The pathology of pseudomyxoma peritonei and appendix tumours

An introduction for patients and their carers

We're Pseudomyxoma Survivor. We're here to provide emotional support and practical advice, through an online community that's proven to make a real difference.

Together we're stronger and can face anything.

We rely on the generosity of people like you to fund our vital work. If you would like to make a donation, you can do so by visiting us at: pseudomyxomasurvivor.org/donate

Pseudomyxoma Survivor is a registered charity in England and Wales, number 1143642.

From our Chair

"Cancer of the appendix?"

"Never heard of that one" is an all too common exchange that for those of us with appendix cancer. Often these exchanges are with medical professionals. Mention pseudomyxoma peritonei (PMP) and people definitely glaze over.

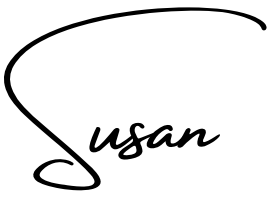
When I was initially diagnosed in 2003, I was told that I had mucinous adenocarcinoma of the appendix, Dukes
stage 4, which acted like a bowel cancer and therefore was to be treated as such.

As I understand it now, cancer of the appendix and PMP are not normally given a Dukes classification. I was confused and found it difficult to articulate to others exactly what my diagnosis was. My friend, a medical doctor, tried to reinterpret what I was telling her and had her suspicions for many years that I really should be seeing a surface malignancy specialist.

Classification of cancers is a complex business and even the experts can disagree. We are fortunate though, that within our community, a classification system has been developed. Norman Carr, MB BS FRCPath FRCPA FAcadMEd, Director of Research and Consultant Histopathologist at the Peritoneal Malignancies Institute, Basingstoke has had his contribution to the classification of Tumours of the Digestive System published by the World Health Organisation (WHO). Many appendiceal cancer specialists refer to and use his system.

We at Pseudomyxoma Survivor are grateful that he took time out of his busy schedule to present to our community. At the presentation, he explained the various types of appendiceal cancers and very patiently answered many questions from patients regarding their own understanding of their pathology. It is fair to say that many had been confused prior to his talk.

Once you can name what it is that you have, it is easier to self-advocate and receive the most viable treatment for you. "Never heard of that one". "Well, let me explain". This booklet will inform the patient of their type of cancer in a non-jargon, user-friendly way. Many thanks to Norman for the content and his support to our community to become their own advocates.



Susan Oliver
Chair
Pseudomyxoma Survivor

What we're going to cover

- What is pathology, and what is its role in patient care?
- What is pseudomyxoma peritonei?
- What kind of appendix tumours are there?

This document is intended as a brief overview for non-medical people and aims to answer these questions.

- Norman Carr, MB BS FRCPath FRCPA FAcadMEd

What is pathology?

MOST PEOPLE THINK OF AUTOPSIES WHEN PATHOLOGY IS MENTIONED, BUT POST MORTEM EXAMINATIONS ARE ONLY A PART OF PATHOLOGY.

In fact, the majority of pathologists are based in hospitals and deal with specimens from living patients. The branch of pathology in which surgical specimens are examined under the microscope is called histopathology.

This booklet will discuss the role of histopathology in diagnosis and treatment of pseudomyxoma peritonei (PMP) and the appendiceal tumours that are the most common cause of PMP.

What happens to a surgical specimen in the histopathology laboratory?

When the surgeon has removed an organ from the body, it is normally placed in a solution of formalin that preserves it and prevents decomposition. This is called fixing the specimen.

The specimen is sent to the histopathology laboratory where it is dissected by a pathologist or trained biomedical scientist.

The aim of specimen dissection is to:

- Record and describe the organs or other material received.
- Look for any features that may be important in prognosis or treatment (for example, in the appendix this might include whether the wall has ruptured)
- Select pieces of tissue for examination under the microscope

For examination under the microscope,

THE SELECTED TISSUE SAMPLES ARE EMBEDDED IN PARAFFIN WAX (SIMILAR TO THE WAX USED TO MAKE CANDLES), WHICH ALLOWS VERY THIN SECTIONS TO BE CUT.

The pieces of tissue are usually about 2cm wide and the sections are about 4µm thick. A human hair is about 20 times thicker.

The thin sections are stained so that the cells become visible under the microscope. The ones used most commonly in the histopathology lab are dyes and immunohistochemical stains. Examples are given on the next page.

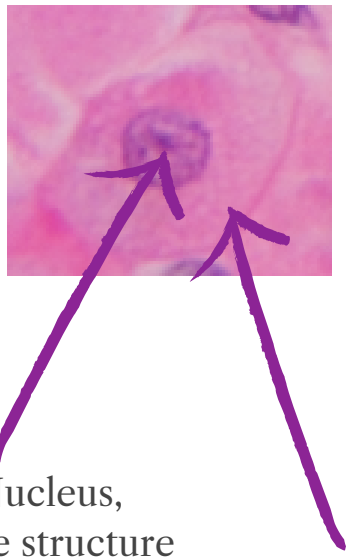
The slides are examined by a pathologist. Pathologists are medically qualified doctors who specialise in this field. The pathologist's report is sent to the surgeon and makes an important contribution to management decisions.

