbol on the left highlights recommendations and statements that are specifically for children, or explains how recommendations should be implemented in this cohort

List of Abbreviations	
CA 125	Cancer Antigen 125
CA 19-9	Carbohydrate Antigen 19-9
CC-Score	Completeness of Cytoreduction Score
CEA	Carcinoembryonic antigen
CT	Computed tomography
HAMN	high-grade appendiceal mucinous neoplasm
HIPEC	Hyperthermic intraperitoneal chemotherapy
CRC	Colorectal carcinoma
LAMN	Low-grade appendiceal mucinous neoplasm
PCI	Sugarbaker peritoneal carcinomatosis index
PMP	Pseudomyxoma peritonei
UICC	Union for International Cancer Control
WHO	World Health Organization

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