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Nationwide Analysis of epidemiological data on peritoneal metastasis provided by the German statutory health insurance

Dissertation

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Zusammenfassung

Die vorliegende Dissertationsarbeit ist die erste epidemiologische Untersuchung und analytische Erfassung von Patienten mit peritonealer Metastasierung in Deutschland. Die Datenanalyse erfolgte auf Basis bundesweiter Abrechnungsdaten der vertragsärztlichen Versorgung. Die peritoneale Metastasierung, auch Peritonealkarzinose genannt, stellt eine klinisch hochkomplexe und prognostisch ungünstige Manifestation überwiegend gastrointestinaler und gynäkologischer Malignome dar und ist zumeist Ausdruck einer fortgeschrittenen Tumorerkrankung. Trotz ihrer hohen klinischen Relevanz liegen bislang keine Erkenntnisse zur ambulanten Versorgungsrealität vor, obwohl ein Großteil der Patienten nach Diagnosestellung im ambulanten Bereich betreut wird. Ziel der Arbeit ist die Untersuchung grundlegender epidemiologischer Daten, und die Einordnung dieser in dem Gesamtkontext, mit besonderem Augenmerk auf fachärztliche Inanspruchnahme und ambulanter diagnostisch-therapeutischer Leistungen. Die Analysen basieren auf bundesweiten Routinedaten gesetzlich Versicherter über mehrere Jahre und berücksichtigen sowohl nationale als auch regionale Versorgungsstrukturen.

Die Ergebnisse zeigen, dass die ambulante Versorgung von Patientinnen und Patienten mit Peritonealkarzinose in Deutschland überwiegend hausärztlich koordiniert wird, während spezialisierte Fachdisziplinen regional sehr unterschiedlich eingebunden sind. Die erfassten Patienten sind vornehmlich weiblich und in höherem Lebensalter. Im Zeitverlauf zeigt sich eine leichte Zunahme der ambulant dokumentierten Fälle dieser Erkrankung. Es lassen sich regional unterschiedliche Inzidenzen (angenäherte Inzidenz) sowie Unterschiede in der Einbindung chirurgischer Fachrichtungen erfassen.

Diese Muster sprechen für strukturelle Unterschiede in Zugang, Versorgungsorganisation und fachärztlicher Verfügbarkeit, mit möglicherweise Benachteiligung des ostdeutschen Raumes. Insgesamt zeigt sich eine im Verhältnis zur Krankheitskomplexität begrenzte Dokumentation spezialisierter ambulanter Diagnostik und Prozeduren. Die im Rahmen dieser Analyse erfassten Daten sind eine Annäherung an die möglichen Inzidenz- und Verteilungsraten von Peritonealkarzinose und geben erste Hinweise auf die ambulante Versorgung für diese

Patientengruppe. Eine systematische Untersuchung und Erfassung von Peritonealkarzinosedaten ist langfristig notwendig, um weitere Trends und Entwicklungen zu untersuchen.

Abstract

Introduction:

Peritoneal metastasis (PM) is a complex clinical condition associated with substantial morbidity and a need for interdisciplinary management. To date, dependable demographic data, including incidence, prevalence and information on outpatient management of PM remain scarce. For the first time, this study offers a comprehensive analysis of outpatient care for PM patients across the German stately-insured population.

Methods:

For the purpose of this study, billing data from Statutory health insurance-accredited physicians and psychotherapists (in accordance with Section 295 of the Fifth Book of the German Social Code (SGB)) from 70.1 million insured patients in Germany were analyzed, encompassing all patients receiving outpatient treatment for PM between the period of 2014 until the end of 2021, including the COVID-19 period. Analysis focused on regional approximated incidence as well as age and sex distribution.

Results:

The provided data indicates that 69.9% of contacts were made with the primary care providers (general/family medicine), 22.8% with their oncologists/hematologists, and 8.2% with their gynecologists. From 2014 to 2021, the 19,359 cases of PM were listed nationwide 2021 which reflected an increase of 5.3% compared to 2014. The approximated incidence rate was higher in eastern Germany than in the western part. A wide spectrum of diagnostic and therapeutic procedures was performed in the outpatient setting.

Discussion:

Outpatient management of patients with PM is complex and involves extensive diagnostic and therapeutic interventions, predominantly coordinated by primary care providers. It remains unclear whether existing expertise and resources are sufficient to address the diverse needs of this patient group throughout disease progression. Further research is warranted to optimize outpatient care structures and interdisciplinary collaboration for PM patients. A systemic approach is needed to monitor epidemiological data for PM.

Abbreviations

BDSG	Federal Data Protection Act
CT scan	Computed tomography
CEA	Carcinoembryonic antigen
CRS	Cytoreductive surgery
CRC	Colorectal carcinoma
DGAV	German Society for General and Visceral Surgery
EBM	Uniform value scale
ECM	Extracellular matrix
ENT	Ear Nose and Throat
GDPR	General Data Protection Regulation
GOÄ	German Fee Schedule for Physicians
HIPEC	Hyperthermic intraperitoneal chemotherapy
ICD-10-GM	International classification of diseases, 10th revision, German modification
IPC	Intraperitoneal chemotherapy
KBV	National Association of Statutory Health Insurance Physicians
MRI	Magnet resonance imaging
PCI	Peritoneal carcinomatosis index
PIPAC	Pressurized intraperitoneal aerosol chemotherapy
PM	Peritoneal metastases
SHI	Statutory health insurance
ZI	Central Research Institute of Ambulatory Health Care in Germany

Table of Contents

List of Figures

List of Tables

1. Introduction

1.1 Definition and Pathophysiology of Peritoneal Metastasis

Peritoneal metastasis (PM) represents a complex and clinically challenging manifestation of advanced malignancy, most commonly arising from gastrointestinal and gynecological cancers, including colorectal, gastric, pancreatic, gallbladder, ovarian carcinomas and others (1). While the peritoneum can host primary malignancies such as malignant peritoneal mesothelioma, most peritoneal malignancies occur as secondary metastatic disease in the context of an established primary tumor (1). Due to its unique biological behavior, dissemination pathways, and clinical implications, PM is now widely regarded as a distinct metastatic entity rather than simply a late stage of systemic disease (2).

Unlike classical distant metastases, which typically develop through hematogenous or lymphatic spread to organs such as the liver, lungs, or bones, PM arises predominantly via transcoelomic dissemination (2-4). While other routes of cancer spread have been proposed, this is the more common view in the current medical and scientific community (5, 6).Tumor cells may directly exfoliate from the surface of the primary tumor into the peritoneal cavity, where they survive in suspension, evade apoptosis, and subsequently adhere to and invade the peritoneal lining (3, 7). This is a complex multistage process which is not necessarily linear and can be either slow or, in other instances, rapid. In the case of rapid disease progression, which often goes along with an increase in total cancer volume, patients often experience rapid clinical deterioration and increased symptoms.

The metastatic spread bypasses vascular dissemination and is led by distinct biological mechanisms, including altered cell adhesion, epithelial–mesenchymal transition, interactions with the peritoneal microenvironment, and evasion of local immune response. A variety of ideas have been proposed to interfere in this multifaceted process (8). In the clinical setting, sometimes the metastatic process appears to be restricted to the abdominal cavity. This pattern, present in many but not all cases, has contributed over recent decades to a more nuanced understanding of PM.

For example, while it used to be common to classify PM as an undifferentiated metastatic spread pattern of solid primary cancer of the abdominal cavity, this view has changed to some degree. Currently, the peritoneal surface is more closely viewed as an organ rather than an outer skin. The partial or complete surgical removal of metastatic spread within “one organ” does not necessarily mean that one is looking at a systemic metastatic constellation. In fact, the commonly observed isolated peritoneal spread might indicate that cells are still somewhat biologically attached to the peritoneal cavity (9-11).

These features further emphasize the concept of PM as a specific metastatic phenotype with its own molecular drivers, spread patterns and therapeutic challenges (2, 3, 7).The heterogeneous nature of PM further complicates its clinical management. Most PM cases originate from advanced gastrointestinal malignancies, particularly colorectal, gastric, pancreatic, and appendiceal cancers (1, 2). This makes it harder to evaluate treatments, coordinate patient flow as well as collect and evaluate basic statistical data on PM. This heterogeneity increases the complexity of evaluating surgical interventions, as cancers of different origins may exhibit significantly different outcomes even at comparable stages. Moreover, there are specific “PM-like” or equivalent forms of malignant peritoneal diseases with unique types of behavior and disease patterns such as mucin-producing tumors e.g. appendiceal neoplasms and pseudomyxoma peritonei (12, 13). These display distinctive patterns of locoregional dissemination characterized by extensive mucin accumulation and often prolonged but highly morbid clinical course (2). In contrast, gastric and pancreatic carcinomas are frequently associated with aggressive tumor biology, limited treatment response, and rapid clinical deterioration once peritoneal involvement develops (2). PM exhibits a large variety of heterogeneity (14). The heterogeneity continues within each cancer entity (15, 16) but also throughout the different entities: in colorectal cancer for example, some tumors show a marked predilection for peritoneal dissemination, whereas others predominantly metastasize via hematogenous routes (2, 3).

Gynecological malignancies, particularly ovarian cancer, represent another major contributor to PM prevalence (3, 7). Ovarian carcinoma is characterized by an insidious onset and the absence of effective population-based screening strategies; therefore, screening is neither recommended nor provided by statutory health insurance (SHI) for average-risk populations, and many patients pre-

sent with advanced-stage disease and extensive peritoneal involvement at diagnosis (17, 18). The high frequency of PM in ovarian cancer reflects both its intrinsic biological tendency toward transcoelomic spread and its anatomical characteristics that facilitate tumor cell dissemination within the peritoneal cavity (3, 17). PM manifestation and its different primary origins might further explain why there is basically no data available on incidence or prevalence for PM. Provided numbers are very rough estimates, assumption on PM extent in the society or small subgroups within one entity (19, 20). This is quite astonishing when considering that PM is a serious diagnosis with devastating consequences for affected patients. The high mortality rates of PM are undeniable. However, the aforementioned challenges in patient classification and grouping may have substantially contributed to the longstanding difficulty in obtaining reliable data on PM.

