



Primary and metastatic peritoneal surface malignancies

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Abstract | Peritoneal surface malignancies comprise a heterogeneous group of primary tumours, including peritoneal mesothelioma, and peritoneal metastases of other tumours, including ovarian, gastric, colorectal, appendicular or pancreatic cancers. The pathophysiology of peritoneal malignancy is complex and not fully understood. The two main hypotheses are the transformation of mesothelial cells (peritoneal primary tumour) and shedding of cells from a primary tumour with implantation of cells in the peritoneal cavity (peritoneal metastasis). Diagnosis is challenging and often requires modern imaging and interventional techniques, including surgical exploration. In the past decade, new treatments and multimodal strategies helped to improve patient survival and quality of life and the premise that peritoneal malignancies are fatal diseases has been dismissed as management strategies, including complete cytoreductive surgery embedded in perioperative systemic chemotherapy, can provide cure in selected patients. Furthermore, intraperitoneal chemotherapy has become an important part of combination treatments. Improving locoregional treatment delivery to enhance penetration to tumour nodules and reduce systemic uptake is one of the most active research areas. The current main challenges involve not only offering the best treatment option and developing intraperitoneal therapies that are equivalent to current systemic therapies but also defining the optimal treatment sequence according to primary tumour, disease extent and patient preferences. New imaging modalities, less invasive surgery, nanomedicines and targeted therapies are the basis for a new era of intraperitoneal therapy and are beginning to show encouraging outcomes.

Sarcoma

A cancer of the connective tissue including bones, nerves, muscles, tendons, cartilage or blood vessels.

Orphan diseases

Diseases that have been ignored, mostly owing to their rarity.

Peritoneal surface malignancies (PSM) comprise a heterogeneous group of quite different cancers in terms of incidence, sensitivity to systemic therapies and prognosis, all of which are unique in their proclivity for peritoneal dissemination. PSM can be primary tumours of the peritoneum (peritoneal mesothelioma and primary peritoneal cancer) or disseminate secondarily as peritoneal metastasis from tumours of other organs, which include those of intraperitoneal origin (tumours of the digestive and female reproductive tract as well as sarcoma) and those of extraperitoneal origin (lung, breast and kidney tumours) (FIG. 1).

Until ~10 years ago, PSM were considered orphan diseases with limited therapeutic options and heralded a poor prognosis¹. The primary reasons for poor patient outcomes are related to diagnosis at an advanced stage and the limited clinical response of most entities to conventional therapeutic options such as systemic chemotherapy. Major innovations over the past two decades include the adoption of novel surgical techniques, such

as peritonectomy procedures and multivisceral resections to obtain complete cytoreduction (defined as absence of macroscopic disease)², and the application of intraperitoneal chemotherapy to address microscopic residual disease^{3–5}. Despite the perception of high morbidity of such procedures, optimization of perioperative care has led to the morbidity and mortality rates of these procedures being equivalent to those of other major abdominal cancer surgeries^{6–9}. Concurrent development of new multidisciplinary strategies involving perioperative systemic chemotherapy¹⁰ and targeted and maintenance therapies¹¹ has dramatically changed the landscapes and the prognoses of these diseases. In selected patients, long-term survival and even cure have become possible and the overall prognosis seems to be equivalent to that of patients with metastatic disease at other sites (such as in the liver or the lungs)¹². In addition to therapies with curative intent, the development of less invasive and better-tolerated treatments can also provide symptomatic relief and improved survival for patients

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<https://doi.org/10.1038/s41572-021-00326-6>

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with advanced disease and, therefore, a more optimistic outlook for patients and their families.

In this Primer, we describe the epidemiology, pathophysiology, diagnosis and prevention of primary peritoneal mesothelioma and primary peritoneal cancer, and of peritoneal metastases of the digestive tract, female reproductive tract and sarcoma as well as of extraperitoneal tumours. We discuss in detail the treatment options, with special emphasis on the quality of life (QoL) of patients with PSM, and close with an outlook on upcoming innovations.

Epidemiology

Incidence and prevalence of PSM vary widely based on the underlying primary tumour, with the highest incidence in patients with ovarian and gastric cancer¹³. As PSM are difficult to detect on cross-sectional imaging and not specifically documented in national registries as no separate code previously existed until recently, estimating their true incidence is difficult. Additionally, sites of metachronous metastases are not captured in most cancer registries, making it challenging to estimate the incidence of isolated peritoneal metastases. The GLOBOCAN registry, which provides estimates of the global incidence of cancer in 185 countries, does not record the incidence of PSM separately¹⁴. The closest approximation of these data comes from cohort studies that report the incidence or prevalence of peritoneal metastases as the proportion of patients with a particular histological subtype^{15,16}. All data relating to the incidence and prevalence of PSM comes from high-income countries in the Western world. The incidence of most common cancers giving rise to PSM, such as ovarian, gastric and colorectal cancers, increases with age and they are more common in the age group ≥ 50 years¹⁴. In the past few decades, the incidence of these cancers has been increasing, especially that of colorectal cancer. However, the overall age-adjusted incidence of PSM seems to be mostly unchanged over the past four decades¹⁷. Of note, the incidence of secondary PSM by far exceeds the incidence of primary PSM. Between 2012 and 2016, the annual age-adjusted incidence of primary peritoneal

malignancies was 4.36 per 1,000,000 persons and that of synchronous secondary peritoneal metastases was 99.0 per 1,000,000 persons in the Czech Republic¹⁷.

PSM secondary to intraperitoneal tumours

The specific incidences of PSM vary depending on the underlying malignancy. Globally, the incidence of ovarian cancer and, therefore, of peritoneal metastases from ovarian cancer has increased in the past decade, with the highest average annual percentage change of 4.4% found in Brazil, which may be associated with an increase in sedentary behaviour^{18,19}. The reported relative incidence of peritoneal metastases from ovarian cancer is 60–70% whereas it is <10% for other gynaecological malignancies²⁰. Although studies on mortality specific to ovarian peritoneal metastases are lacking, overall mortality due to ovarian cancer has declined, most probably because more effective treatments have become available^{21,22}.

For gastrointestinal malignancies, the relative incidence of peritoneal metastases is highest for gastric cancer, at 15–43% (for both synchronous and metachronous metastases), depending on gastric cancer subtype^{23,24}. Although the incidence of gastric cancer is the highest in East Asia (Japan and Mongolia) and Eastern Europe, specific reporting of the incidence of peritoneal metastases from gastric cancer from these regions remains scarce¹⁴. In a registry study from the Netherlands, peritoneal metastasis was detected in 14% of gastric cancers at the time of initial diagnosis, with a median survival time of 4 months^{24,25}. For colorectal cancer, the relative incidence of synchronous peritoneal metastases is 4–15%^{16,26}. Around 8% of patients at the time of primary resection and up to 25% of patients with recurrent colorectal cancer will develop metastatic disease confined to the peritoneal surfaces^{16,27}. Appendiceal mucinous tumours are the most common underlying cause of pseudomyxoma peritonei (PMP), with a reported incidence of 0.4–1.9 per 1,000,000 person-years²⁸.

PSM secondary to extraperitoneal tumours

Compared with intraperitoneal tumours, extraperitoneal tumours rarely cause PSM, and data from population-based studies on the incidence of PSM from these cancers are very scarce. In a population-based study from Ireland, 5,791 patients were diagnosed with PSM from 1994 to 2021, of whom 543 (9%) had an extra-abdominal primary malignancy²⁹. Breast cancer (40.8%), lung cancer (25.6%) and melanoma (9.3%) were the most common extra-abdominal cancers to develop PSM. The actual incidence of PSM from these cancers is low: 1.2% of 1,041 patients with lung cancer treated over a 26-year period in a cohort study from Japan and 0.7% in 3,096 patients with breast cancer treated from 2001 to 2010 in a cohort study from the USA^{30,31}.

PSM of primary peritoneal tumours

A population-based study from Sweden showed an increase of 0.9 to 1.24 per million per year in the incidence of peritoneal mesothelioma in the years 2011–2015 compared with 1993–2003 (REF.³²). Occupational or environmental exposure to asbestos is a risk factor for

Metachronous metastases

Metachronous metastases are diagnosed at least 3 months after diagnosis of the primary tumour, whereas synchronous metastases are diagnosed with the primary tumour or up to 3 months after its diagnosis.

Pseudomyxoma peritonei (PMP)

This syndrome results from the progressive accumulation of mucin in the peritoneal cavity; perforation of an epithelial neoplasm of the appendix is the most common cause.

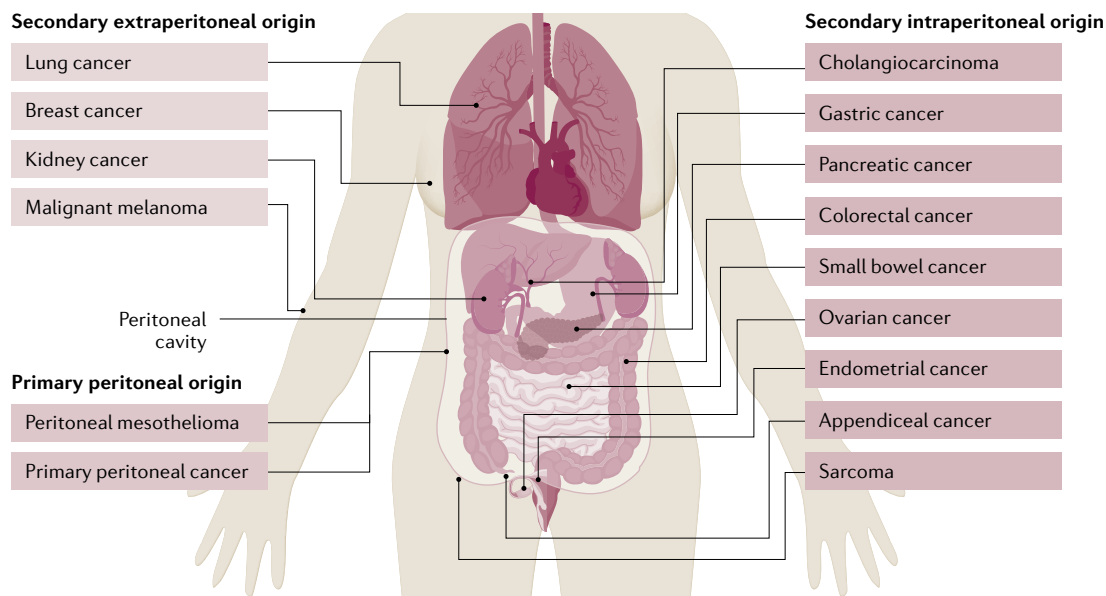


Fig. 1 | Tumours causing peritoneal surface malignancies. Peritoneal surface malignancies are a heterogeneous group of malignancies that can arise from primary tumours of the peritoneum or disseminate secondarily as peritoneal metastases from tumours of intraperitoneal origin and from tumours of extraperitoneal origin.

peritoneal mesothelioma and legislative measures banning its use since the 1980s (for example, in the USA, European Union and Russia) have resulted in a decline in the incidence of mesothelioma in these countries^{33,34}. From 2008 to 2012, the world standardized incidence per 100,000 persons was 0.9 for men and 0.3 for women in the USA, and 1.7 for men and 0.4 for women in Europe. The incidence has declined in the USA since 2012 and in Europe since 2016. The decline is in the range of 10–20% and is seen more in men than in women. For other PSM, no single preventable risk factor can be associated with the risk of developing either the primary tumour or secondary peritoneal metastases.

Trends in prognosis of PSM

Randomized controlled trials and cohort studies show that the survival of patients with peritoneal metastases from various primary sites treated with a combination of locoregional and systemic treatment has improved compared with historical data from patients who received palliative treatment alone^{35–41}. There are several reasons for this trend. The number of patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has increased in the past three decades^{42–45}. The increase in early diagnosis can be attributed to the improvement in imaging modalities and increased awareness⁴⁶. Additionally, more effective systemic therapies for PSM have been developed^{47–49}, enabling PSM resection in more patients. However, these data represent outcomes of subgroups of patients (mainly from high-income countries) and data from population-based studies are very limited.

