Surveillance in individuals at high risk of pancreatic cancer: too early to tell?

Harinck, F.; Canto, M.I.; Schulick, R.; Goggins, M.; Poley, J.W.; Fockens, P.; Kluijt, I.; Bruno, M.

DOI
10.1136/gut.2009.197004

Publication date
2010

Document Version
Final published version

Published in
Gut

We describe our experience of successfully deploying a wireless capsule endoscope (Pillcam, Yoqnean, Israel) in five instances of gastric retention encountered during 205 procedures performed from October 2006 to September 2009. All patients followed standard instructions as suggested by the manufacturers. Individuals with previous history of gastric retention of at least one capsule were included in the study. Written informed consent was obtained from all patients. Endoscopic duodenal deployment was required in five instances, including two patients with suspected Crohn's disease and another 28-year-old female patient who required WCE on three different occasions for recurrent significant anaemia and associated persistently positive faecal occult blood test. In this patient, initial WCE failed due to excessive bowel secretions, the second examination produced poor quality images due to frothy bilious secretions, while the third examination was conducted with prior administration of simethicone suspension and achieved good visualisation. This patient also underwent double-balloon enteroscopy and mesenteric angiography, both being non-contributory.

All patients swallowed the capsule just prior to an oesophagogastroduodenoscopy under conscious sedation using midazolam. The swallowed capsule was identified in the stomach and was captured using the polyp retrieval net (RothNet-Polyp, Mentor, OH, USA, net diameter 3 cm, shaft diameter 2.5 mm) passed down the scope and advanced to the duodenum. Our modified technique involved performing 3–4 moderately forceful 'to-and-fro' movements of the polyp basket net towards the tip of the scope before finally pulling it out. This manoeuvre led to easy breakdown of the net threads without any difficulty, and resultant release of the capsule in the desired location. During these procedures we did not encounter any mechanical or traumatic complications. In all the patients, the capsule subsequently passed to the caecum. Using this slightly modified technique we avoided the potential complications described with the use of an over tube and the use of argon plasma coagulation for cutting the threads of the retrieval basket.[4]

In conclusion, this simple modified technique for the direct duodenal deployment of WCE appears safe and does not influence the video quality of the procedure. This technique, however, needs further evaluation from larger cohorts.

Asghar Qasim, Barbara Ryan, Niall Breslin, Colm O'Morain

Adelaide and Meath Hospital, Trinity College Dublin, Ireland

Correspondence to Dr Asghar Qasim, Adelaide and Meath Hospital, Trinity College Dublin, Ireland; qasima@tcd.ie

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Gut 2010;**59**:1004–1005. doi:10.1136/gut.2009.201665

REFERENCES

1. **Fritscher-Ravens A,** Scherbakov P, Bufler P, *et al*. The feasibility of wireless capsule endoscopy in detecting small intestinal pathology in children under the age of 8 years: a multicentre European study. *Gut* 2009;**58**:1467–72.
2. **Ben-Soussan E,** Savoye G, Antonietti M, *et al*. Factors that affect gastric passage of video capsule. *Gastrointest Endosc* 2005;**62**:785–90.
3. **Carey EJ,** Heigh RI, Fleischer DE. Endoscopic capsule endoscope delivery for patients with dysphagia, anatomical abnormalities, or gastroparesis. *Gastrointest Endosc* 2004;**59**:423–6.
4. **Carr-Locke DL,** Al-Kawas FH, Branch MS, *et al*. Overtube use in gastrointestinal endoscopy. *Gastrointest Endosc* 1996;**43**:767–70.

Authors' response

We thank Qasim *et al* for their contribution.[1] They comment and report on the few cases in adults, in which endoscopic capsule insertion into the duodenum is necessary in 5of 205 patients in their letter.

The problems with trauma to the gut mucosa using the Roth net are certainly encountered in children as well as adults. However, the problems in children are much more marked as the entrance to the oesophagus as well as the pylorus and duodenal lumen are considerably smaller in diameter when compared with adults, resulting in rather obvious difficulties to expel any contents out of the Roth net.

We do not believe that the technique the authors use does indeed differ from our or other experienced examiners' procedure. Usage of the Roth net included to and fro movements to expel the contents on a routine basis. However, the actual reason for the difficulty with this device in small children is the smaller lumen of the small bowel in a 4 year old, which we reported in our paper. In some cases, to and fro movements and even relocation of the capsule into a different area of the basket did not reduce the difficulty in expelling it as opening the basket in this small space proved difficult and was sometimes very hard to achieve. In small children as we showed in our study the 'acorn' type of introducer whether commercially made (Advance ® Introducer, US Endoscopy, Mentor, Ohio, USA) or custom made was much easier to use with little or no trauma to the mucosa as no to and fro movements are necessary and the device has no sharp edges.

