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Pancreatic cancer at the GI Cancer Symposium

Cystic neoplasms of the pancreas are frequently misdiagnosed as pseudocysts 'with potentially disastrous results,' according to Dr Felice Scholl-Sussman (Weill Medical College, NY). Addressing the American Society of Clinical Oncology (ASCO)'s 2004 Gastrointestinal Cancers Symposium (San Francisco, California, USA, 22–24 January 2004), she urged physicians, 'Beware the acute pancreatitis patient!'

She said that 3 out of 4 cystic lesions of the pancreas are non-neoplastic and have no malignant potential. Typically they are pseudocysts, complicating acute or chronic pancreatitis.

However, she studied 101 consecutive patients referred for endoscopic ultrasound (EUS) evaluation of a pancreatic cyst. Of the group, 20% had acute pancreatitis, and within this group, 8 patients (40%) had a mucinous cystic neoplasm (*Proc ASCO Gastrointestinal Cancer Symposium 2004 #120*).

Patients with acute pancreatitis of unclear aetiology should undergo imaging studies and possible EUS to exclude an occult pancreatic cystic neoplasm, she said. They are more common in women, but 'a heightened sense of awareness should be present' for men under 50 years who present with acute pancreatitis and a pancreatic cyst.

• Families with increased incidence of pancreatic cancer show increased incidence of common cancers such as of the breast or prostate, Dr Elizabeth Nicole Omer (University of Utah) told the Symposium (*Proc ASCO Gastrointestinal Cancer Symposium 2004 #83*).

Her group identified 55 kindreds at high risk for pancreatic cancer from the Utah Population Database (UPDB): each kindred had at least 5 cases. Among the kindreds, 1291 pancreatic cancer cases were identified.

Pedigrees of 50 of the original kindreds were searched for other cancers; members of the cohort were followed for cancer risk beginning in 1966. The study found an increased risk of the common cancers of the breast, prostate, lung and colon cancer and melanoma.

• Detection of pancreatic cancer may be possible using simultaneous analysis of multiple serum markers, according to Dr Stephen Winikoff (University of Pittsburgh). The levels of markers IL-6, IL-8, eotaxin, HGF, and IP-10 were significantly different when comparing patients with healthy controls (*Proc ASCO Gastrointestinal Cancer Symposium 2004 #166*).

A logistical regression model, combining levels of the 5 markers, correctly classified 88% of the test set, with a sensitivity and specificity of 87% and 89%.

Dr Winikoff said his group is currently developing Luminex beads that will enable them to expand the panel of biomarkers to include, for example, CA 19-9 and PSCA. 'A sensitive and specific serum-based assay for pancreatic cancer will allow for earlier diagnosis and more rapid detection of recurrence, as well as novel insights into the biology of the disease,' he said.

Preclinical models: an overview

Current and future drug development depends on rational, hypothesis-driven pre-clinical studies, say the editors of a forthcoming *EJC* Special Issue (*EJC* 2004, **40**, 6 '*Preclinical Models in Cancer Drug Discovery and Development*'). The volume evaluates the strengths and weaknesses of contemporary pre-clinical models.

Professor Herbie Newell (University of Newcastle, UK) edited the issue with Professor Ed Sausville (NCI, Bethesda, Maryland, USA). He said that the identification of optimal models for the development of molecularly targeted therapies is 'a significant contemporary issue.'

Professor Newell continued 'Pre-clinical *in vivo* pharmacology in particular can be a bottleneck. With techniques such as high-throughput *in vitro* screening it is possible to generate data on thousands of potentially useful compounds; however, only a small subset can be taken into the clinic.'

An additional issue is that *in vivo* pharmacology must be limited on the grounds of animal welfare, as well as for logistical and financial reasons, he said. The Special Issue highlights the importance of hypothesis-driven studies using fully characterised models as an alternative to the random screening of compounds. 'In drug development, the focus should at all times be on the mechanism by which compounds are acting, and selecting and progressing compounds in light of this information.

Professor Newell concluded 'Before we offer an experimental therapeutic to a patient, there has to be a realistic prospect that it is going to be of benefit. Pre-clinical models are an important aid to estimating potential benefit, and we hope this comprehensive review of contemporary models will be a useful resource for both academia and the pharmaceutical industry.'

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Panel eases US drug approval process

A key advisory panel in the USA has recommended easing the process in which the US Food and Drug Administration (FDA) approves new drugs for treatment of cancer. In December, 2003, the Oncology Drugs Advisory Committee (ODAC) agreed that progression-free survival—also referred to as time-to-tumour progression—could be used as an outcome endpoint in some situations.