1.2 Peritoneal vs. distant metastasis

Despite advances in molecular and translational oncology, it remains incompletely understood why some patients are more prone to PM development (2, 3). While factors such as tumor differentiation, invasive capacity, genomic alterations, and interactions with the peritoneal microenvironment are likely contributing, their exact role and impact have not been fully elucidated (3, 7). Clinical experience indicates that the peritoneal cavity itself is not particularly hospitable to floating cancer nodules. No clear threshold exists for the intraperitoneal burden required to initiate cancer cell adhesion and local manifestation, although its importance is widely acknowledged (21, 22). Data from the experimental setting indicate that cancer cells prefer the extracellular matrix (ECM) to a mesothelial surface which commonly covers the peritoneal cavity. However, this is not the only factor in the overall perspective on PM spread. Beyond the question of total cancer burden and extent of PM spread, the clinical picture can differ significantly. Some patients experience rapidly progressive PM, whereas others develop more indolent disease that nevertheless imposes substantial morbidity over time (1, 2, 23). Evidence increasingly suggests that intrinsic tumor biology plays a decisive role in shaping metastatic formation. Molecular alterations associated with greater invasive capacity, mesothelial adhesion, or altered immune evasion may

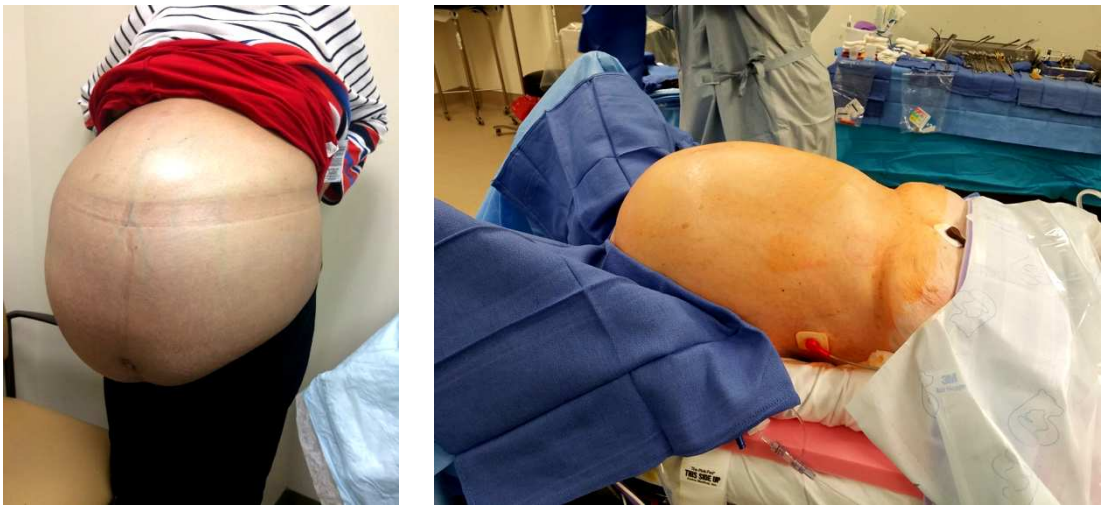
predispose tumor cells to colonize the peritoneal cavity (3, 7). Conversely, tumors that metastasize hematogenously often demonstrate molecular profiles that enable vascular invasion, survival in the bloodstream, and organ-specific colonization (3). These divergent biological pathways underscore the necessity of examining peritoneal metastasis as a pathophysiological process distinct from classical systemic metastasis, with its own prognostic and therapeutic implications (2, 3). A comprehensive understanding of PM must begin with an appreciation of the structural and functional distinctiveness of the peritoneum.

The peritoneal cavity is lined by a continuous monolayer of mesothelial cells that rests upon a complex submesothelial connective tissue matrix containing blood vessels, lymphatic channels, and diverse immune cell populations (24). This structure fulfills several essential physiological roles: it provides a protective and friction-reducing barrier for intra-abdominal organs, regulates peritoneal fluid homeostasis, and serves as a highly active immunologic interface capable of mounting both innate and adaptive responses (24). Paradoxically, these same features might contribute to the cavity's vulnerability to metastatic colonization. The mesothelial layer can undergo rapid changes in response to inflammation or tumor-derived stimuli, becoming more adhesive and permeable; tumor cells may exploit these properties and adhere to mesothelial surfaces with the purpose to invade the underlying stroma under certain conditions (3, 7). Thus, the peritoneal microenvironment forms a unique habitat for metastatic seeds, shaping the clinical behavior of peritoneal disease (3, 7).

1.3 Secondary symptoms

Clinically, PM imposes a particularly severe burden on affected patients. The diffuse spread of tumor deposits along the peritoneal surfaces progressively disrupts gastrointestinal function, frequently resulting in malignant ascites, bowel obstruction, nutritional decline, chronic pain, and profound fatigue, all of which markedly reduce quality of life and independence (1, 2, 23). These symptoms often dominate daily living, leading to significant physical, emotional, and social limitations that extend far beyond the oncologic diagnosis itself (see figure 1). Diagnostic assessment is further complicated by the fact that PM may remain

radiologically occult due to its thin and superficial growth pattern, contributing to delayed diagnosis and underestimation of disease extent in conventional imaging such as computed tomography (CT scan) (25-28). This limitation reinforces the importance of direct surgical evaluation, particularly diagnostic laparoscopy, for accurate disease assessment (24). Taken together, the substantial individual and societal burden of PM underscores the urgent need to better understand this disease entity. Systematic and comprehensive data collection is therefore essential to characterize patient demographics, disease patterns, and care pathways, and to generate dependable, population-specific evidence within the German healthcare system that can inform clinical decision-making and ultimately improve patient-centered care (2, 29).



a) b)

Figure 1: *Clinical appearance of ascites with abdominal distension*
(Source:courtesy of Department of Surgery, University of California, Irvine, USA)
a) preoperative presentation of ascites showing abdominal distention and b) intraoperative presentation of ascites in advanced tumor disease. Presence of ascites as an indicator for advanced tumor dissemination in patients with peritoneal metastasis (PM). The extreme intraabdominal volume can cause severe abdominal pain and discomfort, dyspnea and markedly reduced quality of life.

1.4 Limitations in access to specialized centers

Within Germany, PM management has evolved considerably over the last decades, with increasing recognition of PM as a distinct disease entity and the establishment of structured documentation and quality assessment initiatives for major locoregional procedures [30]. Despite these efforts and significant scientific contributions to improve our current understanding of PM, this tumor entity remains much less known with overall little public awareness. In most cases, patients have never heard about this form of cancer manifestation whereas they usually have at least some understanding of other cancer entities such as colorectal or pancreatic cancers. This also extends to some part into the clinical setting. Oftentimes, PM is presented as a form of locoregional metastasis in the curriculum and does not warrant wider attention from students and young medical graduates. This is further complicated by the lack of specific recommendations and protocols. In clinical practice, a lack of diagnostic and therapeutic algorithms is observed as there are no standard operational procedures or recommended guidelines (Leitlinie) specifically designed for PM patients. In the past, and to

some extent still today, a PM diagnosis has been viewed by many practicing physicians, especially family physicians, as an immediately fatal diagnosis. In the practical setting, many patients are forced to take the initiative and search for specialized doctors and centers that they contact for further help and recommendations.

This leads to an overall heterogeneity including variations in referral patterns, institutional expertise, and access to advanced therapeutic modalities. Treatment efficacy remains limited, which is particularly consequential in a disease where eligibility for complex interventions is time-sensitive and strongly depends on disease extent at presentation (2, 29).

The burden of PM is further intensified by the limited availability of highly specialized peritoneal malignancy programs and the complexity of referral pathways. At this point, it is important to consider the aspect of time-sensitivity. It is not unusual that a significant amount of time passes until patients are actually seen by PM specialists in the hospital setting. Furthermore, it is important to mention that the amount of PM specialists throughout Germany remains limited. While specialized care may provide advanced diagnostics, multidisciplinary evaluation, and access to locoregional therapies, timely referral is nevertheless challenging in many healthcare systems, including in Germany. This is due to geographic constraints, variable referral structures, and limited patient and provider awareness regarding urgency and eligibility windows (2, 29). This is further aggravated by the disease characteristics as highlighted by a low median survival of 3 - 5 months, a fast and progressive deterioration of the patient's ability to receive therapy, the need to travel to reach specialized centers and the center's availability for timely care.

According to the StuDoQ/Peritoneum registry of the German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein und Viszeralchirurgie, DGAV) a total of 52 hospitals in Germany are reported to perform cytoreductive surgery/Hypothermic Intraperitoneal Chemoperusion (CRS/HIPEC), indicating a degree of specialization in PM treatment [30]. However, the level of expertise and procedural volume can substantially vary between centers, ranging from high-volume, specialized university hospitals to institutions performing CRS/HIPEC only sporadically. The level of experience in these centers is not equivalent. In order to perform CRS/HIPEC procedures, which can be very ex-

pensive operations, surgeons must complete extensive training and be highly experienced. A similar level of expertise is required from ICU teams to manage the extensive amount of postoperative challenges following these high-level operations. In the absence of standardized treatment algorithms and recommended guidelines for PM, combined with limited disease awareness, access to specialized PM centers remains challenging. Delayed presentation to expert centers can directly reduce eligibility for aggressive locoregional interventions, thereby perpetuating poor outcomes and increasing psychological distress for patients and families (2, 29).

1.5 Peritoneal carcinomatosis index (PCI) score

The peritoneal carcinomatosis index (PCI) score was first described by Sugarbaker et al. in 1996 (24) and has since become a central component of preoperative assessment, intraoperative decision-making, and outcome stratification in peritoneal surface malignancies. To obtain the PCI score, a diagnostic laparoscopy needs to be performed. During the procedure, the surgeon scans the intraperitoneal cavity for metastatic growth. For this purpose, the abdominal and pelvic cavity is divided into 13 anatomical regions, comprised of nine abdominopelvic regions and four small-bowel regions. In each region, the largest visible tumor nodule is scored according to lesion size: LS-0 (no visible tumor), LS-1 (tumor ≤ 0.5 cm), LS-2 (tumor > 0.5 cm and ≤ 5 cm), and LS-3 (tumor > 5 cm or confluent disease). The individual regional scores are added to yield a total PCI ranging from 0 to 39, with higher scores indicating greater peritoneal tumor burden. Beyond reflecting tumor volume, the PCI captures topographic disease distribution, particularly the involvement of the small bowel, which is a critical determinant of resectability and the likelihood of achieving complete cytoreduction. In general terms, a PCI > 20 is considered as a cut-off value and demonstrates a contraindication for curative surgical procedures like CRS and HIPEC.

While it is consensus that lower PCI scores indicate limited disease and better overall surgical outcomes, it is important to understand that eligibility for CRS and HIPEC as well as cut-off values for PCI scores can vary depending on the primary tumor entity. For example, in colorectal cancers (CRC), a PCI be-

tween 0 and 20 can be considered for CRS and HIPEC, depending on other inclusion criteria, general condition of patient and potential small bowel involvement. However, e.g. in gastric cancer, with respect to its unique tumor biology and rather quick tendency to locally metastasize, the recommended PCI cut-off is at 12 as indicated by Glehen et al. (30). In fact, most PM patients with a primary gastric tumor who benefit from CRS and HIPEC typically show PCI scores of < 7. These differences further highlight the pronounced heterogeneity of PM across tumor entities and emphasize the importance of timely referral to specialized centers.

