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Advances in the Diagnosis and Treatment of Appendiceal Mucinous Neoplasms

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Abstract

Primary appendiceal neoplasms represent a relatively low percentage of all gastrointestinal cancers. A subset of these neoplasms, those of epithelial origin, are characterised by the production of a considerable amount of mucus, which is referred to as appendiceal mucinous neoplasms (AMN). Appendiceal mucinous neoplasms (AMN) have a low incidence, are easily misdiagnosed, depend on postoperative examination for confirmation of the diagnosis, are prone to form a "diagnosis", and have a high incidence of the disease. Furthermore, they are prone to form peritoneal pseudomyxoma peritonei (PMP), are controversial in surgical decision-making, are prone to recurring after surgery alone, and are tricky to manage clinically. In this paper, we review the pathological characteristics, diagnosis and treatment of appendiceal mucinous tumours in the light of recent literature reports, with a view to providing certain references for the clinical diagnosis and treatment of this disease.

Keywords

Appendiceal Mucinous Neoplasms, Pseudomyxoma Peritonei, Cytoreductive Surgery, Hyperthermic Intraperitoneal Chemotherapy

1. Introduction

Appendiceal mucinous neoplasms (AMN) have a very low incidence [1] and have been on the rise in recent years in the younger age groups [2]. Their pathogenesis has not yet been thoroughly investigated, which makes the prevention of this disease quite difficult. The clinical manifestations of appendiceal mucinous tumour are not sufficiently specific, and the early manifestations are similar to those of appendicitis, manifesting as metastatic right lower abdominal pain or fixed right lower abdominal pain. Consequently, this disease is susceptible to

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misdiagnosis. Currently, the accuracy of various preoperative examinations is continuously improving, yet it remains challenging to confirm the diagnosis of AMN before surgery. Postoperative pathological diagnosis is the "gold standard" for AMN. In the absence of an early diagnosis, the appendix may rupture and perforate due to excessive mucus accumulation, with tumour cells being planted in the peritoneum with the mucus into the abdominal cavity to form a peritoneal pseudomyxoma peritonei (PMP). This requires surgical intervention and is prone to recurrence, with the patient's health being significantly compromised by multiple surgeries. Currently, the treatment of AMN in China is a comprehensive approach, primarily surgical. The surgical method is controversial, and there is no unified guideline. Prevention of PMP formation is also an important aspect of AMN treatment. In recent years, hyperthermic intraperitoneal perfusion chemotherapy (HIPEC) has attracted the attention of numerous scholars due to its distinctive efficacy on PMP. Intravenous chemotherapy is ineffective for PMP due to the insufficient blood supply to the peritoneal surface and the existence of the plasma-peritoneal barrier [3]. Intraperitoneal thermal perfusion chemotherapy can be achieved by preparing chemotherapeutic drugs into a perfusion solution, heating it to the appropriate temperature (43˚C) and then infusing it into the abdominal cavity with an intraperitoneal thermal perfusion device to carry out a thermostatic cycle. The perfusion solution kills tumour cells through thermal damage and other mechanisms, while it is weaker for the killing power of normal cells. This results in the death of tumour cells while normal cells survive, and ultimately achieve the purpose of preventing or treating PMP. This article presents the latest developments in the diagnosis and treatment of appendiceal mucinous tumours, based on an analysis of pathological characteristics, diagnosis and treatment of appendiceal mucinous tumours in the context of recent literature reports.

2. Epidemiology

There is a paucity of large-scale epidemiological investigations of AMN in China, with the majority of relevant literature comprising scattered case reports. In the United States, appendiceal tumours account for less than 1% of all gastrointestinal tract tumours, with approximately two to three thousandths of appendiceal specimens confirmed to be AMN [4]. In the United States, appendiceal tumours account for less than 1% of all GI tumours, with approximately two to three percent of appendiceal specimens confirmed to be AMN [5]. AMN is distinct from colorectal cancer (CRC) in that it is a relatively inert tumour that rarely metastasises outside the peritoneal cavity. Long-term statistics indicate that the incidence of AMN in the United States has been on the rise, with a notable increase in the number of cases occurring in younger individuals [6]. In the United States, the incidence of AMN has been increasing and becoming younger, and a similar trend has been observed in the Netherlands [7]. The incidence of AMN in the United States is on the rise and is increasing at a younger age. In

the United States, more than half of AMN patients are women, with the majority being white (70% - 74%) [6] [8]. This gender and racial characteristic has remained consistent for a considerable period of time. It is important to note that this characteristic cannot be simply applied to the country as a whole, given that the white community in the country is too small to be representative. With regard to the presentation of symptoms at the time of peritoneal involvement, it is observed that approximately 53.2% of AMN patients present with symptoms at this stage. Interestingly, the closer to the present, the smaller the proportion of cases in which the tumour is confined, while the proportion of cases with metastases to the peritoneum or to adjacent organs increases yearly [6].

3. Clinical Manifestations

Patients with AMN have no specific clinical manifestations, which often results in delayed diagnosis. In the early stages of the disease, there may be no symptoms, but increased mucus in the appendiceal lumen may give rise to manifestations similar to those of an acute appendix, such as metastatic or fixed right lower abdominal pain. Patients with AMN present with no specific clinical manifestations, which frequently results in delayed diagnosis. In the early stages of the disease, there may be no symptoms, but increased mucus in the appendiceal lumen may give rise to manifestations similar to those of an acute appendix, such as metastatic or fixed right lower abdominal pain. It has been demonstrated that an excess of mucus can result in the perforation of the appendix, with the subsequent development of acute peritonitis. Carret [9] *et al.* reported that 32% of patients presenting with appendiceal tumours were diagnosed with acute appendicitis prior to surgery, with a further 23% being found to have appendiceal tumours as a result of physical examination or surgery of other organs in the abdomen. In the absence of timely intervention, mucinous ascites accumulate in the peritoneal cavity, resulting in a gradual abdominal distension. Additionally, patients may present with chronic abdominal pain, weight loss, anaemia, frequent umbilical or inguinal hernias, and infertility in female patients of childbearing age [10]-[12]. Although AMN has the potential to implant into the peritoneum and omentum and may cause intestinal obstruction, patients presenting with intestinal obstruction as their initial symptom are uncommon [12] [13]. The initial symptom of AMN is intestinal obstruction.

