Pseudomyxoma peritonei

Katharine E Bevan, Faheez Mohamed, Brendan J Moran

Abstract

Pseudomyxoma peritonei (PMP) is an uncommon “borderline malignancy” generally arising from a perforated appendiceal epithelial tumour. Optimal treatment involves a combination of cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC). Controversy persists regarding the pathological classification and its prognostic value. Computed tomography scanning is the optimal preoperative staging technique. Tumour marker elevations correlate with worse prognosis and increased recurrence rates. Following CRS with HIPEC, 5-year survival ranges from 62.5% to 100% for low grade, and 0%-65% for high grade disease. Treatment related morbidity and mortality ranges from 12 to 67.6%, and 0 to 9%, respectively. Surgery and HIPEC are the optimal treatment for PMP which is at best a “borderline” peritoneal malignancy.

Key words: Pseudomyxoma peritonei; Cytoreductive surgery; Heated intraperitoneal chemotherapy; Jelly belly; Appendiceal mucinous tumour; Peritoneal malignancy; Borderline malignancy

INTRODUCTION

Pseudomyxoma peritonei (PMP) is an uncommon clinical entity with an estimated incidence of one to two per million per year[1]. Classically it is characterized by diffuse intra-abdominal gelatinous collections (jelly belly) with mucinous implants on peritoneal surfaces and the omentum[2]. Many cases present unexpectedly at laparoscopy or laparotomy, or may be suspected at cross-sectional imaging during the investigation, or staging, of another pathological entity. Thus all who operate within the abdominal cavity will encounter an occasional case and will be faced with diagnostic and therapeutic uncertainty due to the rarity of PMP and the lack of an evidence base, or consensus, on management.

PMP has generally been considered benign; however its behaviour suggests that it should, at best, be considered a borderline malignancy with disease progression over time, to massive abdominal distension and nutritional compromise in most cases. The long term survival in most patients remains poor with reported 5 and 10 year survival rates of 50% and 10%-30%, respectively[3]. There has recently been a global interest in the management of PMP, particularly in macroscopic removal of tumour by complex surgical techniques combined with heated intraperitoneal chemotherapy (HIPEC)[4-14].

Werth in 1884 coined the term PMP, describing it in association with a mucinous tumour of the ovary[15]. In 1901, Frankel[16] described a case associated with a cyst of the appendix. Since these early reports there has been...
ongoing debate as to the primary origin of PMP, particularly in women. The exact incidence of PMP remains speculative. Both the clinical caseload experience of the two UK national centres (Basingstoke and Manchester), and a recent publication from the Netherlands reporting on a nationwide epidemiological and pathological database, suggests that the incidence of PMP is approximately two per million, per year.[1]

In reality the clinico-pathological entity “PMP syndrome” or “jelly belly” probably represents a spectrum of disease. This ranges from mucinous ascites, in association with a cystadenoma of the appendix (resulting in true PMP); to frank mucinous adenocarcinoma. Additionally intestinal mucinous tumours, particularly colorectal cancers, or indeed any mucinous neoplasm may present with clinical, radiological and pathological features resembling PMP.

**ORIGIN OF PMP**

Most acknowledge that PMP predominantly originates in the appendix in men and increasingly evidence suggests a similar site of origin in females.[17,18]. In women synchronous ovarian and appendiceal disease is common, and PMP appears more prevalent. However immunohistochemistry and molecular genetic techniques support the hypothesis that in the majority of women, the ovarian tumour is metastatic from a perforated appendiceal mucinous tumour.[19-22]. Recently MUC 2 over-expression has been suggested as a molecular marker for PMP of intestinal rather than ovarian origin[20]. From a clinical perspective, Moran and colleagues[2,17] have proposed that it is unlikely that the male and female appendix behave in a different manner and it is likely that there are similar numbers of appendiceal PMP cases in both groups. Personal experience suggests that some of the reported increased female incidence may represent a “Will Rogers” phenomenon[24] with earlier and more precise diagnosis in women[3]. Women with non-specific symptoms are more likely to have cross sectional imaging, particularly to rule out ovarian cancer.

Undoubtedly a proportion of cases arise from other organs[25,26] and it is likely that an ovarian primary is the commonest in this diverse group. PMP has been reported originating from the colon and rectum, the stomach, gallbladder and bile ducts, small intestine, urinary bladder, lung, breast, fallopian tube and pancreas producing large quantities of mucus.

