Indian J Surg Oncol (March 2015) 6(1):57–62
DOI 10.1007/s13193-014-0373-9

REVIEW ARTICLE

Pancreatic Cancer in Chronic Pancreatitis

Puneet Dhar · S. Kalghatgi · Vivek Saraf

Received: 2 July 2014 / Accepted: 17 December 2014 / Published online: 21 January 2015

Abstract Data exists to indicate a definite association between chronic pancreatitis and pancreatic cancer. The strength of this association varies between various causes of pancreatitis, with hereditary and tropical pancreatitis more likely to result in malignancy. Pathogenesis may involve genetic factors, diabetes, smoking and alcohol consumption. Clinically a significant overlap exists between the two conditions, with histology difficult to obtain and interpret in this setting. Biomarkers like CA19-9 and others may be useful, as is a variety of newer imaging modalities. Treatment needs to be individualised as surgery offers the only chance of cure, albeit in but a few.

Keywords Chronic pancreatitis · Pancreatic cancer

Introduction

Chronic pancreatitis (CP) is a debilitating disease of diverse aetiology and equally diverse manifestations. In addition to causing severe pain, diabetes and exocrine insufficiency, CP puts the patient at risk for developing pancreatic cancer (PC). The relationship between CP and pancreatic cancer has been the focus of multiple studies, many of which have indicated a strong association [1, 2]. However, the intricacies of this association, like pathogenesis, temporal progression and risk factors, remain far from clear. The inherent difficulty in differentiating an inflammatory head mass from malignancy in CP compounds the issue. Thus many formal pancreatic resections are performed, some of which may be unnecessary for benign disease. This review attempts to summarize the available data with regards to the association between CP and PC.

P. Dhar (✉) · S. Kalghatgi · V. Saraf
Department of GI and HPB Surgery, Amrita Institute of Medical Sciences, Cochin, India
e-mail: dharpuneet@gmail.com

The Association Between Chronic Pancreatitis and Pancreatic Cancer

In a large multicenter historical cohort study conducted by the International Pancreatitis Study Group, the cumulative risk of PC in patients with CP (predominantly of alcoholic aetiology) was reported as 1.8 % and 4 % at 10 and 20 years respectively [1]. This risk was reported to be independent of age, sex and type of pancreatitis. However, this data was criticized for its retrospective nature and lack of uniformity. In 2002, Malka et al. [3] published the results of a prospective single centre study, which addressed many of the deficiencies plaguing the earlier data, and they reported a definite association between CP and PC with a cumulative incidence of pancreatic cancer of 1.1 % at 5 years and 1.7 % at 10 years. A large nationwide prospective study from India including our hospital [4] found the incidence of cancer in chronic pancreatitis to be 4 %, to be somewhat similar to western alcoholic disease, and less than previously reported in "tropical pancreatitis". [5, 6] Many studies have cast doubts regarding this association by suggesting that these findings may have been confounded by the presence of common etiological factors between CP and PC, like alcohol consumption and cigarette smoking [7, 8], or indeed even common dietary and environmental factors. Despite these concerns, most studies suggest that CP is associated with an increased risk of PC. The link between CP and PC is clearer in certain subtypes of CP like tropical pancreatitis and hereditary pancreatitis.

Tropical pancreatitis is a distinct subtype of CP, which is seen almost exclusively in the developing countries of the tropical world. It is characterised by a younger age at onset, presence of large intraductal calculi, rapid progression into

exocrine insufficiency, and most notably, a high susceptibility to pancreatic cancer [9]. Augustine et al.[10] reported a 8.3 % incidence of pancreatic cancer in patients with tropical pancreatitis, which is much higher than western figures. A low incidence of de novo pancreatic cancer in these geographical areas was presumed, however over the ensuing decades it seems to be a frequent neoplasm even in these regions. PC arising in tropical pancreatitis differs from de novo pancreatic cancer in that it occurs at a younger age and has a poorer prognosis. Chari et al. [6] reported similar findings and concluded that the likelihood of patients with tropical pancreatitis would develop pancreatic cancer was 100 times that of patients without tropical pancreatitis. More recently, a lower incidence of malignancy has been seen, possibly at higher ages [4] and might suggest a shift in patient characteristics such as improved socioeconomic status.

