Message from the President

Pathology: Alive and Kicking

A recent article in Labtimes in which the quality of pathology research was measured (http://www.labtimes.org/labtimes/ranking/2013_07/index.lasso) started as follows: “Not dead yet, Pathology has entered the molecular age and contributes its shares to cancer and neurodegenerative diseases’ research”.

I think the writer meant this as a compliment or at least as a positive remark, but I feel there is a misunderstanding underneath. If you start with not dead yet, you imply that this is not common knowledge, and of course the yet may indicate that it will come anyhow.

Pathology has been declared dead many times but is alive and kicking. That is very obvious for pathologists but not always for others. For many diseases our diagnosis is the firm basis upon which all following medical interventions are based. Our diagnoses become more reliable and more detailed thanks to the use of new or improved techniques but also thanks to the painstaking work of many colleagues who collect data and link that to clinical features. New criteria or markers are introduced almost on a daily basis and it is not always easy to keep up with all that happens. This brings quite some responsibility, which is certainly felt by the ESP.

The ESP organises congresses, courses, provides a Journal, and has an improved educational portal, introduced quality assessment for molecular testing. Furthermore, the ESP interacts with clinicians through links with ESMO, UEG, EUS, and EORTC etc. Is this enough? In my introducing speech in Lisbon I indicated that I like further development of the ESP on two aspects: science and public relations. As is shown in the article in Labtimes we do a lot of good research and incorporate that into our routine practice. We will show lots of that in London and I hope many of you will send abstract of your research. Pathology is a real scientific discipline and we must be proud of that and show it to our colleagues (and not only to clinicians). We will also have in London a session on public relations. I hope many of you will attend, since I hope it is going to be a starting point of new initiatives for reaching to the public and patients.

It is an exiting time to be in pathology and I am sure that it will be for many years. Pathology is changing and there are challenges. We therefore need to have sufficient numbers of pathologists and get the best of the new generation into our profession. This means hard work! We also need to give the young all the chances they need. It is therefore that we have the membership of the ESP for free for residents/trainees. And there are many bursaries for them so they can attend our congress at low cost. I hope to see many of them in London!

Prof. Han van Krieken

Message from the Editor

Dear Colleagues,

This spring issue of the Newsletter, wrapped in a new format, adds to its usual sections the worthy contributions of Prof Gordan Vujanic, our new associate editor. Prof Vujanic brings with him a
wealthy experience as editor-in-chief of the Paediatric Pathology Society (PPS) Newsletter and Honorary Secretary of the PPS during the period 1996-2002. He also served as director of the International Paediatric Pathology Association advanced course (2002-2010), a good reason for charging him with keeping us abreast of the meetings, congresses and books of interest. We heartily welcome him!

Prof Han van Krieken opens the Newsletter placing great emphasis on the kicking liveliness of pathology and its need to pay special attention to both science and public relations. Those two aspects will be cherished at the upcoming European Congress of Pathology in London, whose rich assortment of scientific and social events is outlined by Prof Adrienne M Flanagan, the meeting secretary of the Pathological Society.

In accord with our goal of giving prominence to the various ESP working groups (WGs) Prof Josep Lloreta, chair of the Electron Microscopy WG, explains the unabated importance and current roles of ultrastructural pathology.

Further on, as an expression of the firm rapprochement between pathologists and clinicians, Prof Fátima Carneiro comments on the collaboration between the ESP and the European Society for Medical Oncology (ESMO).

Prof Lloreta’s and Prof Carneiro’s articles bring to mind the varied strains put on today’s pathologists, who must acquire ever more complex knowledge and competences to properly serve patients and effectively deal with clinicians. But, how do our trainees know whether they know all they have to know? In response to that query, Prof Fred T Bosman writes on the EUROPALS progress test and the recent takeover of the project by the ESP.

Finally, Dr Loukas Kaklamanis offers us his very careful selection of medical abstracts (Analecta Medica) and Prof Gordan Vujanic provides most useful information on the meetings and congresses to be held in 2014 and some recently published pathology books. Enjoy!

Prof Aurelio Ariza

Message from the Meeting Secretary of the Pathological Society of Great Britain and Ireland.

We are in the final stages of planning the 2014 European Congress of Pathology to be held in London (August 30th – September 3rd) jointly organised by the Pathological Society of Great Britain and Ireland with the European Society of Pathology. Early March saw the preliminary programme go on line and we are hoping for a large number of abstracts to be submitted for the deadline on the 8th April. The meeting will have an international flavor with speakers and participants from beyond Europe including Canada, China, Japan, and the USA.