4. Preoperative Examination

A preoperative examination does not confirm the diagnosis of AMN. Caspi *et al.* suggest that the intracapsular "onion skin sign" can be a characteristic feature of AMN [14]. Sagebiel *et al.* suggest that calcification of the appendiceal wall could be considered as evidence of the presence of appendiceal epithelial neoplasia, especially in well-differentiated AMN [15]. Lien *et al.* It was proposed that an appendix with an outer diameter of more than 15 mm should be considered as a potential indicator of AMN [16]. According to Lien *et al.*, in the case of AMN

combined with PMP, the sonographic picture shows an indistinct cystic or cystic-solid mass in the pelvic cavity, which is irregular in shape and often combined with "jelly-like" ascites [17]. Wang Yumeng and colleagues posit that the ultrasonographic impression of uneven internal echogenicity, internal calcification, invasion of surrounding tissues, and abdominopelvic effusion can be considered a high-risk indicator of AMN [18]. The computed tomography (CT) manifestation of adolescent mucinous neoplasm (AMN) is a predominantly multicompartmentalised right lower abdominal mass, which may also display a septum. Low-grade and high-grade mucinous tumours of the appendix are characterised by a reduction in solid components and a thin, uniform thickening of the cyst wall and septum. In contrast, mucinous adenocarcinomas of the appendix exhibit an increase in solid components and an uneven thickening of the cyst wall. Enhancement scans reveal mild to moderate strengthening of the cyst wall and septum, with a cystic fluid density of approximately 7-32 HU [19]. When AMN is combined with PMP, enhanced CT reveals multi-room cystic liquid hypodense areas within the abdominal cavity. Mild to moderate enhancement of the cystic wall and septum is observed, while the cystic portion and ascites show no enhancement [20]. MRI is more effective at distinguishing the solid components of the tumour, as well as the internal and external components of the cyst. The cyst, the root tip, the wall nodule, and so forth, can be evaluated more objectively in terms of the boundary and integrity of the tumour. However, in the case of small foci of calcification or the appearance of walled egg-shell-like calcification, the MRI display is not optimal, and in some instances, the foci of calcification cannot be displayed [21]. In the case of colonoscopy, the presence of an intraluminal bulge at the opening of the appendix should prompt the suspicion of an appendiceal tumour [22]. Low-grade appendiceal mucinous neoplasm (LAMN) is characterised by a mucosal appearance that is less aggressive than that of appendiceal mucinous adenocarcinoma (AMCA). The distinguishing feature of appendiceal mucinous adenocarcinoma (AMCA) is that it occurs at the appendiceal opening. Various biomarkers, including CEA, CA125, CA19-9, etc., can be employed to ascertain the severity of the disease and the extent of the disease. CEA, CA125, CA19-9, and other biomarkers can be employed to ascertain the severity of the disease and to predict the resectability of the tumour [23]. A retrospective analysis of 176 patients with primary appendiceal tumours (including 153 cases of AMN) revealed that the presence of elevated serum CEA and CA125 in patients admitted to hospital was indicative of a high risk of peritoneal metastasis. In cases of inflammatory adhesions or even intestinal obstruction caused by excessive mucus produced by AMN, the leukocyte count may be elevated as in ordinary infections. However, such cases occur when there is already a widespread abdominal implantation of the mucus and cancerous cells, requiring surgical intervention, and therefore blood counts may be elevated. However, when this occurs, the mucus and cancer cells are already widely planted in the abdominal cavity, necessitating surgical intervention. Consequently, blood counts are of limited value in diagnosing AMN. Nevertheless, some scholars have iden-

tified potential applications of blood counts in determining the prognosis of AMN patients. Luo Huan and colleagues observed that in patients with primary appendiceal tumours, an admission blood routine with anaemia and a platelet-to-lymphocyte ratio exceeding 190.1 suggested a poor prognosis. The authors hypothesised that anaemia caused hypoxia, which in turn favoured tumour proliferation and angiogenesis [24] [25]. The patient's prognosis may be unfavourable. Liu Qi [26] *et al.* concluded that in patients with a preoperative diagnosis of appendicitis and postoperative pathology suggestive of an appendiceal tumour, the admission blood leukocyte count affects the prognosis of the patients, with a higher value indicating a worse prognosis. The reason for this remains to be investigated, and the study still uses the old names of AMN, such as mucinous cystadenoma and mucinous cystadenocarcinoma, etc. It would be more convincing if the pathological diagnosis could be revised. There is no discernible anomaly in the blood biochemistry of patients with early AMN. However, in the late stage, the mucus and cancer cells will elevate the serum bilirubin if they are extensively distributed and obstruct the bile ducts. Nevertheless, at this juncture, the diagnosis of AMN should not be challenging. Therefore, as in the case of routine blood tests, blood biochemistry is not a significant factor in the diagnosis of AMN.

5. Pathologic Staging and Tumour Staging

The current gold standard for confirming AMN is postoperative pathological diagnosis. The classification and nomenclature of AMN has undergone numerous revisions. The World Health Organization (WHO) classification of appendiceal tumours has been updated to the 5th edition, which includes only two categories of AMN: Low-grade appendiceal mucinous neoplasms (LAMN) and high-grade appendiceal mucinous neoplasms (HAMN) [27]. Furthermore, the close relationship between AMN and PMP resulted in the Oncology Group Peritoneal Surface International (PSOGI) convening a global assembly in Berlin in 2012 [28]. The meeting was attended by 71 members from 13 different countries, including 34 pathologists, 37 medical oncologists, and 37 surgeons. A total of 71 scholars reached a consensus on a set of terms and definitions through the Delphi Method, which classified AMN as LAMN, HAMN, mucinous adenocarcinoma (AMCA), and indolent carcinoma (ICC) [29]. In contrast, the Fifth Edition of the WHO Classification of Tumors of the Digestive System on Tumors of the Appendix, 2019, excludes mucinous adenocarcinoma and indolent mucinous adenocarcinoma (HAMN) from its classification. This edition notes that peritoneal dissemination of mucinous adenocarcinomas and HAMN can occur and that there is no significance in distinguishing between the two [27]. In light of the modifications to the nomenclature of appendiceal tumours and their clinical manifestations, the PSOGI classification has gained greater acceptance. Among these, LAMN serves as the foundation for the classification. Microscopic features of LAMN include a low grade of cellular heterogeneity, the disappearance of the mucosal muscular layer, replacement of the submucosal layer by fibrous tissue,

the presence of push-like infiltration, the original columnar epithelium becoming flattened and of different heights, incomplete appendiceal structure, and the presence of cells and/or mucus outside of the appendix. In addition to the aforementioned characteristics, the microscopic characteristics of HAMN include a high grade of cellular heterogeneity line. Based on the classification of ALMN, AMCA has an increased risk of spreading to the peritoneal cavity. The classification of HAMN has been expanded to include the following ALMN: an invasive infiltrative pattern, which may or may not contain imprinted cells, and is changed to imprinted cell carcinoma if more than half of the cells are imprinted [28]. Should the content of impression cells exceed 50%, it will be transformed into impression cell carcinoma.