Annette Fritscher-Ravens and Peter Milla for the European Paediatric Capsule Study Group.

Annette Fritscher-Ravens,[1] Peter Milla[2]

[1]European Paediatric Capsule Study Group, Homerton University Hospital, London, UK; [2]European Paediatric Capsule Study Group, UCL Institute of Child Health London, UK

Correspondence to Annette Fritscher-Ravens, Department of Gastroenterology, Homerton University Hospital, Homerton Row, London E9 6SR, UK; fri.rav@btopenworld.com

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Gut 2010;**59**:1005. doi:10.1136/gut.2009.206169

REFERENCE

1. **Quasim A,** Ryan B, Breslin N, *et al*. Gastric retention and wireless capsule endoscopy in adults: a modified technique for direct duodenal deployment. *Gut* 2010;**59**:1004–5.

Surveillance in individuals at high risk of pancreatic cancer: too early to tell?

We have read with great interest the publication by Langer *et al*.[1] Pancreatic cancer surveillance of high-risk individuals may have the potential to alter the dismal prognosis of this deadly disease. Although promising, its application is a learning experience and results of pancreatic cancer surveillance studies are eagerly awaited. Although we greatly value the efforts of Langer *et al* we have some comments and questions.

The title of their paper suggests a prospective cohort study with a median follow-up observation period of 5 years. Indeed, the time period in which individuals were included was 5 (and a half) years (between June 2002 and December 2007). However, as we read from the manuscript, the median number of examination visits was 2 (range 1–7), maximally 1 year apart. This is almost similar to a cross-sectional design type of study. Both endoscopic ultrasound (EUS) and MRI were part of the programme, but while 329 MRIs were performed, only 167 EUS investigations were reported. Could the authors clarify these issues to help us understand the median observation time per patient, the median number of MRI and EUS examinations per patient, as well as overall follow-up in patient-years?

The diagnostic yield of screening among 76 individuals was 1.3%, which is much lower than that in an EUS–CT based surveillance programme from the USA[2] (pathologically confirmed neoplasms 10%) and an EUS based surveillance programme from the Netherlands[3] (asymptomatic cancer 6.8%, IPMN (Intraductal Papillary Mucinous Neoplasms)-like lesions 15.9%). This difference might be related to differences in the patient populations; the majority of the individuals included (58%) by Langer *et al* were at moderate risk. In addition, one might question whether some

of the included melanoma–pancreatic cancer syndrome families were even at moderate risk, since they were non-carriers of the CDKN2A mutation. Was mutation analysis obligatory or only offered in families suspected to carry an inherited tumour syndrome? If the former is true, it might be that 50% of those individuals included were not at increased risk of pancreatic cancer.

The yield in the Langer *et al* study was based on the prevalence of neoplasia in patients who had surgery at their institution. Could the authors provide us with additional information regarding the number of individuals who are under close surveillance because of the detection of a potentially premalignant lesion that did not (yet) meet surgical criteria? Moreover, EUS examinations were done by a single very experienced endosonographist. Were EUS investigations and abnormalities photographed or videotaped and reassessed and confirmed by other observers?

In the abstract conclusion, it is stated that the enormous psychological stress for the tested individual should be one of the considerations that pancreatic cancer screening is not justified. We do not agree per se. The issue of psychological stress applies to all types of cancer screening and surveillance programmes. This does not withhold us from running these programmes to prevent cancer deaths. Was the level of psychological stress studied by Langer *et al* and can they provide additional data to substantiate their statement?

Before any definite conclusion can be drawn about the true value of any screening and surveillance programme in individuals at high risk for pancreatic cancer, we need to better understand the spectrum and nature of pancreatic parenchymal and ductal changes, their natural development and progression, and most importantly, their clinical relevance. For this a prospective cohort study including truly high-risk individuals involving an observation period of at least several years is required.

While we do not agree with the conclusion, based on the presented data, that general pancreatic cancer screening in high-risk individuals is not justified, we fully agree with Langer *et al* that any effort in pancreatic cancer screening should only be performed in the setting of board approved, prospective controlled long-term studies with a scientific evaluation to validate the safety and diagnostic accuracy of the screening strategy.