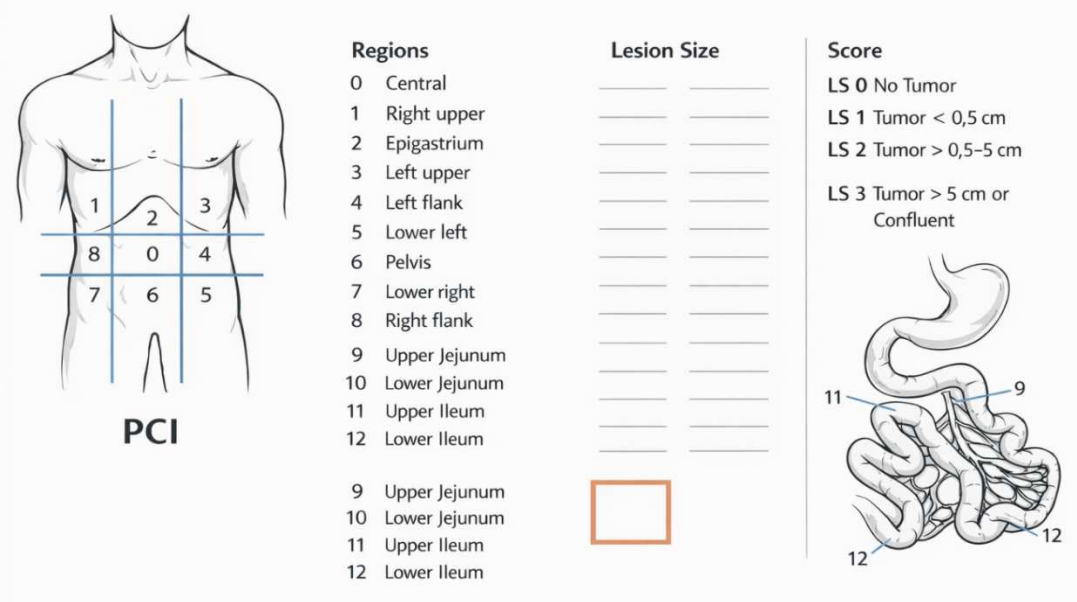


***Figure 2**: Schematic illustration of the Peritoneal Cancer Index (PCI)*
(modified from(24))
The PCI is a standardized scoring system used to objectively quantify the extent and distribution of peritoneal metastases (PM). It is most commonly assessed during diagnostic laparoscopy and constitutes a key parameter in guiding subsequent therapeutic decision-making

1.6 Current therapeutic approaches

1.6.1 CRS and HIPEC

Current PM management has increasingly incorporated specialized locoregional strategies and the application of intraperitoneal chemotherapy (IPC). For many years, PM was a palliative diagnosis without any hope for treatment. With the introduction of CRS and HIPEC (1, 2, 31) by Paul H. Sugarbaker in the 1980s, the landscape in treatments completely changed for PM. For the first time, a potential curative therapy was available for patients with limited disease.

While controversial at the beginning, CRS and HIPEC marked a paradigm shift and changed the clinical understanding of PM. With a timely diagnosis and fast access to specialized care, this once terminal illness can now be potentially cured, at least in selective patients. The most important aspect was the notion that a locoregional metastatic spread is not equivalent to a general metastatic spread throughout the body. The idea of CRS is to provide a complete macroscopic cytoreduction through peritonectomy procedures and, when required, multivisceral resections. The outcome of CRS and HIPEC strongly depends on achieving complete cytoreduction, meaning that all macroscopically visible tumors are removed and an R0 resection is achieved (31, 32). Subsequently, the abdomen is closed following CRS, and HIPEC is administered by means of a heated intraperitoneal chemoperfusion (commonly around 41–42°C) (33, 34). While the surgeon can eliminate all macroscopically visible tumor nodules by means of multivisceral resection, it must be assumed that microscopic tumor residues might persist which can give rise to recurrent tumors. Thus, to eliminate all potentially residual microscopic tumor cells, high locoregional drug concentrations are delivered using hyperthermia-enhanced cytotoxicity to target microscopic residual disease (24, 35, 36). The pharmacologic principle is supported by the peritoneal–plasma barrier concept, which explains why IPC can achieve higher peritoneal than plasma drug levels for selected agents and delivery conditions (24, 35, 36). After an exposure time of 60 to 90 minutes, the chemoliquid is released and chemoperfusion is terminated.

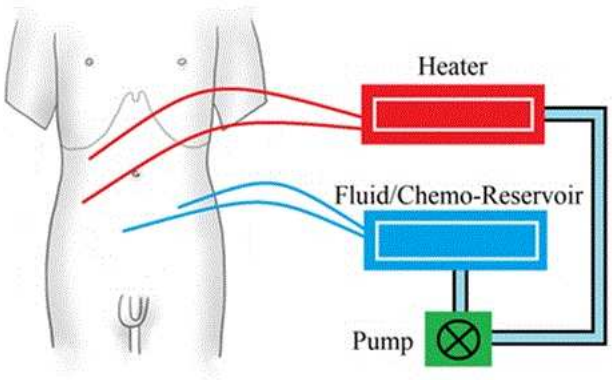


Figure 3: *Schematic illustration of Hyperthermic Intraperitoneal Chemotherapy (HIPEC).* (modified from(37))
A liquid chemotherapeutic solution is heated to approximately 41–43°C and delivered into the abdominal cavity via a controlled pump-driven perfusion system. The solution is continuously circulated within the peritoneal cavity for a defined treatment period, typically lasting 60–90 minutes

CRS and HIPEC are among the most complex procedures in surgical oncology with high morbidity and mortality rates (38-40). Despite a long list of potential complications, it remains the only curative approach. The therapeutic benefit of CRS combined with HIPEC critically depends on rigorous indication setting and careful patient selection (41, 42). Assessment of eligibility for CRS and HIPEC requires fulfillment of several key criteria, including potential resectability with a high likelihood of achieving complete cytoreduction, as evaluated by preoperative imaging and staging laparoscopy, a limited intraperitoneal tumor burden as reflected by a current PCI score, and adequate physiological reserve to tolerate major surgery, including acceptable cardiopulmonary and renal function (41-43). Exclusion criteria commonly include extensive peritoneal disease, diffuse tumor involvement of the small bowel or mesentery, extraperitoneal spread such as distant metastases, severe malnutrition, uncontrolled infection, major decompensated comorbidities, or manifest bowel obstruction (42-44). Due to the individual nature of each case, it finally depends on the surgeon's experience and best estimate whether, under the provided conditions, a patient is a good candidate. Ultimately, this means whether the patient will more likely benefit from the procedure than being harmed by it. Evaluating this requires consideration of many aspects and further illustrates the short time frame in which the patient will remain suitable for a full technical resection. It is important to understand that this window of opportunity is closing more with each day that passes. This emphasizes that timely patient presentation is essential for consideration of CRS and

HIPEC and helps explain why only a selected group of patients ultimately qualify for these procedures.

1.6.2 PIPAC

In 2011, a novel palliative treatment was introduced into the clinical setting called Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). PIPAC was introduced on a large scale initially at the Marienhospital Herne, University Hospital of the Ruhr-University in Bochum. Within a few years, several thousand patients received sometimes multiple rounds of PIPAC. Since then, it has been rapidly adopted internationally as a repeatable laparoscopic drug delivery technique for unresectable PM, particularly in patients who do not qualify for CRS/HIPEC due to disease extent and comorbidity (2). Its rationale is to improve intraperitoneal drug distribution and tissue uptake through aerosolization under pressure, thereby providing symptom control, including reduction of ascites, disease stabilization, and preservation of quality of life in a palliative setting (2). In a broader sense, it is a locoregional form of chemical cytoreduction therapy.

In clinical practice, PIPAC is performed following laparoscopy. After establishment of a capnoperitoneum, the extent of peritoneal disease is documented, commonly including intraoperative assessment of the PCI score, and peritoneal biopsies are obtained for histological evaluation (45, 46). Chemotherapy is subsequently aerosolized into the abdominal cavity using a nebulizer connected to a high-pressure injector while the abdomen remains closed and pressurized for a defined exposure period (45). At the end of the exposure time, the aerosol is evacuated by controlled desufflation through a closed filtration system to ensure occupational safety before completion of the procedure (46, 47). PIPAC is typically administered in repeated cycles, often at intervals of approximately six weeks depending on protocol and combination with systemic therapy. Treatment response is assessed by repeated histological sampling, repeated macroscopic evaluation and PCI documentation during subsequent procedures (48, 49). An analysis of German hospital care reported that in 2019, 534 patients received PIPAC in Germany, with low in-hospital mortality and procedure-related morbidity documented in that dataset (50). Accordingly, PIPAC represents an emerging

component of multimodal palliative therapy, with an expanding role particularly for patients previously limited to systemic therapy (2, 50).

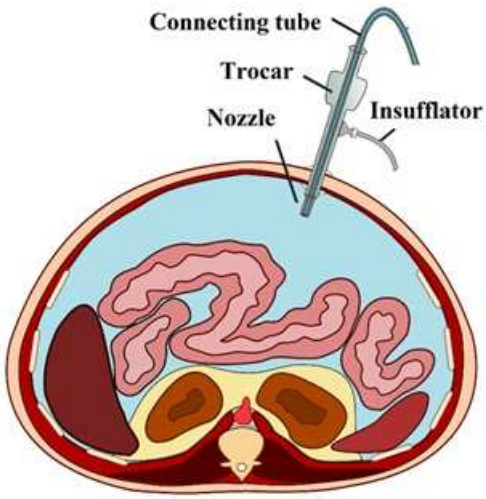


Figure 4: *Schematic illustration of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) (modified from(51))*
PIPAC is performed laparoscopically in a closed abdominal cavity. During the procedure, a chemotherapeutic agent is aerosolized and evenly distributed within the abdomen using a nebulizer connected to a high-pressure injector. After a defined exposure period, the aerosol is safely removed by controlled desufflation through a closed filtration system to protect operating room personnel before the procedure is completed.

1.6.3 The role of palliative systemic chemotherapy

Before the clinical introduction of surgical procedures such as CRS and HIPEC or PIPAC, systemic palliative chemotherapy frequently represented the only active treatment option for patients with PM, and it remains a cornerstone of palliation within contemporary multimodal concepts (2, 24, 35, 36). In this setting, the primary goal of systemic chemotherapy is not to achieve cure, but rather to slow down tumor progression, reduce symptoms, improve quality of life and further preserve the current performance status (2). However, the limitations of systemic therapy in peritoneal disease are substantial. A key challenge is the peritoneal–plasma barrier, which reduce effective drug transfer from plasma into the peritoneal cavity and limit exposure and penetration of superficial tumor nodules at the target site (24, 35, 36).

Beyond pharmacokinetic limitations, systemic chemotherapy in PM is also limited in its efficacy due to strong interindividual variability in treatment response. It is difficult to predict which patients will derive meaningful benefit, while almost

all patients suffer from the side effects associated with chemotherapeutic applications. Thus, the emergence of locoregional palliative options such as PIPAC address an important therapeutic gap by offering local tumor therapy for selected patients, further underscoring the importance of scientific investment and contributions into this difficult tumor entity.

1.6.4 Prognosis

PM is associated with a particularly poor prognosis, reflecting both aggressive tumor biology and the fact that the disease is often diagnosed at an advanced stage (2, 23). In many patients, the natural course of peritoneal spread is predominantly palliative, as the extent of intra-abdominal tumor involvement frequently limits curative treatment approaches (2, 23). Historically, patients receiving supportive care alone have had median survival times measured in only a few months, commonly reported in the range of three to six months, although outcomes vary depending on tumor type and patient cohort (1, 23). One reason for this limited survival is that PM often remains clinically silent in early stages; symptoms typically become apparent only once secondary complications develop, by which time disease burden is usually advanced and difficult to reverse (2, 23). In contrast to other metastatic conditions-such as certain subtypes of metastatic breast cancer, where modern systemic therapies can achieve survival measured in years-PM is characterized by rapid clinical deterioration driven by progressive intraperitoneal tumor growth and widespread involvement of the peritoneal surfaces (52). Disease progression commonly manifests as increasing ascites, recurrent episodes of partial or complete bowel obstruction, progressive abdominal distension, early satiety, and a gradual decline in functional capacity (2, 23). In advanced stages, many patients develop cachexia, refractory ascites, and persistent gastrointestinal obstruction, severely limiting oral intake and often necessitating repeated palliative interventions. Together, these features contribute to a terminal disease trajectory marked by a pronounced decline in physical reserve and quality of life (2, 23).