For example, the report will usually include:

- The diagnosis
- Features that can guide further treatment
- Features that may point to the likely outcome (prognosis)

A dye stain

Dyes stain the cells different colours. The image shows a cell with the combined haematoxylin and eosin stain. Haematoxylin is blue and eosin is pink/red.

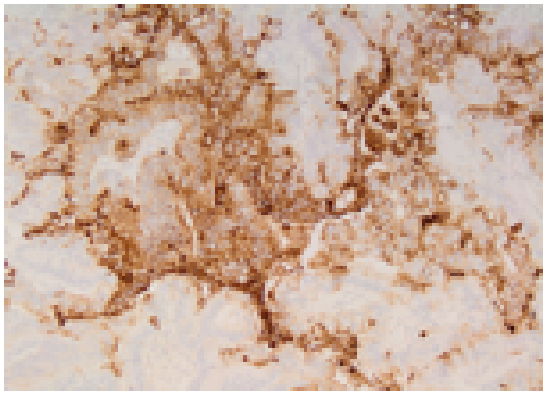


Nucleus, the structure that houses the DNA

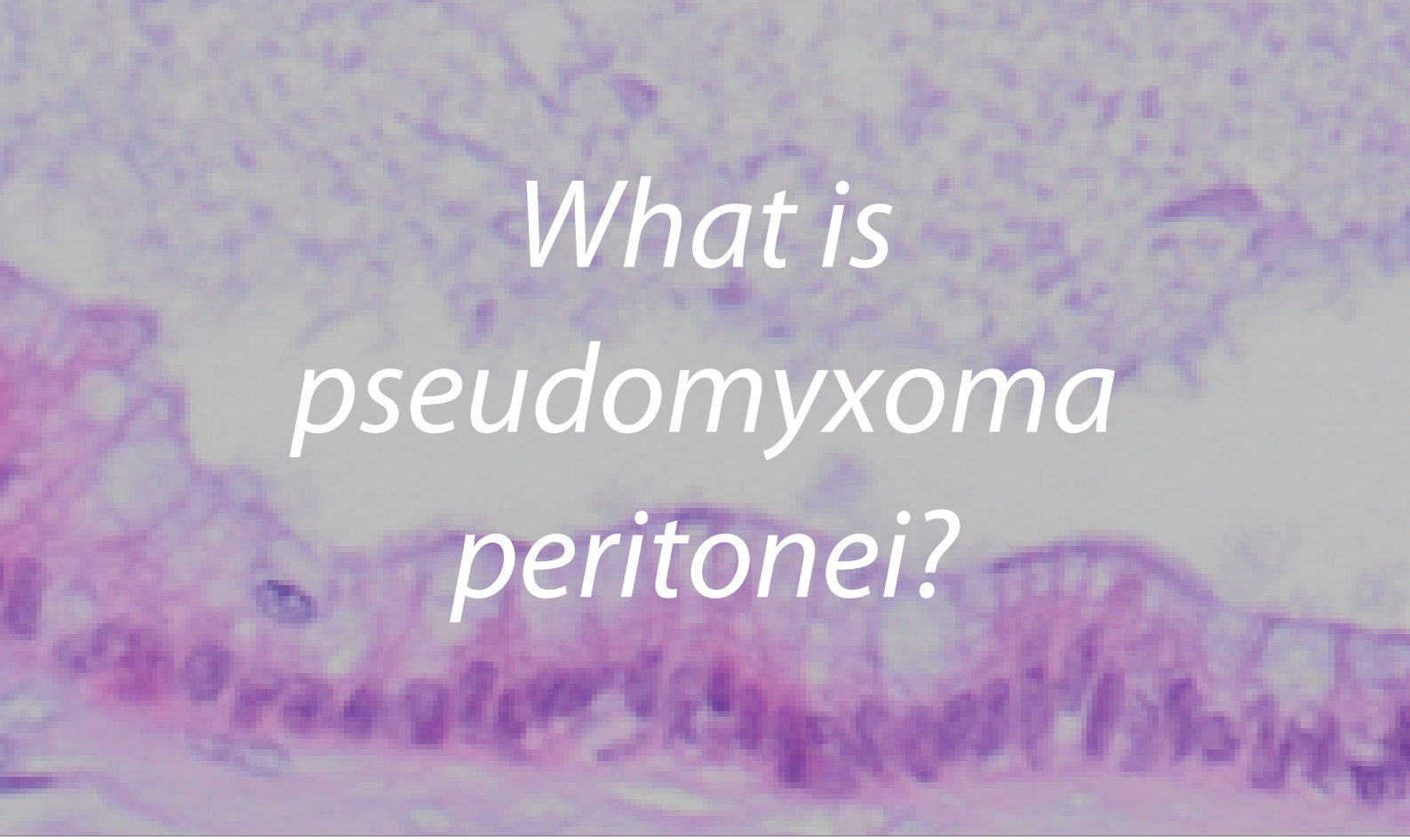
Cytoplasm, where most of the cell's metabolism occurs

An immuno-histochemical stain

Immunohistochemistry specifically identifies individual substances in the specimen. These stains use antibodies that only react with one particular substance. For example, the image shows a cancer in which immunohistochemistry for CEA (a marker of certain types of tumour) is positive.