Hereditary pancreatitis is an autosomal dominant condition caused by a gain of function mutation in the cationic trypsinogen gene (PRSS1). A lifetime risk of 40–55 % of developing pancreatic cancer in patients with hereditary pancreatitis has been reported. [11] Notably, smoking significantly enhanced the risk of malignancy. Similar findings have been reported by the EUROPAC study [12] which concluded that the cumulative risk of pancreatic cancer from symptom onset was 1.5 % at 20 years, going up to 44.0 % at 70 years from symptom onset.

An interesting point of discussion has been of reverse causality—the finding that pancreatic cancer can cause pancreatitis by way of tumour related duct obstruction. Although the association is stronger for acute pancreatitis, it also exists for CP. This has led to concerns that the historical data regarding the association between CP and PC could have been skewed by many of these patients having tumour related pancreatitis rather than pancreatitis causing PC. This has been investigated by International Pancreatic Cancer Case–control Consortium (PanC4) [13], which conducted a pooled analysis of 10 case control studies and reported that up to 38 % of cases of CP with PC had CP because of the PC. But even after deducting this figure, there still existed a 3-fold increased risk of PC in patients with CP.

Pathogenesis of Pancreatic Cancer in Chronic Pancreatitis

It has long been accepted that the chronic inflammatory processes which characterize CP promote metaplasia and neoplastic transformation. Studies have attempted to define the progression of inflammation to malignancy in the setting of chronic pancreatitis [14–16]. It is believed that the cytokines and reactive oxygen species that are generated during inflammation cause DNA damage. Chronic inflammation leads to accumulation of DNA damage, finally progressing to oncogenic mutations in K-ras, p16 and p53 resulting in malignant transformation. However, this explanation is too simplistic considering that malignancy occurs at different rates in different types of CP, thereby suggesting that alternate mechanisms might exist.

Hereditary pancreatitis is associated with multiple mutations in cationic trypsinogen (PRSS1) and idiopathic chronic pancreatitis has mutations in SPINK-1. Both of these mutations have been implicated in the development of PC [16].

Diabetes mellitus is a known risk factor for PC [17–19]. Whether the coexistence of CP with DM increases the overall risk of PC is unclear. In a population based cohort study by Liao et al.[20], risk of PC in patients with CP and DM combined was higher than that for patients with CP alone (HR= 33.52 vs HR=19.4). This finding is confounded by the fact that diabetes could be a manifestation of PC in CP, rather than a risk factor.

The impact of environmental risk factors like tobacco smoking and alcohol consumption on the development of PC in CP cannot be underestimated. Smoking has been shown to markedly increase the risk of malignancy in patients with hereditary pancreatitis, most likely by potentiating the underlying genetic defect. The role of pancreatic stellate cells in development of CP and PC is being increasingly recognized [21]. Stellate cells are activated by ethanol and its metabolites and contribute to tumor progression and resistance to chemotherapy. In addition cholecystokinin receptor over-expression has been found in pancreatic cancers as also in mice models of early PanINs and blocking these receptors halts PanIN progression and reverses fibrosis [22].

Carcinogenesis in chronic pancreatitis is likely to be a multifactorial phenomenon with both genetic and environmental factors working synergistically to generate a microenvironmental milieu favouring progression from inflammation to malignancy. However, the complexity of this interaction has yet to be completely elucidated. Better understanding of these interactions might help in identifying the minority of patients with CP who go on to develop PC.

Detection of Pancreatic Cancer in Chronic Pancreatitis

Pancreatic cancer arising in CP accounts for only 0.1–5 % of all cases of PC [23, 24]. But a disproportionately higher number of pancreatico-duodenectomies are performed in patients with CP due to the difficulty in differentiating an inflammatory head mass from malignancy.