1.7 Patient access to medical care and specialist services

In Germany, statutorily insured patients are entitled to the principle of free choice of physician (“freie Arztwahl”) as regulated by the Social Code Book V (SGB V) (53). This principle is subject to certain restrictions; for example, a change of physician within the same calendar quarter is generally permitted only for justified reasons, and free choice is limited to physicians participating in statutory outpatient care (53, 54). In addition, the model of general practitioner–centered care (“hausarztzentrierte Versorgung”) restricts direct access to specialist care by requiring referral through a general practitioner, a framework that also applies to patients with oncologic diseases (55, 56).

Overall, there are 34 officially recognized medical specialties in Germany (57). The care of patients with PM is multidisciplinary and typically involves several medical specialties, including general practitioners, internists, oncologists, surgeons, gastroenterologists, radiologists, and gynecologists (33, 42). According to the 2024 German physician statistics published by the German Medical Association, there are a total of 63,368 physicians specialized in internal medicine in Germany, of whom 30,563 work in outpatient care (57). Among these, 1,358 physicians hold a specialization in medical oncology, with 617 providing outpatient care. In addition, Germany counts 45,373 general practitioners, of whom 38,498 are active in the ambulatory sector (57). The distribution of further medical specialties relevant to the care of patients with PM is summarized in Table 1.

With approximately 3.7 physicians per 1,000 inhabitants, Germany-alongside Austria and Greece-ranks among the European Union countries with the highest physician density (58). Germany also reports a comparatively high frequency of physician contacts, with an average of around 9–10 physician visits per capita per year (58, 59). This may underestimate actual utilization, as statutory outpatient billing data record a maximum of one case per physician per patient per calendar quarter, irrespective of the number of consultations during that period (54, 60).

Table 1: *Medical speciality infrastructure and physician distribution relevant to PM care in Germany (2024)*

Specialty	Total	Outpatient practice	Inpatient practice
Internal Medicine	63,368	30,563	28,903
General Practice	45,373	38,498	2,565
Surgery	41,839	13,447	25,475
Gynecology	19,736	12,204	6,521
Radiology	10,139	4,681	4,854
Gastroenterology	1,923	926	896
Radiation Oncology	1,670	814	781
Oncology	1,358	617	642

(Source: Own illustration based on data from (54))
This table summarizes the total number of physicians in selected specialties involved in the diagnosis and treatment of PM, differentiated by outpatient and inpatient practice settings. Note: Outpatient practice refers to physicians working in ambulatory care settings, while inpatient practice refers to hospital-based physicians.

1.8 Demographics

To date, reliable population-level estimates on PM incidence in Germany are lacking. A fundamental limitation is that PM is not consistently or systematically recorded in cancer registries, which substantially restricts epidemiological conclusions at the national level (61-63). As a result, available German data on PM are largely derived from procedure- and center-based registries or institutional cohorts, which, while informative for clinical characteristics and outcomes, are not suitable for estimating national incidence. Due to the overall low medium survival, the best approach to look at the extent of PM cases in the population is the annual incidence rate. The prevalence rates (cases of PM at any measured moment) would not adequately reflect the total extent of challenges associated with PM. Given the short median survival of approximately 3–4 months, fewer patients are likely to be affected by PM at any given time than over the course of a full year, which would lead to systematic underreporting and underestimation of overall disease burden.

The most comprehensive German datasets on PM originates from the DGAV StuDoQ|Peritoneum registry, which prospectively documents patients undergoing CRS and HIPEC. These data provide valuable insights into periopera-

tive outcomes and allow entity-specific analyses within selective patient subgroups (29, 64). However, by design, the registry captures a highly selective surgical population treated in specialized centers and therefore does not reflect the true population-level burden of PM in Germany. The most population-oriented German analysis identified is a registry-based cohort study from Bavaria, utilizing data from the Regensburg Tumor Center to examine outcomes in patients with isolated synchronous or metachronous colorectal PM (65). Although Regensburg represents a major national referral center for PM treatment, this study primarily addresses comparative effectiveness and survival outcomes and does not provide nationally generalizable estimates of PM incidence.

Consequently, despite the availability of high-quality clinical and surgical data (29, 64, 65), fundamental epidemiological parameters of PM in Germany, including overall burden, incidence, demographic distribution and development of PM numbers, remain insufficiently characterized. This persistent evidence gap underscores the need for population-based approaches capable of generating reliable demographic and epidemiological estimates to better quantify PM burden and regional variation at the national level.

1.9 Structural Characteristics of PM management

1.9.1 Inpatient Care: Role and Limitations

A central structural feature of PM care in Germany is the disconnect between the high clinical complexity of the disease and the predominantly outpatient reality in which the majority of affected patients spend most of their illness. Inpatient care offers decisive strengths because it provides immediate access to interdisciplinary diagnostics, acute complication management, and complex oncologic interventions that cannot be reliably delivered in ambulatory settings (2, 23, 29). From a clinical perspective, hospitals are uniquely equipped to address the acute complications that define PM burden: bowel obstruction, refractory ascites requiring drainage, severe pain requiring parenteral analgesia, electrolyte disturbances, dehydration, infectious complications, and therapy-related toxicities such as neutropenic infections or renal impairment (2, 23). In addition, key elements of onco-

logic pathway execution—central venous access placement, cross-sectional restaging, diagnostic laparoscopy in selected entities, structured tumor board decision-making, intensive care capability for high-risk interventions, and complication management infrastructure—are primarily available in inpatient settings and are prerequisites for meaningful eligibility assessment and treatment delivery in time-sensitive PM care (24, 29).

1.9.2 Outpatient Care as the predominant care setting

At the same time, outpatient care is the dominant setting in which most patients live with PM, and therefore the setting in which longitudinal symptom management, coordination, and psychosocial support are provided. Primary care physicians and ambulatory specialists play a pivotal role in recognizing evolving disease, initiating supportive measures, coordinating diagnostics, and triggering specialist referrals. However, PM is not a common “index diagnosis” in primary care, and awareness of specialized treatment windows and referral urgency may vary, particularly in the context of limited population-level outpatient data (2, 23). With a persistent structural knowledge gap, systematic outpatient data are essential to characterize which medical specialties are involved, how referral patterns develop, and which diagnostic and supportive interventions are provided in the ambulatory setting.

1.9.3 What this study adds

To date, no reliable data exists on how many patients are diagnosed with PM in Germany or any other medium to larger size country-not even approximated data or estimates are available to the best of my knowledge. This lack of knowledge is particularly alarming given that PM represents a severe, life-threatening condition that is likely to affect thousands of patients each year. Fundamental epidemiological information, including age and sex distribution, regional variation, and overall disease burden, remain unknown and have been missing until recently. Equally unclear is how patients with PM are managed in the outpatient setting: which medical specialties are involved, how care is coordinated, and what diagnostic, therapeutic, and supportive services are actually provided outside of the hospital setting. This absence of data does not only present a knowledge gap, but a critical barrier to adequate patient care. Limited awareness of PM, delayed referral to specialized centers, and insufficient integration of outpatient providers may substantially compromise the quality of care. However, without systematic data, these shortcomings cannot be quantified, evaluated or addressed. The lack of evidence effectively renders the outpatient care of patients with PM invisible within the healthcare system. Motivated by these profound knowledge gaps, this PhD thesis provides the first systematic, population-based analysis of PM in Germany using large-scale statutory health insurance and ambulatory billing data.

The analysis focuses on regional incidence estimates, age- and sex-specific distributions, and reconstruction of outpatient care pathways. Specifically, this work allows to (a) characterize the affected population, (b) identify the involved medical specialties and referral patterns, (c) quantify diagnostic and therapeutic measures beyond hospital care, and (d) evaluate supportive and palliative interventions in the ambulatory sector. By making the outpatient reality of PM visible for the first time, this study lays an essential foundation for evidence-based health policy, improved care structures, and ultimately better outcomes for a patient population that has long remained unrecognized.

2. Materials and Methods

2.1 Study Design and overview

This study was designed as a retrospective, population-based cohort analysis using nationwide ambulatory billing data from SHI-accredited physicians and psychotherapists in Germany. The analysis was conducted in collaboration with the Central Research Institute of Ambulatory Health Care in Germany (Zentralinstitut für die kassenärztliche Versorgung, Zi), the statutory institution responsible for processing and evaluating nationwide outpatient care data according to §295 SGB V. The provided dataset reflects routine clinical practice in the ambulatory sector and enables comprehensive evaluation of healthcare utilization patterns among patients diagnosed with PM.

The most recent dataset available at the time of analysis covered the period from Q1 2014 to Q4 2021, thereby capturing a continuous eight-year observation window, including a substantial portion of the COVID-19 pandemic. This allowed for both longitudinal analysis and examination of temporal trends while ensuring broad generalizability across diverse healthcare environments within Germany.

2.2 Data source and regulatory context

The ZI dataset includes all SHI-billed medical services provided by office-based physicians and psychotherapists in Germany. Because approximately 87% of the German population is insured under SHI, the dataset provides near-population-level coverage. For each claim, the dataset includes: Patient demographics (age, sex, insurance status), diagnoses coded according to International Classification of Diseases, 10th Revision, German Modification (ICD-10-GM) (verified as “assured,” “suspected,” or “status post”), services billed according to the Uniform Value Scale (Einheitlicher Bewertungsmaßstab; EBM), region of service provision, consultation type and specialty group as well as diagnostic services, including laboratory and imaging claims. It is important to note that only ambulatory

billing data are included. Services provided exclusively during inpatient hospital stays are not recorded in §295 SGB V data.

2.3 Case definition and identification of PM cohort

To construct an incident cohort, all patients with a newly coded ICD-10-GM diagnosis corresponding to PM (C78.6 or related metastasis codes explicitly involving the peritoneum) were identified. To ensure incident status, patients were included only if a PM diagnosis appeared for the first time during the study period, and no PM diagnosis had been coded in the four preceding quarters. Using this definition, a total of 151,412 unique patients with newly diagnosed PM between 2014 and 2021 were identified in outpatient care and included in the analysis. Because the dataset reflects outpatient documentation, patients whose first PM diagnosis occurred during hospitalization and who died before entering outpatient follow-up are not captured. This constitutes a structural limitation inherent to SHI ambulatory claims data. Aside from the incident-case definition, no exclusion criteria were applied, and no additional filtering of patient cases was conducted

2.4 Geographic coverage and regional stratification

The dataset encompasses all 16 German federal states, enabling nationwide analysis. To evaluate regional differences in healthcare utilization, states were grouped into predefined macro-regions reflecting historical, demographic, and healthcare-structural characteristics:

1. Western Germany: Schleswig-Holstein, Hamburg, Niedersachsen, Bremen, Nordrhein-Westfalen, Hessen, Rheinland-Pfalz, Saarland, Baden-Württemberg, Bayern.
2. Eastern Germany (former German Democratic Republic): Mecklenburg-Vorpommern, Brandenburg, Sachsen-Anhalt, Thüringen, Sachsen, Berlin. Exclusion of Berlin was marked in some analyses.
3. Southwest Germany (analytically relevant subset): Hessen, Saarland, Rheinland-Pfalz, Bayern, Baden-Württemberg.