The staging of AMN tumours is a matter of ongoing debate within the medical community. In 2017, the American Joint Committee on Cancer (AJCC) proposed that carcinoma in situ (pTis) of LAMN is the stage in which the tumour does not breach the lamina propria and there is no pT1 or pT2. When the tumour breaches the lamina propria and does not extend to the appendiceal mesentery or plasma membrane, it is classified as pT3. This designation encompasses not only the tumour epithelium but also the mucus. pTis is almost unlikely to recur, and patients with pT3 are at risk of peritoneal metastasis, with no clear indication of the level of risk. The staging of LAMN with mucus invasion of the peritoneum must be pT4a, regardless of whether tumour epithelium is present in the mucus. The risk of peritoneal recurrence is significantly higher in patients with tumour epithelial components (36%) than in those without epithelium (3%) [30]. The staging should be based on the conclusions reached following the removal of the appendix in its entirety. In the event that the surgical procedure results in the perforation of the appendix with the development of a tumour, the mucinous component will also be released, leading to an overestimation of the staging. Therefore, it is of paramount importance to maintain the integrity of the appendiceal tumour throughout the operation. The staging of carcinoma in situ in HAMN differs from that of LAMN, which is characterised by a high grade of mucinous epithelium with a "pushed" border. This can infiltrate the solid muscle when growing in a diverticulum-like pattern. HAMN is characterised by a high-grade mucinous epithelium with a "pushing" border. This is staged as T2 if it grows in a diverticulum-like pattern and infiltrates the solid muscle, and T3 if this mucinous epithelium breaks through the plasma membrane or invades the appendiceal meninges. In the event that mucus foci are identified on the peritoneal surface other than the appendix, the tumour is deemed to have distant metastasis (M). The classification of this distant metastasis is as follows: M1a if there is no cellular component in the mucus, M1b if there is a cellular component in the mucus (neoplastic epithelium), and M1c if the mucus is implanted in an organ other than the peritoneum.

Furthermore, the AJCC proposes a grading system for AMN, which was initially proposed by Davison [31] *et al.* The classification is divided into three grades based on the presence or absence of invasive infiltration. LAMN is classi-

fied as highly differentiated (G1) due to the low grade of tumour cytology and the absence of invasive infiltration. It is also classified as moderately differentiated (G2) due to the high grade of tumour cytology and the presence of invasive infiltration, but the absence of imprinted cells. The presence of an invasive infiltrate with an imprinted cell component of more than 95% is designated as poorly differentiated (G3) [32] [33]. Gabriella Esquivel [34] *et al.* analyzed 229 patients based on the AJCC/TNM 8th edition incorporating G (grade) and E (extent of disease). The impact of these 5 clinicopathological variables (T, N, M, G, E) is scored as stages 0 to IV and is reported as the Esquivel Peritoneal Surface Disease Severity Score (E-PSDSS). Their research shows that the E-PSDSS combines specimen examination and reporting according to the College of American Pathologists with the pTNM requirements from the AJCC staging manual. It represents an important prognostic indicator in patients with mucinous appendiceal neoplasms.

6. Molecular Mechanisms

The pathogenesis of AMN remains unclear. The presence of mucin not only determines the pathological diagnosis of AMN, but is also closely associated with PMP. Given the low prevalence of the condition, genetic research for AMN has not advanced significantly. To date, no genetic loci have been identified that determine the pathogenesis of AMN, and there is no anchor point for targeted therapy. Mutations in genes such as TP53, KRAS, and GNAS, which are common in AMN, have been documented in the scientific literature [35]. These mutations are typically observed in LAMN, with HAMN being exceedingly rare, resulting in a paucity of data. The situation of AMCA, Indian Ring Cell Carcinoma, is more complex and requires further investigation. However, Singhi [36] *et al.* found that GNAS mutation expression was prevalent regardless of AMN grade after studying 55 cases of AMN. Of the three main types of mutations, GNAS mutations are thought to be associated with high mucus production [37], KRAS mutations are often considered to be early tumour events [30] [38] and TP53 mutations are very common in tumours such as colorectal. On immunohistochemistry, it has been demonstrated that CK20 (100% positive) and CK7 (71% positive) staining are similar in AMN and CRC [39] [40]. However, it is not necessary to assume that the pathogenesis of AMN is the same as that of CRC. AMN and CRC have significant differences in morbidity and pathologic diagnosis, and AMN is heterogeneous in the sense that it produces large amounts of mucus. Finally, the clinical presentation of both tumours is very different. The clinical presentation of AMN is related to the amount of mucus produced, and the amount of mucus produced is related to the amount of mucus produced. The quantity of mucus produced is straightforward to combine with appendicitis, yet difficult to differentiate from it. Right hemicolon carcinoma is commonly characterised by a right lower abdominal mass and anaemia, while left hemicolon carcinoma and rectal carcinoma are commonly characterised by changes in bowel habits and/or traits. A review of the available literature reveals

a paucity of studies investigating genetic differences between different subgroups of AMN. In conclusion, the low incidence, lack of progression, and high price limit the use of genetic analysis in the clinical treatment of AMN.