The breadth and depth of what is on offer at this conference should make it an attractive meeting for everyone involved in pathology. The programme reflects the motto Understanding Disease of the Pathological Society which has been adopted by the London 2014 meeting. The programme covers virtually all aspect of cellular pathology and includes sessions around the latest developments in translational research and how these will impact on laboratory medicine over the next decade, seminars delivered by experts in their field aimed at covering the most up to date diagnostic information necessary for best clinical practice at the current time. The trainees have organised an exciting set of lectures focussing on molecular pathology demonstrating their interest in disease mechanism and how they see the discipline of pathology transforming over their careers. We expect to attract a strong cohort of undergraduates and to see a large turnout for a
lively debate on the topic of “Pathology Should Not Be a Priority in the Undergraduate Curriculum”.

The social events organised along the Conference are not to be missed. The evening concert in the Central Hall Westminster performed by the famous Royal Philharmonic Orchestra and conducted by Vartan Melkonian should not be missed and we will end with a lively party in the Museum of London at Docklands.

We look forward to seeing you in London.

Prof. Adrienne M Flanagan


A Word from the Chairman

The Electron Microscopy Working Group (EMWG) is opened to all pathologists, pathologists in training, and other biomedical scientists that are interested in the morphological and functional basis of disease, as well as in the still many diagnostic applications of the ultrastructural assessment of cell and tissue samples in different organ systems. Nowadays, ultrastructural pathologists are concentrated in academic institutions and mostly work in electron microscopy (EM) as a part time job, combining it with different diagnostic and research profiles. In recent years, we have witnessed the reduction or the disappearance of some EM laboratories, but it must be emphasized that, in spite of the increasing economic constraints, new EM units have been developed and that referral of cases to centralised laboratories for ultrastructural examination has become a more common practice. On the other hand, a survey of Pathology and Cell Biology journals reveals that EM is used in a remarkable percentage of studies and included in many papers. Furthermore, reference textbooks and monographs contain chapters or sections devoted to the ultrastructural features of diseases whenever indicated. Thus, in spite of the common feeling that the use of EM is dramatically declining, it is less so than it would seem.

In this setting, the EMWG has the mission of redefining and disseminating the current applications of EM in the steadily changing field of Pathology. Moreover, it has the task of identifying and interconnecting all pathologists and other scientists involved in electron microscopic diagnosis and research.

Morphology and morphological-functional correlation is the basic ground on which Pathology has developed over the centuries, and even the more apparently abstract molecular changes take place in a morphological context. EM has traditionally been, and still remains, a powerful tool for understanding physiologic and pathologic changes in cells and tissues. It is therefore an essential research tool in the study of many pathological processes, one that brings an added value to the understanding of the pathogenesis of disease. On the other hand, there are diagnostic ultrastructural clues in many fields, not only the obvious of renal glomerular diseases or ciliary abnormalities, but also in neuropathology, dermatopathology, hematopathology, infectious diseases, connective tissue disorders, and congenital enzymatic defects. In all of them, there are diseases or clinical situations in which a specific diagnosis simply cannot be achieved without EM assessment. There are also many ultrastructural features that, although they are not essential diagnostic clues, constitute relevant or confirmatory data. As new diagnostic tools, new antibodies and other diagnostic tests are developed, the relative weight of all the components in the armamentarium must be revisited. This need for reassessment is constantly reshaping the practice of Pathology, and it also impacts the field of EM. Thus, an ultrastructural key feature may become a complementary one
when a specific test, e.g. a cytogenetic translocation, is found to be decisive. On the other side of the coin, tests that are initially regarded as constant and defining are found to be less specific over time. This is classic for many “promising” antibodies, but it is also true for many “specific” cytogenetic abnormalities that are eventually found in different and often apparently unrelated tumours. Furthermore, the development of new therapeutic strategies poses new demands to pathologists, but are also avenues for new approaches to diagnosis and new ways of combining the available ancillary techniques. In short, the use of electron microscopy in Pathology, like that of any other tool, must be revisited and adapted to the evolving clinical demands and patients’ needs.