4. The city-states Berlin, Hamburg, and Bremen were analyzed separately due to their unique population structures and healthcare densities. Exclusion of Berlin was marked in some analyses.

Due to the unique position of Berlin as a previously split city between east and west and as the capital it was excluded as the city defies criteria that would enable meaningful grouping in the aforementioned categories.

2.5 Study variables and assessed parameters

The analysis examined multiple domains relevant to the epidemiology and healthcare utilization of PM patients.

2.5.1 Demographics

Descriptive analysis of demographics included age distribution (full range and age strata) as well as gender distribution across the PM cohort.

2.5.2 Healthcare Utilization

For the purpose of this study, service use was quantified across specialties, including general practitioners and family physicians, gastroenterologists, surgeons, gynecologists, medical oncologists and hematologists, radiologists, palliative care specialists and other office-based specialists.

Consultation frequency per patient was determined for the incidence quarter and the three subsequent quarters (Q+1, Q+2, Q+3)**.** Each patient was counted once per specialty if at least one billed contact occurred in the defined time window.

2.5.3 Diagnostic Utilization

Diagnostic analyses focused on radiologic procedures, particularly CT scan and MRI of the abdomen as well as the screening of tumor markers, as recorded in EBM-coded laboratory diagnostics.

2.5.4 Regional incidence approximation

Approximate incidence rates of PM per 100,000 inhabitants were calculated by normalizing the number of newly diagnosed PM cases to the population size of each federal state provided by the 2022 German census database. Standard deviations were reported to quantify regional variation.

2.5.5 Consultation ratios

A central analytical parameter was the quotient between specialized physicians (surgeons, oncologists, gynecologists), and primary care physicians (general practitioners, family doctors). This quotient was compared across regions to assess structural differences in access to specialty care.

2.5.6 Normalization of service utilization

To enable cross-regional comparisons, the number of billed services and consultations was normalized to local population size and adjusted for regional PM incidence. This allowed for comparison of utilization intensities independent of regional population density.

2.5.7 Visualization

For descriptive illustration, several figures were generated using Excel (Excel, Windows 11, Microsoft Inc, USA) showing the proportion of PM compared to the size of the total study population in percent or per mille. The dataset covered cases by each medical specialty during the defined observation period. The cal-

culated rate for the incidence is based on approximations from the numbers represented and ultimately derived from aggregated billing records.

2.6 Data handling and quality assurance

All analyses were conducted on anonymized patient-level data. No direct identifiers (names, addresses, insurance numbers) were ever accessible. Data processing followed Zi protocols for: aggregation, validation, error checking, specialty classification and consistency checks across quarters. Systematic errors due to billing irregularities or coding inconsistencies were minimized through Zi's established data-cleaning pipelines.

2.7 Statistical Analysis

Descriptive statistics were used to characterize the cohort and evaluate utilization patterns. These included absolute frequencies and percentages, measures of central tendency (means, medians), measures of dispersion (standard deviations, interquartile ranges and regional incidence per 100,000 inhabitants. Comparisons between regions were descriptive rather than inferential, given the administrative nature of the dataset and the intention to map healthcare structures rather than establish causal associations. All analyses were conducted using R and Python-based statistical platforms within the secure Zi research environment. A Non-parametric test for more than two independent groups was used to evaluate significance (Kruskal-Wallis Test). Significance levels were indicated with *=$p<0.05$, **=$p<0.01$, ***=$p<0.005$, #=$p>0.05$.

2.8 Ethical and legal considerations

This study is based on anonymized secondary data provided by the Zi. According to German legislation and prevailing ethical standards for health-services research using fully anonymized administrative data, no informed consent from individual patients is required. However, to comply with local regulations, ethical approval was obtained by the ethics committee of the medical faculty, Heinrich-Heine University, Düsseldorf (study no.: 2023-2400). All analyses complied with the General Data Protection Regulation (GDPR) and the Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG). Data access was restricted to aggregated, non-identifiable datasets.

3. Results

3.1 Study Population

Over the eight-year observation period from 2014 to 2021, a total of 151,412 patients were listed with PM in the outpatient setting with an increasing trend (Figure 5A). Regional differences in the incidence rates were noted as well (Figure 5B). Of these, 53,241 (35.2%) were male and 98,171 (64.8%) were female, demonstrating a clear predominance of women within the study population. Age distribution further underscored this demographic imbalance. Among all included cases, 11,041 (7.3%) were younger than 50 years, 63,882 (42.2%) were between the ages of 50 and 70, and 76,489 (50.5%) were aged 70 years or older. Notably, female patients were disproportionately represented in both the younger (<50 years) and older (>70 years) age strata, suggesting either entity-specific differences across tumor origins or varying levels of healthcare utilization among women within these age groups (Figure 6A).

Across the entire study period, outpatient care was overwhelmingly provided by general practitioners and family physicians, who accounted for 69.9% of all listed consultations. Oncologists and hematologists represented the second-largest group with 22.8%, followed by gynecologists with 8.2%, and internal medicine specialists with 6.2% of recorded patient contacts. All remaining outpatient disciplines, including radiology, anesthesiology, and surgery, together represented only 11.7% of encounters. These findings collectively indicate that most PM-related care occurs within the primary care setting, with specialized outpatient involvement forming a comparatively small but clinically decisive segment of contacts.

The number of newly diagnosed PM patients showed a slight upward trend during the study period, increasing from 18,383 cases in 2014 to 19,359 cases in 2021. While this increase is modest, it nonetheless aligns with the broader rise in oncologic diagnoses in Germany during the same period and may also reflect increasing diagnostic awareness, improved coding practices, and enhanced life expectancy among cancer patients who subsequently develop metastatic dissemination.

A regional analysis of approximated incidence rates revealed meaningful geographic variations across Germany. The three city-states-particularly Bremen and Hamburg-displayed lower PM incidence rates than larger territorial states. For example, the incidence rate in these city-states was 0.98 per thousand, which was significantly lower than rates observed in Southwest Germany (1.23 per thousand, $p < 0.05$), in former West Germany (1.17 per thousand, $p < 0.05$), and particularly in former East Germany excluding Berlin (1.73 per thousand, $p < 0.01$) (Figure 5B). These findings indicate significant regional heterogeneity that cannot be explained simply through differences in population density. Instead, they highlight possible structural, demographic, and oncologic differences across regions.

3.2 Regional differences in outpatient contact patterns

Substantial differences were observed not only in incidence but also in diagnostic utilization and patterns of outpatient engagement across Germany. A total of 13,082 PM patients underwent at least one CT scan examination during the observation period (Figure 6B). Among the total listed cases within the study group, thoracic CT scans accounted for 40%, while abdominal CT scans constituted 55%, reflecting the central role of abdominal imaging in the diagnostic and follow-up evaluation of PM. An additional 5% of CT examinations were performed for other anatomical regions, including the neurocranium, upper gastrointestinal tract, and spine. At this point it is important to consider that the CT abdomen and thorax as well as the tumor markers (Figure 6C) are often part of the initial staging of many cancer entities. Magnetic resonance imaging (MRI) was performed in 949 patients (Figure 6D), with examinations distributed across abdominal (35%), pelvic (17%), upper gastrointestinal (26%), neurocranial (14%) and spinal (8%) regions. These imaging patterns align with the typical diagnostic requirements of PM, where assessment of abdominal tumor load, metastatic spread, and complications such as obstruction or ascites remain paramount.

Biochemical diagnostic utilization was also evaluated through tumor marker testing. A total of 5,629 PM patients underwent tumor marker assessment. Among the total number, 41% received carcinoembryonic antigen (CEA) testing,

27% were tested for CA 19-9, and 16% for CA-125 (Figure 6C). The distribution of markers largely reflects the heterogeneous origins of PM, including gastrointestinal and gynecological malignancies.

Marked regional differences emerged with respect to PM incidence. While the national mean incidence was 1.39 cases per 1,000 population, the rates differed substantially between federal states. For instance, Hamburg exhibited one of the lowest incidence rates at 0.93 cases per 1,000 (Figure 7A, column 4), whereas Mecklenburg-Vorpommern showed the highest rate at 1.90 cases per 1,000 (Figure 7A, column 13), more than double the lowest value. These disparities underscore the presence of potential demographic or structural factors influencing detection and reporting of PM, as well as differences in cancer epidemiology across Germany.

When analyzing the relative number of outpatient consultations and treatments per region, substantial variations became evident. Larger states understandably tend to show higher absolute numbers of PM-related consultations, which was expected based on differences in population size (Figure 7B, column 2 vs. 5). However, the relationship between encounters with primary care physicians and those with surgeons varied considerably across regions (Figure 7B, column 2 vs. 7). In Nordrhein-Westfalen and Schleswig-Holstein, the ratio of surgeon-to-primary care physician contacts was approximately 1:80 (Figure 7B, column 3, 7, 8), indicating a strong dominance of primary care utilization relative to surgical engagement. In contrast, in Mecklenburg-Vorpommern, this ratio was markedly higher, at 1:10 (Figure 7B, column 13), suggesting substantially more frequent surgical attention relative to primary care interactions. Importantly, the latter region also demonstrated the highest incidence rate nationwide, yet it remains unclear if this is related to the overall high of disease burden.

These cross-regional discrepancies might also suggest differing organizational structures, referral practices, and levels of awareness regarding specialized PM management. However, the data does not provide further clarifications on these points. The comparison reveals that states with lower incidence rates tend to exhibit lower specialty involvement, whereas regions with higher incidence tend to demonstrate increased engagement with surgical disciplines.

3.3 Comparison of consultations among medical disciplines

The calculated quotient of surgeon-to–primary care physician contacts confirmed the general trend that former Eastern Germany demonstrates a substantially higher level of surgical involvement relative to primary care than former West Germany or the city-states. This finding was consistent across most Eastern German states and aligns with the elevated incidence rates observed in this region. Interestingly, this difference was not mirrored in the corresponding quotient for hematology/oncology or gynecology, where the differences between East and West were comparatively small and did not show clear regional clustering. This suggests that regional disparities in access to and utilization of surgical expertise may be more pronounced than those observed for other specialist disciplines.

When examining the relative number of consultations per incident case, values tended to cluster close to the national mean for general practitioners, whose involvement remained consistent across regions. Gynecologists and oncologists demonstrated moderately higher variation, while surgeons showed the greatest variability, with standard deviations indicating wide interregional differences. The underlying causes for the high variation in surgical involvement cannot be fully elucidated from the available dataset, but the magnitude of variation itself is striking and indicates substantial heterogeneity in how PM patients enter and navigate the outpatient healthcare system.

Outpatient procedures-excluding CT and MRI imaging and tumor marker evaluation-also demonstrated a broad procedural spectrum. Within the study population, most contacts were clearly registered with the primary care physician followed by hematology/oncology (Figure 8). Following a noticeable decrease from primary care physicians to hematology/oncology, gynecology represents the next most involved specialty, with another substantial decline compared to hematology/oncology. After gynecology, the following next disciplines had gradually lower numbers (Figure 8).

Across the entire observation period, 9.660 outpatient procedures were recorded in association with PM. Compared to the over 150.000 cases of PM in the study population, this is an overall small number. When categorizing these 9.660 procedures in smaller units, the overall amount of procedures for the vari-

ous categories does not exceed the per mille level when compared to the total study population (Figure 9).