The brown colour is the positive reaction and confirms the presence of CEA in the cancer.



What is pseudomyxoma peritonei?

PMP is an unusual condition in which a mucinous cancer spreads within the abdominal cavity causing mucin (mucus) to accumulate. The cancer usually arises in the appendix, although other sites of origin are encountered occasionally. The primary appendix tumours that can produce PMP are discussed later.

The abdominal cavity is also called the peritoneal cavity, because it is lined by a thin membrane called the peritoneum. This membrane covers the abdominal organs and the inside of the abdomen. The word peritonei reflects the fact that the peritoneum is involved in PMP.

PMP is different from other cancers that involve the abdomen in two main ways:

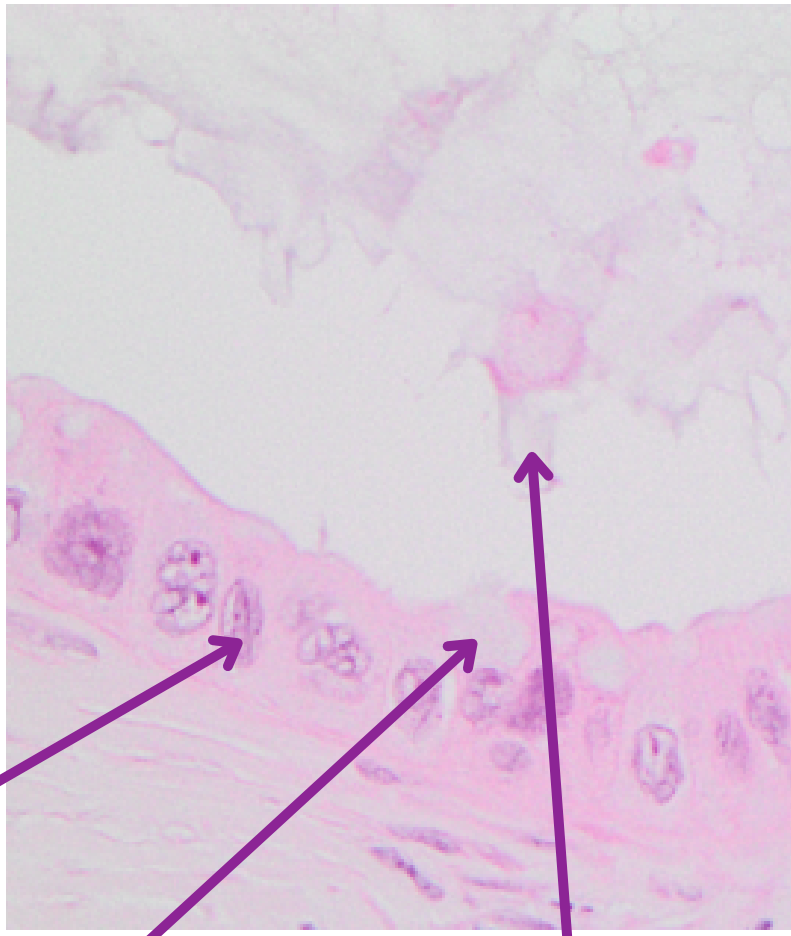
- It distributes itself widely through the abdominal cavity with the production of copious amounts of mucin

- It tends not spread to distant organs such as the lungs or bones (although there are exceptions)

PMP under the microscope

IN PMP, THE CANCER CELLS GROW IN THE ABDOMINAL CAVITY WHERE THEY PRODUCE LARGE AMOUNTS OF MUCIN.

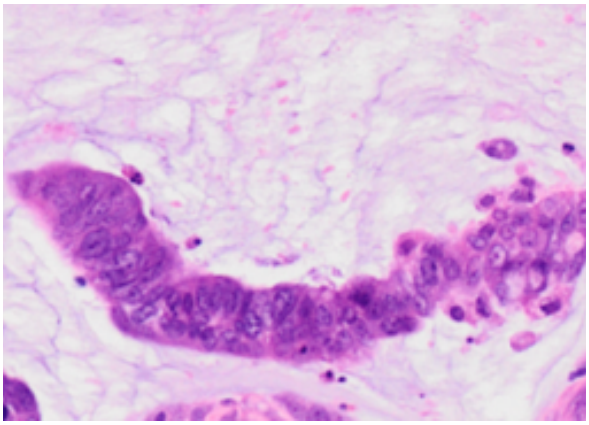
The image shows a typical example stained with haematoxylin and eosin under the microscope.