7. Surgical Decision-Making and Adjuvant Chemotherapy

Given that the incidence of lymph node metastasis in well-differentiated and limited appendiceal tumours is less than 2%, the majority of clinical surgeons believe that a simple appendectomy is sufficient to treat these conditions. The following is an example of a simple appendectomy [4]. In the event that an appendectomy is performed without prior consideration of the tumour and the tumour is subsequently confirmed to be present postoperatively, it cannot be considered to be confined. Consequently, an additional right hemicolectomy is necessary due to the lack of guarantee that there will be no intraoperative mucus spillage. In the absence of an appendectomy, particularly in the event of perforation and implantation, ileoblastectomy and right hemicolectomy should be considered, with conversion to open surgery. It is noteworthy that AMCA and indolent cell carcinoma exhibit adenocarcinoma characteristics and the possibility of lymph node metastasis is high, thus necessitating a right hemicolectomy for both types of AMN upon diagnosis [41]. For AMCA and indolent cell carcinoma, there is a possibility of lymph node metastasis. The surgical treatment of low-grade AMN with peritoneal mucin overflow is still a matter of contention. AMN-derived PMP mucus secretion is highly active, with a mucin/cell ratio that can reach 1000:1 [42]. The ratio of mucin to cells can be as high as 1000:1. The existing literature indicates that the cellular content of the mucus may influence the prognosis of patients with AMN. It has been demonstrated that in patients with AMN-derived PMP, those with a cell density of less than 20% exhibited a greater median overall survival than those with a cell density of 20% or greater. This suggests that low cell density is associated with a more favourable prognosis. Furthermore, the histopathologic type of this type of PMP is also important in suggesting prognosis. MMR protein deficiency is an independent molecular prognostic indicator, with the median survival of patients with MMR protein deficiency being shorter than that of those without deficiency [42] [43]. One possible explanation for this phenomenon is that high cell density indicates a high proliferative capacity of tumour cells, whereas MMR protein deletion suggests a strong genetic predisposition. For relatively early lesions with localized spillage of cellular mucin, combined treatment with cytoreductive surgery (CRS) is recommended. As the spilled mucin may contain tumour cells, the lesion is likely to progress to extensive peritoneal cancer (PC) if treated only with appendectomy or right hemicolectomy. The efficacy of postoperative chemotherapy in AMN is uncertain, and the most commonly used regimens are XELOX (oxaliplatin + capecitabine) and FOLFOX6 (oxaliplatin + fluorouracil) [25].

Given that the diagnosis of AMN cannot be confirmed by all preoperative tests, surgery is not only the most effective way to confirm the diagnosis of AMN, but also the most crucial step in the treatment of AMN. The matter of

surgical decision-making in AMN is still the subject of considerable controversy. In the event that the conditions of well-differentiated and confined lesions are met, it has been observed that the probability of appendiceal tumour metastasis via the lymph node route is less than 2%. Consequently, appendectomy is recommended at this time [4]. It is important to note that AMN has a 5% to 15% probability of rupture preoperatively, and the tumour may also rupture during appendectomy as a result of surgical manipulation. Consequently, the risk of postoperative PMP remains [44]. In the event of peritoneal implantation having occurred preoperatively in AMN, it would be beneficial to ascertain whether it is possible to extend the scope of surgery, such as performing appendectomy and right hemicolectomy. The answer to this question is not yet definitive, and further research is required to the answer to this question is not yet definitive, and further research is required to gain a more comprehensive understanding. In a retrospective study of 50 patients with LAMN, Li *et al.* [45] found that 30 patients underwent appendectomy, 13 underwent cecal resection, and 7 patients underwent right hemicolectomy. All patients demonstrated no evidence of recurrence during the four-year follow-up period. In a retrospective study with both large-scale and multicentre characteristics, Young [46] and several scholars compared the survival rates of patients with AMN with different surgical modalities. Their findings indicated that the survival rates were similar between the appendectomy, cecal resection, and right hemicolectomy groups. SA total of 501 patients with primary appendiceal tumours were included in the study. Following multivariate analysis, it was found that there was no significant difference in survival between patients who underwent right hemicolectomy and those who had an appendicectomy alone. Furthermore, intraoperative rapid cryopathology was found to be a valuable tool in guiding surgical decision-making. This test allows for right hemicolectomy to be performed if appendiceal lymph node metastasis, distal ileal lymph node metastasis, distal colonic lymph node metastasis, and positive tumour margins are detected, while ensuring that there is no residual tumour. It appears that an appendectomy is a more advisable option than a right hemicolectomy. However, it will take time for this conclusion to be universally recognised, particularly internationally. This is due to the low incidence of AMN and the numerous updates to the pathological diagnostic criteria. Additionally, the sample size of surgical cases collected over a wide span of time makes it challenging to correct the diagnosis in retrospect. The Chinese Expert Consensus on Multidisciplinary Comprehensive Treatment of Appendiceal Tumours (2021 Edition) states that during surgery, medical appendiceal perforation and tumour implantation should be avoided. If laparoscopic surgery is being performed, it is recommended that the procedure be intermediate and open. At this time, simple appendectomy is also not recommended, and right hemicolectomy is one of the feasible options [47] [48].