The three largest categories included urological examinations and procedures (15.2%), gastrointestinal endoscopy (22%), and vascular ultrasound (23.2%). The prominent top two specific procedures listed were gastroscopy and duplex ultrasonography of the abdominal and retroperitoneal organs. Gastroscopy might be related to attempts for gastral decompression procedures or placement of gastral feeding tubes while the duplex ultrasonography of abdominal and retroperitoneal organs might be related to abdominal ultrasound examinations routinely done in patient with PM. Although urological procedures represent a relatively high proportion compared to other interventions, they include a heterogeneous range of measures, most likely aimed at ensuring drainage and preserving renal function by preventing mechanical obstruction.

Additional frequently documented procedures included therapeutic or diagnostic punctures (12.9%), possibly related to abdominal decompression in patients with malignant peritoneal effusions, irradiation-related services (7.2%), and cardiological diagnostics (5.7%). These procedural categories reflect the range of organ systems affected by PM and the broad diagnostic and supportive care needs of this patient population.

Despite the diversity of outpatient procedures documented, the overall number of such interventions still remains unexpectedly low across the eight-year observation period. For instance, the entire dataset included only 9,660 outpatient procedures, even though 19,359 new PM diagnoses were recorded in 2021 alone. This discrepancy highlights a notable gap between the overall disease burden and the procedural activity documented in the outpatient sector. The reasons for this gap remain speculative but may include the short survival time associated with PM, a rapid transition of many patients to inpatient or palliative settings shortly after diagnosis, limited outpatient procedural capacity, or under-coding of certain interventions in the ambulatory sector.

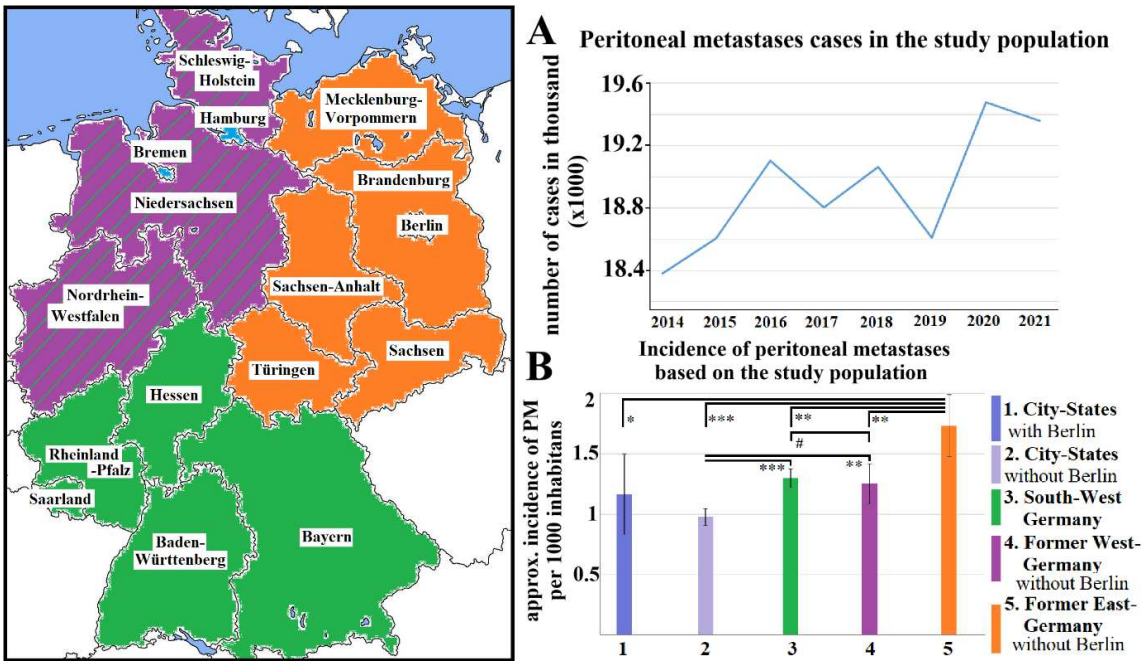


Figure 5: *Map of Germany showing federal states and their grouping into regions*
(Source: Own illustration based on (54))
Western Germany (green and purple) includes Schleswig-Holstein, Hamburg, Niedersachsen, Bremen, Nordrhein-Westfalen, Hessen, Rheinland-Pfalz, Saarland, Baden-Württemberg, and Bayern. Eastern Germany (orange) includes Mecklenburg-Vorpommern, Brandenburg, Sachsen-Anhalt, Thüringen, Sachsen, and Berlin. (A) Overall approximated incidence rates of peritoneal metastasis (PM) based in the study population. Note a sharp increase in incidence rates in 2020 (B) Approximated incidence rates based on the study population for the grouped regions. Statistical significance was defined as follows: *p<0.05, **p<0.01 and ***p<0.005; *#p* > 0.05, with p-value <0.05 considered to be statistically significant.

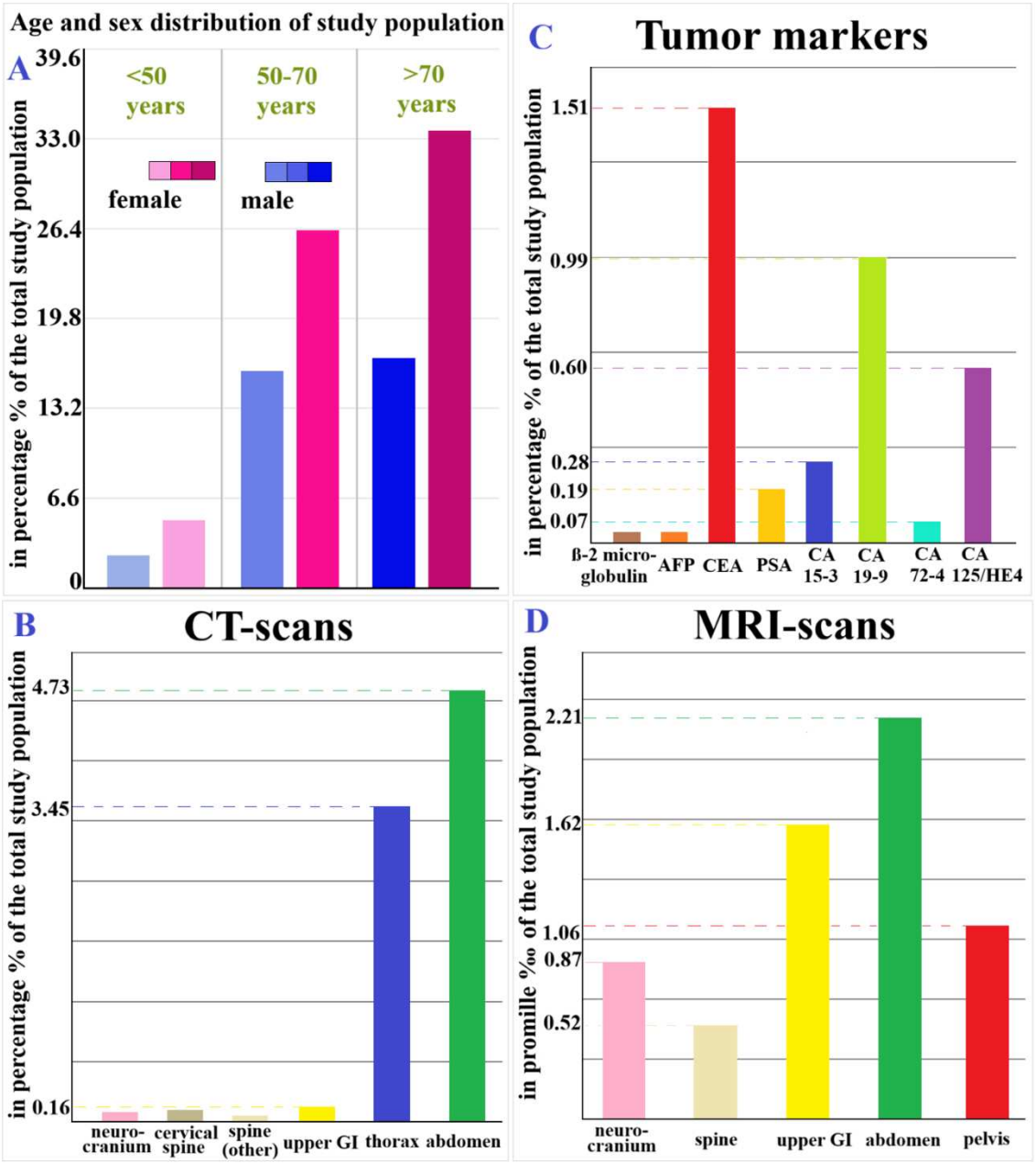


Figure 6: *Demographic characteristics and diagnostic work-up of the study population*
(Source: Own illustration based on data from (54))
(A) Age and gender distribution of the study population. A higher volume of female cases is observed across all ages in the study population. (B) Distribution of tumor markers in serum listed for the study population (C) Computed tomography (CT) scans listed by body region for the study population. (D) magnetic resonance imaging (MRI) scans listed by body region for the study population.

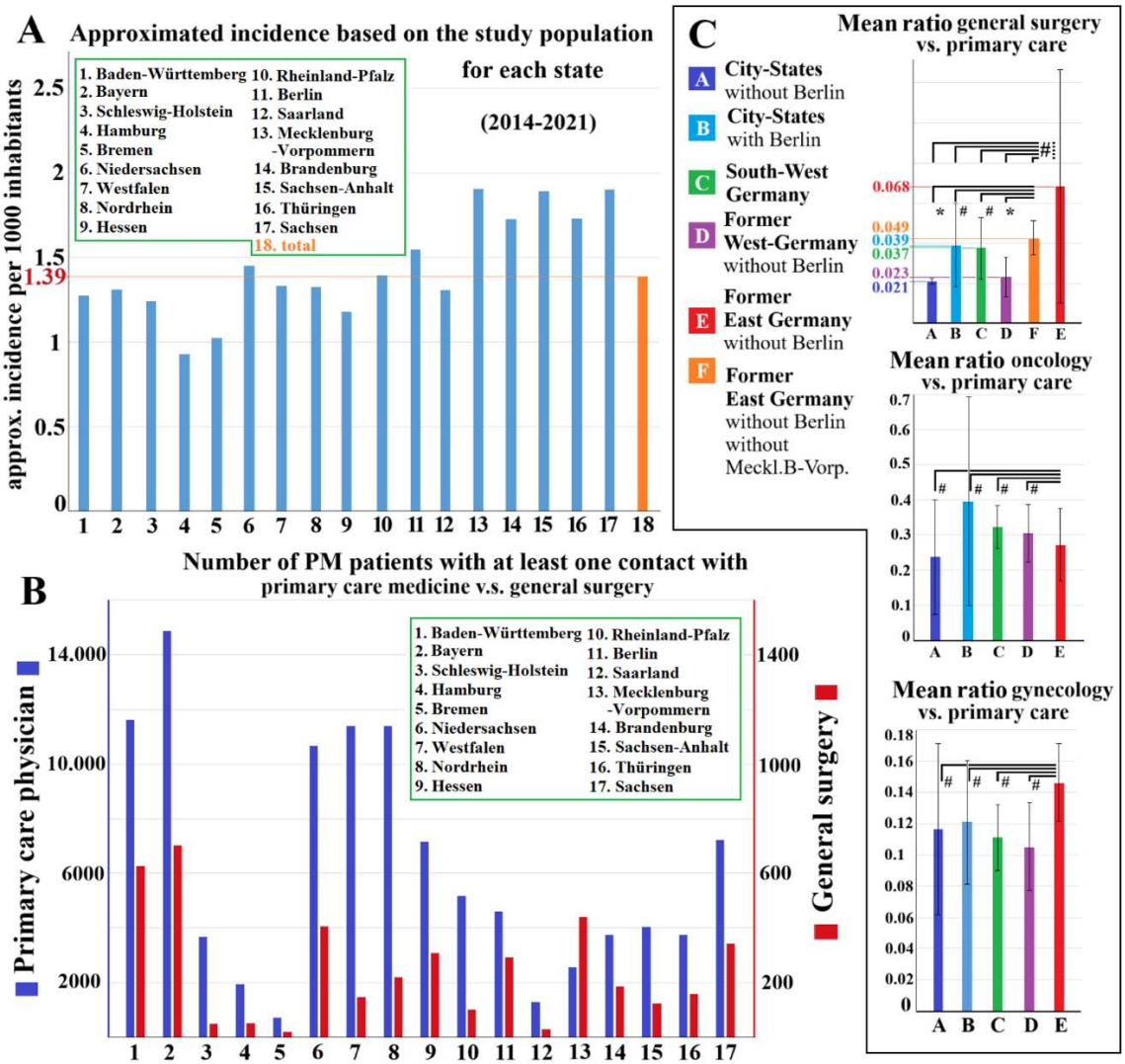


Figure 7: *Regional Variations in PM Incidence and Healthcare Utilization Across German Federal States (2014-2021)*