At the meeting, the panel voted 11 to 8 in favour of progression-free survival as the basis for approving drugs for treatment of patients with metastatic lung cancer. However the committee rejected expanding the recommendation to drugs for locally advanced lung cancer. (The panel have previously rejected the use of progression-free survival for measuring the effect of drugs designed to treat advanced colon cancer).

"I don't think the action changes much in the way drugs are approved" says David Johnson, Vanderbilt University, TN, USA. "The gold standard for drug approval remains as survival benefit." At the meeting, Grant Williams of the FDA, outlined some of the advantages and disadvantages of using progression-free survival. "Checking the time-to-progression is complex, and requires that the protocol, case report form, and statistical analysis plan are checked in conjuction with time from randomisation to first evidence of progression", comments Williams. "Its advantages are that time-to-progression is measured in all patients and is assessed before crossover. However, time-to-tumour progression doesn't always correlate with survival."

Johnson, a former member of ODAC, said that although the FDA is anxious to accelerate the approval process, progression-free survival might not be the best method. He also added that after resection, the appearance of a tumour in a patient is a definitive event, whereas progression-free survival in patients who do not have their tumour exised is often based on vague interpretations of radiographs or CT scans. Johnson suggests that the use of response rate would be a better marker.

ODAC members also recommended that progression-free survival would be acceptable in accelerated approvals for drugs for treatment of patients with lung cancer, but not in full approvals for drugs in a non-metastatic lung cancer setting. The committee did not specify an absolute time-frame in which progression-free survival would be considered significant, but it did suggest that for a drug to be approved it would have to extend progression-free survival for a period that "substantially" exceeds 2 months.

Edward Susman

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ASCO Commission on Tobacco

The American Society of Clinical Oncology (ASCO) is setting up an independent blue ribbon commission which it says will study the social, medical, legal and economic dimensions of the tobacco problem, both domestically and globally.

The commission will be made up of representatives from government, educational and scientific organisations, advocacy groups and the private sector. It aims to identify appropriate schemes for regulating tobacco products, determine which agencies in the federal government should take charge of tobacco control and establish what scientific and medical research is required to better understand tobacco addiction.

According to ASCO, the Commission 'will develop its preliminary findings, hold public meetings for testimony and comments, and issue its final recommendations, to be catalogued in a report outlining a strategy for achieving immediate reduction of tobacco use and, ultimately, a tobacco-free world'.

'Need for radical change' in oral cancer

New prognostic and predictive factors may allow much-needed progress in the treatment of oral cancer, say German researchers. Despite significant development in the multimodal treatment of the disease 'survival rates have remained at a disappointingly stable level,' they say in a review article (*Oral Oncology 2004*, **40**: *110–119*).

The incidence of oral cancer, and its attributable mortality, has escalated in Europe in recent decades 'with a striking upward trend in younger males, especially in some Eastern and central European countries.' It 'is expected to become a public health problem in the foreseeable future,' they say.

In Western countries the main aetiological factors include alcohol consumption, tobacco use and poor oral hygiene, acting on a genetically susceptible individual. Chewing betel quid is an important risk factor in Asia. Viral infections, such as with the human papillomaviruses (HPV), and infections with Candida albicans are contributory.

One of the reasons for the lack of progress in oral cancer, the German researchers say, is that the tumour-node-metastasis (TNM) system, supplemented with conventional histopathological tumour grading 'have proven to be unsatisfactory prognostic indicators.'

For the future, assessment of the biological aggressiveness of individual tumours is showing promise, particularly the unravelling of the significance of the invasive tumour front (ITF). This entails examination exclusively of the tumour-host interface. In squamous cell carcinomas of the oral cavity, ITF grading is based on the assessment of qualitative histological parameters such as the degree of keratinisation, nuclear polymorphism, pattern of invasion and lymphocytic infiltration.

Incorporation of such tools into a prognostic system 'will better reflect the biological diversity of oral cancer and more accurately predict clinical outcome and/or response to a particular type of adjuvant therapy' they conclude.

RT 'slightly improves survival' after breast-conserving surgery

Radiotherapy after breast-conserving therapy only slightly improves survival, according to a new pooled analysis of randomised controlled trials (RCTs). It substantially reduces the risk of local recurrence, Belgian researchers found (*JNCI* 2004, **96**, *115–121*).

