World Journal of Gastrointestinal Pathophysiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4291/wjgp.v6.i2.29

World J Gastrointest Pathophysiol 2015 May 15; 6(2): 29-32
ISSN 2150-5330 (online)

EDITORIAL

Cystic tumors of the pancreas: Opportunities and risks

Marco Del Chiaro, Caroline Verbeke

Marco Del Chiaro, Pancreatic Surgery Unit, Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institute at Center for Digestive Diseases, Karolinska University Hospital, 14186 Stockholm, Sweden
Caroline Verbeke, Department of Pathology, Institute of Clinical Medicine, University of Oslo, 0316 Oslo, Norway
Caroline Verbeke, Department of Pathology, Karolinska Institute, 14186 Stockholm, Sweden
Author contributions: Del Chiaro M and Verbeke C equally contributed to this paper.
Conflict-of-interest: None.

Correspondence to: Marco Del Chiaro, MD, PhD, FACS, Associate Professor of Surgery, Head of Pancreatic Surgery Unit, Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institute at Center for Digestive Diseases, Karolinska University Hospital, K53, 14186 Stockholm, Sweden. marco.del.chiaro@ki.se
Telephone: +46-8-58580000
Fax: +46-8-58586366
Received: January 18, 2015
Peer-review started: January 20, 2015
First decision: February 7, 2015
Revised: February 21, 2015
Accepted: March 16, 2015
Article in press: March 18, 2015
Published online: May 15, 2015

Abstract

Pancreatic cystic neoplasms (PCNs) are a high prevalence disease. It is estimated that about 20% of the general population is affected by PCNs. Some of those lesions can progress till cancer, while others behave in a benign fashion. In particular intraductal papillary mucinous neoplasms of the pancreas can be considered as the pancreatic analogon to colonic polyps. Treatment of these precursor lesions at an early stage can potentially reduce pancreas cancer mortality and introduce a new "era" of preemptive pancreatic surgery. However, only few of those lesions have an aggressive behavior. The accuracy of preoperative diagnosis, *i.e.*, the distinction between the various PCNs is around 60%, and the ability to predict the future outcome is also less accurate. For this reason, a significant number of patients are currently over-treated with an unnecessary, high-risk surgery. Furthermore, the majority of patients with PCN are on life-long follow-up with imaging modality, which has huge cost implications for the Health Care System for limited benefits considering that a significant proportion of PCNs are or behave like benign lesions. The current guidelines for the diagnosis and management of PCNs are more based on expert opinion than on evidence. For all those reasons, the management of cystic tumors of the pancreas remains a controversial area of pancreatology. On one hand, the detection of PCNs and the surgical treatment of pre-cancerous neoplasms can be considered a big opportunity to reduce pancreatic cancer related mortality. On the other hand, PCNs are associated with a considerable risk of under- or over- treatment of patients and incur high costs for the Health Care System.

Key words: Pancreatic cystic neoplasms; Mucinous cystic neoplasia; Preemptive pancreatic surgery; Pancreas; Intraductal papillary mucinous neoplasia

Core tip: The present paper is an editorial focused on the critical problems regarding the management strategy of pancreatic cystic neoplasms (PCNs). Being a pre-cancerous condition in most of the cases, PCNs represent a unique opportunity to prevent pancreatic cancer and to develop preemptive pancreatic surgery programs. However, the lack of predictive factors of the behaviour of these lesions, the low accuracy of

pre-operative diagnostics, and the limited knowledge regarding the natural history of those lesions, result in a substantial risk for under- and over-treatment of patients with PCN and represent a high cost factor for the Health Care organization. The paper underscores the critical importance of both the current management of PCNs and the need for future research.

Del Chiaro M, Verbeke C. Cystic tumors of the pancreas: Opportunities and risks. *World J Gastrointest Pathophysiol* 2015; 6(2): 29-32 Available from: URL: http://www.wjgnet.com/2150-5330/full/v6/i2/29.htm DOI: http://dx.doi.org/10.4291/wjgp.v6.i2.29

EDITORIAL

Pancreatic cystic neoplasms (PCNs) represent disease with a high prevalence. Recent series report an overall prevalence of 20%[1,2], whereby the majority of these neoplasms are discovered incidentally. The most frequent PCNs are represented by three distinct tumor entities: Intraductal papillary mucinous neoplasia (IPMN), mucinous cystic neoplasia (MCN) and serous cystic neoplasia (SCN). The first two neoplastic entities can progress to cancer, whereas SCN is almost always benign.