Risk factors

In general, secondary peritoneal metastases arise when the primary tumour is at an advanced stage. The T stage of the primary tumour, regional lymph node

involvement, histological subtype and positive peritoneal fluid cytology are some of the risk factors for peritoneal metastases that are common to most of the underlying primary tumours^{50–52}.

Over the past few decades, a high number of cancer risk genes for many gastrointestinal and gynaecological malignancies have been discovered. Around 10% of colorectal cancers and 20–25% of ovarian cancers are associated with germline genetic disorders^{53,54}. Defects in DNA repair pathways, such as homologous recombination repair and mismatch repair, are the most frequently described molecular mechanisms related to inherited cancers. Homologous recombination repair deficiency is often related to the *BRCA1* and/or *BRCA2* mutations, whereas mismatch repair deficiency is commonly associated with Lynch syndrome. *BRCA1* and *BRCA2* germline mutations account for 15% of unselected epithelial ovarian cancers and are also associated with gastrointestinal cancers, such as pancreatic, colorectal and gastric cancer, but the clinical importance in gastrointestinal cancers is not yet clear. Lynch syndrome is characterized by a germline mutation in a mismatch repair gene (*MLH1*, *MSH2*, *MSH6* or *PMS2*) or a germline deletion in *EPCAM* leading to inactivation of *MSH2*. Lynch syndrome accounts for 3% of colorectal cancers (usually located on the right side) but also for some extracolonic cancers such as endometrial, small bowel, gastric, hepatobiliary tract, ureteral and ovarian cancer⁶⁰. Other mutations linked with colorectal cancer include *APC* involved in familial adenomatous polyposis^{53,55}. Hereditary diffuse gastric cancer is linked to mutations of *CDH1*, which encodes the cell–cell adhesion protein E-cadherin⁵⁶. Individuals with this genetic syndrome frequently develop signet ring cell carcinoma, which has a high risk of peritoneal metastases. For malignant mesothelioma, germline *BAP1* mutations have been shown to increase the risk of developing peritoneal

T stage

The invasion depth of a primary tumour into the wall of the affected organ.

Cytology

Exam of single cell types in fluid specimens.

Familial adenomatous polyposis

A rare genetic condition resulting from a defect of *APC* leading to multiple polyps throughout the colon and associated with a near 100% risk of developing bowel cancer.

Microvilli

Small finger-like projections that increase the surface area of some cell types, including mesothelial cells.

Peritoneal cavity

The anatomical space in the abdomen and pelvis lined by peritoneum.

Mesothelial cells

Specialized cells that line certain body cavities or organs; these multifunctional cells have various functions, including the lubrication of surfaces and absorption of excess fluids.

mesothelioma after asbestos exposure⁵⁷. Owing to the increased awareness of hereditary cancer risk, improved access to genetic counselling, surveillance and prophylactic risk-reducing surgery, a decrease in the incidence of these diseases and their secondary peritoneal metastases can be expected^{58–61}.

Mechanisms/Pathophysiology**Peritoneal anatomy and physiology**

The peritoneum is the largest and most complex serous membrane of the human body. The visceral peritoneum, covering the intra-abdominal organs and mesentery, forms a continuous layer with the parietal peritoneum, which lines the abdominal wall and pelvic cavities (FIG. 2). As a large sac, it covers abdominal organs that are tethered but still retain considerable mobility. The peritoneal surface area in adult women is $\sim 1.7\text{ m}^2$ (slightly more, on average, in men) but, when the enormous array of microvilli (≥ 300 per mesothelial cell) is considered, the total area is likely much larger. This has important implications for the role of the peritoneum as a transport barrier in intraperitoneal chemotherapy⁶². The peritoneum is a closed-sac system in men, whereas it is an open-sac system in women where the fallopian tubes and ovaries are continuous with the peritoneal cavity. It is involved in the exchange of nutrients, metabolites and gases⁶³, and serves as a barrier to infectious agents and as a line of defence through the transfer of innate and adaptive immune cells, cytokines and chemokines.

Most knowledge of the peritoneum is informed by studies in animal models^{64–69}. Scanning electron microscopy and histological and immunohistochemical examination confirm that the morphology of the mammalian peritoneum is similar across species. Histologically, the peritoneum consists of a monolayer of mesothelial cells

supported by a basement membrane that rests on a layer of connective tissue, also referred to as the submesothelium or stroma⁷⁰. Morphologically, the mesothelial cells are predominantly squamous-like, flattened with microvilli but cuboidal mesothelial cells exist in some areas of the abdominal cavity. Mesothelial cells have both mesodermal (vimentin and desmin expression) and epithelial (cytokeratin expression) features⁷¹.

The peritoneum provides a slippery, non-adhesive surface through the microvilli of mesothelial cells, which produce large amounts of phosphatidylcholine and hyaluronic acid, forming the glycocalyx together with associated plasma proteins⁷². Mesothelial cells produce humoral factors, such as complement C3 and C4 and human β -defensins, which, together with recruited cellular components of the immune system, comprise the peritoneal fluid protective mechanism^{73–76}. The peritoneum also participates in immune responses against peritoneal pathogens that access the abdominal cavity. Mesothelial cells generate a chemotactic cytokine gradient from the basal to the apical side of the mesothelial lining, including IL-6 (REFS^{77–79}), IL-8 (REFS^{78,80}), IL-10 (REF⁷⁹), IL-15 (REF⁸¹), monocyte chemoattractant protein 1 (MCP1)⁸² and stromal cell-derived factor 1 (SDF1)⁸³. The mesothelial cell membrane also expresses receptors related to innate immunity such as Toll-like receptors^{80,82,84} and nucleotide-binding oligomerization domain (NOD)-like receptors⁸². Leukocyte migration over the mesothelial lining is facilitated by integrins and adhesion molecules such as vascular cell adhesion molecule 1 (VCAM1)^{78,85–87} and intercellular adhesion molecule 1 (ICAM1)^{78,87}. Mesothelial cells participate in antigen presentation through presentation of major histocompatibility complex class II (MHC II) on their cell surface, both in an unstimulated state and after IFN γ stimulation^{88–90}.

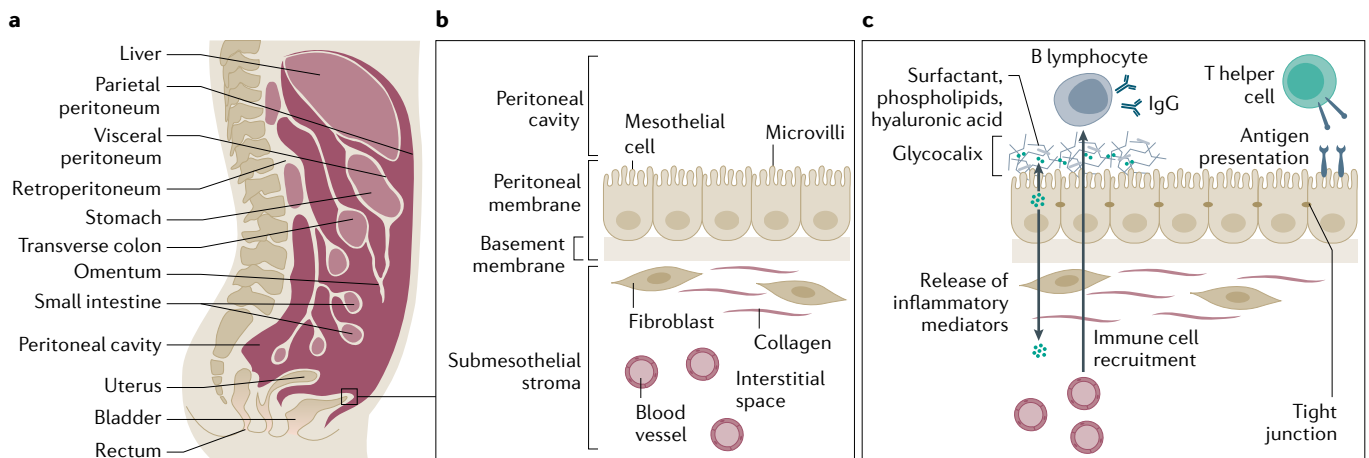


Fig. 2 | Peritoneal anatomy and physiology. a | The peritoneum is a serous membrane consisting of a single layer of mesothelial cells with complex apical and basal interactions. It forms a peritoneal sac that covers the abdominal organs. The visceral peritoneum describes the layer of the peritoneum adjacent to the abdominal organs, and the parietal peritoneum is the layer that adheres to the abdominal wall. The peritoneal cavity is the (virtual) space between these two layers that is filled with a small amount of serous fluid in the healthy state. **b** | The healthy peritoneal cavity is lined by mesothelial cells that express hundreds of microvilli per cell, which enable nutrient, waste and gas exchange as well as some organ mobility.

The mesothelial cells are supported by a basement membrane, which consists of a laminin polymer and a collagen IV network. Numerous other cells contribute to a dynamic submesothelial stroma that responds to mechanical stress, cellular damage and infection. **c** | Immune cells may traffic to the mesenchymal apical surface, which is protected by a complex chemical mix predominated by a glycocalyx, despite close cellular connections via tight junctions. Depending on the health status of the peritoneum and the presence of antigens, various inflammatory mediators can be released in both directions. Parts **a** and **b** adapted from REF.⁴⁰⁶, Springer Nature Limited.

Peritoneal injury and repair

In the context of chronic (long-term peritoneal dialysis) or acute (surgical) peritoneal tissue injury, mesothelial cells have a dynamic role in tissue repair and scarring^{91,92} and regulate macrophage emigration from a site of inflammation⁹⁰; they can promote procoagulant^{93,94}, fibrinogenic and fibrinolytic mediators⁹⁵. The repair process is facilitated by the production of an extracellular matrix (ECM) of type I, III, and IV collagen, elastin, fibronectin, laminin, and proteoglycans^{91,92}. The repair process is modulated via expression of tumour necrosis factor (TNF)⁹⁶, IL-1 β ⁹⁷, epidermal growth factor (EGF)⁹⁸ and transforming growth factor- β (TGF β)^{99,100}. Overexpression of TGF β in particular has been linked to the formation of adhesions and fibrosis¹⁰¹.

Clinically and experimentally, chronic inflammation of the peritoneal surface is observed following repeated and prolonged peritoneal dialysis for renal failure, which, in turn, gives rise to peritoneal fibrosis through the mechanism of epithelial-to-mesenchymal transition (EMT) of the mesothelial cells¹⁰². The TGF β and hypoxia-inducible factor (HIF) pathways are involved in this process^{91,92} and are likely to be central to several diseases of the peritoneum. Specifically, EMT of mesothelial cells has also been suggested to be involved in the pathogenesis of peritoneal metastases^{103,104}.

Peritoneal metastasis and carcinomatosis

Peritoneal metastasis and carcinomatosis development can be conceptualized as a stepwise process that starts with malignant cells gaining access to the peritoneal cavity. The origin of this malignant cell population can be situated either within the peritoneal cavity (most commonly from gastrointestinal cancer, ovarian cancer and malignant mesothelioma) or outside of the peritoneal cavity.

Detachment of cells from the primary tumour. In most patients, the first step in the cascade resulting in peritoneal metastases is shedding of tumour cells from the surface of the primary cancer (FIG. 3), which can occur spontaneously from locally advanced or perforated tumours, or can have iatrogenic causes^{105–108}. Downregulation of cell–cell adhesion molecules, such as E-cadherin (CDH1) via the transcription factor TWIST, promotes cancer cell detachment^{109,110}. Loss of E-cadherin is a requisite for EMT, which results in a motile and invasive cellular phenotype¹¹¹. Spontaneous shedding of loose cells is further facilitated by the elevated interstitial fluid pressure in most solid tumours¹¹². This biomechanical property of malignant tissue is explained by rapid cellular proliferation, defective lymphatic drainage, fibrosis and contraction of the interstitial matrix, and increased osmotic pressure generated by anaerobic glycolysis and leakage of plasma proteins^{113,114}. In addition, inadvertent cutting into tumour tissue or by sectioning blood, lymphatic or biliary channels that drain the tumour tissue has been shown to promote locoregional tumour cell dissemination^{115,116}.