Clinical features could be similar in early stages. When features of definite malignancy appear, there is a high chance of it being an advanced disease. In a small series from Eastern India – it was found that the presence of anorexia, weight loss and worsening of glycaemic control in long standing diabetics suggested malignancy, but all these patients had advanced malignancy. [25] The occurrence of obstructive jaundice

increases the suspicion for malignancy, but benign obstruction is at least as frequent a cause. It is likely that a high grade or rapid increase or severe cholestatic symptoms would suggest malignancy, but it would then likely be advanced. In an early report from our department, jaundice was found in 7 of 61 operated patients, with 4 of them eventually proving to be benign. Additionally 5 patients had clinically obvious metastatic malignancy (supraclavicular nodes, umbilical nodules or ascites).[26] In a series from Trivandrum, 23 cases of malignancy in chronic pancreatitis were compared to 118 de novo pancreatic cancers during the same period. It was found that intractable pain, weight loss and worsening of diabetes was present in 60 % of dual disease with higher propensity for the head region for local or peritoneal spread, whilst jaundice, pruritis and weight loss was commonest in de novo cancers, with a higher incidence of liver metastases. [27]

Obtaining pathological confirmation has traditionally been a contentious issue. Difficulty in access, poor yield, risk of bleeding or pancreatic fistula, possibility of seeding, and increased difficulty in diagnosis in the presence of chronic pancreatitis all contribute, and many clinicians don't insist on it as a requirement even for major surgery and occasionally this may be justified. However, an interesting study from France analysed all CP patients who were recommended resection by a multidisciplinary meeting for suspicion of cancer, but without histologic pre-operative proof. They found no difference in clinical features in those patients with subsequent confirmation of malignancy and the benign cases. [28] Interestingly most of the postop morbidity occurred in the group without malignancy – this would argue for a better preop diagnosis and augur against the usual cavalier surgical attitude of "cut it out and see"!

Biomarkers to Predict Malignancy in CP with Head Mass

CA 19-9 has been the most widely investigated tumour marker for pancreatic cancer. However, in the setting of CP, it has obvious limitations since it can be elevated in many causes of obstructive jaundice (both benign and malignant) especially when associated with cholangitis, and rarely in chronic pancreatitis itself [29]. The utility of CA19-9 in differentiating an inflammatory head mass in CP from a malignant mass has been frequently investigated. Perumal et al. [30] reported that CA19-9 was the single most important risk factor in predicting malignancy in CP with a head mass and a level>127 IU/ml had a sensitivity of 85.7 % and specificity of 96.5 % in predicting malignancy. However the study concluded that the CA19-9 level is best considered along with other parameters, like serum bilirubin level, CBD diameter and MPD diameter for highest predictive accuracy. Bedi et al. [31] reported that CA 19-9 levels>300 IU/ml were 100 % specific for predicting malignancy in CP with head mass but such high levels were seen in only 6 patients in the study. Another prospective study from Karnataka also showed an incremental specificity and stressed the value of its elevation particularly in non-jaundiced patients. [32] A postoperative elevation after normalisation, may also suggest recurrence. Our institute reported no statistically significant difference in the two groups, although elevation above 1500 was seen only in malignancy.[26]

Attempts have been made to improve the utility of CA19-9 in differentiating benign from malignant head masses by combining it with other serum markers. Maire et al. [33] investigated the value of detecting KRAS2 mutations in circulating DNA for diagnosing malignancy in this setting. The authors concluded that the finding of a normal CA 19-9 level and absence of KRAS2 mutations makes the diagnosis of pancreatic cancer extremely unlikely.

Plasma micro-RNA's are increasingly being utilized for the detection of pancreatic cancer arising in CP. Liu et al. [34] reported a sensitivity of 88.4 % and specificity of 96.3 % in differentiating PC from CP using a combination of micro-RNA and CA 19-9.

More recently, a monoclonal antibody PAM4 (Clivatuzumab), has been found to be positive in a large proportion of patients with pancreatic cancer, but not in chronic pancreatitis unless there were precursor lesions like PanINs.[35] This could have significant impact on labelled imaging and therapeutic potential as well. The antibody is likely to exert its effect on the specific mucin species MUC5AC.[36] Using CA19-9 along with PAM4 may increase its accuracy. Another candidate biomarker under investigation is CD1D – an altered gene measured in the pancreatic aspirate after secretin stimulation [37].

Despite all these measures, it can be remarkably difficult to conclusively differentiate an inflammatory mass from a malignant mass. In such situations, the onus lies on the treating clinician to weigh various factors and form an opinion and proceed accordingly.