The tumour cell surfaces lack adhesion molecules preventing random adherence to peritoneal surfaces and, being surrounded by mucus, move with the normal flow of peritoneal fluid. The distinctive feature of PMP is its characteristic “redistribution” within the peritoneal cavity[27]. In contrast to most carcinoma cells of gastrointestinal tract origin that implant in a random fashion near the site of perforation; PMP demonstrates a nomadic pattern of migration with epithelial cells accumulating at specific abdominal and pelvic sites. The intraperitoneal distribution of PMP is determined by physical factors, namely the movement and absorption of peritoneal fluid and gravity. The open lymphatic lacunae on the under surface of the right hemidiaphragm and the lymphoid aggregates in the omentum, absorb fluid, leading to bulky accumulations as the mucus is absorbed and epithelial cells “filtered out” and concentrated. From a clinical perspective, the concentrated tumour masses result in “scalloping” of the liver and an “omental cake”.

Gravity also plays a role, especially in the early stages, as mucus and cells concentrate by gravitational forces. Dependent portions of the abdomen and pelvis such as the recto-vesical pouch, the right retro-hepatic space and the paracolic gutters, accumulate tumour cells[27].

As the disease progresses and becomes generalized redistribution extends to the left hemidiaphragm, engulfs the spleen and stomach, and spreads throughout the peritoneal cavity. The resultant gastrointestinal tract compression eventually culminates in bowel obstruction and terminal starvation.

A pathognomonic feature of favourable PMP is the complete, or nearly complete, absence of tumour masses on the freely mobile intestinal surfaces, especially the small bowel but to a lesser extent the stomach and transverse colon. Normal peristalsis, together with poor adherence properties of the epithelial tumour cells results in “bowel sparing”. In contrast the parts of the gastro-intestinal tract fixed to the retroperitoneum, such as the gastric pylorus and antrum, the ileocecal and rectosigmoid regions, are often heavily diseased and commonly require resection to remove macroscopic tumour involving the bowel[28].

Smeenk et al[28] recently made the important observation that there remains much confusion in the terminology of what exactly constitutes PMP. There is no debate when the abdomen is full of mucinous ascites originating from a primary appendiceal tumour. Other variations are more difficult to categorize, ranging from an unperforated mucocele, to local perforation with disease apparently confined to the pelvis or right iliac fossa, through to disseminated intra-abdominal disease. More than 50% of cases present before the full-blown manifestation of the disease. In essence a patient with a perforated appendiceal tumour with mucus, and/or epithelial cells, either on the serosa of the appendix or anywhere in the peritoneal cavity is at risk of developing PMP[29]. Most cases will develop within 2-5 years of initial appendiceal perforation[29]. Early on these patients are asymptomatic and disease is only detectable by cross-sectional imaging or direct peritoneal

**PATHOPHYSIOLOGY OF PMP**

The sequence of events culminating in PMP is thought to involve growth of an appendiceal adenoma progressing to occlude the appendiceal lumen with distension of the appendix by mucus and mucinous tumour cells[11]. The appendix eventually ruptures, often initially by a “blow out” and subsequent slow leak of mucus containing epithelial cells from the adenoma. In most cases appendicular perforation is an occult event. The epithelial cells within the peritoneal cavity continue to proliferate
inspection at laparoscopy or laparotomy.

For this reason a recent review outlined the management of an unexpected appendiceal tumour\[30\]. It recommended a colonoscopy, to exclude synchronous colonic neoplasia, with a baseline computed tomography (CT) and tumour markers (CEA, CA125 CA19-9). Annual tumour marker measurements and cross-sectional imaging [CT or magnetic resonance imaging (MRI)] for 5 years were suggested. At any interval a laparoscopy should be considered if uncertainty exists (such as elevated tumour markers or a CT abnormality).

PATHOLOGICAL CLASSIFICATION

Controversy persists over the classification of epithelial appendiceal neoplasms and their relationship to PMP. High grade colonic mucinous neoplasms, adenocarcinomas of the appendix and mucinous adenocarcinomas originating from any other intra-abdominal organ (particularly the colon) can mimic the clinical, radiological, and pathological features of pseudomyxoma peritonei\[31\]. Additionally, there appears to be a spectrum of disease from low to high-grade, though the pathological appearances of the tumour may not correlate with its clinical behaviour\[32\].