The progression model of mucinous neoplasms, in particular of IPMN, is very similar to that of colonic polyps. The latter neoplasms can progress from a benign and non-invasive adenoma with mild dysplasia through stages with increasing grades of dysplasia and eventually transform into invasive cancer[3]. For this reason, PCNs, and in particular IPMNs, offer today an extraordinary opportunity to detect pancreatic cancer progression and perform preemptive pancreatic surgery[4].

PCNs are easy detectable with conventional and commonly used abdominal imaging modalities, *i.e.*, computed tomography, magnetic resonance and ultrasonography. They are frequently discovered at an early, often asymptomatic stage. Of particular interest is the fact that IPMNs are significantly more common in the subpopulation of patients that are at increased risk for pancreatic cancer, such as individuals with a positive family history[5]. Furthermore, data from the literature suggest that IPMN of the pancreas can be associated with an increased risk of extrapancreatic malignancies[6], hence their diagnosis can prompt the investigation and early detection of tumors in other organs. However, a recent multicentre study analyzing the incidence of extrapancreatic malignancies in IPMN patients seems to question this association[7].

In clinical practice, the concept that PCNs may be considered as the pancreatic analogon to colonic polyps, *i.e.*, lesions suitable for preemptive surgery and cancer prevention, presents with many difficulties and potential risks.

First of all, considering the low incidence of pancreatic cancer in the general population, it is obvious that only few of the PCNs really progress to invasive carcinoma. It is estimated that only about 24% of all resected BD-IPMNs are malignant[8]. In a recent series of 90 consecutive resected MCNs of the pancreas, only 4.4% were associated with invasive carcinoma[9]. The risk of progression to cancer is shown to be only 1.4% following 5 years' surveillance of non-resected BD-IPMN[10]. The accuracy of pre-operative diagnosis remains poor, also in highly specialized tertiary referral centers. It is estimated that for PCNs the pre-operative diagnostic is around 63%, however, erroneous diagnosis has a clinical impact (for example unnecessary surgery) in only 8.5% of the cases[11]. Several recent studies demonstrate that even with the use of fine needle aspiration (FNA) during endoscopic ultrasound, the accuracy of the pre-operative diagnostic work-up does not significantly increase[11]. The sensitivity of FNA cytology is around 38%[12], while combined biochemistry and cytology provides a correct diagnosis in only 33%[13,14]. For this reason, there is a concrete danger of over- or under-estimation of the risk of malignant transformation in some lesions and, as a consequence, of over- or under-treatment of the patients. New diagnostic approaches based on molecular and genetic analysis of the cystic fluid seem to be promising for the future, but are not yet extensively used in clinical practice[15,16].

Unfortunately, this lack of accurate diagnostic modalities results for the majority of patients with PCNs in the need of frequent, expensive and life-long radiologic assessment.

In recent years, two new guidelines partially changed the management of patients with PCNs[8,17]. Even though both are similar in many aspects, there are also some significant differences. Limiting our attention to the treatment of IPMN and MCN, it can be said that the European Guidelines are less aggressive from a surgical point of view, and that they suggest a less aggressive surveillance program for patients who are not a candidate for resection. Of note, both guidelines are mostly based on expert opinion and - by default - founded on only a very low grade of evidence.

Today we know that IPMNs with involvement of main pancreatic duct (main-duct and mixed type) are associated with an increased cancer risk[8,17], and for this reason these tumors should be resected in every patient fit for surgery. However, the surgical approach and extent of resection is not well defined. In the near future, new endoscopic methods, such as pancreatoscopy, may possibly change our clinical practice[18]. The clinical decision process is also complex for patients with PCNs that do no involve the main pancreatic duct. IPMNs involving only the branch ducts are difficult to handle. The risk for cancer is lower than for main-duct or mixed type IPMN, and according to large studies the incidence of cancer during follow-

