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Editorial

Diagnosis of early pancreatic cancer

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Pancreatic cancer has one of the poorest prognoses of all gastrointestinal malignancies. About 8-12 per 100.000 individuals develop ductal adenocarcinoma each year and the vast majority of these will have a median survival of 6 months, with less than 10% of patients being alive after 12 months and an overall 5 year survival rate of almost zero[1]. With this cancer, mortality almost equals incidence.

Chemotherapy and radiotherapy have failed so far to improve survival, leaving surgical resection at an early stage as the only treatment that can offer a possibility of cure. Pancreatic surgery has made considerable technical progress during the last decade, mostly as a consequence of greater subspecialisation and better postoperative intensive care. In experienced centres, mortality rates are now less than 5% and from the technical point of view, even locally advanced tumors can now be safely removed[2]. Despite technical advances, improvement in long-term survival after pancreatic resection for cancer is less obvious and a 5-year overall survival rate remains about 10%[2,3]. Most of the patients who undergo potentially curative resection will die within the first two postoperative years due to local recurrence or distant metastasis.

There are two reasons for the small progress in survival of patients suffering from pancreatic adenocarcinoma. One is the lack of symptoms in early stage tumors, which makes early diagnosis a wishful dream. The second and even more important reason is that pancreatic cancer is characterized by extremely aggressive biological behavior with an intense propensity to spread locally and metastasize distally. Thus, even very small tumors may already have positive lymph nodes.

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Although the reasons for this aggressive biological behavior are not yet clearly established, it seems that pancreatic cancer has the unique characteristic of carrying a number of genetic abnormalities that directly promote cancer cells proliferation and enhance tumor cell invasiveness and metastasis formation. These include inactivation of the tumor suppressor gene p16, which is followed by the inactivation of p53 and DPC4 tumor suppressor genes[4]. Activation of the K-ras oncogene is found in most pancreatic carcinomas and appears to be an early event in the process of carcinogenesis[5]. Furthermore, pancreatic cancer is characterized by the increased expression of various growth factors and their receptors, which confer a distinct growth advantage to cancer cells[6].

Today we know that pancreatic adenocarcinoma, similar to other cancers, arises from precursor ductal epithelial lesions also known as pancreatic intraductal neoplasia (PanIN). PanIN has the same genetic alterations found in cancer. A standard classification system has recently been established, according to which Pan IN is divided into 3 grades: Pan IN I is intraepithelial ductal hyperplasia, Pan IN II is low-grade dysplasia and Pan IN III is high-grade dysplasia or carcinoma in situ[7]. The exact process, as well as the latent period for the development of cancer, is largely unknown.

Based on the above, the term "early pancreatic cancer" includes the carcinoma in situ (Pan IN grade III) and very small tumors (<1cm in diameter) with no lymph node metastasis.

It is obvious that the detection of pancreatic cancer at this stage is possible only after the application of a screening methodology. Currently there is no effective strategy applicable to the general population or even to those at increased risk. No reliable tumor marker has proved to be useful for screening purposes, due to poor specificity and sensitivity. Recently evaluated molecular markers such as K-ras gene mutations in the pancreatic

juice are not suitable as a single diagnostic marker as they lack specificity for cancer[8]. The screening modalities available at the moment are actually the imaging examinations that are used for diagnosis, namely EUS, ERCP, CT, MRCP/MRI, which are neither sensitive nor specific enough for the diagnosis of dysplasia or tumors less than 1 cm.

A number of hereditary cancer syndromes have been identified and screening strategies targeted at high risk individuals are under evaluation. It is estimated that 5%-15% of patients with pancreatic cancer may have an inherited predisposition to develop the disease and the lifetime risk of pancreatic cancer in some individuals may approach 50%. Secondary screening came up as a need to ease the fears of cancer that members of families with inherited predisposition to pancreatic cancer often experience. In all cases, screening strategies should weigh the increased risk of cancer derived from that particular syndrome against the potential morbidity, the inconvenience and the cost associated with screening.

Over the last years, centres in Europe and USA have started to enroll high-risk family members in an annual clinical screening programme[9-13]. Most of the centers use EUS or MRI/MRCP as the first-line imaging procedures leaving ERCP and CT for the individuals who have abnormal findings on their initial tests or have symptoms. So far, a number of family members were identified as having dysplastic changes and proceeded to pancreatectomy. Follow-up of these patients now extends up to 4 years in some patients and all remain free of cancer. It is, of course, very early to draw any firm conclusions about the benefits of secondary screening strategies in high-risk individuals but definitely they offer the best potential for early detection of pancreatic cancer and its precursor lesions. Moreover, the detailed study of such cases will increase understanding on pancreatic carcinogenesis and improve the diagnosis of the much more common sporadic pancreatic cancer. Advances in the understanding of the molecular alterations in pancreatic cancer will lead to the development of new diagnostic tests and, hopefully, will provide the basis for a molecular screening programme.

REFERENCES

1. Andren-Sandberg A, Backman PL. Demography and Epidemiology of pancreatic cancer in: Pancreatic Tumors, achievements and prospective. Edited by by Dervenis and Bassi, G. Thieme Verlag, Stuttgart 2000; 16-26.
2. Di Magno EP, Reber HA., Tempero MA. American Gastroenterological Association: Technical review on the epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. Gastroenterology 1999; 117:1463-1484.
3. Jonson C. Prognosis in pancreatic cancer. Lancet 1997; 349:1027-1028.
4. Hruban RH, Iacobuzio-Donahue C, Wilentz Re, *et al*. Molecular pathology of pancreatic cancer. Cancer J 2001; 7:1-23.
5. Scarpa A, Moore PS, Rigaud G, Zamboni G. Genetic anomalies of Pancreatic cancer in Pancreatic Tumors, achievements and prospective. Edited by by Dervenis and Bassi, G. Thieme Verlag, Stuttgart 2000; 37-49.
6. Kleeff J, Friess H, Korck M, Buchler M. The role of growth factors and growth factor receptors in pancreatic cancer. In Pancreatic Tumors, achievements and prospective. Edited by by Dervenis and Bassi, G. Thieme Verlag, Stuttgart 2000; 50-62.
7. Hurban RH, Adsay NV, Albores-Saavedra J, *et al*. Pancreatic intraepithelial neoplasia. A new nomenclature and classification system for pancreatic duct lesions. Am J Surg Pathol 2001; 25:579-586.
8. Matsumoto S, Harada H, Tanaka J, *et al*. Evaluation of cytology and tumor markers of pure pancreatic juice for the diagnosis of pancreatic cancer at early stages. Pancreas 1994; 6:741-747.
9. Rulyak SJ, Brentnall TA. Inherited pancreatic cancer: surveillance and treatment strategies for affected families. Pancreatology 2001; 1:477-485.
10. Howes N, Greenhalf W, Neoptolemos J. Screening for early pancreatic ductal adenocarcinoma in hereditary pancreatitis. Med Clin N Am 2000; 84(3):719-738
11. Lynch HT, Brand RE, Deter CA, *et al*. Hereditary pancreatic cancer. Pancreatology 2001; 1:466-471.
12. Ellis I, Lerch MM, Whitcomb DC. Genetic testing for hereditary pancreatitis: Guidlines for indications, counseling, consent and privacy issues Pancreatology 2001; 1:405-415.
13. Applebaum SE, Kant JA, Whitcomb DC. Genetic testing: counseling, laboratory and regulatory issues and the EUROPAC protocol for ethical research in multicenter studies of inherited pancreatic diseases. Med Clin N Am 2000; 84(3):575-588.