8. AMN-Derived PMP Treatment

For a considerable period, treatments for PMP of AMN origin consisted of re-

peated drainage of mucus ascites, which undoubtedly made the patients very miserable. Subsequently, tumour cytoreductive surgery (CRS) was developed on the basis of right hemicolectomy, but the patients still suffered from recurrences. In the 1980s, Spratt *et al.* demonstrated that the administration of heated chemotherapeutic agents into the peritoneal cavity in conjunction with CRS and continued for a period of time, also known as intraperitoneal chemotherapy, resulted in a reduction in the recurrence of PMPs [39] [49]. In the 1990s, Sugarbaker, Jacquet *et al.* established the concept of hot intraperitoneal perfusion chemotherapy (HIPEC) [43] [50] [51]. The objective of intraperitoneal heat infusion chemotherapy is to administer high doses of heated chemotherapy directly into the abdominal cavity, with minimal systemic effects. Intraperitoneal heat chemotherapy is typically employed in patients with complete CRS and minimal or no underlying disease. Once the abdomen has been opened intraoperatively, the high-dose chemotherapeutic drugs are heated to approximately 40˚C - 42˚C. The abdominal cavity is then filled, the abdominal incision is left open, or it can be temporarily sutured for the purpose of protecting healthcare workers. This allows the chemotherapeutic drugs to fully kill residual cancer cells without leaving any dead space. It has been demonstrated that in addition to cytotoxicity, the heat effect can also induce the production of heat shock protein, thereby activating the body's immune system to actively kill cancer cells [52]-[54]. In addition to cytotoxicity, it has been demonstrated that the heat effect can also induce the production of heat shock proteins and cause the body's immune system to actively kill cancer cells. Animal studies have demonstrated that hyperthermia may enhance the cytotoxicity of chemotherapeutic drugs [54]. The study demonstrated that hyperthermia may enhance the cytotoxicity of chemotherapy drugs. It is crucial to acknowledge that this form of open HIPEC may result in the generation of aerosols containing chemotherapeutic drugs, which may potentially induce adverse effects if inhaled by intraoperative healthcare workers. Consequently, postoperative closed HIPEC has also been developed. A retrospective analysis was conducted on 670 patients with peritoneal cancer who underwent closed HIPEC for a total of 4249 times, with no deaths during treatment. The incidence of HIPEC-associated adverse effects, such as treatment failure, intolerable pain, cytotoxic peritoneal inflammation, intestinal obstruction, and intestinal perforation, was less than 3% [55]. This evidence indicates that closed HIPEC is a safer procedure than open intraoperative surgery. In the event of peritoneal spread in patients with advanced malignant peritoneal neoplasm (AMN), complete attenuation of tumour cells is an important predictor of survival. The degree of postoperative tumour cytoreduction is determined by the completeness of cytoreduction (CC) scoring method. The CC scoring system is scored according to the size of the residual tumour. The CC score is based on the size of the residual tumour, with no peritoneal residual tumour scored as 0, residual tumour < 2.5 mm in diameter scored as 1, 2.5 mm to 2.5 cm in diameter scored as 2, and more than 2.5 cm in diameter, or the lesion could not be resected scored as 3. Scores of 0 and 1 are

considered as satisfactory cytoreduction of the tumour. In 1996, Sugarbaker and Jacquet proposed the peritoneal carcinomatosis index (PCI) as a means of assessing the size and extent of peritoneal implants [56] [57]. The PCI scoring system will divide the abdomen into zones 0 to 9 according to the nine-point division of the abdomen. The umbilical region will be designated zone 0, with this zone serving as the central reference point. Zones 1 to 8 will be counted clockwise from the right quarter rib region, while zones 9 to 12 will be designated for the upper jejunum, lower jejunum, upper ileum, and lower ileum. Each partition included organs within the corresponding region in addition to the peritoneum. The size of the implant foci was used to assign a score, with no implant foci being assigned a score of 0, implant foci less than 0.5 cm being assigned a score of 1, more than 5 cm being assigned a score of 3, and between 0.5 cm and 5 cm being assigned a score of 2. The cumulative total of the scores for each of the 13 zones was assigned a score of PCI. The total score ranged from 0 to 39, with higher scores indicating a greater tumour load. A PCI score exceeding 20 renders it exceedingly challenging for the surgeon to achieve a satisfactory CRS outcome for the patient [58]. Chua Chua [59] *et al.* retrospectively evaluated 2298 patients with AMN with peritoneal metastases in 16 specialized centers. Their findings indicated that failure to achieve a satisfactory CRS suggests a poor prognosis, and patients with a high PCI score also have a poor prognosis. HIPEC significantly improves progression-free survival (PFS) in patients with AMN, but is associated with an improvement in overall survival (OS). The use of HIPEC was found to significantly improve progression-free survival (PFS) in patients with AMN, although it did not result in an overall survival (OS) benefit.

9. Neoadjuvant and Palliative Chemotherapy

The administration of neoadjuvant chemotherapy for AMN is somewhat complex and requires a delicate balance. Currently, AMN is not a reliable preoperative diagnosis, whereas CRC can be diagnosed by colonoscopy and subsequently treated with chemotherapy to minimise the size of the cancerous lesion. This approach is challenging in AMN due to the lack of reliable diagnostic tools. It is theoretically possible to perform a pathological examination prior to surgery on patients with AMN, using a biopsy of the rectum. This can be guided by ultrasound or CT to ensure accurate placement. However, this has the potential to cause new problems. In cases of PMP of appendiceal origin, the commonly used puncture needles may be unable to aspirate the optimal specimen due to excessive mucus. Even if the needle is replaced by a coarser one, the tumour tissue may be encapsulated by the mucus, which may also be disappointing. Furthermore, wounds created by the coarser needles are more challenging to heal than those created by the finer needles. In the most extreme cases, fistulas may form and lead to abdominal infections. Laparotomy also presents a comparable quandary. Laparoscopic biopsy appears to be a promising option, but if acute myeloid leukaemia (AML) is highly suspected during the examination, is it advisable to take a biopsy and withdraw from the scope instead of cytoreductive

surgery (CRS)? To date, no studies have demonstrated that neoadjuvant chemotherapy improves overall survival (OS) or progression-free survival (PFS) in patients with AMN. For patients with AMN who have intraoperatively detected unresectable tumours or who cannot tolerate CRS, experts suggest that palliative systemic chemotherapy may still be attempted [60] [61]. For patients with AMN who have unresectable tumours identified during surgery or who are unable to tolerate CRS, experts recommend that palliative systemic chemotherapy may still be attempted.

10. Summary and Outlook

HIPEC represents a complex surgical procedure with a high incidence of morbidity and mortality. In the context of such a lethal disease, the risk is considered acceptable. A multitude of studies have reported disparate rates of operative and postoperative complications. In a systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for PMP, the overall morbidity rate was found to vary from 33% to 56%, while the overall mortality rate ranged from 0% to 18%. The mean hospital stay was found to range from 26 to 29 days, with a median hospital stay of 16 to 21 days.