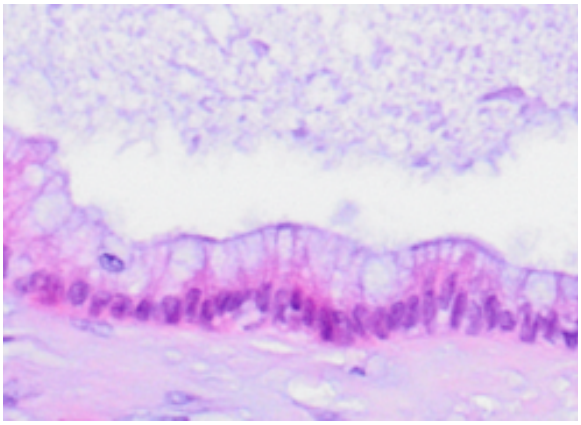
Grading PMP

Grade refers to the aggressiveness of a cancer. In PMP, high grade lesions tend to grow quickly and patients are more likely to be offered chemotherapy. Low grade lesions grow more slowly and sometimes may be present for years without causing serious problems.

High grade PMP is characterised by cells that look very abnormal and may be seen to infiltrate adjacent tissue. The cells of low grade PMP look more normal.



High grade PMP



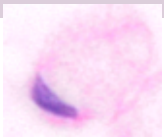
Low grade PMP

Pathological terminology

Unfortunately, medical terms can sometimes be confusing and there are often multiple names for the same condition. PMP is no exception and has been classified in different ways over the years. The current classification, endorsed by the World Health Organization (WHO), is shown in the Table. It uses the term “mucinous carcinoma peritonei”, which is the same as “PMP”.

Category	WHO grade	Typical histological features
Low-grade mucinous carcinoma peritonei	G1	Strips of mucinous cells showing relatively few abnormal features lying within abundant mucin
High-grade mucinous carcinoma peritonei	G2	High-grade features involving at least 10% of the tumour
High-grade mucinous carcinoma peritonei with signet ring cells	G3	Signet ring cells present (signet ring cells are a type of cell associated with worse prognosis)