In this regard, one of the features contributed by the EMWG in the several recent European Congresses of Pathology is the organization of multidisciplinary symposia on monographic topics. Thus, renal tumours were addressed in Helsinki (2011), spindle cell tumours in Prague (2012), and the relatively heterogeneous group of Alk-associated neoplasms in Lisbon (2013). In these very well attended sessions, the reviews of the ultrastructural aspects of the different tumour entities are combined with lectures on the respective histopathological, immunohistochemical, cytogenetic, and molecular features. Usually, the program is complemented with a lecture by a renowned oncologist that gives an updated review on the therapeutic implications of pathological data. The next symposium, to be held in the ECP in London, will be devoted to pulmonary and pleural tumours using a similar approach.

As stated above, another main goal of the EMWG is to serve as a forum for every electron microscopist, be it as a full time or a part time job, and regardless of their academic background. Thus, we are planning to identify who and where is working in EM, both at the diagnostic and research levels. We will focus mainly on European electron microscopists, but will welcome candidate members from any continent. In this short note, we would like to ask that every single pathologist or scientist with any activity in EM would send an e-mail to the chairman of the EM. This e-mail should contain very few data: given and family name, contact data, institution, academic background (pathologist, biologist, etc.) and main tissues examined and main areas of interest (e.g. kidney, muscle, skin, microorganisms, etc.). We look forward to welcoming many new members to the EMWG and to the ESP in the near future. Indeed, the EMWG is willing to serve as a platform for collaboration, consultation, and continuing medical education among whoever is interested in this technique. From Morgagni’s era to the present, each meaningful technical advance has been introduced in Pathology without sacrificing previous tools and methods, but rather adjusting them to the new scenarios. The future of Electron Microscopy, similar to the future of Pathology, is in the hands of those that work in it. The strength of a solid morphologic background is one of the keys to this future: we must strive to maintain and enrich it and to pass it onto the young generations. 

Prof. Josep Lloreta Trull

Collaboration between the ESP and the European Society for Medical Oncology (ESMO).

When I took over the Presidency of the ESP, in September 2011, I announced that one of the areas I would dedicate special attention during my term of office would be the “Reinforcement of the internationalization of the ESP, with the establishment of solid links with International Organizations and Societies”.
This decision was put in action and it was possible to establish collaborations with the European Organisation for Research and Treatment of Cancer (EORTC), the European Society for Medical Oncology (ESMO), the United European Gastroenterology (UEG) and the European Crohn's and Colitis Organization (ECCO).

The collaboration with the ESMO has been extremely fruitful, expressed in the Memorandum of Understanding (MoU) signed by the two Societies, the organization of joint meetings, the collaboration in the Rare Cancers Europe (RCE) initiative and the nomination of ESP Pathologists for the ESMO Faculties.

The purpose of the Memorandum of Understanding is to "increase collaboration, mutual recognition, and shared culturally sensitive approaches to the work of both organizations. The collaboration focuses on relevant clinical practice issues, research activities and on communication with each other about eventual strategies to develop and to support and promote medical oncology and pathology". The ESP representatives for the collaboration with ESMO are Prof. Han van Krieken, in his quality of ESP President, and Prof. Paolo dei Tos.

Joint ESP/ESMO meetings have been organized in the ESMO Congress, Vienna, 2012, on “Molecular diagnostics for personalized cancer treatment” and in the 25th European Congress of Pathology, Lisbon 2013, on “The role of pathology in new forms of clinical trials”. Other joint sessions are being organized for the 26th European Congress of Pathology, London 2014, on “Molecular classification of tumours: Disease entity or target recognition?” and the ESMO Congress, Madrid 2014, on “Tissue markers for immuno-oncology”.

Another important aspect in the frame of ESP/ESMO is the active participation of the ESP in Rare Cancers Europe (RCE) initiative, a collaboration in which Prof. Paolo dei Tos is the ESP representative. RCE is a multi-stakeholder initiative, led by the ESMO, aiming to address issues of particular relevance in rare cancers, including late or incorrect diagnosis. During the 24th European Congress of Pathology, Prague 2012, a short survey was developed by the ESP and RCE aiming to get a better understanding of rare cancer-related issues and to identify challenges for Pathologists.

More recently, a Consensus Meeting on Rare Cancers (“Pathology in rare cancers”) was held in February 2014, in Brussels, jointly organised by Rare Cancers Europe (RCE), the ESP and the ESMO. This workshop produced a consensus paper based on available evidence and intensive expert discussion on issues related to accurate and timely diagnosis of individual rare cancers. The paper will be published in a scientific journal and used as the basis of an awareness campaign at the EU level.