Imaging and Guided Pathology

Ultrasound is the usual first investigation and can rule out advanced disease and guide biopsy in these cases, frequently unsuccessfully! However CT Scan is the basic workhorse in suggesting and identifying cancer in CP and is the most commonly used tool in this setting. Even though multi-detector contrast enhanced CT has improved pancreas resolution and diagnosis, most features of contour, vascular or ductal abnormalities occur in advanced disease. Early lesions can still be missed whilst still curable. A recent triple phase study showed that peak enhancement in cancer occurs earlier with early washout, whereas contrast appearance was delayed in chronic pancreatitis [38]. MRI is believed by many to be at least as good especially when CT contrast needs to be avoided.

Diffusion weighted imaging may be of some help, and a recent report showed improved characterisation of normal pancreas, focal pancreatitis and PC using quantified Apparent diffusion coefficient (ADC) histogram analysis, as a marker of tissue heterogeneity.[39]

Endoscopic Ultrasound (EUS) has the potential to be the most sensitive of the current imaging techniques to pick up small pancreatic tumours (even less than 2 cm) within pancreatitis, and thus diagnose it at a relatively curable stage. However, it may still be difficult to justify a diagnosis of malignancy in a candidate lesion, without taking some tissue sample. EUS is one of the safest ways to guide cytology or tissue diagnosis, since, if it does turn out to be malignant, and requires surgery – the entry tract can also be removed with the specimen. Its accuracy can be improved using contrast enhancement and Doppler. EUS elastography also appears promising with malignant masses showing higher strain ratios and lower mass elasticity than inflammatory lesions. Yet, one of the largest single centre studies showed no discriminatory benefit [40].

Despite the poorer anatomical detail for Positron Emission Tomographic (PET) scan, its fusion with CT scan heralded excitement in potentially identifying a more proliferative tumour of PC which would be FDG avid in a background of fibrosis that occurs in CP which should show a reduced uptake. The real world studies have yielded conflicting results and although many reports show some usefulness [41], the anticipated hype has not been clinically met unequivocally. False positivity can occur due to the variable and unpredictable avidity of the component of acute inflammation in the background fibrotic process, and also in autoimmune pancreatitis or Tuberculosis, where uptake is high. False negativity can occur in diabetes, hyperglycaemia and islet cell tumours. A recent meta-analysis did not find PET to offer a clear clinical benefit. As its cost reduces, it is likely to be utilised increasingly, to look for signs of inoperability like distant metastases, recurrences, and as a problem-solving tool when CT and EUS are equivocal. [42]

Management of Pancreatic Head Mass

Indications for surgery in chronic pancreatitis continue to be on standard lines – that is when complications occur, or in intractable pain. Since the patients are younger and fitter, there is a higher likelihood that the morbidity and longer sequelae of resectional surgery can significantly hamper their quality of life. So if a malignancy is reasonably excluded, there is a considerable drive to do conservative drainage operations or minimal resection to prolong the effects of drainage. Major resections are generally suggested only for proven malignancy or in recurrence after conservative surgery.

Fortunately, a pancreatic head resection can effectively palliate pain and other complications of chronic pancreatitis and should still be done, if there is at least a reasonable suspicion of malignancy. However this comes at a higher cost in terms of morbidity and occasional mortality and equipoise may be difficult to achieve! It is frequently argued in favour of resection, that in chronic pancreatitis, the risk of pancreatic fistula (the most dreaded complication) may be lower because of a firmer gland. Whilst it is certainly true that many series attest to this reduction in fistula rates, what is probably underreported is the higher morbidity of the resectional component of dense fibrotic adhesions to adjacent structures and in venous compression. The long-term outcome of treatment in this specific subset of patients of PC in CP is also unclear - while some suggest a uniformly bleak outcome in preoperatively diagnosed cancer, some contrary optimistic reports may tend to exaggerate the likely benefits. For instance, it is possible that many of the cures of resection are incidental and in patients without preoperative suspicions! A real world multicentre outcome report of a prospective cohort would help in clarifying this issue and in planning treatment strategy, especially in the borderline resectable where imaging suggests locally advanced disease! A peculiar conundrum exists in such patients who have minimal or no symptoms – their indication for surgery is solely the doubt of malignancy. If they are non-malignant, they don't need an operation, and if they are malignant, they are unlikely to be cured with one!