a signet ring cell →

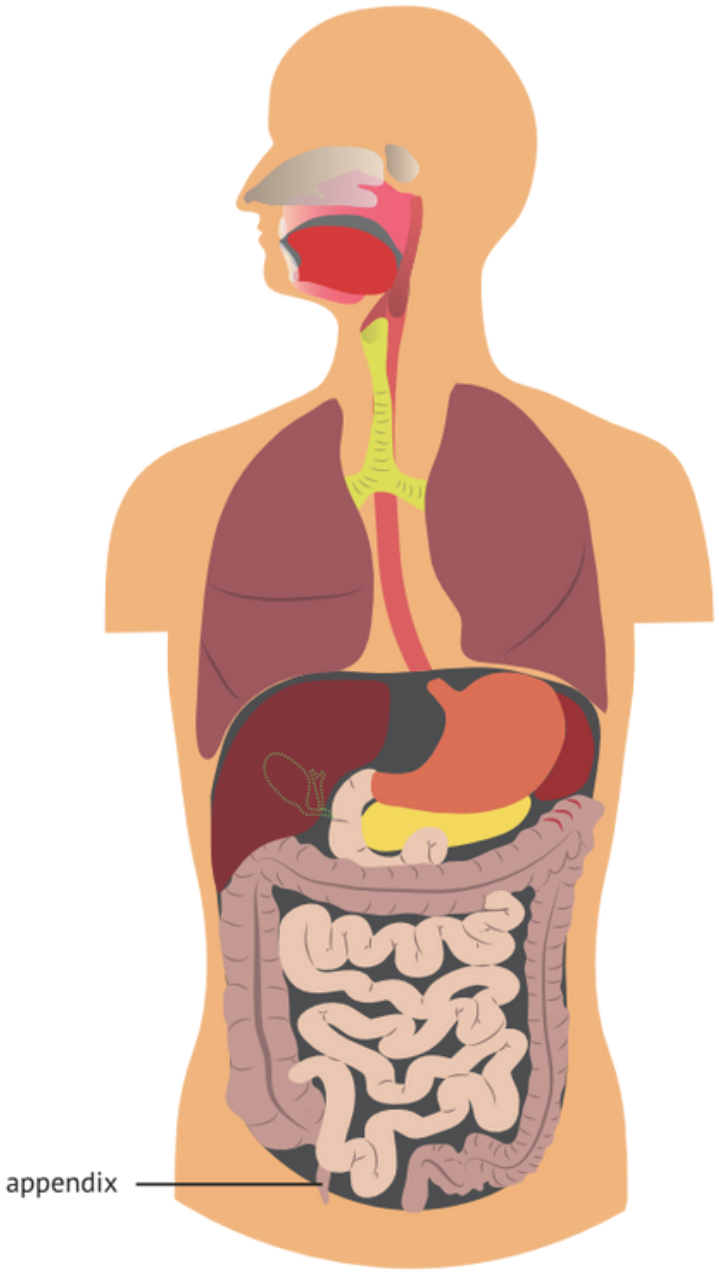


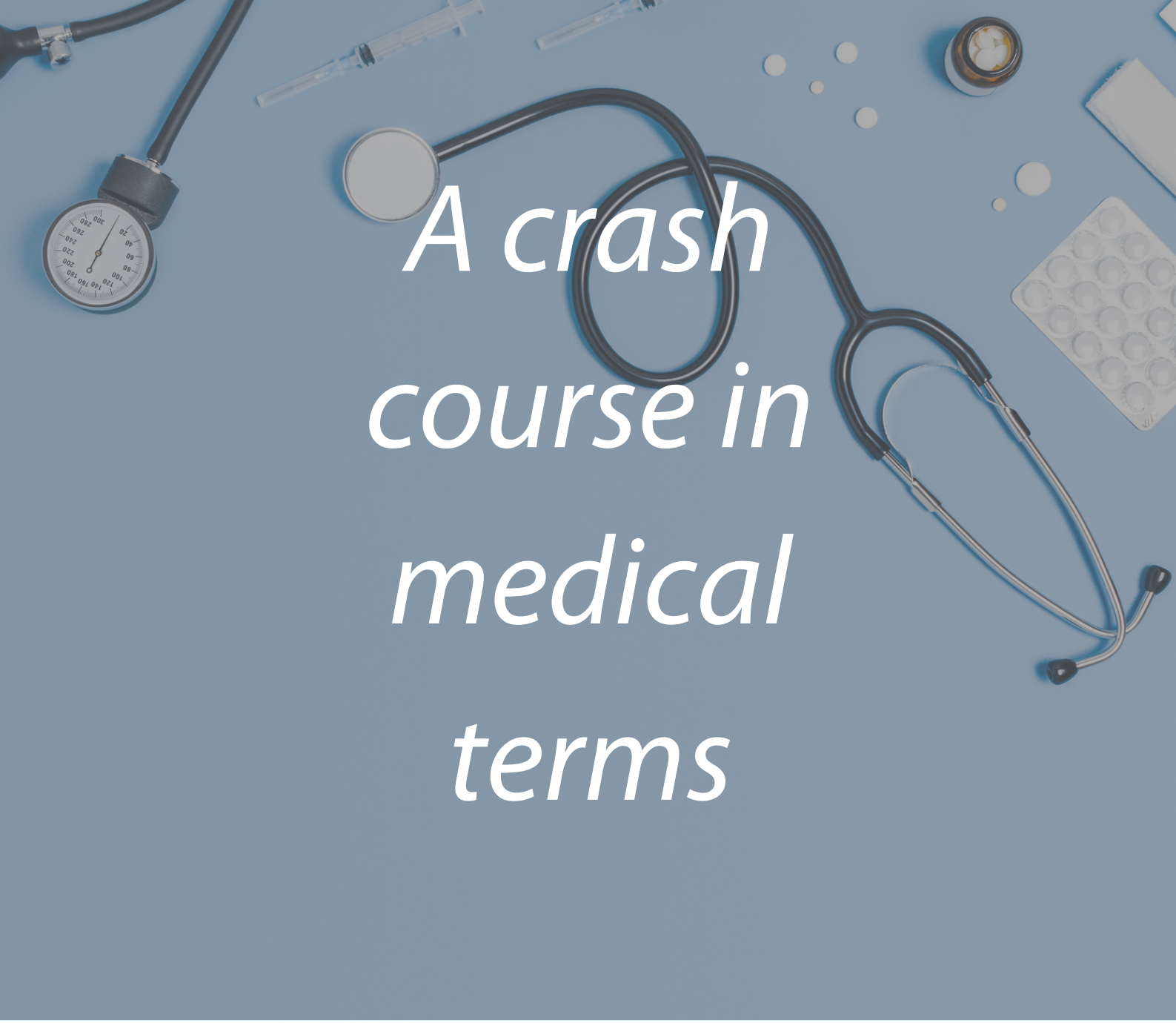
What kind of appendix tumours are there?

THE APPENDIX IS A WORM-LIKE OUTPOUCHING AT THE UPSTREAM END OF THE LARGE INTESTINE.

Once thought be vestigial with no particular function, we now know it has evolved as a lymphoid organ that plays a part in immune reactions, similar to the tonsils. It also acts as a reservoir for the “good bacteria” that normally live in our intestines.

Because it is a small organ, cancer of the appendix is much less common than, say, cancer of the large intestine. However, it is prone to specific types of tumour that are peculiar to it. This document will focus on the tumours that can lead to PMP.