These difficulties in pathological classification of PMP have led to diverse reports with ongoing confusion as to outcomes following intervention. Thus, many series include all cases of PMP, of whatever origin, and include patients with mucinous adenocarcinoma of the appendix.

Others report only on classical pseudomyxoma, from appendiceal low-grade tumours, generally cystadenomas. Ronnett and colleagues, in a retrospective review of a series of patients who had undergone complete cytoreduction by Sugarbaker's group, reported a pathological system commonly quoted in the literature\[33\]. They classified low-grade tumours as disseminated peritoneal adenomucinosis (DPAM) and high-grade tumours as peritoneal mucinous carcinomatosis (PMCA), with an intermediate group (IG) demonstrating a mixture of DPAM and PMCA. Survival was significantly higher in the low-grade (DPAM) as compared with the high-grade tumours (IG and PMCA). They were unable to show a statistically significant difference between the IG and PMCA groups and subsequently grouped these together\[34\]. Dichotomous categorizations of mucinous tumours of the appendix have been adopted by others and what is emerging is that optimal outcomes result from the management of PMP originating from low-grade appendiceal mucinous tumours\[35\].

These pathological classifications are important as they give some indication of prognosis following cytoreductive surgery (CRS) and HIPEC. Patients with low grade tumours (DPAM, MCP low grade etc) appear to obtain maximum survival benefit from aggressive locoregional treatments while those with PMCA behave more like peritoneal carcinomatosis of colorectal origin\[36\].

CLINICAL PRESENTATION OF PMP

The clinical presentation of PMP has been poorly defined due to few reports with large patient populations. The majority of patients are diagnosed during, or after, a laparotomy or laparoscopy, for suspected appendicitis, peritonitis or gynaecological cancer.

In a series of 410 patients with appendiceal tumours, 217 had the diagnosis of PMP with histological confirmation\[37\]. Overall, 27% presented with suspected appendicitis, 23% with increasing abdominal distension and 14% with a new onset hernia. In women, PMP was most commonly diagnosed during investigation of an ovarian mass (39%).

Moran has recently suggested an increasing number being detected at cross-sectional imaging either for investigation of abdominal symptoms or incidental abnormalities noted on staging, or investigational imaging for unrelated pathology\[38\].

PRE-OPERATIVE ASSESSMENT

Imaging

CT is currently the optimal imaging modality for the diagnosis and staging of PMP\[39\]. CT or ultrasound (US)-guided biopsy may be useful, although the relatively acellular material is often difficult to diagnose with certainty. CT-scan findings may be pathognomonic for PMP, particularly when radiologic techniques combine oral, rectal and intravenous contrast. Typical CT appearances include areas of low attenuation, with islands of higher attenuation due to solid elements within mucinous material. Classically “scalloping” of visceral surfaces, particularly of the liver and spleen (Figures 1 and 2), distinguishes mucinous from fluid ascites\[39\].

The pattern of disease distribution is characteristic and should suggest the diagnosis. Once PMP has involved the abdomino-pelvic regions, it fills those sites where peristalsis is limited by peritoneal attachment (ileo-caecal region, ligament of Treitz, sigmoid colon) and finally occupies the remaining abdominal cavity. When the peritoneal cavity is completely or almost completely filled with PMP, CT-scan findings become less specific and the characteristic pattern of PMP cannot be appreciated. In most cases the striking feature is the relative sparing of the small bowel and its mesentery or “compartmentalization” in the central abdomen by a large omental cake and massive mucinous ascites\[39\].

Contrast-enhanced CT can assist in predicting the likelihood of complete cytoreduction\[39\]. Jacquet reported two radiological findings that predicted incomplete cytoreduction, segmental obstruction of the small bowel and tumour masses more than 5cm in width on the small bowel and its mesentery (exclusive of the distal ileum). With these findings on preoperative CT scans, patients had an 88% probability of incomplete resection and those without a 92% probability of complete resection\[39\].

The role of MRI in staging PMP is under investigation. A recent report on the use of delayed gadolinium enhanced MRI seems promising in staging and patient selection for cytoreductive surgery\[34\] but requires further evaluation.

Positron emission tomography (PET) and PET CT are
of limited value for low-grade mucinous lesions, though may be helpful in more aggressive variants by detecting systemic metastases.