Additionally, it is unclear if a total pancreatectomy should always be done in confirmed cancers associated with pancreatitis, in view of the likely field change. This is also relevant, since islet cell harvesting and auto-transplantation is not a realistic option when malignancy is present.

Role of Screening, Surveillance and Prevention of Cancer in Patients with CP

In a meta-analysis conducted by Raimondi et al.[43] it was estimated that 5 % of patients with CP will develop PC over a 20-year period. This does not seem to justify screening. Additional confounders are a difficulty in confirming diagnosis, invasiveness and morbidity of a biopsy and the rather bleak outlook in the majority of patients with this malignancy. Yet efforts continue in this direction, since the disease tends to affect patients in the prime of their life and malignancy could be a common cause of mortality in CP.

Surveillance can be done in those with a higher potential for malignancy:

1. Radiological – especially if high risk lesions like IPMN especially with high grade dysplasia, previous pancreatic cancer, susceptible genetic conditions (HNPCC, Peutz Jeghers syndrome)

2. Cytogenetic - e.g., if PanIN-3 precursor lesions (pancreatic tail can be sampled in the radiologically suspicious case and a total pancreatectomy done if positive.
3. Biomarker positivity

Prevention – some risk factors are modifiable to (at least) delay the onset of PC in CP – cigarette smoking, obesity and Diabetes. The antidiabetic drug metformin has shown inhibition of experimental tumour induction, and its use is clinically associated with lower risk for pancreatic cancer. It could thus offer useful chemoprevention even in non-diabetics [17]

Is there a benefit from surgery in prevention? It sounds attractive to hypothesise that treatment of pancreatitis by reducing inflammation could delay oncogenesis! Indeed large cohorts of operated patients of chronic pancreatitis have NOT reported a higher postoperative incidence of cancer (apart from those cancers wrongly diagnosed as benign), even from groups reporting a high overall rate of malignancy. Whether this is a reporting bias, can only be known by prospective multi-center studies.