The analysis was based on 15 RCTs with a total of 9422 patients. Patients who did not have radiotherapy after breast conserving surgery were 3 times more likely to have an ipsilateral recurrence than those who had both treatments. Data on 8206 patients showed they also had a slightly increased mortality rate (relative risk 1.086).

In an accompanying editorial, Dr Katherine Vallis and Dr Ian Tannock (University of Toronto, Canada), point out that the survival gains associated with radiotherapy after mastectomy are substantial. 'It is surprising that improvements in survival resulting from the use of radiotherapy after breast conserving surgery are not larger,' they write.

A difference in the radiotherapy given is a potential explanation. After mastectomy, radiotherapy is administered to the regional lymph nodes and chest wall, whereas it is only given to the residual breast after breast-conserving therapy. Local recurrence may be more likely in the chest wall after mastectomy than in the residual breast after breast conserving therapy.

However, the meta-analysis is internally consistent, with all but 2 trials showing a trend in favour of a survival benefit. Furthermore, modern high-precision radiotherapy techniques such as intensity-modulated radiotherapy and partial-breast irradiation will help avoid irradiation of the heart. This will further improve the risk-benefit ratio associated with radiotherapy, say Dr Vallis and Dr Tannock.

Groups of patients with good prognostic factors may not require radiotherapy to reduce the rate of recurrence after breast-conserving surgery. These patients are likely to have high rates of survival and any gains in absolute survival from radiotherapy would probably be small.

However, the Belgian meta-analysis 'reinforces the view that the large majority of patients undergoing breast-conserving surgery should also receive radiotherapy,' they say.

Screening information 'is severely biased'

Information on mammographic screening run by professional advocacy groups and governmental organisations is 'severely biased in favour of screening,' say Danish researchers. 'Few websites live up to accepted standards for informed consent,' they say (*bmj.com* 2004, **328**, *148*).

Lead researcher of this study, Dr Peter Gøtzche (Nordic Cochrane Centre, Copenhagen, Denmark) previously co-authored a review (*Lancet* 2001, **358**, *1340–2*) that questioned the value of screening. It identified harms related to overdiagnosis and overtreatment. The *BMJ* study examined whether current information given 'was balanced and reflected the recent findings.'

The study included 27 websites in Scandinavian and English-speaking countries. Advocacy groups ran 13 of the sites, governmental institutions 11 and consumer organisations, 3.

The consumer sites 'were much more balanced and comprehensive than other sites', the researchers found. For example, overdiagnosis and overtreatment were mentioned by only 4 sites overall, but by all 3 of the consumer group sites. 'The most important harms of screening-overdiagnosis and overtreatment- seem to be the best kept secret about screening', they say.

The study found that governmental and advocacy sites all recommended mammography screening, at least implicitly, whereas the consumer sites questioned the value of screening.

Researchers also criticised the way data was presented. 'To mention that screening reduces the risk of dying from breast cancer by 30% (relative risk reduction) is much more impressive than the equivalent finding-reported in the same overview-that the absolute risk of dying from breast cancer is reduced by 0.1% after 10 years,' they write.

The symmetry of information should be respected for cumulative risks, they said. If the lifetime risk of getting breast cancer is noted then the lifetime risk of getting a false positive diagnosis should also be noted rather than the risk at each screening round.

'It is worrying that so few websites live up to accepted standards for informed consent since it is possible to persuade people to accept or decline cancer screening by withholding or including particular information items,' the researchers write.

'No evidence' that patients in trials do best

Little generalisable evidence exists to support the widespread belief that participation in trials directly improves outcomes for cancer patients, say researchers from Boston, US. In its absence, cancer patients should be encouraged to enrol 'on the basis of trials unquestioned role in improving treatment for future patients' (*Lancet* 2004, **363**, *263–79*).

The researchers identified 26 comparisons of outcomes among cancer patients enrolled and not enrolled in clinical trials. Half showed a trial effect, but the researchers say that 'showing a causal relation between trial participation and improved outcome is difficult.'

A true trial effect could be caused by a protocol effect (the way treatment is delivered), incidental aspects of care, changes in doctor or patient behaviour on the basis of the knowledge that they are under observation, and placebo effect. However, improved outcomes could result from differences in baseline characteristics, bias in how data was gathered, or publication bias. An experimental treatment effect would raise ethical issues 'in view of the requirement for equipoise or uncertainty in randomised clinical trials,' they say.