A crash course in medical terms

IF YOU ARE NOT FAMILIAR WITH THE WORDS USED BY DOCTORS WHEN DESCRIBING TUMOURS, HERE ARE SOME DEFINITIONS:

Benign

Cannot spread to distant parts of the body

Malignant

Can spread to distant parts of the body

Tumour

A mass due to autonomous growth of cells, whether benign or malignant

Neoplasm

Another word for tumour

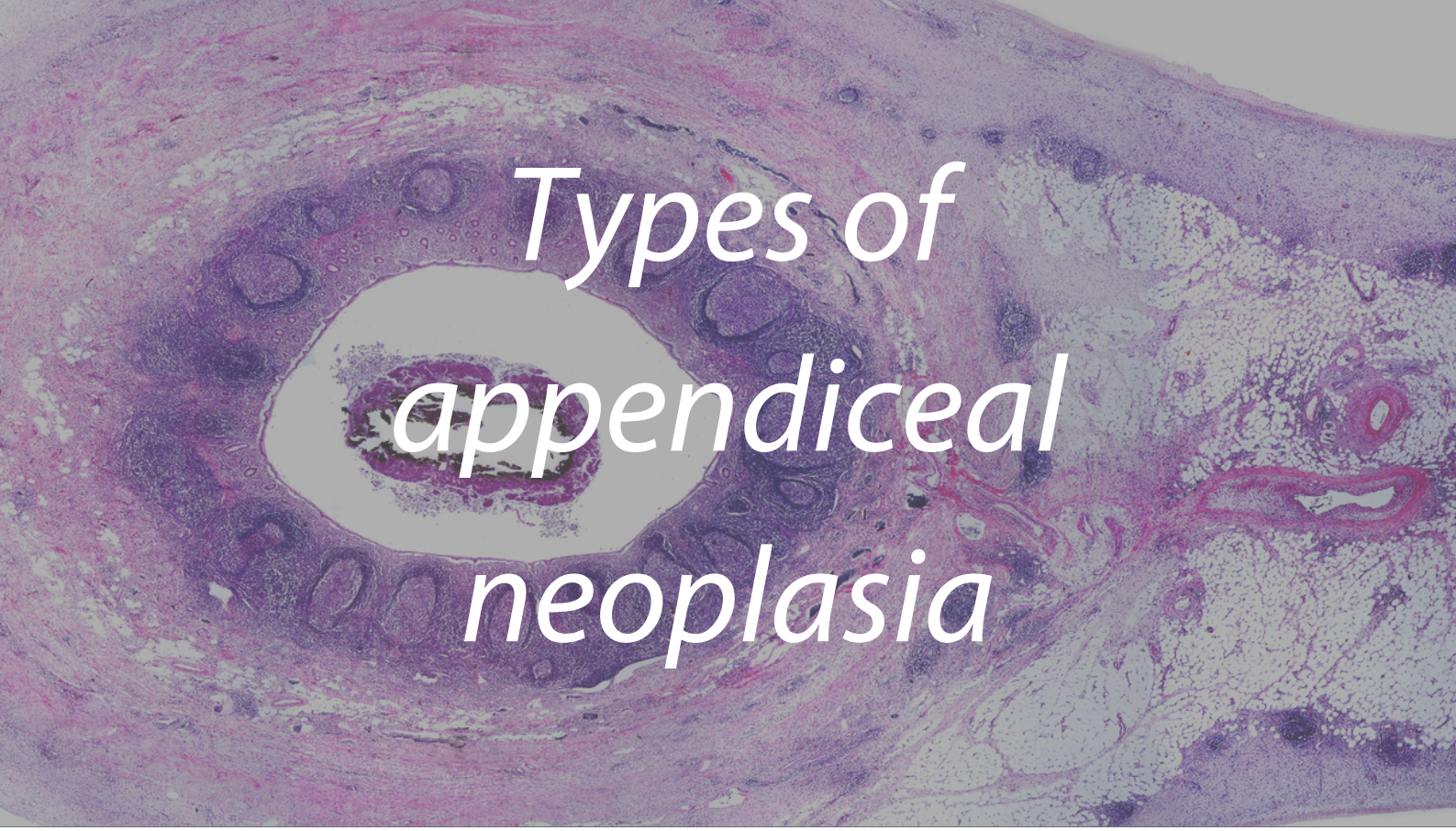
Cancer

A malignant tumour

Lesion

Anything abnormal on or in the body, not just neoplasms

Neoplasms are classified according the type of normal cell they resemble. For example, adenocarcinoma is a type of cancer resembling glands (adeno = gland and carcinoma = cancer of lining cells). Tumours are called mucinous if more than 50% of the mass consists of mucin.



Types of appendiceal neoplasia

THE MAIN TYPES OF NEOPLASM ARISING IN THE APPENDIX ARE

Mucinous appendiceal neoplasms

these are the type that are the usual source of PMP

Goblet cell adenocarcinomas

rare and occasionally show PMP-like spread

Non-mucinous adenocarcinomas

can spread to peritoneum but do not cause PMP

Neuroendocrine neoplasms

do not cause PMP

Mucinous appendiceal neoplasms

THERE ARE FOUR MAIN TYPES OF MUCINOUS APPENDICEAL NEOPLASM. THEY ARE CLASSIFIED BY GRADE AND TYPE OF INVASION AS SHOWN IN THE TABLE.