(Source: Own illustration based on data from (54))

*(*A) Approximated PM incidence for each federal state in Germany (2014–2021). The red column indicates the mean value for the provided date. (B) Relative number of contacts and treatments by primary care providers (blue columns) versus surgeons (red columns) in each federal state. (C) Ratio of PM patients contacting general surgeons vs. primary care providers, oncologists vs. primary care providers, and gynecologists vs. primary care providers in the outpatient setting. Statistical significance was defined as follows: *p<0.05 and **p<0.01, ***p<0.005; *#p* > 0.05, with p-value <0.05 considered to be statistically significant.

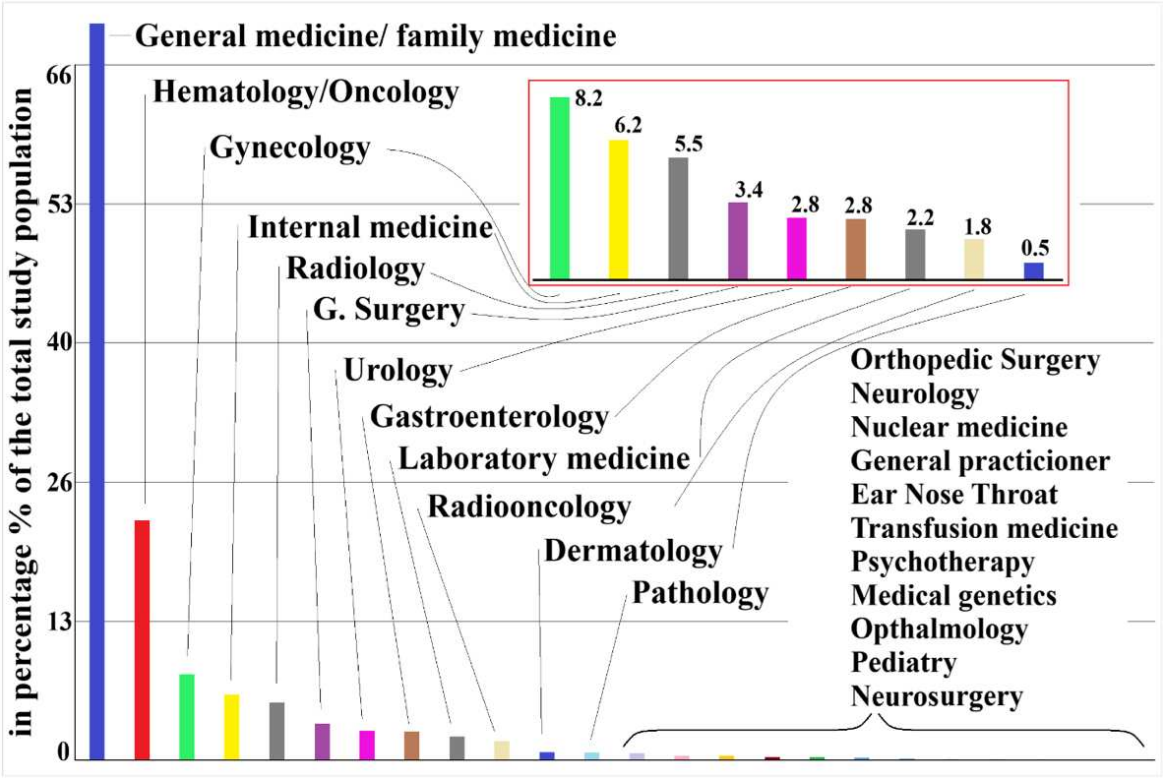


Figure 8: *Distribution of Outpatient Care Physician Contact per Speciality*
(Source: Own illustration based on data from (54))
(A–D) Relative number of contacts with outpatient care physicians per incidence and population: (A) primary care, (B) gynecology, (C) oncology, and (D) surgery. (E) Relative number of diagnostic and therapeutic contacts in PM patients. Colored blocks represent categories of similar contacts (including procedures and interventions): green – urogenital and kidney-related procedures; light brown – therapeutic radiation; brown – endoscopic procedures; pink – diagnostic and therapeutic punctures; orange – cardiological examinations; yellow – vascular examinations; blue – ear, nose, and throat (ENT) examinations; purple – ophthalmological examinations; grey – genetic and molecular biology examinations; reddish/pink – miscellaneous examinations and procedures

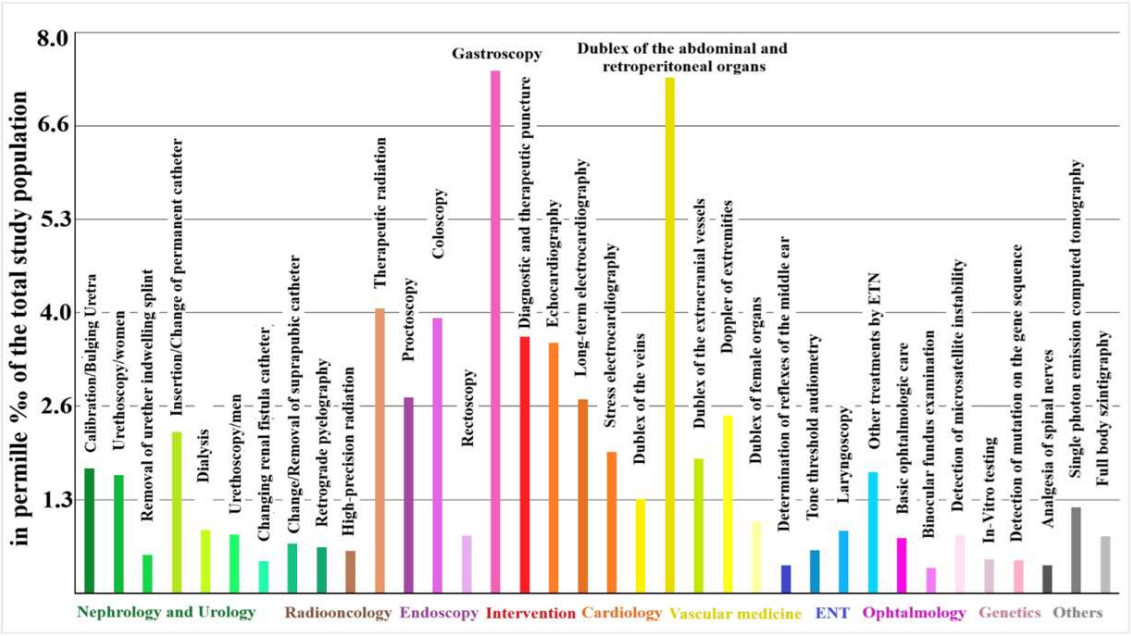


Figure 9: *Prevalence of clinical interventions and diagnostics categorized by medical specialty (Source: Own illustration based on data from (54))*

Distribution of procedures and diagnostics for the study population in relation to the size of the overall study group. The groups were colored according to discipline or diagnostic setting. The green columns reflect procedures from nephrology and urology followed by the other disciplines. The y-axis is reflective of the overall numbers in relation to the total number of the study group.

4. Discussion

4.1 Approximated incidence numbers for PM

For the first time in Germany, the present study aimed to generate a comprehensive population-level overview of the epidemiology and outpatient care patterns of patients diagnosed with PM. By analyzing nationwide SHI billing data covering approximately 70 million insured individuals per year, this work provides the most extensive empirical insight to date into the outpatient disease trajectory of PM patients worldwide. The analysis encompasses approximated incidence rates, demographic characteristics, regional variation, diagnostic utilization, and involvement of medical specialties. Although the applied metrics are an estimate and do not reflect the correct measured incidence rate, they are the most accurate number that has ever been available for a large population. This approach enables PM to be examined not merely as a terminal manifestation of advanced solid malignancies but as a distinct clinical entity with specific epidemiologic characteristics and substantial implications for health-services planning.

Across the eight-year observation period, between 18,000 and 19,000 incident outpatient PM diagnoses were documented annually. It is important to mention that approximately 10 million out of 80 million are missing in this data set. Moreover, we can assume that not all outpatient physicians might have listed the diagnosis PM for each patient that suffers from PM as they are not obligated to do so. Therefore, we must assume that the numbers provided are rather estimated at the lower levels and that the actual numbers are indeed much higher. Still, the current figures substantially exceed prior estimates derived from localized institutional cohorts or registry-based analyses restricted to individual primary tumor entities (37, 66, 67). It must be emphasized, however, that the underlying dataset comprises exclusively statutory health insurance billing data. This leads to a different form of bias in the data. Services reimbursed through selective contracts are not captured, nor are privately insured individuals or statutorily insured patients who did not seek medical care. These limitations are discussed in detail in Section 4.2. Consequently, all reported incidence figures must be interpreted as approximations rather than absolute population values.

Given the characteristically poor prognosis and short median survival associated with PM which is often measured in months rather than years (68, 69), incidence and prevalence values are expected to be closely aligned. In fact, due to the overall low medium life-expectancy, the potential prevalence rate might be less significant than the actual incidence. Under these circumstances, annual incidence may serve as a better proxy to quantify the disease more accurately than the prevalence. At this point, it is important to consider that PM would have to be "viewed" or rather "categorized" by the physician as a separate entity or diagnosis than distant metastasis. Despite these aspects, the numbers provided underscore the substantial societal and healthcare impact of PM, which has historically been underrepresented in national cancer statistics.

Over the study period, a modest upward trend in newly diagnosed PM cases was observed, increasing from 18,383 cases in 2014 to 19,359 cases in 2021. Although this increase is relatively small, it parallels the overall rise in cancer diagnoses in Germany during the same timeframe (70). Potential contributing factors include demographic aging, improved survival of patients with primary malignancies who subsequently develop metastatic disease, enhanced diagnostic awareness, and improved coding practices. Additional explanations, such as population changes resulting from migration and delayed access to care in certain subpopulations, cannot be excluded. Importantly, given the observational nature of the data, no causal explanation regarding the drivers of this trend can be drawn, and it is likely that multiple interacting factors contribute to the observed increase. The extent of potential confounding factors is substantial, and their overall impact on the numbers provided is difficult to quantify.