In some patients, peritoneal metastases arise from primary tumours outside of the peritoneal cavity such

as lung cancer, breast cancer or malignant melanoma²⁹. The pathophysiology of peritoneal spread from extra-abdominal primary cancers is not fully understood but must involve systemic (vascular and/or lymphatic) routes.

Peritoneal transport. Free cancer cells in the peritoneal cavity are subject to passive movement dictated by gravity and excursion of the diaphragm. As a result, cells usually follow a predictable path towards the pelvis and, from the pelvis, along the right paracolic gutter towards the sub-diaphragmatic spaces and the mesentery of the ileum¹¹⁷. Cancer cells also have active motility provided by lamellipodia and filipodia, whose mechanical force is generated by polymerization of actin microfilaments¹¹⁸. In ovarian and colorectal cancer, multi-cell clusters rather than isolated cancer cells can disseminate^{119,120}. Presumably, these clusters may arise by aggregation of single cells or by shedding as clumps from the primary tumour.

Mesothelial adhesion. Free peritoneal cancer cells adhere to either the mesothelial lining or to the underlying ECM through specific adhesion molecules, including VCAM1, ICAM1 and PECAM1 (REFS^{78,121}) (FIG. 3b,c). In vitro, mesothelial adhesion of colorectal tumour cells is mediated by the interaction of mesothelial ICAM1 and CD43 (sialophorin) rather than β_2 integrin, the most ubiquitous ligand of ICAM1 (REF.¹²²). This interaction is exacerbated by the presence of damage to the mesothelial layer, whereby loss of cell junction integrity and mesothelial cells delaminate and expose the underlying basement membrane^{66,69}.

In several cancer types, mesothelial adhesion was shown to be mediated by glycan-binding selectins expressed by mesothelial cells^{123–125}. In addition, migrating cancer cells can be mechanically captured by neutrophil extracellular traps, a meshwork of decondensed DNA produced by activated neutrophils¹²⁶. Adhesion between tumour cells and ECM components seems to be mediated primarily by the β_1 integrin subunit¹²⁷. In the pathogenesis of ovarian peritoneal metastases, the ECM components versican and hyaluronan interact with CD44, the hyaluronan ligand expressed by ovarian cancer cells¹²⁸. In addition, mesothelin, a glycoprotein physiologically expressed by mesothelial cells, was identified as a ligand for carbohydrate antigen 125 (CA125) and may have a role in peritoneal progression of ovarian cancer¹²⁹.

It is unclear why the omentum is a preferential site of peritoneal tumour growth¹³⁰. The mechanisms underlying this tropism are not fully elucidated but it has been suggested that cancer growth is stimulated by the fatty acids stored in omental adipocytes and by the pro-angiogenic environment of the omental ‘milky spots’, which consist of immune aggregates and a dense capillary network^{131–133}. Tumour cell binding may be mediated by a network of collagen I fibres overlaying the milky spots and by the expression of the pro-angiogenic vascular endothelial growth factor receptor 3 (VEGFR3) by omental microvessels¹³⁴. In female patients, mucinous signet ring cell carcinomas at a location other than the

Adhesions

Connective tissue that joins adjacent anatomical structures; adhesions typically form as a result of an inflammatory process or after surgery.

Paracolic gutter

The space lateral to the colon and the abdominal wall.

Mesentery

The connective tissue that supports the intestines and contains blood vessels and draining lymphatics.

Omentum

A fold of peritoneum and fatty tissue connecting the stomach with the transverse colon (greater omentum) and the porta hepatis (lesser omentum).

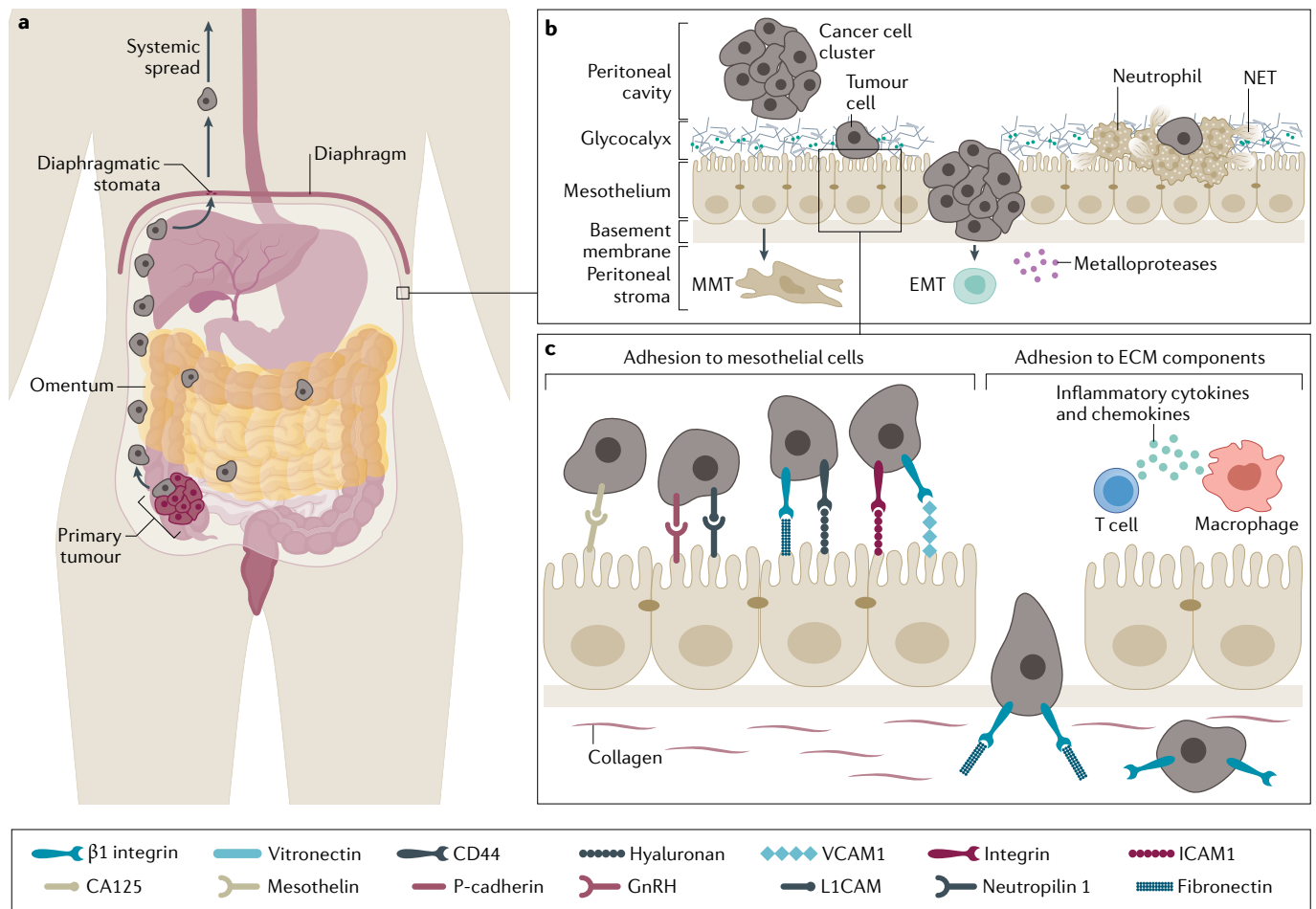


Fig. 3 | Metastatic spread to the peritoneum. a | The development of peritoneal carcinomatosis depends on mechanical forces, including gravity and diaphragmatic excursion, and on interactions between tumour cells, mesothelial cells and the underlying extracellular matrix (ECM). Individual or clusters of cancer cells are shed from the surface of the primary tumour (right colon cancer in this example). Subsequently, transcoelomic spread occurs, mainly in the direction of the pelvis and the right diaphragm. For reasons that are incompletely understood, there is a striking tropism for the greater omentum. At the surface of the diaphragm, the peritoneal cavity is in direct communication with lymphatic channels through stomata, enabling systemic dissemination of peritoneal metastases. **b** | Cancer cells present in the peritoneal cavity adhere to the mesothelial lining and to the underlying matrix through active (receptor mediated) and passive mechanisms. Tumour cells may become mechanically trapped in neutrophil extracellular traps

(NETs), expressed by activated neutrophils. In colorectal and ovarian cancer, collective invasion of clusters of cells has been reported. Invasion of the submesothelial stroma is facilitated by the action of metalloproteases and by mechanical or chemical damage to the mesothelial integrity. In addition, the process of epithelial-to-mesenchymal transition (EMT) provides cancer cells with a fibroblast-like, motile and invasive phenotype. Interestingly, some data suggest that the mesothelial cells also undergo mesenchymal transition (mesothelial-to-mesenchymal transition; MMT), enabling them to contribute to metastasis formation. **c** | Tumour cells express various receptors and ligands that enable close interactions with and binding to mesothelial cells and ECM components. The expression of these ligands and receptors is enhanced in the presence of inflammatory cytokines and chemokines. CA125, carbohydrate antigen 125; ICAM1, intercellular adhesion molecule 1; VCAM1, vascular cell adhesion molecule 1.

ovaries may give rise to ovarian metastases described as Krukenberg tumours. Depending on the primary malignancy, the pathogenesis of Krukenberg metastases may involve transcoelomic, lymphatic or haematogenous pathways¹³⁵.

The expression of mesothelial adhesion molecules (and the resulting cancer cell adhesion) may be considerably enhanced by inflammatory stimuli induced by infection or surgical trauma¹³⁶. For example, mesothelial expression of ICAM1 is stimulated by pro-inflammatory cytokines, including TNE, IL-1 β , IL-6 and EGF¹³⁷. Furthermore, malignant cells can become trapped in exudated fibrin matrices, and exudated plasma proteins, such as fibronectin and vitronectin, can act as bridging

molecules between endothelial cells, smooth muscle cells and cancer cells via the $\alpha_5\beta_1$ integrin and $\alpha_v\beta_3$ integrin receptors¹³⁸.

Alterations in mesothelial binding may also be caused by mechanical factors. In vitro, elevation of the ambient pressure (for example, by establishing a pneumoperitoneum during surgery) increases adhesion of colon cancer cells to matrix proteins¹³⁹. Additionally, elevated intraperitoneal pressure causes contraction of mesothelial cells, resulting in increased exposure of ECM binding sites⁶⁹. Further to the mechanical effects on mesothelial structure, in preclinical studies, the acidification and dehydration associated with CO₂ gas inflation during laparoscopic surgery promote tumour

Pneumoperitoneum

The consequence of air or CO₂ filling the peritoneal cavity; the creation of artificial space is required for minimal invasive surgery.

Spiral CT

High-resolution cross-sectional imaging modality on the basis of CT with a faster machine rotating continuously around the body, enabling more rapid acquisition and higher image resolution.

growth and invasiveness but this has not been observed in the clinical setting^{140,141}.

Invasion of the submesothelial tissue. Loose tumour cells gain access to submesothelial tissue at areas of peritoneal discontinuity or mesothelial cell contraction. Alternatively, tumour cells can induce apoptosis of mesothelial cells. For example, in vitro, colorectal cancer cells induced FAS-dependent apoptosis of cultured human mesothelial cells¹⁴². Once the mesothelial barrier is breached, tumour cells degrade the underlying matrix by the secretion of several proteases such as matrix metalloproteinases^{143,144}. Interestingly, the phenotype and genotype of the established peritoneal metastases may differ substantially from those of the primary tumour. For example, gene expression studies of peritoneal tumours derived from colorectal cancer suggest preferential development of consensus molecular subtype 4 (CMS4) peritoneal tumours, representing cancers enriched for stromal and ECM elements¹⁴⁵.