Currently, the ESP is extending the collaboration with the ESMO in the frame of educational initiatives. In this setting, the ESP has been nominating Pathologists for the ESMO Faculties, an initiative that was most welcome by the Chairs of the ESP Working Groups.

I think that the ESP was able to establish a solid and fruitful collaboration with the ESMO. An example to follow!

Prof. Fátima Carneiro

Do You Know What You Need to Know?

Many of you will have noticed the repeated announcements by ESP office emails of the EUROPALS Progress test, which was offered in the second half of November until early December 2013. Some of you even took the test. Many of you might have wondered what this is. If you are one of them, it is a pity that you did not participate: the best way to find out would have been to simply
take it! For all of you who without much ado directed the messages to the trashcan and for those of you who took the test but want some background information: let’s talk about it a little bit.

**EAPCP**

The European Association of Pathology Chairs and Program Directors (EAPCP) was created in 2005 as an initiative of prof. Jan van den Tweel. His conviction, shared by many leading pathologists in Europe, was that even though the Union Européen de Médecins Specialistes (which meanwhile we all know as the UEMS) as a political body created within the EU infrastructures was responsible for coordination of postgraduate medical specialty training in Europe, an association of pathologists with responsibility for directing an Academic Department of Pathology or a Training Program might contribute significantly to the further development of our discipline in Europe. It did not take the EAPCP long to find out that training programmes in Europe are extremely heterogeneous and that harmonizing them was at best a distant dream, in view of the fact that the responsibility for accreditation of training programs and for certification of medical specialists remains entirely in each individual country. Pragmatists as pathologists are, the solution chosen by EAPCP to contribute to harmonization was the creation of a progress test. In 2009 the EAPCP submitted a grant application to the EU for support for the creation of the progress test. The project was called European Pathology Assessment and Learning System (indeed, EUROPALS as acronym). One of its main deliverables was the EUROPALS progress test.

**Progress test??**

Now what is this progress test all about? Well, the idea is rather simple. It did not make sense to try and create tests at intermediate level to assess progress: the differences between the training programs being such that intermediate levels would be incomparable. So the idea was to create a test at exit level for all trainees. Trainees at an entry level would not have an outstand score but the score would go up per year, as an indication of the progress made. Ultimately, the exit level would have to be the same all over Europe. With good coverage of the learning objectives, selective test items and wide adherence to this approach to evaluation, ultimately the progress test might become one of the instruments in Europe wide accreditation of medical specialists. Good coverage of the learning objectives implies their detailed definition, which the EAPCP achieved in a document describing the profile of todays European pathologist. Selective test items implies adherence of many program directors in making test items (mostly multiple choice questions assessing knowledge, image recognition skills and microscopy competence using virtual slides) but also a working group responsible for fine tuning of the test items. Wide adherence appeared to be a totally different matter. This was created through the EAPCP initiative. Getting many trainees (we have more than 1500 of them in Europe!) to take the test was to be achieved by making the test easy to subscribe to, fun to do and anonymous, an effective feed-back tool for the trainee: do you know what you need to know? Also certified pathologists would be encouraged to take the test, allowing them to regularly assess their basic knowledge.

**Test characteristics**

Between 2009 and 2014 we ran the test 6 times with a number of participants up to 650 per test. The tests consisted of between 80-100 questions, partly knowledge oriented multiple choice questions, partly still image based and partly virtual slide based, as well as extended matching questions. The questions did not only test diagnostic histopathology knowledge, but also molecular pathology items and understanding of mechanism of disease. The testee immediately received feed-back upon completion of the test. Testees were requested to fill out a brief questionnaire, to allow those compiling the test to use the feed-back to improve on the test. In the
In the spring of 2013 we ran a Gastro-intestinal pathology specialty test and this will be repeated in May 2014 with a Hematopathology specialty test, which will be announced shortly. The progress test for 2014 will be run as usual in November.

Experience gained

What has been our experience so far? Well, the principle functions: up to 650 trainees/pathologists participated in the test and the feedback we received was generally positive. The use of virtual slides has improved over time and recent experience indicates that almost all participants had no difficulties in reading the slides on-line. The level of the test is perceived as high, as the obtained scores (the Table shows the 2013 list) indicate with a mean score (% of correctly answered questions) in the fifties. There is quite a bit of molecular pathology and disease mechanisms in the test, which is by some participants perceived as too much. This is, however, intentional: we are in the middle of a molecular revolution that will not leave our discipline untouched. Moreover, diagnostic pathology is not only ‘reading the sides’ but also ‘understanding disease’.