Conflict of Interest The authors declare that there is no conflict of interest

References

1. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andren-Sandberg A, Domellof L (1993) Pancreatitis and the risk of pancreatic cancer. International pancreatitis study group. N Engl J Med 328(20):1433–7
2. Ekbom A, McLaughlin JK, Nyren O (1993) Pancreatitis and the risk of pancreatic cancer. N Engl J Med 329(20):1502–3
3. Farrow B, Sugiyama Y, Chen A, Uffort E, Nealon W, Mark Evers B (2004) Inflammatory mechanisms contributing to pancreatic cancer development. Ann Surg 239(6):763–9, discussion 769-71
4. Balakrishnan V, Unnikrishnan AG, Thomas V, Choudhuri G, Veeraraju P, Singh SP, Garg P, Pai CG, Devi RN, Bhasin D, Jayanthi V, Premalatha N, Chacko A, Kar P, Rai RR, Rajan R, Subhalal N, Mehta R, Mishra SP, Dwivedi M, Vinayakumar KR, Jain AK, Biswas K, Mathai S, Varghese J, Ramesh H, Alexander T, Philip J, Raj VV, Vinodkumar A, Mukevar S, Sawant P, Nair P, Kumar H, Sudhindran S, Dhar P, Sudheer OV, Sundaram KR, Tantri BV, Singh D, Nath TR (2008) Chronic pancreatitis. A prospective nationwide study of 1,086 subjects from India. JOP 9(5):593–600
5. Mori M, Hariharan M, Anandakumar M, Tsutsumi M, Ishikawa O, Konishi Y et al (1999) A case control study on the risk factors for pancreatic diseases in Kerala, India. Hepatogastroenterology 46:25–3
6. Chari ST, Mohan V, Pitchumoni CS, Viswanathan M, Madanagopalan N, Lowenfels AB (1994) Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. Pancreas 9(1):62–6
7. Karlson BM, Ekbom A, Josefsson S, McLaughlin JK, Fraumeni JF Jr, Nyren O (1997) The risk of pancreatic cancer following pancreatitis: an association due to confounding? Gastroenterology 113(2): 587–92
8. Ekbom A, McLaughlin JK, Karlsson BM, Nyren O, Gridley G, Adami HO, Fraumeni JF Jr (1994) Pancreatitis and pancreatic cancer: a population-based study. J Natl Cancer Inst 86(8):625–7
9. Balakrishnan V, Nair P, Radhakrishnan L, Narayanan VA (2006) Tropical pancreatitis - a distinct entity, or merely a type of chronic pancreatitis? Indian J Gastroenterol 25(2):74–81
10. Augustine P, Ramesh H (1992) Is tropical pancreatitis premalignant? Am J Gastroenterol 87(8):1005–8
11. Yadav D, Lowenfels AB (2013) The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 144(6):1252–61
12. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, Truninger K, Ammann R, Cavallini G, Charnley RM, Uomo G, Delhaye M, Spicak J, Drumm B, Jansen J, Mountford R, Whitcomb DC, Neoptolemos JP, European Registry of Hereditary, and C. Pancreatic (2004) Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2(3):252–61
13. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, Silverman DT, Ji BT, Gallinger S, Holly EA, Fontham EH, Maisonneuve P, Bueno-de-Mesquita HB, Ghadirian P, Kurtz RC, Ludwig E, Yu H, Lowenfels AB, Seminara D, Petersen GM, La Vecchia C, Boffetta P (2012) Pancreatitis and pancreatic cancer risk: a pooled analysis in the international pancreatic cancer case-control consortium (PanC4). Ann Oncol 23(11):2964–70
14. Whitcomb D, Greer J (2009) Germ-line mutations, pancreatic inflammation, and pancreatic cancer. Clin Gastroenterol Hepatol 7(11 Suppl):S29–34
15. Greer JB, Whitcomb DC (2009) Inflammation and pancreatic cancer: an evidence-based review. Curr Opin Pharmacol 9(4):411–8
16. Kolodecik T, Shugrue C, Ashat M, Thrower EC (2013) Risk factors for pancreatic cancer: underlying mechanisms and potential targets. Front Physiol 4:415
17. Li D (2012) Diabetes and pancreatic cancer. Mol Carcinog 51(1):64–74
18. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D (2005) Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 294(22):2872–8
19. Fisher WE (2001) Diabetes: risk factor for the development of pancreatic cancer or manifestation of the disease? World J Surg 25(4): 503–8
20. Liao KF, Lai SW, Li CI, Chen WC (2012) Diabetes mellitus correlates with increased risk of pancreatic cancer: a population-based cohort study in Taiwan. J Gastroenterol Hepatol 27(4):709–13
21. Tod J, Jenei V, Thomas G, Fine D (2013) Tumor-stromal interactions in pancreatic cancer. Pancreatology 13(1):1–7
22. Andersen DK, Andren-Sandberg A, Duell EJ, Goggins M, Korc M, Petersen GM, Smith JP, Whitcomb DC (2013) Pancreatitis-diabetes-pancreatic cancer. Summary of an NIDDK-NCI workshop. Pancreas 42:1227–37
23. Gold EB, Cameron JL (1993) Chronic pancreatitis and pancreatic cancer. N Engl J Med 328(20):1485–6
24. Fernandez E, La Vecchia C, Porta M, Negri E, d'Avanzo B, Boyle P (1995) Pancreatitis and the risk of pancreatic cancer. Pancreas 11(2): 185–9
25. Chakraborty PP, Dutta D, Biswas K, Sanyal T, Ghosh S, Mukhopadhyay S, Chowdhury S (2012) Pancreatic carcinoma in fibrocalcific pancreatic diabetes: an eastern India perspective. Indian J Endocrinol Metab 16:S486–8
26. Sudhindran S, Krishnan P (2006) Early detection of malignancy in tropical pancreatitis – is it possible? In: Balakrishnan V (ed) Chronic pancreatitis and pancreatic diabetes in India. L.G. Creations, Bangalore, pp 364–70
27. Hariharan M, Subhalal N, Anandakumar M, Chellam VG, Iype S (2006) Chronic calcific pancreatitis of the tropics with carcinoma. In: Balakrishnan V (ed) Chronic pancreatitis and pancreatic diabetes in India. L.G. Creations, Bangalore, pp 147–54