Systemic metastasis. Cancer cells that have disseminated to the peritoneal cavity can access the lymphatic system through specialized lymphatic stomata, which are localized mainly on the diaphragmatic surface, falciform ligament of the liver and pelvic side wall¹⁴⁶. These stomata are 8–10 µm² round-to-oval gaps between cuboidal mesothelial cells and communicate directly with the lumen of a lymphatic vessel or lacuna¹⁴⁷. In a rabbit model, passage of cancer cells from the peritoneal cavity via the stomata into the lymphatic cisterna was seen¹⁴⁸. A similar observation was made in patients with gastric cancer, in whom passage of cancer cells into submesothelial lymphatic vessels was documented using scanning electron microscopy¹⁴⁹. Importantly, both the density and diameter of the stomata and, therefore, the peritoneal absorptive capacity may increase by raised intraperitoneal pressure or by molecular mediators such as VEGF and nitric oxide¹⁵⁰.

Symptoms associated with peritoneal metastases. The most common symptoms developing in patients with (extensive) peritoneal metastases include ascites formation, obstructive symptoms and pain. The pathophysiology of malignant ascites is complex and multifactorial and the result of an imbalance between peritoneal fluid production and absorption¹⁴⁵. Obstruction of peritoneal lymphatics and stomata by invaded cancer cells impairs fluid resorption, while increased fluid filtration results from dilated peritoneal microvessels and enhanced vessel wall permeability, caused mainly by tumour-originating VEGF¹⁵¹. Abdominal pain in patients with

peritoneal metastases may be caused by ascites and the resulting abdominal distention, obstruction of the gastrointestinal or urinary tracts, and cancer infiltration of somatic and visceral afferent peritoneal nerves¹⁴⁵.

Diagnosis, screening and prevention**Clinical presentation**

The clinical presentation of PSM varies depending on the origin and extent of the disease. At the onset, symptoms can be specific to the primary cancer for gastrointestinal malignancies, for which abdominal pain and distension are common in most patients. At late stage disease, at which ovarian cancer is diagnosed in 70% of cases, unspecific symptoms (abdominal distension, fatigue, nausea, anorexia, weight loss and constipation) increase in frequency in up to 85% of patients. Clinical examination may identify palpable mass and ascites as usual signs^{1,152}.

Imaging modalities

Early diagnosis of PSM can be hampered by challenges in radiological detection. PSM imaging requires both modern technology and advanced reporting expertise¹⁵³. Technological prerequisites include high spatial resolution for the often-small lesions combined with high contrast resolution (PSM have the same attenuation as normal peritoneum and bowel) and minimal motion artefact. An interobserver variability of 30–73% in CT detection sensitivity has been reported and appropriate specialty-specific training is lacking¹⁵⁴.

In addition to its use in the diagnosis of PSM, imaging is a key factor in determining the surgical resectability of disease and predicting survival outcomes^{155,156}. Anatomical sites that are crucial in assessing the feasibility of complete resection, such as small bowel mesentery and hepatic hilum, remain difficult to characterize^{153,157,158}.

Ultrasonography has a limited role in diagnosis in general medical practice when concerning features, such as ascites or an omental cake, might trigger a high level of suspicion of underlying PSM. However, ultrasonography has no role in staging of PSM¹⁵⁹, for which CT, PET-CT and MRI are preferred imaging modalities (TABLE 1).

Multidetector or spiral CT with multiplanar reconstruction has emerged as the primary imaging modality in PSM, facilitated by its widespread availability and high speed of acquisition. A meta-analysis reported a pooled sensitivity of 0.68 (0.46–0.84) and a specificity of 0.88 (0.81–0.93) of CT in PSM¹⁶⁰. The sensitivity of CT depends on the size and location of cancerous lesions. The detection rate of lesions <0.5 cm is only 11%¹⁶¹ and

Table 1 | **Imaging modalities and their performance for peritoneal surface malignancies**

Imaging modality	Accuracy	Positive predictive value	Negative predictive value	Sensitivity	Specificity	Refs
CT	0.804	0.758	0.821	0.61	0.902	154–156,160–162
PET-CT	0.76	0.905	0.652	0.656	0.908	160,162,164,165
MRI	0.875	0.877	0.873	0.895	0.851	45,155,160,168

Although differences in appreciating peritoneal metastases of different malignancies are commonly described in the literature, these have never been quantified with accuracy or compared between different primary malignancies.

CT accuracy is reduced owing to the complex anatomy in the pelvis, visceral peritoneum and right subphrenic space¹⁶². For colorectal cancer PSM, the radiological peritoneal cancer index (PCI) by CT, as determined by a specialized radiologist in a PSM expert centre, correlates with the surgical or pathological PCI in only two-thirds of patients¹⁵⁵. The PCI is the most accepted method of estimating tumour burden in the peritoneal cavity and is closely related to prognosis and success of CRS and HIPEC. The largest lesion in each of 13 anatomical sites in the peritoneal cavity is given a score of 1–3 according to its size. This includes nine sites in the peritoneal cavity (sites 0–8) and four small bowel and mesenteric sites (sites 9–12). The sum of the scores gives a PCI of between 0 and 39 (REF.¹⁶³).

PET–CT with the tracer ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) is an imaging modality that combines functional and morphological imaging techniques to increase accuracy. According to a meta-analysis, the sensitivity and specificity of PET–CT for PSM were 84% and 98%, respectively¹⁶⁴. It has a higher interobserver reproducibility than CT and helps in selecting potential candidates

for CRS by excluding extra-abdominal disease. However, PET–CT has a longer acquisition time than CT and underperforms in mucinous PSM¹⁶⁵.

ImmunoPET is a potentially paradigm-shifting molecular imaging modality combining the targeting capability of monoclonal antibodies and the inherent sensitivity of the PET technique¹⁶⁶. Combining the same monoclonal antibody with a chemotherapeutic conjugate can leverage this imaging modality into a therapeutic strategy^{166,167} (FIG. 4). This strategy is currently under investigation for folate receptor- α (FRA)-based immunoPET and its therapeutic implications for epithelial ovarian cancer PSM¹⁶⁷.

The role of MRI has considerably evolved with the development of specific PSM imaging protocols^{45,153}. Functional diffusion-weighted sequences have greatly added to morphological (T2-weighted and gadolinium-enhanced) sequences and improved PSM diagnosis, staging and follow-up¹⁶⁸. The combination of CT and MRI improved the preoperative estimation of PCI and the diagnosis of non-resectability of PSM¹⁶⁹. The use of MRI to identify small bowel involvement

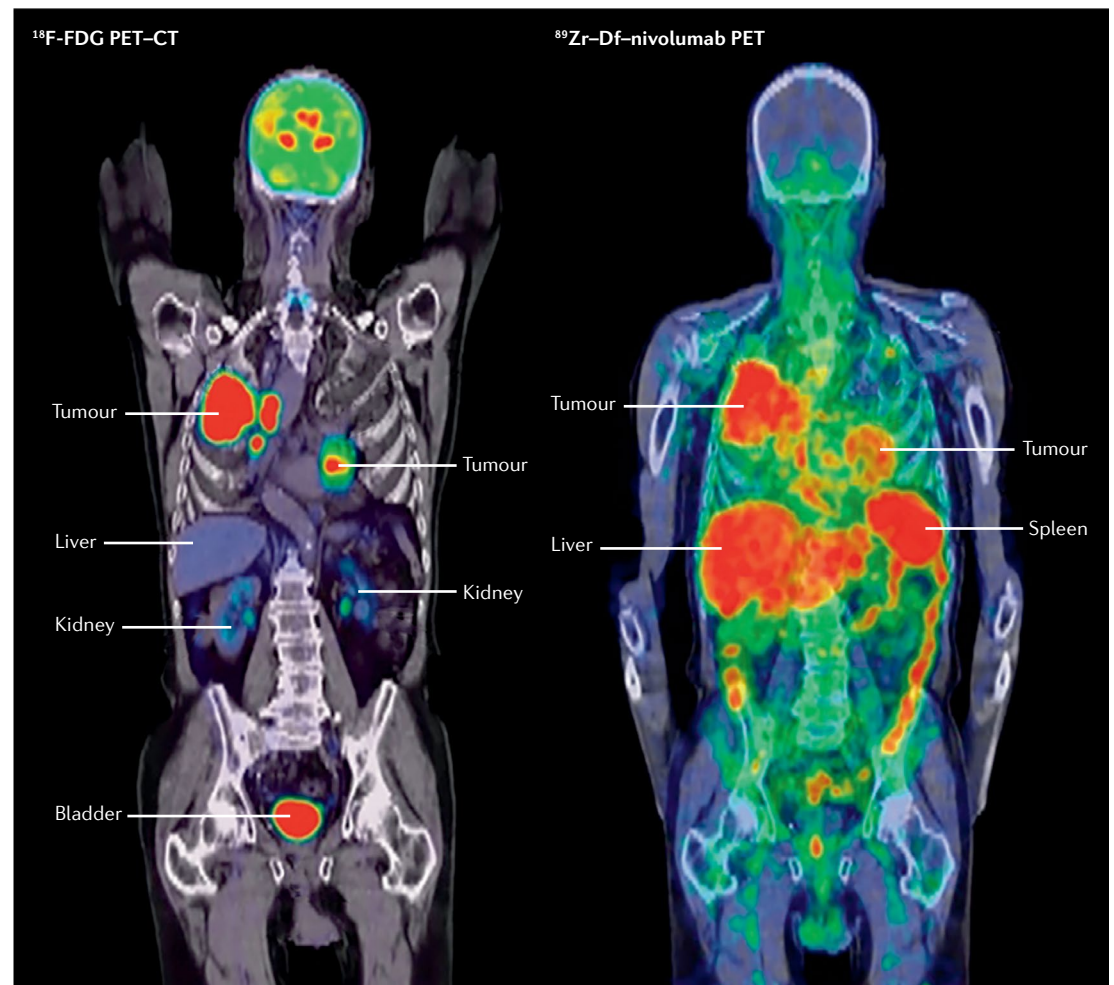


Fig. 4 | **ImmunoPET imaging.** Comparison of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET–CT (left image) with immunoPET (right image) for the same patient. Molecular imaging via immunoPET enables the combination of the precision of tissue targeting via a specific monoclonal antibody with the sensitivity of PET, resulting in better delineation of malignancy.

benefits from a more experienced radiologist¹⁷⁰. However, high costs, limited availability, motion artefacts, ascites and long learning curves restrict its widespread application. The emerging field of radiomics can further increase its role¹⁷¹.

Tumour markers

Tumour markers can be used in PSM diagnosis, prognosis and treatment response¹⁷². Routinely used tumour markers are carcinoembryonic antigen (CEA) and CA19-9 for gastrointestinal cancers at diagnosis and during follow-up. Diagnostic accuracies of CEA and CA19-9 are 66% and 71%, respectively, in gastrointestinal tract malignancies¹⁷³. CA125, which is highly specific for ovarian malignancies and mesothelioma can also be a useful marker of disease diagnosis and follow-up¹⁷³⁻¹⁷⁵. Serum CA125 and CA72-4 are clinically useful markers in diagnosis, evaluating the efficacy of chemotherapy and predicting the prognosis of patients with peritoneal dissemination from gastric cancer¹⁷⁶.

In the context of PMP, when preoperative levels of CEA, CA19-9 and CA125 are not elevated, a complete CRS can be achieved in 97% of patients. Conversely, if these markers are elevated, the success of complete CRS drops to 50%^{173,175,177}. Finally, one important clinical use of tumour markers is the evaluation of chemotherapy efficacy, and some data suggest that the survival time of responders to chemotherapy (assessed by the four tumour markers CEA, CA19-9, CA125 and CA72-4) was longer than that of non-responders^{176,178}.

Endoscopy

As PSM is often attributable to cancers of the upper or lower gastrointestinal tract, endoscopic procedures are a valuable diagnostic tool to determine the primary tumour location and obtain relevant biopsy samples¹⁷⁹⁻¹⁸¹. In symptomatic patients, the thorough selection of patients for endoscopic examination increases the probability of obtaining relevant findings^{182,183}. Endoscopy may enable the differentiation of extrinsic compression through disease from intrinsic stenosis in patients with PSM. That is, disease from outside the lumen of the gastrointestinal tract may lead to obstructive symptoms by pushing on the bowel compared with disease within the lumen of the bowel leading to a reduction in lumen size¹⁸⁴.