**Tumour markers-CEA, CA125, CA19.9**
The prognostic value of tumour markers in patients undergoing CRS and HIPEC has been evaluated. Baratti reported that normal preoperative CA125 correlated to the likelihood of achieving adequate CRS on univariate analysis, and that increased baseline CA19.9 was an independent predictor of shorter progression-free survival on multivariate analysis. van Ruth et al. reported that elevated CA19.9 after surgery, or rising levels during follow-up, related to disease recurrence. Survival was related to preoperative CEA and CA19.9 levels among 532 patients studied by Carmignani et al. Both markers, measured at the time of disease recurrence, correlated with survival after a second cytoreduction with HIPEC. Alexander-Sefre et al. reported a significantly reduced recurrence-free interval for patients who had an elevated baseline CEA prior to complete cytoreduction, but also for patients with at least one elevated marker (among CEA, CA125 and CA19.9).

**Laparoscopy**
When a patient presents with increasing abdominal girth as a result of presumed malignant ascites, the diagnosis is usually established with paracentesis, or laparoscopy and biopsy. If possible, paracentesis, or laparoscopy, should be performed through the midline as these sites can be excised by a midline abdominal incision. Ideally no lateral puncture or port sites should be used as this may result in abdominal wall tumour seeding, reducing the probability of disease eradication. Laparoscopic access and visualization may be compromised by disease extent, in particular a large omental "cake", rendering accurate laparoscopic assessment impossible.

**TREATMENT OF PMP**
The indolent behaviour of PMP led some to advocate no active treatment, although it is increasingly accepted that most patients with PMP, untreated, will progress to terminal starvation through intestinal obstruction by mucinous ascites.

**Surgical treatment**
Traditional surgical management of patients with PMP involved repeated interval debulking for symptomatic relief, with limited expectation of long-term survival and no prospect of cure. The rarity of PMP has resulted in limited reports on accurate historical controls of uniformly treated patients. In 1994, Gough et al. reported from the Mayo clinic, a 10-year survival of 32% in 56 patients who underwent serial debulking and selective, intra-peritoneal radiotherapy, or chemotherapy, between 1957 and 1983. In 2005, Miner et al. reported a 10-year survival of 21% (12% disease free) in 97 patients treated by serial debulking, systemic chemotherapy and/or delayed intermittent intra-peritoneal 5-fluorouracil over a 22-year period in Memorial Sloan Kettering. Misdraji et al. reported on 107 patients with a median survival of 7.5 years, and a 20-year survival of 25% after serial debulking and perioperative intra-peritoneal chemotherapy. The proportion who received aggressive locoregional treatment is not reported.

Sugarbaker et al. introduced and popularized the approach combining CRS (aiming for macroscopic complete tumour removal) with HIPEC to address residual microscopic disease. Patients must be medically fit to safely undergo CRS with HIPEC. Patients with peritoneal carcinomatosis with an ECOG (Eastern Co-operative Oncology Group) performance score of 2 to 3 have significantly poorer overall survival after CRS and HIPEC, compared to those with an ECOG score of 1.

The rationale for HIPEC is to target residual microscopic disease or small volume macroscopic nodules (ideally less than 2-3 mm in size).

**OUTCOMES AFTER CRS AND HIPEC FOR PMP**
Sugarbaker et al. published a series of 385 patients in 1999. Of these, 205 received HIPEC. Survival advantages in those who had complete vs incomplete cytoreduction (80%...
Recent reports suggest that the initial high morbidity (80% vs 28%) were reported but there was no report on the effect of the introduction of HIPEC.

Glehen et al. [34] analysed the data from the same institution over a 30-year period and interestingly found a survival benefit for patients who had an incomplete cytoreduction with HIPEC in addition to Early Postoperative Intraperitoneal Chemotherapy (EPIC) compared with those who had no chemotherapy (27.2% vs 7.3% 5-year survival). However this comparison is likely to include a major selection bias in favour of those who had chemotherapy.

Recent updates by Glehen et al. [34] reported a median survival of 156 mo, with 5 and 10 year survival of 72% and 55% respectively in 501 PMP patients. The majority (approx. 70%) had complete cytoreduction. The uniform treatment approach has shown improved 10 year survival, as compared with historical controls [35].