The commonest is **LAMN** and this tumour is the most frequent cause of PMP.

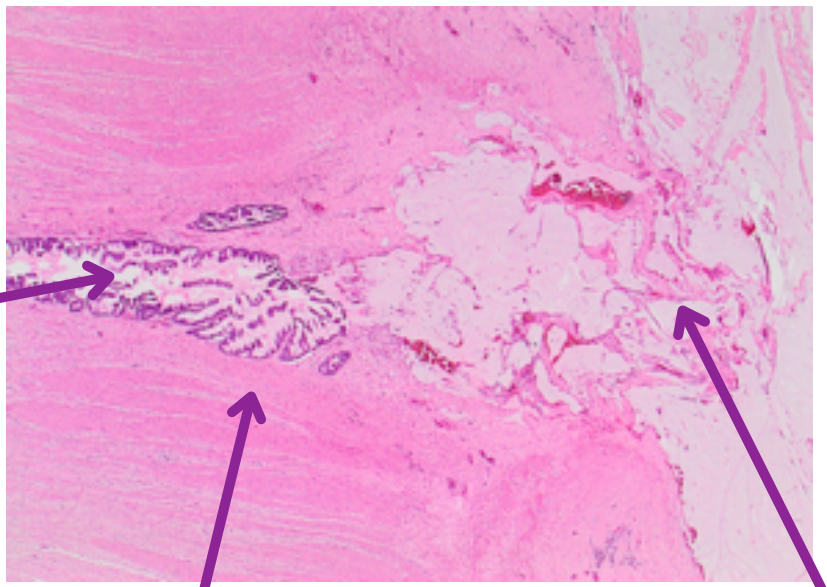
HAMN is rare. Despite its name, it is not as aggressive as mucinous adenocarcinoma, which by definition shows infiltrative invasion of surrounding tissues.

As mentioned earlier, **signet ring cells** are associated with poor prognosis statistically and have the highest grade.

	Type of appendiceal neoplasm	Cells	Type of invasion	WHO Grade
1	Low-grade appendiceal mucinous neoplasm (LAMN)	Low grade	Pushing	G1
2	High-grade appendiceal mucinous neoplasm (HAMN)	High grade	Pushing	G2
3	Mucinous adenocarcinoma	Any grade	Infiltrative	G2
4	Mucinous adenocarcinoma with signet ring cells	Signet ring cells present	Infiltrative	G3

PMP occurs when cells from a mucinous appendiceal neoplasm enter the abdominal cavity

The image is a low-power view of a section stained with haematoxylin and eosin. It shows an LAMN of the appendix that has ruptured due to pushing invasion through the appendiceal wall. The neoplastic cells can then escape into the abdomen, where they can grow and produce PMP.



Discordant histology

THE GRADE OF THE PERITONEAL DISEASE USUALLY MATCHES THAT OF THE APPENDICEAL PRIMARY,

but occasionally the grade differs (e.g. LAMN with high-grade mucinous carcinoma peritonei). This is termed "**discordant histology**".

Therefore, the appendiceal primary and peritoneal disease should be graded separately and independently. It appears that prognosis is more related to the histology of the peritoneal disease.

Another example of discordance is seen when low grade PMP is found at the first operation but high grade PMP is found at a subsequent operation. Presumably, this represents progression of the disease with increasing genetic abnormalities over time.

The role of the pathologist in PMP

THE PATHOLOGIST IS PART OF THE MULTIDISCIPLINARY TEAM OF SURGEONS, NURSES, RADIOLOGISTS, ONCOLOGISTS, PHYSIOTHERAPISTS, DIETITIANS, PSYCHOLOGISTS AND OTHERS.

Pathologists are particularly involved at two points in the care pathway.

1. **At the time of initial diagnosis**

   The pathologist may make the diagnosis of PMP based on a biopsy taken from the abdominal disease, or identify and classify a cancer in an appendectomy specimen.

2. **At the time of surgical treatment**

   Assuming it is in the patient's best interests, the treatment usually offered for PMP in specialist centres is cytoreductive surgery with heated intraperitoneal chemotherapy. The organs removed during surgery are sent for histopathology and the pathologist will issue a report covering features to guide management, such as the grade of the PMP and whether lymph nodes are involved.

New developments and future directions

Novel treatments for cancer are being introduced all the time. For example, some cancers, including high grade PMP and appendiceal adenocarcinomas, may be treated with drugs such as cetuximab that are directed against the epidermal growth factor receptor on cancer cells.