The prognosis of appendiceal mucinous neoplasms is related to pathological staging, whether it is confined or not, whether complete tumor cell reduction is performed or not, whether or not to receive intraperitoneal hyperthermic perfusion chemotherapy after peritoneal invasion, etc. The effect of neoadjuvant chemotherapy and postoperative chemotherapy is still unsatisfactory, and the comprehensive treatment plan of CRS+HIPEC for non-confined AMN is still the mainstream for a short period of time. The outcome of the PMP treatment process is highly variable. The combined use of CRS and HIPEC is considered the optimal therapeutic approach for patients with PMP. It is necessary to develop surgical expertise and refine patient selection criteria in order to enhance the efficacy of the treatment. This can only be achieved through the centralisation of patients' treatment in specialised units or centres. Future breakthroughs in the prevention and diagnosis of this disease will be a clearer understanding of the pathogenesis, earlier detection means, and so forth.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Liang, J.W., Wang, Z., Zhou, Z.X., *et al.* (2012) Clinicopathological Characteristics and Prognosis of Primary Appendiceal Adenocarcinoma. *Chinese Journal of Cancer*, **34**, 616-619.

[2] Shaib, W.L., Goodman, M., Chen, Z., *et al.* (2017) Incidence and Survival of Appendiceal Mucinous Neoplasms: A SEER Analysis. *American Journal of Clinical Oncology*, **40**, 569-573. https://doi.org/10.1097/COC.0000000000000210

[3] Lv, J.F. and Tang, Q.C. (2021) The 2021 Edition of Expert Consensus on Multidisciplinary Comprehensive Treatment of Appendiceal Tumours in China Presents a Comprehensive Overview of the Latest Developments in This Field. *The Chinese Electronic Journal of Colorectal Diseases*, **10**, 225-231.

[4] Moaven, O., Votanopoulos, K.I., Shen, P., *et al.* (2020) Health-Related Quality of Life after Cytoreductive Surgery/HIPEC for Mucinous Appendiceal Cancer. Results of a Multicenter Randomized Trial Comparing Oxaliplatin and Mitomycin. *Annals of Surgical Oncology*, **27**, 772-780. https://doi.org/10.1245/s10434-019-08064-6

[5] Ali Shamseddine, *et al.* (2017) Appendiceal Mucinous Neoplasms: Diagnosis and Management. *The Oncologist*, **22**, 1107-1116. https://doi.org/10.1634/theoncologist.2017-0081

[6] Fackche, N., Schmocker, R.K., Kubi, B., *et al.* (2021) The Utility of Preoperative Tumor Markers in Peritoneal Carcinomatosis from Primary Appendiceal Adenocarcinoma: An Analysis from the US HIPEC Collaborative. *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract*, **25**, 2908-2919.

[7] Van Den Heuvel, M.G.W., Lemmens, V.E.P.P., Verhoeven, R.H.A., *et al.* (2013) The Incidence of Mucinous Appendiceal Malignancies: A Population-Based Study. *International Journal of Colorectal Disease*, **28**, 1307-1310. https://doi.org/10.1007/s00384-013-1714-9

[8] Overman, M.J., Fournier, K., Hu, C.Y., *et al.* (2013) Improving the AJCC/TNM Staging for Adenocarcinomas of the Appendix: The Prognostic Impact of Histological Grade. *Annals of Surgery*, **257**, 1072-1078. https://doi.org/10.1097/SLA.0b013e318269d680

[9] Carr, N.J., McCarthy, W.F. and Sobin, L.H. (1995) Epithelial Noncarcinoid Tumors and Tumor-Like Lesions of the Appendix. A Clinicopathologic Study of 184 Patients with a Multivariate Analysis of Prognostic Factors. *Cancer*, **75**, 757-768. https://doi.org/10.1002/1097-0142(19950201)75:3%3C757::AID-CNCR2820750303%3E3.0.CO;2-F

[10] Ito, H., Osteen, R.T., Bleday, R., *et al.* (2004) Appendiceal Adenocarcinoma: Long-Term Outcomes after Surgical Therapy. *Diseases of the Colon and Rectum*, **47**, 474-480. https://doi.org/10.1007/s10350-003-0077-7

[11] Garg, P.K., Prasad, D., Aggarwal, S., *et al.* (2011) Acute Intestinal Obstruction: An Unusual Complication of Mucocele of Appendix. *European Review for Medical and Pharmacological Sciences*, **15**, 99-102.

[12] Muramoto., T., Kamijo, K., Sano, M., Ibuki, Y., Mori, A. and Kobayashi, Y. (2022) A Case of Low-Grade Appendiceal Mucinous Neoplasm of Its Difficultly to Distinguish from a Right Ovarian Tumor Due to Postmenopause. *Open Journal of Obstetrics and Gynecology*, **12**, 1140-1146. https://doi.org/10.4236/ojog.2022.1211098

[13] Young, R.H. (2004) Pseudomyxoma Peritonei and Selected Other Aspects of the Spread of Appendiceal Neoplasms. *Seminars in Diagnostic Pathology*, **21**, 134-150.

[14] Rutledge, R.H. and Alexander, J.W. (1992) Primary Appendiceal Malignancies: Rare but Important. *Surgery*, **111**, 244-250. https://doi.org/10.1053/j.semdp.2004.12.002

[15] Caspi, B., Cassif, E., Auslender, R., *et al.* (2004) The Onion Skin Sign: A Specific Sonographic Marker of Appendiceal Mucocele. Journal of Ultrasound in Medicine: Official Journal of the American Institute of Ultrasound in Medicine, **23**, 117-121. https://doi.org/10.7863/jum.2004.23.1.117

[16] Sagebiel, T.L., Mohamed, A., Matamoros, A., *et al.* (2017) Utility of Appendiceal

Calcifications Detected on Computed Tomography as a Predictor for an Underlying Appendiceal Epithelial Neoplasm. *Annals of Surgical Oncology*, **24**, 3667-3672. https://doi.org/10.1245/s10434-017-6052-7

[17] Lien, W.C., Huang, S.P., Chi, C.L., *et al.* (2006) Appendiceal Outer Diameter as an Indicator for Differentiating Appendiceal Mucocele from Appendicitis. *The American Journal of Emergency Medicine*, **24**, 801-805. https://doi.org/10.1016/j.ajem.2006.04.003

[18] Bao, Y.J., Wei, X.L., Wang, C.T., *et al.* (2023) Value of Ultrasound in the Diagnosis and Differential Diagnosis of Appendiceal Mucinous Tumor. *China Modern General Surgery Progress*, **26**, 466-469.

[19] Wang, Y.M., Li, Y. and Liu, Dong. (2023) Value of Ultrasound in Risk Assessment of Appendiceal Mucinous Tumors. *Chinese Journal of Ultrasound Medicine*, **39**, 787-790.