Surgical exploration

Owing to the unspecific symptomatology and challenging radiological detection of PSM, surgical exploration can be beneficial in selected patients. Evaluation of the extent of the disease and assessment of its potential surgical resectability are the two major objectives of this approach^{185,186}. Exploration is commonly undertaken in a minimally invasive manner using multi-port or single-port laparoscopy¹⁸⁷. The extent of the disease throughout the peritoneal cavity is expressed through the PCI and can be established at different time points during disease management to identify occult PSM, decide the need for neoadjuvant therapy, or evaluate response to treatment and inclusion in clinical trials¹⁸⁸. Diagnostic laparoscopy is required to establish the PCI

and can exclude from surgery up to 54% of patients who have been classified as non-resectable¹⁸⁹⁻¹⁹⁴.

The rate of open-and-close laparotomies in which surgery is recognized to be futile owing to the presence of advanced disease is estimated to be 13–38% even after preoperative laparoscopic evaluation because of small bowel or porta hepatitis involvement, which is difficult to assess by laparoscopy¹⁸⁹⁻¹⁹⁴. However, PCI evaluation by laparotomy remains the reference for patients with colorectal cancer PSM as laparoscopic evaluation failed to diagnose 18% of PSM in high-risk patients in one study¹⁹⁵.

Histological assessment and cytology

Pathological sampling in PSM can be performed under radiological or laparoscopic guidance. Exploratory laparoscopy may be the more comprehensive technique for both cytology and histology as it enables multiple sampling^{196,197}.

Pathological assessment is a key factor for the integrative management of peritoneal malignancies. At initial diagnosis, expertise in PSM is particularly required in rare peritoneal diseases such as PMP and peritoneal mesothelioma. Both entities have a high variability of pathological features resulting in borderline and malignant subtypes.

Histological assessment. In PMP, both the primary tumour usually located in the appendix¹⁹⁸ and peritoneal dissemination are classified separately into up to four grades according to the Peritoneal Surface Oncology Group International (PSOGI) consensus for classification and pathological reporting of PMP and the WHO classification 2019 (REFS^{199,200}).

For peritoneal mesothelioma, the histological classification distinguishes between diffuse malignant peritoneal mesothelioma and the borderline forms well-differentiated peritoneal mesothelioma and multicystic peritoneal mesothelioma²⁰¹. The interobserver variation is small among expert pathologists but is not known for general pathologists²⁰². Thus, PSOGI recommends a mandatory review of peritoneal mesothelioma specimens by a pathologist experienced in PSM²⁰¹. Distinction among categories for both PMP and mesothelioma is crucial as it informs the choice of treatment.

For other primary cancers, the evaluation of PSM histological features includes sidedness and mutations. Sidedness of the tumour has prognostic relevance for both colorectal and gastric cancer, although its role is not clear for their PSM²⁰³⁻²⁰⁷. Out of the large panel of possible mutations, only few have therapeutic relevance, for example, microsatellite instability status in many gastrointestinal malignancies, which is associated with response to immunotherapy²⁰⁸. In metastatic colorectal cancer, microsatellite instability status, RAS mutations and BRAF mutations are routinely assessed²⁰⁹. Human epidermal growth factor receptor 2 (HER2) status was initially assessed in gastric cancer at any stage but is also becoming relevant in colorectal malignancies^{210,211}. In ovarian cancer primary tumours, germline and somatic *BRCA1* and *BRCA2* mutations have therapeutic relevance for poly(ADP-ribose) polymerase (PARP)

inhibition as is also the case with the homologous deficiency repair assay that helps in selecting patients for this maintenance therapy^{212,213}.

In The Cancer Genome Atlas, molecular subtypes were identified for some frequent malignancies, including primary colorectal and gastric cancer primary tumours^{214,215}. Some data indicate that the colorectal cancer subtype CMS4 is more frequently involved in PSM than other subtypes but no therapeutic implications have yet been established²¹⁶. In advanced gastric cancer, molecular subtypes have a prognostic association with survival but their therapeutic relevance is currently limited²¹⁷.

Treatment response can be assessed for different primary tumours and metastatic sites²¹⁸. In PSM of gastrointestinal origin, the Peritoneal Regression Grading System (PRGS) scores the presence of residual tumour cells and regressive features and has demonstrated reproducibility^{219,220}; however, the system has no correlation with survival and its value as a surrogate survival criterion is unknown. In PSM of gynaecological origin, including ovarian cancer, the chemotherapy response score is based on the presence of fibroinflammatory elements and/or the limited viability of the tumour cells and has shown prognostic value^{221,222}.

Cytological assessment. Peritoneal cytology is a diagnostic and prognostic tool with low sensitivity owing to variability in sampling modalities²²³. Peritoneal lavage cytology is performed by introducing, stirring and aspirating from the abdominal cavity a variable quantity of saline solution but serous effusion cytology can also be performed in patients with ascites²²⁴. In gastric cancer PSM, it may guide treatment either as an indicator of response to neoadjuvant or intraperitoneal chemotherapy³⁸ or as a criterion for inclusion in prophylactic HIPEC and pressurized intraperitoneal aerosol chemotherapy (PIPAC) studies. In the combined progression index based on cytology and PRGS, positive cytology associated with a high PRGS is an independent factor of worse survival outcomes¹⁹⁷. In most PSM, except those of gastric cancer origin, changes in treatment strategy on the basis of histological or cytological response are currently exploratory based on analogies with other metastatic sites.

Prevention and screening

In advanced colorectal cancer, there are high-risk (synchronous ovarian metastases and perforated primary tumour) and low-risk (T4 status, positive peritoneal lavage, mucinous subtype and signet cells) factors for developing metachronous PSM²²⁵ as well as a predictive model²²⁶. Owing to the difficulty of establishing early diagnosis of PSM, several preventive strategies were designed and tested based on these factors.

The role of systemic chemotherapy in the prevention of metachronous colorectal cancer PSM is still unclear as very few trials of adjuvant systemic chemotherapy have investigated site-specific recurrence patterns. In an early study in patients at high risk with resected colorectal cancer receiving systemic FOLFOX-based or FOLFIRI-based adjuvant chemotherapy²²⁷, PSM were

found at second-look surgery in the first year in 56% of 41 patients without any biochemical or radiological sign of recurrence. In a meta-analysis of data from 17,313 patients with pancreatic cancer receiving curative-intent pancreatic resection and systemic chemotherapy, 13.5% had initial tumour recurrence in the peritoneum²²⁸.

Another potential prophylactic strategy to prevent metachronous PSM is extensive intraoperative peritoneal lavage aiming to remove exfoliated tumour cells from the abdominal cavity. This approach has mostly been investigated in the context of high-risk gastric cancer for which positive lavage cytology is associated with an increased risk of developing metachronous peritoneal metastases²²⁹. In the EXPEL trial in 800 patients with gastric cancer randomly allocated to either gastrectomy alone or gastrectomy plus extensive intraoperative peritoneal lavage, the 3-year overall survival in the two groups was similar²³⁰.

In addition, intraperitoneal chemotherapy during surgery was hypothesized to be beneficial in preventing peritoneal metastases. In the early study in high-risk patients with resected colorectal cancer discussed above, 18 of 24 patients who were free of macroscopic peritoneal metastases at second-look received HIPEC and only 1 patient subsequently presented with peritoneal metastases²²⁷; by contrast, 3 of the 6 patients who did not receive HIPEC had peritoneal recurrence. Subsequently, the proactive, upfront approach of combining colorectal resection with HIPEC in high-risk colorectal cancer was investigated in two randomized controlled trials. However, prophylactic HIPEC with oxaliplatin failed to demonstrate superiority in reducing peritoneal metastases in the COLOPEC²³¹ and PROPHYLOCHIP-PRODIGE 15 (REF. 232) trials compared with standard follow-up after surgery²³³. Two more randomized trials, PROMENADE (oxaliplatin-based HIPEC) and HIPECT4 (mitomycin-based HIPEC), are ongoing²³⁴. For gastric cancer, recurrence at the peritoneal surface is common after curative-intent gastrectomy. Three randomized trials^{235–237} and several non-randomized trials investigated whether prophylactic HIPEC could reduce peritoneal recurrence and improve survival²³⁸. The studies demonstrated safety of this procedure and suggested decreased peritoneal recurrence and improved survival.

The identification of frequent mutations of cancer risk genes for many gastrointestinal and gynaecological malignancies has enabled the development of preventive strategies²³⁹. Testing for mutations in *BRCA1*, *BRCA2*, *CDH1* and the DNA mismatch repair pathway has traditionally been guided by personal or family history²⁴⁰. Now, next-generation sequencing technology enables simultaneous assessment of many genes and the use of gene panels in clinical practice²¹². However, the use of this approach depends on economic availability and the socio-cultural perception of genetic heritage; for example, in some cultures, there may be reluctance to seek further information on genetic abnormality²⁴¹.

National cancer screening programmes vary depending on the world region. Colorectal cancer screening is widely implemented and resulted in incidence and mortality reduction²⁴². Gastric or oesophago-gastric cancer

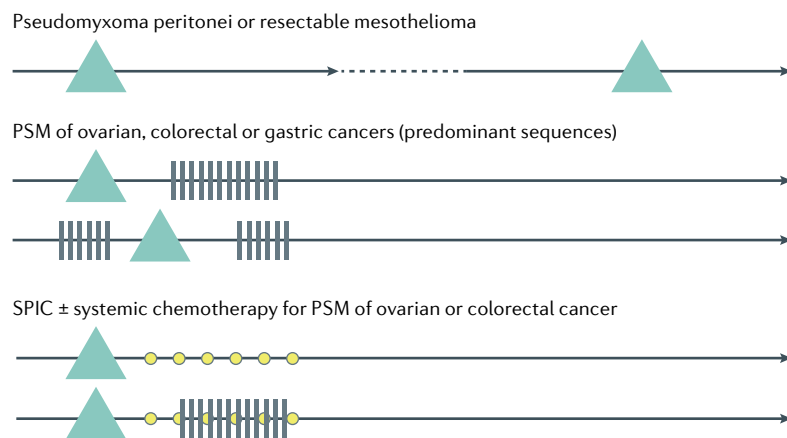
FOLFOX

A systemic chemotherapy regimen including folinic acid (FOL), 5-fluorouracil (F), and oxaliplatin (OX), which can benefit from the addition of a targeted treatment such as an anti-epidermal growth factor receptor or an anti-vascular endothelial growth factor agent; different doses and duration of administration, especially of 5-fluorouracil, are in use.

FOLFIRI

A systemic chemotherapy regimen including folinic acid (FOL), 5-fluorouracil (F) and irinotecan (IRI), which can benefit from the addition of a targeted treatment such as an anti-epidermal growth factor receptor or an anti-vascular endothelial growth factor agent.

Curative intent



Palliative intent or borderline

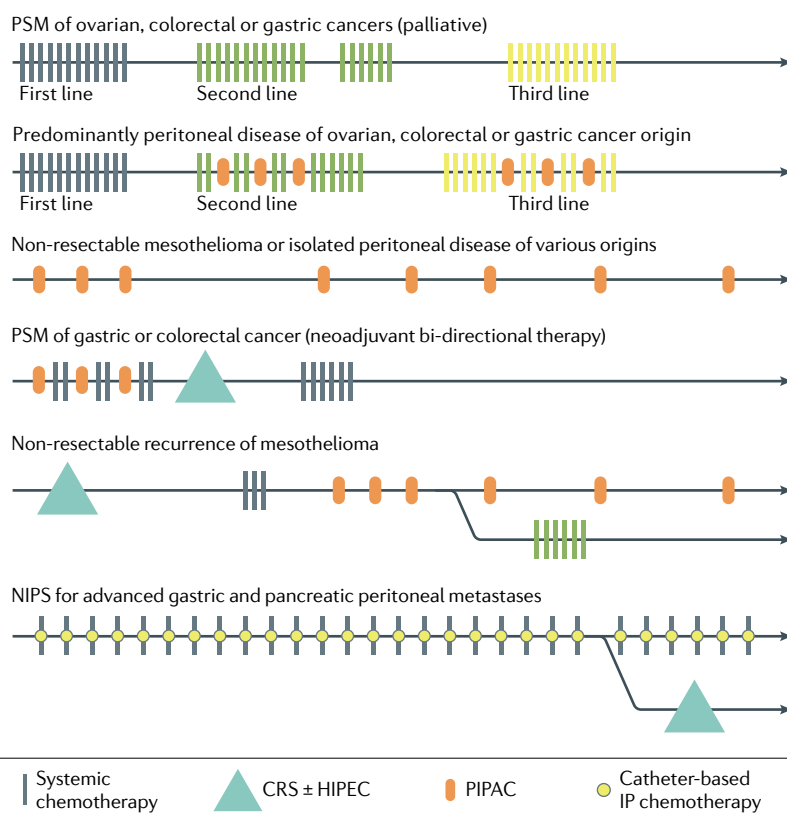


Fig. 5 | Typical treatment sequences for patients with PSM. The main treatment modalities currently used for the treatment of peritoneal surface malignancies (PSM) are systemic chemotherapy, cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC), pressurized intraperitoneal aerosol chemotherapy (PIPAC) and catheter-based intraperitoneal (IP) chemotherapy. These treatments can be combined or applied sequentially according to the underlying primary tumour, the disease extent, and the individual patient's condition and preferences. These typical treatment sequences represent the most frequently encountered situations for patients with PSM. NIPS, neoadjuvant intraperitoneal and systemic chemotherapy; SPIC, sequential postoperative intraperitoneal chemotherapy.

the incidence of PSM associated with these primary tumours.