28. Merdrignac A, Sulpice L, Rayar M, Rohou T, Quéhen E, Zamreek A, Boudjema K, Meunier B (2014) Pancreatic head cancer in patients with chronic pancreatitis. Hepatobiliary Pancreat Dis Int 13(2):192–197
29. Nouts A, Levy P, Voitot H, Bernades P (1998) Diagnostic value of serum Ca 19-9 antigen in chronic pancreatitis and pancreatic adenocarcinoma. Gastroenterol Clin Biol 22(2):152–9
30. Perumal S, Palaniappan R, Pillai SA, Velayutham V, Sathyanesan J (2013) Predictors of malignancy in chronic calcific pancreatitis with head mass. World J Gastrointest Surg 5(4):97–103
31. Bedi MM, Gandhi MD, Jacob G, Lekha V, Venugopal A, Ramesh H (2009) CA 19-9 to differentiate benign and malignant masses in chronic pancreatitis: is there any benefit? Indian J Gastroenterol 28(1):24–7
32. Sivarman A, Muthukrishnan A, Senguttvan NB, Suchak SA, Kannan U (2011) Predictors of malignancy in pancreatic head mass: a prospective study. Pan Afr Med J 9:30
33. Maire F, Micard S, Hammel P, Voitot H, Levy P, Cugnenc PH, Ruszniewski P, Puig PL (2002) Differential diagnosis between chronic pancreatitis and pancreatic cancer: value of the detection of KRAS2 mutations in circulating DNA. Br J Cancer 87(5):551–4
34. Liu J, Gao J, Du Y, Li Z, Ren Y, Gu J, Wang X, Gong Y, Wang W, Kong X (2012) Combination of plasma microRNAs with serum CA19-9 for early detection of pancreatic cancer. Int J Cancer 131(3):683–91
35. Pancreatic Cancer Action / Pancreatic Cancer / News / New blood test can "differentiate between pancreatic cancer and chronic pancreatitis". http://pancreaticcanceraction.org/news/blood-test-differentiate-pancreatic-cancer-chronic-pancreatitis. Accessed 12th June 2014.
36. Gold DV, Newsome G, Liu D, Goldenberg DM (2013) Mapping PAM4 (clivatuzumab), a monoclonal antibody in clinical trials for early detection and therapy of pancreatic ductal adenocarcinoma, to MUC5AC mucin. Mol Cancer 12:143
37. New markers shed light on pancreatic cancer. http://www.mayoclinic.org/medical-professionals/clinical-updates/digestive-diseases/new-markers-shed-light-on-pancreatic-cancer. Accessed 12th June 2014.
38. Yamada Y, Mori H, Matsumoto S, Kiyosue H, Hori Y, Hongo N (2010) Pancreatic adenocarcinoma versus chronic pancreatitis: differentiation with triple-phase helical CT. Abdom Imaging 35:163–71
39. Ma X, Zhao X, Ouyang H, Sun F, Zhang H, Zhou C (2013) Quantified ADC histogram analysis: a new method for differentiating mass-forming focal pancreatitis from pancreatic cancer. Acta Radiol. Oct 28
40. Dawwas MF, Tasha H, Leeds JS, Nayar MK, Oppong KW (2012) Diagnostic accuracy of quantitative EUS elastography for discriminating malignant from benign solid pancreatic masses: a prospective, single-center study. Gastrointest Endosc 76:953–61
41. Santhosh S, Mittal BR, Bhasin D, Srinivasan R, Rana S, Das A, Nada R, Bhattacharya A, Gupta R, Kapoor R (2013) Role of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in the characterization of pancreatic masses: experience from tropics. J Gastroenterol Hepatol 28:255–61
42. Rijkers AP, Valkema R, Duivenvoorden HJ, van Eijck CH (2014) Usefulness of F-18-fluorodeoxyglucose positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. Eur J Surg Oncol 40:794–804
43. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R (2010) Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol 24(3):349–58