However, a common gene that is mutated in cancer cells is RAS, and these particular drugs are not effective in cancers with RAS mutations. Therefore, testing for RAS status is now part of the histopathological assessment of tissue from patients with these tumours. Furthermore, research into drugs that might actively target mutated RAS genes is ongoing.

Our abilities to detect genetic abnormalities in cancer cells are constantly improving. Research into the abnormal genes of PMP is in its infancy, but one day could lead to new treatments.

Thank You...

Pseudomyxoma Survivor is dedicated to supporting those affected by pseudomyxoma peritonei (PMP), appendix cancer and other peritoneal surface malignancies through practical and emotional support. We also raise awareness and support research.

As survivors and carers, information here is from our perspective – we are not health care professionals. We are all individuals, everyone is different. We recommend that you take advice from your doctors for specific information.

Contact Information

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Website:
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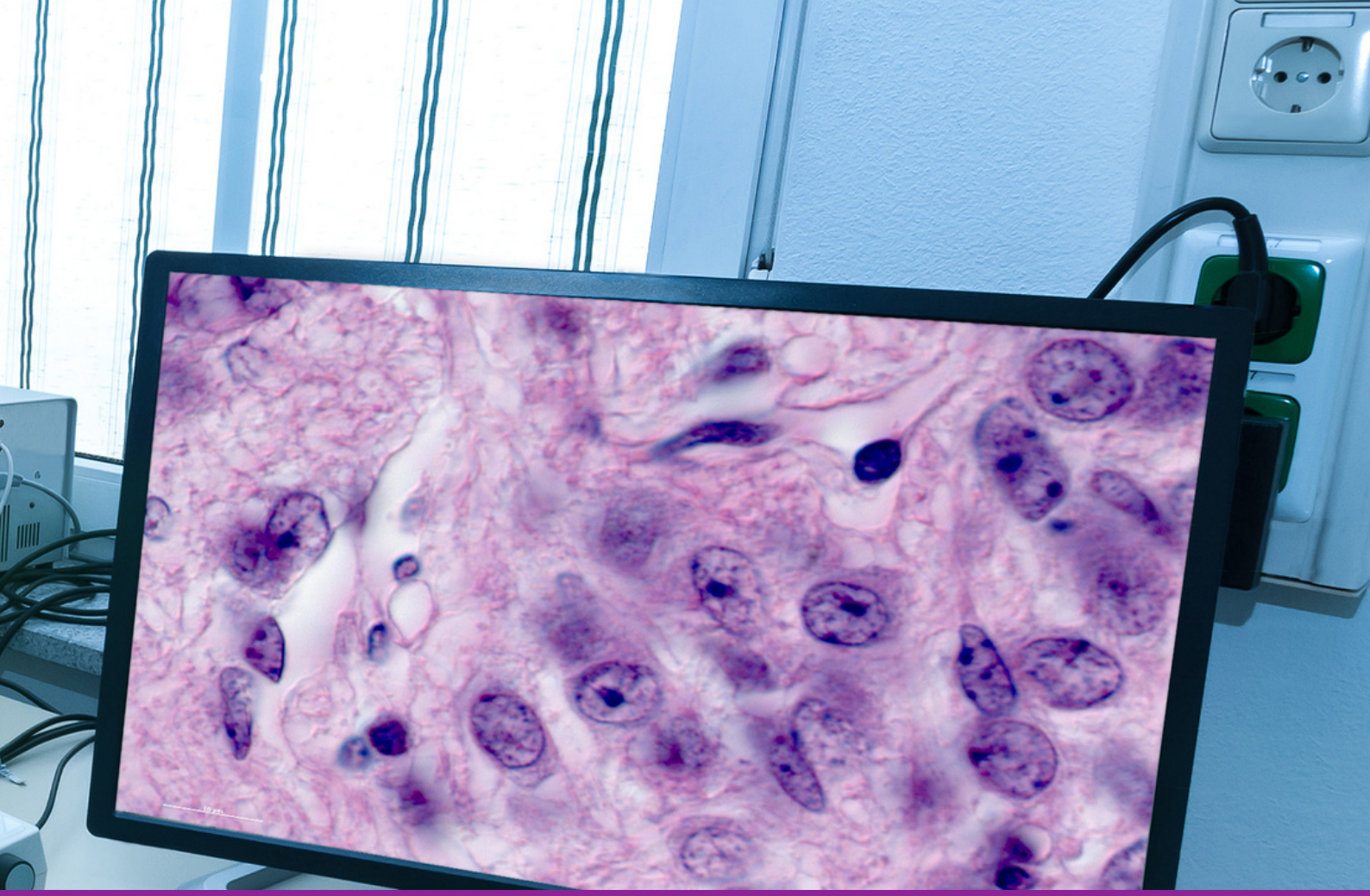

As a consequence of the difficulty of diagnosis, many patients are initially misdiagnosed, some being given very grave life expectancies and little support. The primary aims of Pseudomyxoma Survivor are to raise awareness, both in the medical profession and the wider community, and to provide support to those affected by the disease.

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