[20] Zhang, D., Wang, H.X., Zhang, P.G., *et al.* (2017) Study on Imaging Manifestations and Pathological Correlation of Appendiceal Mucinous Tumor. *Journal of Practical Radiology*, **33**, 69-71, 102.

[21] Hu, Y., Ruan, Z.B., Zheng, X., *et al.* (2020) CT Presentation and Clinical Analysis of Appendiceal Mucinous Tumor. *Chinese Journal of General Surgery*, **35**, 71-72.

[22] Jeffrey, R.B., Wentland, A.L. and Olcott, E.W. (2018) Sonography of the Cecum: Gateway to the Right Lower Quadrant. *Ultrasound Quarterly*, **34**, 133-140. https://doi.org/10.1097/RUQ.0000000000000332

[23] Kuang, L., Zhao, Z.F., Ma, S.R., *et al.* (2015) Enteroscopic and Ultrasonographic Endoscopic Diagnosis of Appendiceal Mucus Cyst. *Chinese Journal of Gastrointestinal Endoscopy*, **32**, 813-816.

[24] Liang, L., Fang, J., Han, X., *et al.* (2021) Prognostic Value of CEA, CA19-9, CA125, CA724, and CA242 in Serum and Ascites in Pseudomyxoma Peritonei. *Frontiers in Oncology*, **11**, Article 594763. https://doi.org/10.3389/fonc.2021.594763

[25] Sun, R.M. (2022) Analysis of Risk Factors and Clinicopathological Characteristics and Prognosis of Primary Appendiceal Tumor Combined with Peritoneal Metastasis. Master's Thesis, Zhengzhou University.

[26] Luo, H., Li, J.X., Gou, H.X., *et al.* (2023) Analysis of Clinical Characteristics, Treatment and Prognostic Factors of Primary Appendiceal Tumors. *Chinese Journal of Basic and Clinical Surgery*, **30**, 721-727.

[27] Liu, Q., Fuan, Z.F., Wang, H.M., *et al.* (2020) Diagnosis, Treatment and Prognosis of Appendiceal Tumor. *Chinese Journal of General Surgery*, **35**, 296-299.

[28] Wang, L.P. (2020) Updates and Advances in Appendiceal Tumor Classification - Fifth Edition of the WHO Classification of Digestive Tumors on Appendiceal Tumors, 2019. *Journal of Diagnostic Pathology*, **27**, 289-294.

[29] Zhao, L.H. and Xiao, H.L. (2017) Interpretation of the International Peritoneal Surface Tumor Organization's Consensus on the Classification and Pathology Report of Peritoneal Pseudomucinous Tumors and Related Appendiceal Tumors. *Journal of Diagnostic Pathology*, **24**, 241-244.

[30] Carr, N.J., Cecil, T.D., Mohamed, F., *et al.* (2016) A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *The American Journal of Surgical Pathology*, **40**, 14-26. https://doi.org/10.1097/PAS.0000000000000535

[31] Valasek, M.A. and Pai, R.K. (2018) An Update on the Diagnosis, Grading, and

Staging of Appendiceal Mucinous Neoplasms. *Advances in Anatomic Pathology*, **25**, 38-60. https://doi.org/10.1097/PAP.0000000000000178

[32] Davison, J.M., Choudry, H.A., Pingpank, J.F., *et al.* (2014) Clinicopathologic and Molecular Analysis of Disseminated Appendiceal Mucinous Neoplasms: Identification of Factors Predicting Survival and Proposed Criteria for a Three-Tiered Assessment of Tumor Grade. *Modern Pathology*: *An Official Journal of the United States and Canadian Academy of Pathology*, *Inc*, **27**, 1521-1539. https://doi.org/10.1038/modpathol.2014.37

[33] Wang, L.R., Ye, J.X. and Shi, X.Y. (2020) Progress in the Pathologic Diagnosis and Mechanism of Appendiceal Mucinous Tumors. *Journal of Clinical and Experimental Pathology*, **36**, 178-181.

[34] Esquivel, G., Qiu, J., Spellman, J. and Esquivel, J. (2023) Incorporation of the 8th Edition AJCC/TNM Staging of Carcinoma of the Appendix into the Esquivel Peritoneal Surface Disease Severity Score (E-PSDSS) in 229 Patients with Mucinous Appendiceal Neoplasms. *Open Journal of Gastroenterology*, **13**, 1-11. https://doi.org/10.4236/ojgas.2023.131001

[35] Ge, P.P. and Xu, L.J. (2022) Diagnostic and Therapeutic Study of Appendiceal Mucinous Tumor. *Medical Information*, **35**, 157-160. https://doi.org/10.1097/IAE.0000000000000150

[36] Singhi, A.D., Davison, J.M., Choudry, H.A., *et al.* (2014) GNAS Is Frequently Mutated in Both Low-Grade and High-Grade Disseminated Appendiceal Mucinous Neoplasms but Does Not Affect Survival. *Human Pathology*, **45**, 1737-1743. https://doi.org/10.1016/j.humpath.2014.04.018

[37] Alakus, H., Babicky, M.L., Ghosh, P., *et al.* (2014) Genome-Wide Mutational Landscape of Mucinous Carcinomatosis Peritonei of Appendiceal Origin. *Genome Medicine*, **6**, Article No. 43. https://doi.org/10.1186/gm559

[38] Pai, R.K., Hartman, D.J., Gonzalo, D.H., *et al.* (2014) Serrated Lesions of the Appendix Frequently Harbor KRAS Mutations and Not BRAF Mutations Indicating a Distinctly Different Serrated Neoplastic Pathway in the Appendix. *Human Pathology*, **45**, 227-235. https://doi.org/10.1016/j.humpath.2013.10.021

[39] Ji, H., Isacson, C., Seidman, J.D., *et al.* (2002) Cytokeratins 7 and 20, Dpc4, and MUC5AC in the Distinction of Metastatic Mucinous Carcinomas in the Ovary from Primary Ovarian Mucinous Tumors: Dpc4 Assists in Identifying Metastatic Pancreatic Carcinomas. *International Journal of Gynecological Pathology*, **21**, 391-400. https://doi.org/10.1097/00004347-200210000-00009

[40] Kinzler, K.W. and Vogelstein, B. (1996) Lessons from Hereditary Colorectal Cancer. *Cell*, **87**, 159-170. https://doi.org/10.1016/S0092-8674(00)81333-1

[41] Professional Committee of Colorectal Tumor of Chinese Physicians Association (2021) Expert Consensus on Multidisciplinary Comprehensive Treatment of Appendiceal Tumors in China (2021 Edition). *Chinese Electronic Journal of Colorectal Diseases*, **10**, 225-231.