No clear strategy exists for patients with disease not amenable to CRS, either at pre-operative assessment or intra-operatively, because of tumour extent and distribution, or serious co-morbidity, or age. There is increasing evidence that these patients benefit from a major palliative resection with reasonable intermediate-term survival of 43% at 2 years and 15% at 5 years and improved quality of life [8,34]. In these situations an extended right hemicolectomy, greater omentectomy and splenectomy with an ileocolic anastomosis, or alternatively a total colectomy and end ileostomy may be advisable. Glehen et al. [34] recommended a combination of comprehensive surgical debulking with HIPEC, except for patients with signet ring histology or lymph node involvement, in their experience.

Mean operating times range from 6 to 12.6 h [6,12,56] and with such complex procedures morbidity and mortality are considerable. Major morbidity includes anastomotic leakage, enteric and pancreatic fistulation, pneumonia, thromboembolism, and intra-abdominal abscesses. Many patients have had previous abdominal surgery prior to definitive resection with reasonable intermediate-term survival of 43% at 2 years and 15% at 5 years and improved quality of life [8,34]. In these situations an extended right hemicolectomy, greater omentectomy and splenectomy with an ileocolic anastomosis, or alternatively a total colectomy and end ileostomy may be advisable. Glehen et al. [34] recommended a combination of comprehensive surgical debulking with HIPEC, except for patients with signet ring histology or lymph node involvement, in their experience with 174 patients who had incomplete cytoreduction.

**MORBIDITY AND MORTALITY OF CRS WITH HIPEC**

Mean operating times range from 6 to 12.6 h [6,12,56] and with such complex procedures morbidity and mortality are considerable. Major morbidity includes anastomotic leakage, enteric and pancreatic fistulation, pneumonia, thromboembolism, and intra-abdominal abscesses. Many patients have had previous abdominal surgery prior to definitive cytoreduction increasing the risk of complications from adhesiolysis and distorted anatomy resulting in a high incidence of small bowel fistulae [30] and significant blood loss [55].

Neutropenic sepsis is a potentially serious complication usually presenting around day 10 following intraperitoneal Mitomycin C, due to bone marrow toxicity [30]. Septic complications may herald, or result from, neutropenia and require prompt treatment.

Re-operation rates for postoperative complications range from 11% [29] to 21% [8] with mortality rates ranging between 0% and 14% [29]. Median hospital stay range from 16 to 21 d [27].

**INFLUENCE OF THE LEARNING CURVE**

Recent reports suggest that the initial high morbidity and mortality seen with CRS and HIPEC decreases with increasing experience [30,34]. This is most marked in specialized centres and includes improvements in patient selection, surgical expertise and postoperative management [30].

**FOLLOW UP AND MANAGEMENT OF PROGRESSIVE DISEASE**

Follow up depends upon the likelihood of recurrent or progressive disease and treatment options. A baseline CT scan 3 mo postoperatively, then 6 monthly, will facilitate detection of recurrence or surveillance of progressive disease [31,64], though we consider this over zealous. Baseline elevated tumour markers CEA, CA 19.9 and CA 125 may indicate an increased risk of recurrent disease in patients who are secretors [30]. The author’s policy has been annual CT and tumour marker measurements, beginning one year after surgery, based on the hypothesis that very early recurrences are unlikely to be amenable to salvage.

Elective second look surgery when recurrence, or progression, is suspected may be beneficial in selected patients. Esquivel and Sugarbaker reported a 5 year survival of 74% for patients with peritoneal spread of appendiceal malignancy treated with further CRS and HIPEC [30]. Mohamed et al. [34] reported a 5 year survival of 70% from initial surgery in 45 patients treated with 3 or more reoperations. Yan and colleagues reported overall survival of 75% at 10 years from time of initial surgery following repeat cytoreductive surgery for both DPAM and non-DPAM [36].

**CONCLUSION**

PMP is uncommon and generally originates from a perforated appendiceal tumour. The optimal treatment involves a combination of surgery and HIPEC. The treatment strategy is complex, associated with significant morbidity and mortality and a substantial institutional, and individual, “learning curve” [36].

The long-term outcomes for CRS with HIPEC in PMP are impressive for patients with low-grade histology amenable to complete cytoreduction. Increasing numbers of medium to large case series reports reflect an improved awareness and understanding of the disease and a global recognition, and reporting, of the learning curve and outcomes.