Femme Harinck,[1] Marcia Irene Canto,[2,*,§] Richard Schulick,[2,§,±] Michael Goggins,[2,*,¶,§] Jan-Werner Poley,[1] Paul Fockens,[3] Irma Kluijt,[4] Marco Bruno[1]

[1]Department of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands; [2]Departments of *Medicine (Gastroenterology), ¶Pathology, §Oncology and, ±Surgery, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA; [3]Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, the Netherlands; [4]Family Cancer Clinic, Netherlands Cancer Institute, Amsterdam, the Netherlands

Correspondence to M J Bruno, Department of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, 's Gravendijkwal 230, Rotterdam 3015 CE, the Netherlands; m.bruno@erasmusmc.nl

Contributions by Femme Harinck, Jan-Werner Poley, Paul Fockens, Irma Kluijt, and Marco Bruno are on behalf of the Dutch research group of pancreatic cancer screening in high-risk individuals. Contributions by Marcia Irene Canto, Richard Schulick, and Michael Goggins are on behalf of the Johns Hopkins multidisciplinary pancreatic cancer screening group and Sol Goldman Pancreatic Cancer Center.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Gut 2010;**59**:1005–1006. doi:10.1136/gut.2009.197004

REFERENCES

1. **Langer P,** Kann PH, Fendrich V, *et al*. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut* 2009;**58**:1410–18.
2. **Canto MI,** Goggins M, Hruban RH, *et al*. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol* 2006;**4**:766–81; quiz 665.
3. **Poley JW,** Kluijt I, Gouma DJ, *et al*. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol* 2009;**104**:2175–81.

Authors' response

We read with interest the letter by Harinck *et al*[1] as a response to our paper[2] and are grateful for the opportunity to respond.

Harinck *et al* offer the criticism that the trial was not prospective as suggested by the title of our paper and the median number of examination visits was only two, with a maximum of 1 year apart. As described in our paper this was a peer-reviewed, board-approved trial that was designed as a prospective study for a period of at least 10 years in cooperation with the Institute of Biometry and Epidemiology of the Philipps-University Marburg. Since the study is still ongoing the number of screened individuals at risk (IAR) is continually increasing. The median number of MRI per patient was 4 (2–12) and of endoscopic ultrasonography (EUS) examinations 2 (1–7), maximally 4.5 years but not 1 year apart. The median observation time per patient was 24 (1–66) months, and the overall follow-up was 152 patient years, respectively. As stated in detail in the methods section every IAR received examinations with two different types of MRI techniques per visit, which explains the different numbers of investigations.

Harinck *et al* suggest that our low diagnostic yield (1.3%) compared to the studies by Canto *et al* (10%,[3]) and Poley *et al* (23.7%,[4]) is among other reasons related to different patient populations. Indeed the number of high risk individuals (>10-fold,[5]) was 45/78 in the Canto study compared to 33/76 in our cohort. Nevertheless, it is unlikely that this was the only reason for the lower yield in our study. The yield of the Canto study[3] is an over-estimation when employing the criteria used in our study, since two patients with PanIN 1–2 lesions, which are not unequivocal precancerous lesions, were as well included when calculating the yield. The cited Dutch study[4] reported the results of a first and one time only screening of 44 IAR, of whom 15.9% had only an EUS diagnosis of intraductal papillary mucinous neoplasm (IPMN)-like lesions. This may as well represent an over-estimation, since in our view it is not correct to classify each hypoechoic or cystic lesion visualised by EUS as IPMN. From IAR that received pancreatic resection for suspicious lesion in our trial we gained the experience that some of the cystic lesions may represent non-malignant cysts or atypical serous cystadenoma. With improving technology and expertise EUS investigators will discover an increasing number of sono-morphological alterations in the pancreas of screened individuals even in normal controls with yet unknown clinical significance. However, we cannot exclude the possibility that we may indeed have underestimated the prevalence of preneoplastic lesions in our study. While it is unlikely that all 21 IAR with detectable small lesions currently being followed have true preneoplastic lesions, some of them will have. We recently operated two (one moderate risk, one high risk) of these 21 IAR due to the change of their lesions. One had multifocal PanIN 2 and IPMN lesions and the other one a PanIN 3 lesion among multifocal PanIN lesions. Intriguingly, the most dysplastic histological lesion in both cases did not correspond to the preoperatively detected lesions and were not visible in preoperative imaging (unpublished).

Harinck *et al* questioned the EUS-screening approach, and in particular the experience and the number of independent investigators. Indeed, all EUS examinations in our programme were performed by one very experienced endosonographist (PHK). According to the protocol standard sections and abnormalities were documented by serial photographs. All examinations were then independently re-assessed and confirmed by another experienced endosonographist (TMG).

Harinck *et al* also discussed the possibility that our paper carries a message that will increase the number of cancer deaths by questioning the relevance of screening for pancreatic cancer in IAR and by pointing out that IAR are exposed to significant psychological stress. Of course, both observations will not refrain us from conducting a screening programme for IAR from pancreatic cancer families in the setting of a board

Surveillance in individuals at high risk of pancreatic cancer: too early to tell?

Femme Harinck, Marcia Irene Canto, Richard Schulick, et al.

Gut 2010 59: 1005
doi: 10.1136/gut.2009.197004