up seems to be very low[10]. If there are multiple lesions, the diagnosis of IPMN is likely, and the current guidelines for the management of these patients seem to be safe. More challenging is the diagnosis of a single cystic lesion, as it may prove difficult to confidently exclude a series of differentials. For this reason, some authors suggested enucleation of these lesions as a combined diagnostic and therapeutic option in selected cases[19,20]. Currently, in absence of risk factors for malignancy and/or worrisome features on radiological assessment, cystic lesions of the pancreas (IPMN and MCN) can be conservatively treated as long as the diameter does not exceed 4 cm[17]. The timing of follow-up remains controversial, but considering that the cancer risk gradually increases over time, a more aggressive follow-up can be suggested after 5 years since initial diagnosis[17]. However, the majority of these patients remain nowadays under life-long follow-up with imaging modalities. Considering the prevalence of these neoplasms, it is obvious that patient surveillance represents a tremendous cost factor for the health care system. In view of the low rate of progression to cancer, the current follow-up approach is probably not cost effective.

In conclusion, PCNs offer today the only opportunity to reduce in the short to medium term the mortality related to pancreatic cancer. However, to realize this, we have to overcome obstacles and improve our current results. First and foremost, we need more accurate diagnostic tools in order to make a correct pre-operative diagnosis and overcome the problems of patient over-treatment and surgery-related mortality and morbidity. We need new markers that reliably predict the progression of PCN to cancer, such that the indication for surgical treatment or follow-up can be tailored to the cancer risk in the individual patient. Less costly imaging modalities that are suitable for surveillance of large patient populations are urgently needed. Only when progress regarding these important issues has been achieved, may an effective preemptive surgical program for pancreatic cancer come into realization, which will require minimally invasive techniques performed at highly specialized centers[21].

REFERENCES

1 **Laffan TA**, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, Johnson PT, Fishman EK, Hruban RH. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008; **191**: 802-807 [PMID: 18716113 DOI: 10.2214/AJR.07.3340]

2 **Zhang XM**, Mitchell DG, Dohke M, Holland GA, Parker L. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. *Radiology* 2002; **223**: 547-553 [PMID: 11997566 DOI: 10.1148/radiol.2232010815]

3 **Shi C**, Hruban RH. Intraductal papillary mucinous neoplasm. *Hum Pathol* 2012; **43**: 1-16 [PMID: 21777948 DOI: 10.1016/j.humpath.2011.04.003]

4 **Del Chiaro M**, Segersvärd R, Lohr M, Verbeke C. Early detection and prevention of pancreatic cancer: is it really possible today? *World J Gastroenterol* 2014; **20**: 12118-12131 [PMID: 25232247 DOI: 10.3748/wjg.v20.i34.12118]

5 **Brune K**, Abe T, Canto M, O'Malley L, Klein AP, Maitra A, Volkan Adsay N, Fishman EK, Cameron JL, Yeo CJ, Kern SE, Goggins M, Hruban RH. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. *Am J Surg Pathol* 2006; **30**: 1067-1076 [PMID: 16931950]

6 **Larghi A**, Panic N, Capurso G, Leoncini E, Arzani D, Salvia R, Del Chiaro M, Frulloni L, Arcidiacono PG, Zerbi A, Manta R, Fabbri C, Ventrucci M, Tarantino I, Piciucchi M, Carnuccio A, Boggi U, Costamagna G, Delle Fave G, Pezzilli R, Bassi C, Bulajic M, Ricciardi W, Boccia S. Prevalence and risk factors of extrapancreatic malignancies in a large cohort of patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas. *Ann Oncol* 2013; **24**: 1907-1911 [PMID: 23676419 DOI: 10.1093/annonc/mdt184]

7 **Marchegiani G,** Malleo G, D'Haese JG, Wenzel P, Keskin M, Pugliese L, Borin A, Benning V, Nilsson L, Oruc N, Segersvärd R, Friess H, Schmid R, Löhr M, Maisonneuve P, Bassi C, Ceyhan GO, Salvia R, Del Chiaro M. Association Between Pancreatic Intraductal Papillary Mucinous Neoplasms and Extrapancreatic Malignancies. *Clin Gastroenterol Hepatol* 2014 Dec 2; Epub ahead of print [PMID: 25478920 DOI: 10.1016/j.cgh.2014.11.029]

8 **Tanaka M**, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012; **12**: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]

9 **Park JW**, Jang JY, Kang MJ, Kwon W, Chang YR, Kim SW. Mucinous cystic neoplasm of the pancreas: is surgical resection recommended for all surgically fit patients? *Pancreatology* 2014; **14**: 131-136 [PMID: 24650968 DOI: 10.1016/j.pan.2013.12.006]