An emerging network of specialized centres may facilitate multicentre studies on aspects of chemotherapy type, duration and temperature to help allay the criticisms of many surgical, and in particular, medical oncologists on the lack of good scientific evidence in PMP management.

All surgeons who operate in the abdomen will occasionally encounter a patient with PMP. In this unexpected event the best strategy to facilitate subsequent attempts at complete cytoreduction is to take generous biopsies, remove the appendix if accessible and refrain from major resectional interventions. Following recovery and histological confirmation of the clinical diagnosis, an opinion should be sought from a specialized assessment and treatment centre.
REFERENCES

1 Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. Eur J Surg Oncol 2006; 34: 196-201

2 Moran BJ, Cecil TD. The etiology, clinical presentation, and management of pseudomyxoma peritonei. Surg Oncol Clin N Am 2003; 12: 585-603

3 Hinson FL, Ambrose NS. Pseudomyxoma peritonei. Br J Surg 1998; 85: 1332-1339

4 Sugarbaker PH. Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol 1999; 6: 727-731

5 Witkamp AJ, de Bree E, Kaag MM, Boot H, Beijnen JH, van Slooten GW, van Coevorden F, Zoetmulder FA. Extensive cytoreductive surgery followed by intra-operative hyperthermic intraperitoneal chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis of colorectal origin. Eur J Cancer 2001; 37: 979-984

6 Güner Z, Schmidt U, Dahlke MH, Schlitt HJ, Klempnauer J, Piso P. Cytoreductive surgery and intraperitoneal chemotherapy for pseudomyxoma peritonei. Int J Colorectal Dis 2005; 20: 155-160

7 Loungnarath R, Causereit S, Bossard N, Faheez M, Sayag-Martinez F, Abulafia O, Eliakim R. Pseudomyxoma peritonei syndrome. A review of current literature. Gynecol Obstet Invest 2001; 51: 73-80

8 Sugarbaker PH. Intraperitoneal cancer dissemination: mechanisms of the patterns of spread. Cancer Metastasis Rev 2003; 22: 465-472.

9 Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FA. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg 2007; 245: 104-109

10 Baratti D, Kusamura S, Nonaka D, Langer M, Andreola S, Favaro M, Gavazzi C, Laterza B, Deraco M. Pseudomyxoma peritonei: clinical pathological and biological prognostic factors in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol 2006; 13: 624-634

11 Murphy EM, Sexton R, Moran BJ. Early results of surgery in 123 patients with pseudomyxoma peritonei from a perforated appendiceal neoplasm. Dis Colon Rectum 2007; 50: 37-42

12 Elias D, Honoré C, Ciuchendéa R, Billard V, Raynard B, Lo Dico R, Dromain C, Duvald P, Goéré D. Peritoneal pseudomyxoma: results of a systematic policy of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Br J Surg 2008; 95: 1164-1171

13 Ronnett BM, Shmookler BM, Diener-West M, Sugarbaker PH, Kurman RJ. Immunohistochemical evidence supporting the appendiceal origin of pseudomyxoma peritonei in women. Int J Gynecol Pathol 1997; 16: 1-9

14 Szych C, Staebeier A, Costello DC, Wu R, Cho KR, Ronnett BM. Molecular genetic evidence supporting the clonality and appendiceal origin of Pseudomyxoma peritonei in women. Am J Pathol 1999; 154: 1849-1855

15 Chuaqui RF, Zhuang Z, Emmert-Buck MR, Bryant BR, Tavassoli FA, Merino MJ. Genetic analysis of synchronous mucinous tumors of the ovary and appendix. Hum Pathol 1996; 27: 165-171.

16 Guerrieri C, Fradlund B, Tisted S, Gilleooley JF, Boerdy R. Mucinous tumors of the verminform appendix and ovary, and pseudomyxoma peritonei: histogenetic implications of cytokeratin 7 expression. Hum Pathol 1997; 28: 1039-1045

17 Ferreira CR, Carvalho JP, Soares FA, Siqueira SA, Carvalho FM. Mucinous ovarian tumors associated with pseudomyxoma peritonei of adenomucinosis type: immunohistochemical evidence that they are secondary tumors. Int J Gynecol Cancer 2008; 18: 59-65

18 Feinstein AR, Susin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985; 312: 1604-1608

19 de Bree E, Witkamp AJ, Zoetmulder FA. Peroperative hyperthermic intraperitoneal chemotherapy (HIPEC) for advanced gastric cancer. Eur J Surg Oncol 2006; 26: 630-632

20 Smeenk RM, Vos A, Verwaal VJ, Horenblas S, Zoetmulder FA. Pseudomyxoma peritonei and the urinary tract: involvement and treatment related complications. J Surg Oncol 2006; 93: 20-23.