4.2 Significance of SHI data

Germany's healthcare system is characterized by a dual insurance structure comprising statutory health insurance and private health insurance. SHI covers approximately 87–90% of the population, corresponding to roughly 74–75 million individuals, whereas 10–11% (approximately 8.7–9 million individuals) are fully privately insured (statistics from the National Association of Statutory Health Insurance Physicians, Kassenärztliche Bundesvereinigung, KBV, 2023). Therefore, the presented analysis captures most of the German population but does not represent complete population coverage. These figures are derived from official statistics published by the KBV (71).

In contrast to SHI, private health insurance in Germany is highly fragmented, consisting of approximately 40 independent insurance providers. There is no legal mandate for centralized data aggregation, nor is there a standardized infrastructure comparable to that of statutory health insurance. Moreover, billing mechanisms differ fundamentally. While SHI physicians submit claims directly to insurance funds using standardized diagnostic coding (ICD-10-GM), privately insured patients receive invoices and can choose whether or not to submit them for reimbursement. Consequently, insurance providers only receive partial information, and diagnostic coding is neither mandatory nor standardized under the German Fee Schedule for Physicians (Gebührenordnung für Ärzte, GOÄ). As a result, diagnostic information for privately insured patients is often incomplete, inconsistent, or entirely absent.

These structural characteristics render comprehensive epidemiologic analyses of privately insured patients unfeasible. Accordingly, the present dissertation necessarily relies exclusively on SHI data. It must therefore be assumed that the true incidence and prevalence of PM in Germany exceed the estimates presented here, as approximately one tenth of the population is not captured. This limitation likely results in a systematic underestimation of the true disease burden.

4.3 Differences in gender distribution

A pronounced predominance of female patients was observed, with nearly twice as many women affected by PM as men across both younger (<50 years) and older (>70 years) age groups. This consistent pattern suggests that the observed gender disparity is unlikely to be explained by age structure alone. Instead, it may reflect entity-specific differences in underlying primary tumors or gender-specific healthcare utilization patterns.

One plausible explanation is the substantial contribution of ovarian carcinoma, a malignancy that frequently presents with peritoneal dissemination and lacks effective population-based screening strategies (67, 72). Ovarian cancer is often diagnosed at an advanced stage, commonly following nonspecific symptoms such as abdominal pain or ascites, conditions closely associated with PM (72, 73). The high proportion of gynecologic involvement observed in this study further supports this interpretation. Nevertheless, the magnitude of gender imbalance remains striking and warrants further investigation. Future research should aim to clarify the relative contributions of tumor-specific epidemiology, biological sex differences, and healthcare-seeking behavior. Our now improved understanding of PM further supports the ongoing need for effective early detection strategies and tailored surveillance approaches for gynecologic malignancies in aging female populations.

4.4 Outpatient care and specialists

Outpatient care for PM patients was predominantly provided by general practitioners and family physicians, who accounted for nearly 70% of all PM-related consultations. This finding highlights the central role of primary care in the German healthcare system and is consistent with the principles of general practitioner–centered care (“hausarztzentrierte Versorgung”), which prioritizes primary care coordination and requires referral for specialist access (74).

While this structure supports continuity of care, it also places substantial responsibility on primary care providers to recognize complex oncologic conditions and initiate appropriate referrals. Given rapid advances in PM management,

including evolving multimodal treatment concepts, this highlights the need for targeted education and decision-support tools for primary care physicians.

Oncologists and hematologists accounted for 22.8% of outpatient contacts, a notable finding given the relatively small number of ambulatory oncologists in Germany (approximately 617 nationwide). Despite this limited workforce, access to oncologic outpatient care appears comparatively adequate for PM patients. Gynecologists (8.2%) and general internists (6.2%) constituted the next most frequently involved specialties. The prominent role of gynecologists further supports the observed female predominance and the relevance of gynecologic primary tumors-particularly ovarian cancer-in the epidemiology of PM.

4.5 Regional demographics

Marked geographic variation in PM incidence was observed across Germany. Regional disparities in healthcare access, physician density, and specialist availability-particularly between former Eastern and Western Germany-have been extensively documented (75-77). Rural and structurally disadvantaged regions are often characterized by lower physician density and reduced access to specialized services, while primary care physicians may compensate by assuming broader scopes of practice (74).

Until now, it has remained unclear how these structural disparities affect patients with complex oncologic conditions such as PM. The present analysis demonstrates significantly higher estimated incidence rates in former Eastern German states compared with Western states and city-states. These differences may reflect variations in healthcare infrastructure, availability of specialized centers, and access to diagnostic and therapeutic services (75-77).

However, it is important to consider that in many cases, PM is a late-stage manifestation of gastrointestinal or gynecological cancer entities that might not have advanced to a stage 4 if they had been detected earlier. This fact should be independent of age, gender or exposure to any risk factor.

Interestingly, the city-states-particularly Hamburg and Bremen-displayed lower PM incidence rates than larger territorial states. These differences cannot

be explained by population density alone and likely reflect a combination of demographic composition, referral patterns, and regional oncologic structures.

States in former Eastern Germany demonstrated the highest estimated incidence values. These findings might be explained by a complex interplay of demographic aging, higher baseline cancer incidence but they could also be related to delayed diagnosis, and reduced access to specialized care. Data on inhabitants per physician suggest higher patient loads in former Eastern German states.

To what extent these findings are influenced by the availability of advanced locoregional therapies, such as CRS, HIPEC, or PIPAC, remain unknown.

However, it must be noted that these treatments are predominantly offered in high-volume academic centers, which are unevenly distributed across Germany (51, 78). Patients in rural or structurally disadvantaged regions may therefore face logistical barriers that delay diagnosis and limit access to multidisciplinary evaluation.

Table 2 offers important insight into how physician density varies among German federal states.

Table 2: *Physician density across German federal states in 2024, expressed as the number of inhabitants per practicing physician.*

Federal State	Inhabitants per practicing physician
Hamburg	124
Berlin	146
Bremen	156
Saarland	178
Bavaria	185
Mecklenburg–Western Pomerania	188
North Rhine–Westphalia	191
Schleswig-Holstein	195
Saxony	199
Hesse	199
Baden-Württemberg	200
Rhineland-Palatinate	204
Thuringia	210
Saxony-Anhalt	211
Lower Saxony	226
Brandenburg	237

(Source: Own Illustration based on data from (54))
Lower values indicate higher physician availability.

4.6 Regional differences in outpatient contact patterns

Analysis of diagnostic utilization revealed notable gaps in outpatient evaluation. Cross-sectional imaging using CT and MRI is essential for diagnosis, staging, operability assessment, and treatment planning in PM (69, 70). Nevertheless, outpatient imaging was documented in only a minority of cases, suggesting that diagnostics may predominantly occur in inpatient settings or that access barriers and delays exist in ambulatory care.

Across the entire observation period, only 9,660 outpatient procedures were recorded, despite nearly 19,400 new PM diagnoses in 2021 alone. This discrepancy highlights a substantial gap between disease burden and documented outpatient procedural activity. Potential explanations include short sur-

vival, rapid transition to inpatient or palliative care, limited outpatient procedural capacity, and undercoding of ambulatory interventions.

Tumor marker assessments were also infrequently coded, despite their routine role in surveillance of colorectal and ovarian malignancies. This finding suggests limited integration of oncology-specific diagnostics into outpatient management pathways.

Marked regional variation was observed in patterns of outpatient consultations. While larger states showed higher absolute numbers of contacts, the ratio of primary care to surgical consultations differed substantially. Regions such as Nordrhein-Westfalen and Schleswig-Holstein demonstrated very low surgeon-to-primary care ratios, whereas Mecklenburg-Vorpommern showed markedly higher surgical involvement. Notably, this region also exhibited the highest PM incidence, suggesting a potential association between disease burden and specialist engagement.

4.7 Access to specialized PM centers

Hospital-based analyses indicate that only 534 patients received PIPAC treatment in Germany in 2019 (50). When contrasted with an estimated annual PM incidence of 18,000–19,000 cases, this represents a remarkably small proportion of potentially eligible patients. Given the expanding role of PIPAC as part of multimodal palliative treatment strategies, particularly for patients not amenable to CRS or HIPEC (2, 50), this discrepancy points to significant gaps in access, awareness, and referral to specialized PM centers.

4.8 Limitations of this study

4.8.1 Limitations in epidemiologic and clinical characteristics

PM arises from a heterogeneous spectrum of primary tumors, including colorectal, gastric, pancreatic, ovarian, appendiceal, and gallbladder cancers, as well as rarer entities such as mesothelioma and cancers of unknown primary origin (37, 66). The likelihood of peritoneal dissemination varies widely by tumor type, ranging from up to 60–75% in advanced ovarian cancer to approximately 20–25% in colorectal cancer (67). The absence of tumor-specific information in the present dataset precludes stratified analyses and represents an important limitation. Future studies integrating tumor registry data are needed to clarify the relative contribution of different primary malignancies. It is also important to mention that the criteria of diagnosing PM is not specified in the clinical setting. PM is either diagnosed by an abdominal CT- scan, a prior diagnostic or therapeutic laparoscopy or malignant abdominal effusions. These are the major ways to establish the diagnosis of PM. Yet many cases might be overseen here, since not all patients exhibit malignant abdominal effusions, receive laparoscopy or display detectable PM in abdominal CT scans.

4.8.2 Health-policy and structural implications

Beyond clinical considerations, the findings have important health-policy implications. PM is characterized by rapid progression, high symptom burden, and complex multidisciplinary treatment requirements (68, 69). These features underscore the need for policy initiatives aimed at improving equitable access to diagnostics and specialized care. National guidelines should incorporate PM-specific referral criteria, and healthcare systems should prioritize regional networks and outreach structures to support patients in underserved areas. Improved epidemiologic surveillance is critical, as current cancer registries insufficiently capture metastatic patterns such as PM.

4.8.3 Strengths and limitations of this study

Key strengths of this study include its nationwide scope, large sample size, exclusive outpatient focus, and inclusion of all 16 federal states. These features make it possible to identify structural patterns that remain unobserved in institutional cohorts. Limitations include reliance on administrative billing data, potential undercoding of PM, exclusion of inpatient-only care, absence of privately insured patients and granular clinical variables such as tumor stage, treatment intent, and survival outcomes.

4.9 Conclusions and outlook

This study demonstrates that PM is a substantial factor in society and the German health system with nearly 20,000 newly documented outpatient cases annually. Despite its severity, PM remains underrecognized, inconsistently coded, and unevenly managed across regions. Outpatient care is dominated by primary care providers, with limited specialist involvement and pronounced regional disparities in diagnostic utilization and referral patterns.

These findings underscore the need for improved national strategies to standardize PM recognition, optimize diagnostic pathways, and ensure equitable access to specialized care. Future research should focus on integrating metastatic disease into cancer surveillance systems, evaluating the impact of emerging intraperitoneal therapies on outcomes, and refining referral pathways to ensure timely, evidence-based care for all affected patients.

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