Preventive strategies proposed to individuals with high-risk mutations include intensive screening and/or preventive surgery. For example, bilateral salpingo-oophorectomy can reduce the risk of epithelial ovarian cancer diagnosis by up to 96%^{244,245}. The procedure should be performed earlier for those with *BRCA1* mutations owing to the higher risk and earlier onset of the disease²⁴⁶. Prophylactic total colectomy is performed for those with familial adenomatous polyposis, usually before 25 years of age but is not recommended for Lynch syndrome⁶⁰. Prophylactic total gastrectomy is recommended to those with a *CDH1* mutation at age 20–30 years or 5 years earlier than the age of the youngest affected family member^{247,248}; 87% of patients who undergo prophylactic gastrectomy owing to *CDH1* mutation have evidence of malignancy^{247,249}.

Management

Treatment modalities

Management of PSM is an interdisciplinary challenge, often requiring individually adapted treatment concepts and optimized patient selection. The overall treatment strategy should evaluate curative management and should be discussed in a multidisciplinary tumour board to define adapted treatment sequences (FIG. 5). Typical modalities used in PSM management include systemic therapy, locoregional treatment (CRS and intraperitoneal chemotherapy), and supportive and palliative care measures.

Systemic therapy. Complications and sequelae of PSM, such as digestive disorders, cachexia and renal impairment, can challenge or prohibit effective systemic drug treatment²⁵⁰. An analysis of data from two prospective clinical trials of systemic chemotherapy in patients with colorectal cancer PSM showed reduced response rates of these metastases in comparison with those at other locations²⁵¹. One potential explanation is the reduced blood supply to the peritoneum and, accordingly, to the diseased peritoneum²⁵², which limits perfusion and drug delivery. Preclinical data have shown the importance of angiogenesis for tumour growth and dissemination to the peritoneum. These findings have laid the basis for the clinical evaluation of agents targeting VEGF signalling pathways in patients with ovarian cancer and other cancers spreading to the peritoneum such as colorectal or breast cancer²⁵³.

Specific therapeutic regimens tailored for PSM are scarce. However, systemic chemotherapy is an important component of the oncological strategy and depends on primary tumour origin, the extent of peritoneal spread, the option of CRS, and the patient's performance status and organ function. In addition, biologically targeted drugs and immunotherapy have become available and are now in broad use for the treatment of metastatic disease in general. Unfortunately, trials of systemic targeted treatments and immunotherapy specifically for peritoneal metastases are lacking. Subgroup analyses from large trials with broad inclusion criteria are typically exploratory and underpowered. Thus, knowledge about

screening is common in Asia and has led to reduced mortality from these cancers²⁴³. Earlier detection of these gastrointestinal cancers may have a beneficial effect on

Box 1 | Intraperitoneal treatment modalities

Intraperitoneal treatment modalities include hyperthermic intraperitoneal chemotherapy (HIPEC), pressurized intraperitoneal aerosol chemotherapy (PIPAC), neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) and early postoperative intraperitoneal chemotherapy (EPIC), which have different characteristics and indications.

HIPEC

- Applied as single administration after cytoreductive surgery (CRS) by use of a perfusion machine. Circulation of the heated chemotherapy solution can be performed using either an open (termed Coliseum) or a closed technique for a duration of 60–120 min and at a temperature of 40–43 °C.
- Indications: Curative.
- Potential other indications: Palliative, neoadjuvant and adjuvant.

PIPAC

- Applied repeatedly by laparoscopy using a two-trocar technique. PIPAC is not combined with CRS. Administration of chemotherapy is achieved via a high-pressure injector and a procedure-specific aerosolizer, creating a therapeutic aerosol with improved distribution and tissue entry.
- Indications: Palliative.
- Potential other indications: Neoadjuvant, adjuvant.

NIPS

- Long-course combination treatment of intraperitoneal and intravenous chemotherapy using implanted catheter access ports.
- Indications: Neoadjuvant.

EPIC

- Administered typically after CRS and HIPEC by use of intraoperatively placed intraperitoneal catheters to extend intraperitoneal drug exposure over 5 days postoperatively.
- Indications: Adjuvant.

Comparison of main features, advantages and disadvantages

Feature	HIPEC	PIPAC	NIPS	EPIC
Potency of drug	++	+	+++	+++
Intraperitoneal concentration	++	++	++	++
Duration of tumour exposure	+	+	+++	+++
Depth of drug infiltration	+++	+++	++	++
Frequency and duration	++	++	+++	+++
Drug distribution	+++	+++	++	++
Combination with heat	+++	+	#	#
Minimally invasive surgery	+	+++	#	#
Repeated pathological evaluation of tumour response	+	+++	#	#
Cost	+++	++	+	+
Potential toxicity	+	+	++	+++

+, low; ++, medium; +++, strong; #, not applicable.

the efficacy of specific targeted drugs or immunotherapy are scarce.

Endocrine therapy, including in the form of selective oestrogen-receptor modulators, oestrogen-receptor blocking agents or aromatase inhibitors, combined with cyclin-dependent kinase 4 and 6 (CDK4 and CDK6) inhibitors, is an option in hormone-dependent cancers such as in breast cancer²⁵⁴. HER2-directed treatment is available for HER2⁺ breast and gastric cancers^{255,256}. PARP inhibitors are used in the treatment of cancers that are deficient in their DNA damage response such

as epithelial ovarian cancer or pancreatic ductal adenocarcinoma with *BRCA1* and/or *BRCA2* mutations^{257,258}. Tropomyosin receptor kinase (TRK) inhibition is possible in cancers with TRK fusions²⁵⁹, and immune-checkpoint inhibition is used in colorectal and non-colorectal cancers with high microsatellite instability^{260,261}.

Of note, molecularly targeted treatments and immunotherapy are dynamically evolving fields, and enabling access for patients to clinical research projects and drug therapy studies is important. Specialty-specific oncologists should be involved in multidisciplinary treatment considerations. The treatment centre should have access to a qualified molecular tumour board to discuss and recommend molecularly stratified and personalized treatment according to the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) guidelines^{262,263}. The ultimate goal is to ensure best outcomes for patients whose tumours display actionable molecular alterations.

Cytoreductive surgery. CRS is the principal component of curative treatment in PSM and aims to resect all visible tumour implants within the abdomen. Peritonectomy procedures and visceral resections are performed to surgically eradicate cancer on peritoneal surfaces²⁶⁴. The surgery comprises midline laparotomy and starts with an exhaustive exploration of the peritoneal cavity to evaluate the disease extent through the PCI¹⁸⁷. At the end of surgery, completeness of cytoreduction according to the CC score (CC-0, no residual nodule; CC-1, <2.5 mm; CC-2, <25 mm; and CC-3, >25 mm) must be determined¹⁸⁶. Postoperative surgical and medical complications are routinely evaluated within 90 days according to the Clavien–Dindo classification or the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)^{265,266}. In selected patients, a laparoscopic and minimally invasive approach can be used²⁶⁷. Morbidity and mortality following CRS in large cohort studies differ between centres (15–50% and 0.8–5%, respectively)^{268,269} but were estimated to be between 25–27% and 0–2%, respectively, in prospective randomized controlled trials^{36,45}. These rates are close to those reported for other types of major surgery⁶. Morbidity and mortality can be considerably decreased in high-volume centres and by optimizing perioperative care using standardized pathways^{7,9}.

Intraperitoneal chemotherapy. Several modalities of intraperitoneal chemotherapy can be used in patients with PSM (BOX 1) and can be combined into sequences (FIG. 5). HIPEC can be used in selected patients immediately at the end of CRS if complete resection was achieved or as a palliative treatment to control the ascites²⁷⁰. Early postoperative intraperitoneal chemotherapy is an option during the early postoperative period before adhesions develop. It has been in use for colorectal cancer with peritoneal metastases and for ovarian cancer with peritoneal metastases²⁷¹. It can also be used in combination with CRS and HIPEC to treat patients with PSM of multiple origins, including gastric, colorectal and appendiceal cancers, as an additional therapy^{5,272}. Intraperitoneal chemotherapy can also be

delivered as a neoadjuvant treatment combined with systemic chemotherapy²⁷³ or as an adjuvant treatment via an intraperitoneal port²⁷⁴. PIPAC describes a modality in which agents are administered via aerosolization at the point of laparoscopy³.

Commonly reported adverse effects from the use of intraperitoneal chemotherapy agents are bleeding, nephrotoxicity, haematological toxicity and some rare presentation of allergic reaction in addition to the adverse events related to CRS^{36,275–278}.

Disease-specific management

Management strategies differ according to the malignancy that caused PSM (Supplementary Tables 1, 2). The multidisciplinary tumour board usually select the treatment sequences of perioperative chemotherapy, surgery, and intraperitoneal chemotherapy and define the neoadjuvant and adjuvant therapy according to the type of PSM, while considering whether treatment has curative or palliative intent.

PMP and appendiceal cancer. CRS and HIPEC offer the best outcome for PMP and mucinous appendiceal tumours^{279–281}. As many patients with PMP present with extensive disease, adequate surgical skills and experience are required to balance the extent of surgery and the risk of complications. This complex treatment has a surgical learning curve with a peak reached after approximately 130 procedures²⁸². Following complete CRS and HIPEC, prognosis is highly dependent on the histopathological characteristics of the tumour. In one analysis, median survival was not reached in those with low-grade PMP, whereas it was <30 months in those with high-grade PMP³⁵. A large retrospective propensity analysis reported the beneficial effect of CRS combined with HIPEC compared with CRS alone²⁸³. This benefit was seen regardless of residual disease or histopathological grade. Various HIPEC protocols were used and survival advantages were reported with intraperitoneal cisplatin plus mitomycin C or intraperitoneal oxaliplatin plus intravenous 5-FU combinations.

Some patients present with histologically low grade but non-resectable, non-metastatic PMP and slow-growing abdominal tumours causing bowel obstruction that require total parenteral nutrition. Multivisceral transplantation may be an option for strictly selected patients and should involve teams specialized in PSM and in transplantation²⁸⁴.

Recurrence is common in PMP and the progressive accumulation of mucin with poor response to systemic treatments is debilitating. The combination of bromelain and acetylcysteine (BroMac) seems to have synergistic activity in the dissolution of tumour-produced mucin in the preclinical setting^{285,286}. The first clinical study reported considerable mucolytic activity and a manageable safety profile, giving hope for patients with inoperable PMP or recurrence²⁸⁷. New approaches, such as iterative intraperitoneal chemotherapy, have been explored in patients with high-grade, unresectable appendiceal cancer, including goblet cell adenocarcinomas, and demonstrated promising results; however, further investigations are necessary²⁸⁸.