21 Sugarbaker PH. Pseudomyxoma peritonei. A cancer whose biology is characterized by a redistribution phenomenon. Ann Surg 1994; 219: 109-111

22 Carmignani CP, Sugarbaker TA, Bromley CM, Sugarbaker PH. Intrahepatic cancer dissemination: mechanisms of the patterns of spread. Cancer Metastasis Rev 2003; 22: 465-472.

23 Smeenk RM, Bruin SC, van Velthuysen ML, Verwaal VJ. Pseudomyxoma peritonei. Curr Prob Surg 2008; 45: 527-575

24 Murphy EM, Farquharson SM, Moran BJ. Management of an unexpected appendiceal neoplasm. Br J Surg 2006; 93: 783-792

25 Sugarbaker PH, Ronnett BM, Archer A, Averbach AM, Bland R, Chang D, Dalton RR, Ettinghausen SE, Jacquet P, Jelinek J, Koslowe P, Kurman RJ, Smeenk RM, Stephens AD, Steves MA, Stuart OA, White S, Zahn CM, Zoetmulder FA. Pseudomyxoma peritonei syndrome. Adv Surg 1996; 30: 233-280

26 Mohamed F, Gething S, Haibma M, Brun EA, Sugarbaker PH. Clinically aggressive pseudomyxoma peritonei: a variant of a histologically indolent process. J Surg Oncol 2004; 86: 10-15

27 Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol 1995; 19: 1390-1408

28 Misdradj J, Yantiss RK, Greame-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. Am J Surg Pathol 2003; 27: 1089-1103

29 Bradley RF, Stewart JH 4th, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol 2006; 30: 551-559

30 Bevan KE et al. Pseudomyxoma peritonei
have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. Cancer 2001; 92: 85-91.

37 Esquivel J, Sugarbaker PH. Clinical presentation of the Pseudomyxoma peritonei syndrome. Br J Surg 2000; 87: 1414-1418.

38 jacquet P, Jelinek JS, Chand D, Koslowe P, Sugarbaker PH. Abdominal computed tomographic scan in the selection of patients with mucinous peritoneal carcinomatosis for cytoreductive surgery. J Am Coll Surg 1995; 181: 530-538.

39 Sulkin TV, O’Neill H, Amin AI, Moran B. CT in pseudomyxoma peritonei: a review of 17 cases. Clin Radiol 2002; 57: 608-613.

40 Low RN, Barone RM, Gurney JM, Muller WD. Mucinous appendiceal neoplasms: preoperative MR staging and classification compared with surgical and histopathologic findings. AJR Am J Roentgenol 2008; 190: 656-665.

41 Stewart JH 4th, Shen P, Levine EA. Intrapерitoneal hyperthermic chemotherapy for peritoneal surface malignancy: current status and future directions. Ann Surg Oncol 2005; 12: 765-777.

42 Baratti D, Kusamura S, Martiñetti A, Seregni E, Laterza B, Oliva DG, Deraco M. Prognostic value of circulating tumor markers in patients with pseudomyxoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2007; 14: 2300-2308.

43 van Ruth S, Hart AA, Bonfrer JM, Verwaal VJ, Zoetmulder FA. Prognostic value of baseline and serial carcinoembryonic antigen and carbohydrate antigen 19.9 measurements in patients with pseudomyxoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2002; 9: 961-967.

44 Carmignani CP, Hampton R, Sugarbaker CE, Chang D, Sugarbaker PH. Utility of CEA and CA 19-9 tumor markers in diagnosis and prognostic assessment of mucinous epithelial cancers of the appendix. J Surg Oncol 2004; 87: 162-166.

45 Alexander-Sefre F, Chandrakumaran K, Banerjee S, Sexton R, Thomas JM, Moran B. Elevated tumour markers prior to complete tumour removal in patients with pseudomyxoma peritonei predict early recurrence. Colorectal Dis 2005; 7: 382-386.

46 Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome. Lancet Oncol 2006; 7: 69-76.