[42] O'Connell, J.T., Tomlinson, J.S., Roberts, A.A., *et al.* (2002) Pseudomyxoma Peritonei Is a Disease of MUC2-Expressing Goblet Cells. *The American Journal of Pathology*, **161**, 551-564. https://doi.org/10.1016/S0002-9440(10)64211-3

[43] Gad, Z., Nassar, O., Soliman, H., Mohamed, S. and Mohamed, M. (2018) Outcome of Management of Pseudomyxoma Peritonei: National Cancer Institute Experience. *Journal of Cancer Therapy*, **9**, 323-337. https://doi.org/10.4236/jct.2018.94030

[44] Rouchaud, A., Glas, L., Gayet, M., *et al.* (2014) Appendiceal Mucinous Cystadenoma. *Diagnostic and Interventional Imaging*, **95**, 113-116.

https://doi.org/10.1016/j.diii.2013.07.015

[45] Li, X., Zhou, J., Dong, M., *et al.* (2018) Management and Prognosis of Low-Grade Appendiceal Mucinous Neoplasms: A Clinicopathologic Analysis of 50 Cases. *European Journal of Surgical Oncology*, **44**, 1640-1645. https://doi.org/10.1016/j.ejso.2018.06.037

[46] Young, S., Sueda, S.K., Hotta, M., *et al.* (2020) Surgical Management of Appendiceal Mucinous Neoplasm: Is Appendectomy Sufficient. *Journal of Surgical Oncology*, **122**, 1173-1178. https://doi.org/10.1002/jso.26108

[47] Liu, Q., Fuan, Z.F., Wang, H.M., *et al.* (2020) Diagnosis, Treatment and Prognosis of Appendiceal Tumours. *Chinese Journal of General Surgery*, **35**, 296-299.

[48] Yan, F., Lin, Y., Zhou, Q., *et al.* (2020) Pathological Prognostic Factors of Pseudomyxoma Peritonei: Comprehensive Clinicopathological Analysis of 155 Cases. *Human Pathology*, **97**, 9-18. https://doi.org/10.1016/j.humpath.2019.12.008

[49] Spratt, J.S., Adcock, R.A., Muskovin, M., *et al.* (1980) Clinical Delivery System for Intraperitoneal Hyperthermic Chemotherapy. *Cancer Research*, **40**, 256-260.

[50] Sugarbaker, P.H. (1995) Peritonectomy Procedures. *Annals of Surgery*, **221**, 29-42. https://doi.org/10.1097/00000658-199501000-00004

[51] Jacquet, P., Stephens, A.D., Averbach, A.M., *et al.* (1996) Analysis of Morbidity and Mortality in 60 Patients with Peritoneal Carcinomatosis Treated by Cytoreductive Surgery and Heated Intraoperative Intraperitoneal Chemotherapy. *Cancer*, **77**, 2622-2629. https://doi.org/10.1002/(SICI)1097-0142(19960615)77:12%3C2622::AID-CNCR28%3E3.0.CO;2-T

[52] Gerweck, L.E. (1985) Hyperthermia in Cancer Therapy: The Biological Basis and Unresolved Questions. *Cancer Research*, **45**, 3408-3414.

[53] Lindquist, S. (1986) The Heat-Shock Response. *Annual Review of Biochemistry*, **55**, 1151-1191. https://doi.org/10.1146/annurev.biochem.55.1.1151

[54] Oleson, J.R., Calderwood, S.K., Coughlin, C.T., *et al.* (1988) Biological and Clinical Aspects of Hyperthermia in Cancer Therapy. *American Journal of Clinical Oncology*, **11**, 368-380. https://doi.org/10.1097/00000421-198806000-00013

[55] Liu, L., Zhang, N., Min, J., *et al.* (2016) Retrospective Analysis on the Safety of 5,759 Times of Bedside Hyperthermic Intra-Peritoneal or Intra-Pleural Chemotherapy (HIPEC). *Oncotarget*, **7**, 21570-21578. https://doi.org/10.18632/oncotarget.7622

[56] Archer, A.G., Sugarbaker, P.H. and Jelinek, J.S. (1996) Radiology of Peritoneal Carcinomatosis. *Cancer Treatment and Research*, **82**, 263-288. https://doi.org/10.1007/978-1-4613-1247-5_17

[57] Jacquet, P. and Sugarbaker, P.H. (1996) Clinical Research Methodologies in Diagnosis and Staging of Patients with Peritoneal Carcinomatosis. *Cancer Treatment and Research*, **82**, 359-374. https://doi.org/10.1007/978-1-4613-1247-5_23

[58] Sugarbaker, P.H. and Jablonski, K.A. (1995) Prognostic Features of 51 Colorectal and 130 Appendiceal Cancer Patients with Peritoneal Carcinomatosis Treated by Cytoreductive Surgery and Intraperitoneal Chemotherapy. *Annals of Surgery*, **221**, 124-132. https://doi.org/10.1097/00000658-199502000-00002

[59] Chua, T.C., Moran, B.J., Sugarbaker, P.H., *et al.* (2012) Early and Long-Term Outcome Data of Patients with Pseudomyxoma Peritonei from Appendiceal Origin Treated by a Strategy of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. *Journal of Clinical Oncology*, **30**, 2449-2456. https://doi.org/10.1200/JCO.2011.39.7166

[60] Yan, T.D., Links, M., Xu, Z.Y., *et al.* (2006) Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Pseudomyxoma Peritonei from Appendiceal Mucinous Neoplasms. *The British Journal of Surgery*, **93**, 1270-1276. https://doi.org/10.1002/bjs.5427

[61] Chicago Consensus Working Group (2020) The Chicago Consensus on Peritoneal Surface Malignancies: Management of Appendiceal Neoplasms. *Cancer*, **126**, 2525-2533. https://doi.org/10.1002/cncr.32881