Malignant peritoneal mesothelioma. Systemic chemotherapy has not been shown to be effective in prolonging survival in malignant peritoneal mesothelioma (MPM)²⁸⁹. The use of cisplatin or gemcitabine combined with the chemotherapeutic pemetrexed, which together constitute the standard therapy, resulted in a median overall survival of ≤27 months²⁹⁰. The use of bevacizumab, a monoclonal antibody blocking angiogenesis by targeting vascular endothelial growth factor A, can be considered following promising findings in pleural mesothelioma²⁹¹. Immune-checkpoint inhibitors, such as nivolumab (anti-PDL1) and ipilimumab (anti-CLTA4), have demonstrated benefit in patients with pleural mesothelioma but their value in patients with MPM is incompletely studied²⁹². Other targeted therapies, such as an anti-mesothelin antibody or pulsed dendritic cells, are promising but still under investigation²⁹³.

Combination treatment comprising CRS and HIPEC results in a median overall survival of 53 months in patients with MPM according to one multi-institutional analysis²⁹⁴. The main prognostic factors are tumour characteristics (histological subtype and Ki-67 expression), completeness of cytoreduction (CC score) and nodal status^{37,295,296}. CRS and HIPEC with cisplatin plus doxorubicin shows a trend towards a survival advantage and is recommended by PSOGI²⁰¹.

For patients not amenable to complete CRS at initial diagnosis, the use of front-line intraperitoneal chemotherapy can be an option, such as PIPAC with cisplatin plus doxorubicin or intraperitoneal pemetrexed combined with systemic chemotherapy. Conversions to curative surgery have been reported in >50% of patients^{297,298}. One randomized trial, MESOTIP, is currently evaluating PIPAC as neoadjuvant treatment²⁹⁹. Long-term normothermic intraperitoneal chemotherapy using pemetrexed may also provide increased survival of 75% at 5 years²⁷⁴.

PSM of colorectal origin. In colorectal PSM, data from an early randomized trial found a significant survival benefit with CRS plus mitomycin C-based HIPEC followed by systemic chemotherapy versus systemic chemotherapy alone (22.4 versus 12.6 months; $P=0.032$); other prospective cohorts have validated these results^{41,300–302}. In addition, a significant survival benefit was seen in patients who had undergone CRS followed by intraperitoneal chemotherapy compared with those who received systemic chemotherapy alone (25 versus 18 months; $P=0.04$)³⁰³. The PRODIGE 7 trial tested CRS plus oxaliplatin-based HIPEC compared with CRS alone and failed to demonstrate an improvement in overall survival or recurrence-free survival³⁶. CRS combined with modern systemic chemotherapy in expert centres achieved a better than expected median overall survival of 41 months in the PRODIGE 7 trial³⁶. This finding highlighted the major role of completeness of CRS as the principal prognostic factor of patient outcome. HIPEC with high-dose oxaliplatin, which increases the risk of intraperitoneal bleeding²⁷⁵, and for a too short duration of 30 min (REF.233) was not appropriate and should be abandoned following three negative phase III trials^{36,231,304}. Future trials should further investigate

the role and optimal type of HIPEC in colorectal PSM management, which remains controversial³⁰⁵.

PSM of gastric origin. Peritoneal metastases are common in the late stage of gastric cancer²⁴ and these patients have a poor prognosis despite systemic chemotherapy³⁰⁶. An analysis of results in prospective databases suggested a survival benefit of adding HIPEC to CRS in patients strictly selected for localized PSM³⁰⁷. Other studies also reported long-term survival following the use of HIPEC in patients with a CC-0 CRS and a PCI <6 (REFS^{307–309}). New approaches for patients with gastric cancer and PSM, such as repeated HIPEC in a phase II trial, have demonstrated promising results and further trials are in progress^{310,311}. The role of CRS and HIPEC compared with palliative chemotherapy is under evaluation in the PERISCOPE II phase III trial³¹². For non-resectable peritoneal metastases from gastric cancer, palliative intraperitoneal chemotherapy provided encouraging survival results. The combination of systemic chemotherapy with PIPAC using cisplatin and doxorubicin resulted in a median survival of 19.1 months and 14.3% of patients became eligible for curative procedures^{298,313}. Neoadjuvant intraperitoneal and systemic chemotherapy or palliative intraperitoneal chemotherapy using docetaxel or paclitaxel seem to further reduce peritoneal progression and improve survival^{38,314–316}. The PHOENIX-GC trial suggested a clinical benefit of intraperitoneal paclitaxel treatment³⁸.

PSM of ovarian, fallopian tube and primary peritoneal cancer origin. Primary CRS followed by systemic chemotherapy is the standard of care for patients with PSM of ovarian, fallopian tube and primary peritoneal cancer origin. The term debulking surgery refers to a procedure in which the goal of optimal debulking is to leave residual disease <1 cm (REF³¹⁷). When complete CRS is not possible owing to disease extent or location, poor general health status or condition, neoadjuvant systemic chemotherapy should be delivered for 3–4 cycles before reconsidering indication for complete surgical resection (interval surgery)^{318,319}. Of note, the goal of CRS initially and at the interval setting should be complete removal of macroscopic disease³²⁰. The role of pelvic and para-aortic lymphadenectomy remains controversial. One randomized trial demonstrated that it can be safely omitted in patients without evidence of node involvement³²¹.

Despite encouraging evidence for the use of HIPEC in combination with CRS from a meta-analysis of nine comparative studies³²², the use of HIPEC is recommended only as an option at the interval setting in most countries. In this setting, the open-label phase III OVHIPEC trial demonstrated that HIPEC with cisplatin increased disease-free survival by ~4 months and overall survival by ~12 months without increasing morbidity⁴⁵.

The benefit of CRS on overall survival in case of disease recurrence has been demonstrated in strictly selected patients with PSM of ovarian, fallopian tube and primary peritoneal cancer origin^{323,324}. The criteria for selection of the best candidates for CRS include good performance status, platinum treatment-free interval of <6 months, complete resection at the primary surgery

and absence of large ascites volumes. However, these criteria are only positive predictors if complete resection is achieved, which can be an option in specialized centres^{325,326}.

The role of CRS combined with HIPEC seems promising, especially for platinum-resistant ovarian cancer^{327,328}. In one randomized study, CRS plus HIPEC followed by systemic chemotherapy versus CRS only followed by systemic chemotherapy resulted in a median survival of 19.4 months versus 11.2 months ($P < 0.05$), respectively³²⁷. Its role is being investigated also by the ongoing randomized controlled trial HIPOVA-01 (REF³²⁹).

The utility of PIPAC with cisplatin and doxorubicin for recurrent ovarian, fallopian tube and peritoneal cancer PSM has been validated in a phase I study³³⁰. This treatment demonstrated safety and potential benefit as a palliative option in patients with recurrent disease: 62% of patients had an objective tumour response; histological tumour regression and PCI improvement were observed in 76% who underwent three courses of PIPAC; and no grade 4 adverse events or death related to treatment were observed^{331,332}. This modality is being investigated in the ongoing phase III trial PIPAC-OV3 (REF³³¹).

PSM of rare origins. Limited data are available for cancers that rarely present with peritoneal metastases or that are rarely eligible for curative resection (mainly due to extraperitoneal dissemination) such as pancreatic, biliary tract, breast, lung and neuroendocrine tumours as well as sarcoma³³³. For these rare PSM, a worldwide analysis led by PSOGI observed promising, but sporadic, long-term survival in strictly selected patients in centres specialized in PSM management. Common selection criteria for curative procedures include the possibility of complete CRS, low PCI, no extra-abdominal metastases, favourable tumour biology or long-term control with systemic chemotherapy³³⁴.

For pancreatic peritoneal metastases, two case reports on treatment with CRS and HIPEC using mitomycin C showed overall survival of 48 and 70 months³³⁵, but a small case series of seven patients treated with CRS and cisplatin-based HIPEC observed overall survival of 16 months, which was associated with a high rate of complications and did not alter disease progression³³⁶. Furthermore, in the PSOGI analysis, PSM of pancreatic origin was a negative prognostic factor³³³. For peritoneal metastases from cholangiocarcinoma, an analysis of a prospective multicentre database for 34 patients treated by CRS and HIPEC and 21 patients treated with systemic chemotherapy found a median overall survival of 21.4 and 9.3 months for the CRS and HIPEC group and the chemotherapy group, respectively³³⁴. Peritoneal metastases from breast cancer are extremely rare and ~82% of patients with peritoneal metastases also have other metastatic sites³¹. A case series of 5 patients treated with CRS and HIPEC with a median elapsed time between breast cancer diagnosis and peritoneal disease of 18 years observed a 56-month overall survival³³⁷. Furthermore, a cohort study that included 73 patients with gastrointestinal metastasis, of whom 32 presented with PSM only, found that surgical resection did not

considerably extend overall survival³³⁸. In the few reports for peritoneal sarcomatosis from different histotypes (7–60 patients)^{339–343}, overall survival was 12–34 months and prognostic factors included completeness of CRS and the extent of peritoneal involvement according to PCI³⁴⁴. The PSOGI analysis included 189 patients with different histotypes, of whom 29% had 5-year overall survival and 14% had 5-year disease-free survival, concluding that the most prognostic factor was CRS and that the role of HIPEC remains to be determined³³³. Finally, neuroendocrine PSM mostly associated with extraperitoneal involvement negatively influences prognosis^{345,346}. The European Neuroendocrine Tumour Society (ENETS) consensus guidelines indicate that these patients should receive aggressive CRS in high-volume centres if complete resection can be achieved³⁴⁷; the role of HIPEC in this indication is not clear³⁴⁸. In the PSOGI analysis, 40% of 127 patients treated with CRS and HIPEC had 5-year overall survival³³³.

Quality of life

The well-being and QoL of patients with cancer is determined by a complex interplay of disease-related and treatment-related effects on somatic and psychological symptoms and functioning. Oncological treatments can have positive or negative effects on QoL and this balance tends to shift over time. QoL should therefore be regarded as a longitudinal measure^{349–351}.

Peritoneal metastases are more frequently symptomatic than metastases at other sites and abdominal pain, nausea and ascites can have profound negative effects on QoL³⁵². In untreated patients, disease tends to progress rapidly with aggravation of symptoms and a dramatic decline in QoL especially during the last 3 months of life³⁵³. In this context, bowel obstruction deserves particular mention, as physical and psychological suffering accompanies loss of essential functions of living as

well as lack of treatment options and consequent loss of hope³⁵⁰.

Systemic chemotherapy remains the standard treatment for metastatic disease. While survival benefits remain modest for peritoneal metastases compared with metastases at other sites, systemic chemotherapy can have a profound negative effect on QoL, particularly in patients with a good performance status^{354,355}. A close partnership between doctors, patients and their families with transparent and honest information on expected benefits, potential risks and treatment options is therefore of utmost importance to define the optimal treatment for the individual patient by shared decision-making. Frequently, there is already a profound misunderstanding between patients and care providers concerning the intent of treatment and prognosis^{356–358}. Although patients with potentially curable disease are more likely to accept treatment-related adverse effects with effects on QoL and functioning, priorities and expectations might be very different in the palliative setting. Indeed, QoL and patient-related outcome and experience measures are increasingly used in routine clinical practice and as primary outcomes in research in the palliative setting. Several tools are available to assess these outcomes but none of them is specific for patients with PSM³⁵¹. Thus, ongoing international efforts concentrate on the creation of dedicated tools to measure QoL and patient-related outcome measures specifically for patients with PSM. These tools will have to be validated in different countries to account for socio-cultural diversity^{359,360}.

CRS combined with HIPEC is performed in most patients with a curative intent. With a potential for cure and long-term survival, a high risk of perioperative morbidity and mortality seems acceptable^{6,45,361–363}. In addition, patients have to be aware of a transitory deterioration of QoL lasting ~6 months after surgery before getting back to baseline performance and surpassing QoL and symptom scores of patients undergoing systemic palliative chemotherapy^{364–366}.

In the palliative setting and in patients with limited life expectancy, QoL gains more importance when evaluating treatment options. PIPAC has been shown to be a safe and feasible treatment option in patients with therapy-refractory disease who are not candidates for a potentially curative approach^{3,353}. In this desperate setting, about two-thirds of patients will have an objective treatment response with no negative effect on QoL. Symptoms improve in >50% of repeatedly treated patients who can gain additional quality lifetime and hope^{3,350,353} (BOX 2).