47 Friedland JS, Allardice JT, Wyatt AP. Pseudomyxoma peritonei. JR Soc Med 1986; 79: 480-482.

48 Sugarbaker PH. Pseudomyxoma peritonei. Cancer Treat Res 1996; 81: 105-119.

49 Gough DB, Donohue JH, Schutt AJ, Gonchoroff N, Geelten JR, Wilson TO, Naesens JM, O’Brien PC, van Heerden JA. Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. Ann Surg 1994; 219: 112-119.

50 Minner TJ, Shi J, Jaques DP, Klimstra DS, Brennan MF, Coit DG. Long-term survival following treatment of pseudomyxoma peritonei: an analysis of surgical therapy. Ann Surg 2005; 241: 300-308.

51 Sugarbaker PH. Surgical treatment of peritoneal carcinomatosis: 1988 Du Pont lecture. Can J Surg 1989; 32: 164-170.

52 Sugarbaker PH, Kern K, Lack E. Malignant pseudomyxoma peritonei of colonic origin. Natural history and presentation of a curative approach to treatment. Dis Colon Rectum 1987; 30: 772-779.

53 Barakat RR, Sabbatini P, Bhaskaran D, Revzin M, Smith A, Venkatraman E, Aghajanian C, Hensley M, Soignet S, Brown C, Soslowsky R, Markman M, Hoskins WJ, Spriggs D. Intrapерitoneal chemotherapy for ovarian carcinoma: results of long-term follow-up. J Clin Oncol 2002; 20: 694-698.

54 Gleich O, Mohamed F, Sugarbaker PH. Incomplete cytoreduction in 174 patients with peritoneal carcinomatosis from appendiceal malignancy. Ann Surg 2004; 239: 278-285.

55 González-Moreno S, Sugarbaker PH. Right hemicolecotomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. Br J Surg 2004; 91: 304-311.

56 Deraco M, Baratti D, Inglese MG, Allaria B, Andreola S, Gavazzi C, Kusamura S. Peritoneectomy and intraperitoneal hyperthermic perfusion (IPHP): a strategy that has confirmed its efficacy in patients with pseudomyxoma peritonei. Ann Surg Oncol 2004; 11: 393-398.

57 Smeenk RM, Verwaal VJ, Zoetmulder FA. Toxicity and mortality of cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei—a report of 103 procedures. Eur J Surg Oncol 2006; 32: 188-190.

58 Verwaal VJ, van Tinteren H, Ruth SV, Zoetmulder FA. Toxicity of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy. J Surg Oncol 2004; 85: 61-67.

59 Sugarbaker PH, Alderman R, Edwards G, Marquardt CE, Gushchin V, Esquivel J, Chang D. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol 2006; 13: 635-644.

60 Cavalieri F, Valle M, De Rosa B, Federici O, Giannarelli D, Garofalo A. [Peritoneectomy and chemohyperthermia in the treatment of peritoneal carcinomatosis: learning curve]. Suppl Tumori 2005; 4: S119-S121.

61 Moran BJ. Decision-making and technical factors account for the learning curve in complex surgery. J Public Health (Oxf) 2006; 28: 375-378.

62 Smeenk RM, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. Br J Surg 2007; 94: 1408-1414.

63 Yan TD, Links M, Fransi S, Jacques T, Black D, Saunders V, Morris DL. Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy—a journey to becoming a Nationally Funded Peritoneectomy Center. Ann Surg Oncol 2007; 14: 2270-2280.

64 Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FA. Progression of pseudomyxoma peritonei after combined modality treatment: management and outcome. Ann Surg Oncol 2007; 14: 493-499.

65 Esquivel J, Sugarbaker PH. Second-look surgery in patients with peritoneal dissemination from appendiceal malignancy: analysis of prognostic factors in 98 patients. Ann Surg 2001; 234: 198-205.

66 Mohamed F, Chang D, Sugarbaker PH. Third look surgery and beyond for appendiceal malignancy with peritoneal dissemination. J Surg Oncol 2003; 85: S-12; discussion 12-13.

67 Yan TD, Bijelic L, Sugarbaker PH. Critical analysis of treatment failure after complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from appendiceal mucinous neoplasms. Ann Surg Oncol 2007; 14: 2289-2299.

68 Moran BJ. Establishment of a peritoneal malignancy treatment centre in the United Kingdom. Eur J Surg Oncol 2006; 32: 614-618.