Methodological difficulties with most studies suggest the need for cautious interpretation, but none found trial participation to be harmful. 'Until more convincing evidence for a trial effect is available, recruitment messages to patients considering trials should focus on their contribution to advances in treatment,' they conclude.

Impact of lung cancer diagnosis

Patients with lung cancer need psychological support at the time of diagnosis, say French researchers (*Lung Cancer* 2004, **43**, *175–182*). They found that patients' emotional and social functioning was impaired by the diagnosis alone.

Little is known about the quality of life (QoL) of patients with lung cancer who are not included in clinical trials, or of the impact of the disclosure of the diagnosis.

The study included 70 patients admitted to University Hospital, Bordeaux, France, for exploration of an abnormal chest X-ray, no previous history of cancer and a performance status of 2 or less. They answered the EORTC Quality of Life Questionnaire (EORTC QLQ-C30) before and after their diagnosis was disclosed- a median of 22 days after hospitalisation.

Patients showed most deterioration in emotional and social functioning. Their responses indicated 'considerable moral anguish', the researchers said. 'Psychological support is needed to detect psychological symptoms, reactive anxiety or depression,' they wrote. 'Pharmacological and non-pharmacological treatments should be considered early and include psychotherapy.'

Communicating sad, bad and difficult news

Ambiguity is common in cancer consultations and may mean that the wrong meaning is conveyed, researchers say (Lancet 2004, **363**, 312–19). Patients may be alarmed or falsely reassured by words or phrases that have different meanings in the lay, rather than medical setting.

Describing nodes as 'positive' or 'negative', for example, or saying, 'the disease is progressing' can communicate the reverse of the true situation, especially, the researchers say, if non-verbal communication 'has not been congruent with the intended message.'

Communicating bad news about diagnosis or recurrence, or discussing the transition from curative treatment to palliative care 'are not simple tasks,' the researchers acknowledge. Time constraints in some health-care systems, together with political imperatives to meet targets and contain costs increase the difficulty.

However, they stress its importance. 'Patients' perceptions of the way in which doctors deliver bad news alter understanding, decisions about treatment options, and later adjustment,' they say.

More attention needs to be paid to the team approach in communication. 'Team members frequently have little awareness about each other's informational roles and responsibilities. Furthermore, what has been communicated about the diagnosis and prognosis is not well documented in hospital records, and collusion with relatives to deceive patients about the reality of their situation is still evident,' they say.

Salt increases risk of gastric cancer

A regular diet of highly salted food doubles the risk of gastric cancer among men, say Japanese researchers (*BJC* 2004, **90**, *1*). The increase was almost as great among women.

The 11-year study included 18,684 men and 20,381 women in four districts of Japan: Iwate, Aklita, Nagano and Okinawa. They completed questionnaires on their dietary, drinking and smoking habits.

Stomach cancer was reported in 358 men and 128 women during the study period. The scientists, from the National Cancer Centre Research Institute in Kashiwa, found that men with the lowest salt intake had a risk of gastric cancer of one in 1000, per year. This doubled to one in 500 among those with the highest salt intake.

Among women, those with a low salt intake had a risk of one in 2000 per year, which rose to one in 1300 for those with the highest intake.

Study leader Dr Shoichiro Tsugane, said, 'Although there is a steady decline in its incidence, gastric cancer is still the most common form of cancer in Japan. In addition to salt intake, our study also shows that smoking and low consumption of fruit and vegetables increases the risk of stomach cancer particularly in men.'

Salting, pickling and smoking are traditionally popular ways of preparing food in Japan. As the Japanese diet has become increasingly westernised, there has been a noticeable drop in the rates of stomach cancer.

'Most cancer patients' take complementary therapies

More than half of all cancer patients were taking herbal remedies, food supplements or both in a study at the Royal Marsden Hospital, London. Most had not discussed it with the clinician overseeing their conventional treatment.

The study included 300 patients, who completed multiple-choice questionnaires. Common remedies taken included echinacea, evening primrose oil and gingko. The most popular supplements were combinations of vitamins, cod liver oils and selenium.

Around one third of the patients taking the remedies were unsure of its purpose, and 11 percent said they took supplements higher than the recommended doses. More than 12 percent had been given health warnings from pharmacists, most often, lymphoma patients taking Echinacea. Previous studies have suggested that it may compromise some treatments for lymphoma and leukaemia.

Dr Ursula Werneke (Homerton Hospital, London) led the study, which she said highlights the importance for conventional healthcare professionals to discuss complementary medicine with their patients. Clinicians must be properly briefed on how health remedies interact with standard treatment, she said.