Outlook

Personalized medicine

Organoids are a 3D cell culture method using patient tissues to create a personalized tumour model to study patient-specific characteristics³⁶⁷. Patient-derived organoids to test chemosensitivity and predict treatment resistance and response have been explored^{368,369}, including for colorectal PSM¹⁴⁵. However, more efficient models to grow organoids need to be developed. This methodology is a promising approach to personalized

Box 2 | Patient experience

My husband and I have been married for 61 years. We only had one daughter because of our busy professional lives. When we retired, we started travelling Europe in our camping car, enjoying each other's company. He was a veteran of war with some old injuries and under treatment for a severe heart condition from the age of 64. All these did not prevent us from living well.

When the diagnosis of appendiceal adenocarcinoma with mucinous peritoneal metastases came, he was 80 and most of the big centres in our region refused to treat him. They dismissed him with little hope because of his age, heart problems and advanced disease. We eventually moved further away for a third opinion, while his status was altering as he could only walk with a cane. When PIPAC [post-pressurized intraperitoneal aerosol chemotherapy] was proposed, we answered 'yes' right away. All we asked for was another couple of years together, watching our grandson growing a little older.

After the first two PIPAC, his general status improved dramatically and we could return to an almost normal life. In total, he underwent 15 PIPAC and, in the time intervals between them, we visited France and Spain in our camping car sharing many joyful moments. He was able to honour umpire invitations for a French National Competition. We also spent time with the entire family and friends.

When PIPAC stopped being an option due to non-access, we still had some time left to be grateful for having each other and to prepare the last moments. He died quietly a couple of days after our 61st wedding anniversary, 3 years after the diagnosis of an end-stage disease.

This statement was provided by Jeanine, the wife of a patient with peritoneal surface malignancy.

intraperitoneal therapy but the clonal pressures and considerable heterogeneity that occur during therapy are substantial barriers to widespread adoption.

In addition, other models for testing chemosensitivity have been developed over the past few years, including xenograft, 2D cell monolayer, and 3D sphere and 3D ex vivo tumour models. In one study, chemosensitivity evaluated with 3D ex vivo models correlated more accurately with the response to chemotherapy in in vivo mouse models than the other models³⁷⁰.

Nanomedicines for intraperitoneal therapy

Major drawbacks of intraperitoneal therapies are the rapid clearance of chemotherapeutics from the peritoneal cavity to the systemic circulation³⁷¹ and low tumour-targeting specificity. Nanomedicines (nanoparticles of 1–1,000 nm size) are widely used as delivery vehicles for therapeutic molecules, such as small molecules, proteins or nucleic acids, and are a promising platform when applied via different routes. For example, nanoparticle albumin-bound (nab) paclitaxel and liposomal doxorubicin are approved for intravenous use in clinical oncology and nucleic acid-based nanomedicines, such as coronavirus disease 2019 (COVID-19) vaccines, are administered intramuscularly^{372,373}. Paclitaxel is a hydrophobic chemotherapy compound with a high molecular weight that has characteristic retention within the peritoneal space following intraperitoneal administration, making it an attractive molecule for the treatment of gastric PSM³⁷⁴.

In the past decade, the intraperitoneal use of nanomedicines has received increasing attention. Several studies have demonstrated benefits of intraperitoneal delivery, particularly for nucleic acids^{375–377}; however, rapid clearance remains an unsolved problem. Sustained-release or depot systems loaded with nanoparticles or applying nanomedicines using the PIPAC technology^{378–380} have shown promising results in animal models but clinical data are lacking. The difficulty in the first strategy lies in the large surface area of the peritoneum and the need for homogenous distribution of the nanotherapeutics while preventing adhesion to tissues that may lead to inflammation^{381,382}. The second strategy offers the advantage of uniform distribution of the medication in the peritoneum but it is unclear whether tumour killing is as effective as that of chemotherapeutics in humans and whether it can be applied to using nucleic acid agents.

Alternatively, the residence time of intraperitoneal drugs may be prolonged by incorporation in injectable depots and hydrogels, which enable loading conventional chemotherapy or nanoparticles in an entangled polymer network^{383,384}. In addition to their potential to control drug release, certain hydrogels have the benefit of preventing postsurgical peritoneal adhesion formation³⁸⁵. Other biomaterials for intraperitoneal drug delivery include sustained-release implantable matrices and nanotextiles^{386,387}. These slow-release platforms enable a metronomic dosing strategy, which enhances antitumour efficacy with minimal systemic toxicity³⁸⁷. Clinical studies are awaited to establish their utility in patients with PSM.

Oncolytic viruses are highly versatile therapeutic platforms that can be genetically engineered to provide targeted anticancer and/or immune-modulating effects. Advantages of oncolytic viruses include selective replication in tumour cells, induction of immunogenic cell death and activation of immune responses³⁸⁸. The effects of oncolytic virus therapy on the tumour microenvironment enables synergism with immune-checkpoint inhibitors³⁸⁹. Several studies have investigated the use of intraperitoneal delivery of oncolytic viruses in animal models of PSM and results from the first trials in humans are already available³⁹⁰. Intraperitoneal oncolytic vaccinia virus expressing an IL-15–IL-15R α complex increased cytotoxic function of CD8⁺ T cells and improved survival in a mouse colorectal PSM model³⁹¹. Another study in a colorectal PSM mouse model found that intraperitoneal delivery of vaccinia virus encoding murine GM-CSF activated dendritic cells and CD8⁺ T cells, resulting in synergistic action when combined with immune-checkpoint inhibitors³⁹². Clearly, oncolytic virus approaches hold promise in the treatment of patients with PSM.

Surgical innovation

Malignant disease can remain in the peritoneum at the end of a supposedly CC-0 CRS despite a macroscopically normal looking peritoneum. Up to 27.2%, 12.2% and 26.6–50% of patients with PSM of ovarian cancer, appendiceal cancer or mesothelioma origin, respectively, had malignancy in randomly selected peritoneal biopsy samples³⁹³. Thus, tools to achieve a more precise peritonectomy must be developed.

Near-infrared, fluorescence-guided surgery has great potential in the field of PSM. Some of the most popular uses of this technique are to assess bowel anastomosis perfusion or for sentinel node navigation³⁹⁴, but one of the most innovative and promising uses is the real-time detection of cancerous tissue using targeted or 'smart' fluorescent dyes. In addition to indocyanine green (the most commonly used fluorophore), which was shown to increase detection of PSM by up to 30% in patients with colorectal cancer³⁹⁵, fluorescence-guided surgery using targeted dyes has the potential to become routine to optimize CRS³⁹⁶. For example, use of a fluorescent dye targeting FRA, which is overexpressed in up to 95% of epithelial ovarian cancers, improved the number of tumour nodules detected by surgeons almost fivefold compared with standard observation³⁹⁷. So-called smart dyes are now being tested, including new tumour-targeted near-infrared dyes that may enable quicker, deeper and stronger imaging applications³⁹⁶.

Robotic peritonectomy has rarely been reported despite the advantages that robotic surgery offers in accomplishing complex abdominal procedures, and a complete, standardized description of robotic peritonectomy is not available so far, only reports of partial peritonectomies^{398,399}.

Whether patients with non-resectable PSM from an aggressive primary tumour or no response or progression despite PIPAC treatment could benefit from ePIPAC (electrostatic precipitation PIPAC)⁴⁰⁰ is currently being investigated. Deeper penetration of the

chemotherapy has been observed but whether this correlates with an increased response rate or improvement in survival remains unclear⁴⁰¹. Other technologies such as hPIPAC (hyperthermic PIPAC) are currently at early stages of research⁴⁰².

Challenge of trials in surgical oncology

The design of clinical studies to evaluate the efficacy of surgery in patients with PSM is hampered by considerable heterogeneity. PSM can have various origins and, among the most common causes, such as colorectal and ovarian cancer, specific genetic and molecular landscapes can affect treatment response. In addition, the outcome of clinical trials that include a study group with complex surgery might be substantially affected by bias that is difficult to control, including variability in skill, experience, surgical technique and methods of adjuvant intraperitoneal drug delivery or HIPEC^{403,404}.

In addition, in phase III randomized oncology trials, overall survival is commonly regarded as the optimal hard end point because of its undisputed significance and precision of measurement. However, in surgical oncology trials, its importance is affected by frequent crossover, long accrual times for cancers that are less lethal, and by subsequent therapy in patients who often have survival periods of years after initial surgery and

receive multiple additional systemic treatments. In patients with PSM, progression-free survival is the preferred trial end point, either as a surrogate of overall survival if progression-free survival has been proven to correlate with overall survival, or because of the clinical benefit of preventing or delaying peritoneal disease recurrence, which is known to cause potentially serious morbidity. Disadvantages of the use of progression-free survival include the difficulty to timely and accurately diagnose recurrent peritoneal disease and that it does not always correlate with overall survival⁴⁰⁵.

The understanding, investigation and treatment of primary and metastatic PSM has greatly improved in the past few years and further exciting developments are expected. However, challenges remain. It is important not only to offer the best treatment option and develop intraperitoneal therapies that live up to the quality of current systemic therapies but also to define the optimal treatment sequence according to primary tumour, disease extent and patient preferences. New imaging modalities, less invasive surgery, nanomedicines and targeted therapies are the basis on which a new era of intraperitoneal therapy is being built, which will bring long-term improvements in patient outcomes.

Published online: 16 December 2021

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Acknowledgements

The authors thank Jeanine for their contribution in Box 2.

Author contributions

Introduction (D.C.-G., M.H. and F.L.); Epidemiology (D.C.-G., M.H., A.B., K.K.T. and M.C.); Mechanisms/Pathophysiology (D.C.-G., M.H., W.C. and R.R.); Diagnosis/Screening/Prevention (D.C.-G., M.H., M.A., O.G., F.L., O.S. and K.V.D.S.); Management (D.C.-G., M.H., M.A., O.G. and F.L.); Quality of life (D.C.-G., M.H., A.B., O.S. and K.V.D.S.); Outlook (D.C.-G., M.H., W.C. and R.R.); Overview of the Primer (D.C.-G.).

Competing interests

R.R. has received group research and engineering support from Fisher and Paykel. K.V.D.S. is a board member of the European Society of Surgical Oncology (ESSO) and an executive committee member of the Peritoneal Surface Oncology Group International (PSOGI). D.C.-G. holds honorary functions within ESSO as member of the Boards of directors, the Spanish Society of Surgical Oncology (SEOG) as member of the Boards of Directors, the Spanish Federation of Oncologic Societies (FESEO) as secretary and member of the Boards of Directors, the International Society for the Study of Pleura and Peritoneum (ISSPP) as member of the communication committee, and the Enhanced Recovery After Surgery (ERAS) society and is responsible for the ERAS HIPEC website content. A.B. is on the review committee of the Department of Science and Technology of India, and declares no financial or non-financial competing interests. M.A. is a member of the ISSPP Education committee. M.H. has received research funding (institution) from Nestlé health science, speaker honorary (institution) from MSD, Nestlé, Fresenius, Capnomed and Encare, is a board member of the ERAS society and is chair of education of the ISSPP. O.G. is a consultant for GAMIDA (financial competing interest), Director of RENAPE, and President of BIG RENAPE association (non-financial competing interests). O.S. holds honorary functions with ESSO (member of the Communication committee), ISSPP (Public Relations committee), the French Society of Surgical Oncology (executive board), the French National Network for Peritoneum (RENAPE; board member) and the Romanian Students' Society of Surgery (honorary president). W.C. is Board member of the Belgian Society of Surgical Oncology and Royal Belgian Society of Surgery, and Editor-in-Chief of *Acta Chirurgica Belgica*, and Associate editor of *European Surgical Research* and *International Journal of Hyperthermia*. F.L., K.K.T. and M.C. declares no competing interests.

Peer review information

Nature Reviews Disease Primers thanks Peter Cashin, Yasuhiro Koda, Winston Spencer Liaw, Beate Rau and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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Supplementary information

The online version contains supplementary material available at <https://doi.org/10.1038/s41572-021-00326-6>.

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