10 **Malleo G**, Marchegiani G, Borin A, Capelli P, Accordini F, Butturini G, Pederzoli P, Bassi C, Salvia R. Observational Study of the Incidence of Pancreatic and Extrapancreatic Malignancies During Surveillance of Patients With Branch-Duct Intraductal Papillary Mucinous Neoplasm. *Ann Surg* 2015; **261**: 984-990 [PMID: 25493361]

11 **Del Chiaro M**, Segersvärd R, Pozzi Mucelli R, Rangelova E, Kartalis N, Ansorge C, Arnelo U, Blomberg J, Löhr M, Verbeke C. Comparison of preoperative conference-based diagnosis with histology of cystic tumors of the pancreas. *Ann Surg Oncol* 2014; **21**: 1539-1544 [PMID: 24385209 DOI: 10.1245/s10434-013-3465-9]

12 **Cizginer S**, Turner BG, Bilge AR, Karaca C, Pitman MB, Brugge WR. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. *Pancreas* 2011; **40**: 1024-1028 [PMID: 21775920 DOI: 10.1097/MPA.0b013e31821bd62f]

13 **de Jong K**, Poley JW, van Hooft JE, Visser M, Bruno MJ, Fockens P. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cystic lesions provides inadequate material for cytology and laboratory analysis: initial results from a prospective study. *Endoscopy* 2011; **43**: 585-590 [PMID: 21611945 DOI: 10.1055/s-0030-1256440]

14 **Jabbar KS**, Verbeke C, Hyltander AG, Sjövall H, Hansson GC, Sadik R. Proteomic mucin profiling for the identification of cystic precursors of pancreatic cancer. *J Natl Cancer Inst* 2014; **106**: djt439 [PMID: 24523528 DOI: 10.1093/jnci/djt439]

15 **Al-Haddad MA**, Kowalski T, Siddiqui A, Mertz HR, Mallat D, Haddad N, Malhotra N, Sadowski B, Lybik MJ, Patel SN, Okoh E, Rosenkranz L, Karasik M, Golioto M, Linder J, Catalano MF. Integrated molecular pathology accurately determines the malignant potential of pancreatic cysts. *Endoscopy* 2015; **47**: 136-146 [PMID: 25314329 DOI: 10.1055/s-0034-1390742]

16 **Kung JS**, Lopez OA, McCoy EE, Reicher S, Eysselein VE. Fluid genetic analyses predict the biological behavior of pancreatic cysts: three-year experience. *JOP* 2014; **15**: 427-432 [PMID: 25262708 DOI: 10.6092/1590-8577/2426]

17 **Del Chiaro M**, Verbeke C, Salvia R, Klöppel G, Werner J, McKay C, Friess H, Manfredi R, Van Cutsem E, Löhr M, Segersvärd R. European experts consensus statement on cystic tumours of the pancreas. *Dig Liver Dis* 2013; **45**: 703-711 [PMID: 23415799 DOI: 10.1016/j.dld.2013.01.010]

18 **Arnelo U**, Siiki A, Swahn F, Segersvärd R, Enochsson L, del

Chiaro M, Lundell L, Verbeke CS, Löhr JM. Single-operator pancreatoscopy is helpful in the evaluation of suspected intraductal papillary mucinous neoplasms (IPMN). *Pancreatology* 2014; **14**: 510-514 [PMID: 25287157 DOI: 10.1016/j.pan.2014.08.007]

19 **Del Chiaro M**, Albiin N, Segersvärd R. Enucleation of branch duct-IPMN in a transplant patient. *Pancreatology* 2013; **13**: 312-313 [PMID: 23858563]

20 **Fritz S**, Klauss M, Bergmann F, Hackert T, Hartwig W, Strobel O, Bundy BD, Büchler MW, Werner J. Small (Sendai negative) branch-duct IPMNs: not harmless. *Ann Surg* 2012; **256**: 313-320 [PMID: 22791105 DOI: 10.1097/SLA.0b013e31825d355f]

21 **Del Chiaro M**, Segersvärd R. The state of the art of robotic pancreatectomy. *Biomed Res Int* 2014; **2014**: 920492 [PMID: 24982913 DOI: 10.1155/2014/920492]

P- Reviewer: Eysselein VE, Guo XZ, Sumi S **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com