'The real problem is that doctors may not have the expert knowledge needed to deal with so many potential risks when patients are mixing conventional treatment with alternative remedies. They need to avoid uncritical encouragement,' she said.

There may be insufficient time to discuss complementary medicine in routine outpatient clinics, and she acknowledged, 'Patients will not always accept their doctors' opinions and may argue that conventional cancer treatment is equally toxic.'

PODIUM

The needs of the next generation

Dr Pamela Kearns is a consultant paediatric oncologist at University of Bristol, UK. Her special interests include the molecular pharmacology of leukaemia, new drug development, phase I and phase II trials. She co-chaired a young oncologists' session at ECCO-12 in Copenhagen.

Dr Pamela Kearns

What are the big issues facing young oncologists?
Training is a key area of concern. On the plus side, training schemes have become better defined, and there is now more emphasis on formal training rather than service provision alone. However, the move throughout Europe to reduce the length of training and get doctors into consultant posts earlier in their careers is creating anxiety. Career choices are now made very early on and it is questionable whether trainees have time to gain the broad clinical experience they need. Flexibility is being lost, and trainees are less able to spend time in related specialties.

This is compounded by the European Directive reducing the hours junior doctors can work. It's good to see working conditions improve but it reduces still further the opportunities for clinical exposure.

What impact is the Directive having?
In practice, unless the Directive is accompanied by an increase in the number of doctors, it is not viable. It means that junior doctors have to walk away from a job even though the work is not finished. They don't find it satisfying and it is not good for their training. Conversely, young consultants entering a consultant-led service, where the issues of the Directive have yet to be addressed are faced with working 60–80 hour weeks.

We are probably in a period of transition. The legislation comes first and the practical solutions come later. We're not there yet.

Does reduced training impact careers in the longer term?
Possibly. It's universally accepted that the multidisciplinary approach is the way forward, but in adult oncology, the opportunities for surgeons, radiation oncologists and clinical oncologists to train together is very limited. In order for them to understand each other's specialties, they need time together in training, to help them later to communicate, work together and collaborate in clinical trials.

Is the situation uniform throughout Europe?
Young oncologists in EU countries are facing the same challenges. However, not all have the resources for big oncology centres and oncologists have to train elsewhere. They are needed to support the service at home, but they have to have enough time away to ensure that their training objectives are met.

Training needs to be uniform throughout Europe to improve mobility. At the moment, each country has its own requirements, and it is not easy to work out whether someone coming from another country has achieved the necessary objectives.

How important is laboratory training for young oncologists?
A moot point. Some oncologists- I'm one of them- feel that for clinicians who have no intention of pursuing a career in academic medicine, it's hard to reconcile spending 3 or more years on a laboratory-based PhD when training time is so limited. The opposing view is that because we are moving towards molecular-based diagnostics and treatment, a basic understanding of the laboratory structure is an important part of training. Academic careers must certainly be encouraged, but there may need to be shorter courses or diplomas to keep 'non-academic' clinicians up to date.

What are the problems faced by young academic oncologists?
The difficulty is balancing time spent on academic work with time spent in the clinic. Usually a certain percentage of time is allocated to clinical work, with the rest spent on research and teaching. In practice, many have a full time clinical commitment, with research and teaching done on top. This has to change. Universities are expecting more from clinical academics in terms of publications in high impact journals, but this cannot happen without time dedicated to research.

Are there any advantages in completing training earlier?
It means that people are in a position to develop treatments and make changes at a time in their life when they have the energy to accomplish it. But young oncologists need support in the early stages of their career. The Flims Alumni Club—with the support of FECS provides forums which draw together young academically-minded oncologists to exchange ideas, offer mutual support, and set up collaborative links across Europe.

What are the challenges for the future?
The way we give chemotherapy is changing. With new agents such as the anti-angiogenesis compounds and tyrosine kinase inhibitors, we may be using more cytostatic treatments, leading to more prolonged, stable disease. We'll need new ways of evaluating drugs, and new endpoints.

A few years ago, a retiring oncologist was talking about progress in cancer treatment and management during her career. I thought then that I would not experience anything similar, but I was wrong. The move towards individual, tailored chemotherapy, and new approaches to treatment and management are tremendously exciting. The internet and email has made national and international collaboration much easier; today's young oncologists will be defined by their enthusiasm for collaboration.

See *www.flimsalumni.org*