Does the test assess progress? To a certain extent the answer is yes! As Table 1 shows, the score goes up gradually but less so than we expected.

What the table does not show is the test scores per country. Between countries significant differences in scores have been noted and this can be exploited even to assess differences between training programmes within a country. As it was not our primary intention to do this, this potential use has not been further explored but there is no doubt that with Europe-wide participation in the test it would allow the individual testee a comfortable self-assessment test, training programmes a possibility to compare their performance with that of other training programmes and the UEMS European Board of Pathology (who offer the annual Boards Examination as a rule the day before the European Congress of Pathology) to use the test as one of the assessment tools for final certification.

What’s next?

Based upon the experience gained we will continue as originally foreseen. Only, the ‘we’ has changed. As the EAPCP after the EU subsidy expired no longer has the means to continue, the ESP has decided to take over the project. The Education Subcommittee will assume responsibility for creating the annual test, which will be offered through the ESP Education Portal. A working group for writing the test items is in the making (if you want to be part of this do not hesitate to be in touch with the ESP office admin@esp-pathology.org or with prof. Helmut Popper, chair of the Education Subcommittee). The discussion with UEMS European Board of Pathology continues, in order to get to a more coordinated approach. How exactly this will be done still needs some more reflection. That is the reason why the theme of the symposium dedicated to postgraduate training during the 2014 European Congress of Pathology (ECP London 2014) is ‘Certification in a European context’, with the progress test as one of the items to be discussed.

Prof. Fred T Bosman

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<th>Year of Training</th>
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Which Physicians Are the Most Overweight?

In the latest US Centers for Disease Control and Prevention (CDC) report on obesity, about 35% of the US population is obese, which is a body mass index (BMI) of ≥ 30.[1] Although far fewer physicians of the total number who responded to the Medscape survey are obese (8%), being overweight is still a problem for 34% of them.

The pathologist percentage, with 38% of them reporting being overweight to obese, was slightly lower than the middle of the specialty rankings. General surgeons report being the most overweight physicians, with 49% confessing to being overweight to obese (BMI > 25). Family physicians follow closely at 48%. Dermatologists are the least heavy, with less than a quarter of them (23%) reporting a BMI > 25, followed by 29% of ophthalmologists.
Are Pathologists Happier at Home or at Work?

A majority (63%) of pathologists report being very to extremely happy at home, with only 45% of them reporting the same level of happiness at work. (When looking at gender among all physicians who responded, there was almost no difference between men and women in their ratings of happiness either at work or at home.)

2. Focal Amplification of the Androgen Receptor Gene in Hormone-naive Human Prostate Cancer.

S Merson, Z H Yang, D Brewer, et al. on behalf of the Transatlantic Prostate Group.

British Journal of Cancer 2014;110:1655-1662

Background:

Androgen receptor (AR)-gene amplification, found in 20–30% of castration-resistant prostate cancer (CRPCa) is proposed to develop as a consequence of hormone-deprivation therapy and be a prime cause of treatment failure. Here we investigate AR-gene amplification in cancers before hormone deprivation therapy.

Methods:
A tissue microarray (TMA) series of 596 hormone-naive prostate cancers (HNPCas) was screened for chromosome X and AR-gene locus-specific copy number alterations using four-colour fluorescence in situ hybridisation.

Results:

Both high level gain in chromosome X (≥4 fold; n=4, 0.7%) and locus-specific amplification of the AR-gene (n=6, 1%) were detected at low frequencies in HNPCa TMAs. Fluorescence in situ hybridisation mapping whole sections taken from the original HNPCa specimen blocks demonstrated that AR-gene amplifications exist in small foci of cells (≤600 nm, ≤1% of tumour volume). Patients with AR gene-locus-specific copy number gains had poorer prostate cancer-specific survival.

Conclusion:

Small clonal foci of cancer containing high level gain of the androgen receptor (AR)-gene develop before hormone deprivation therapy. Their small size makes detection by TMA inefficient and suggests a higher prevalence than that reported herein. It is hypothesised that a large proportion of AR-amplified CRPCa could pre-date hormone deprivation therapy and that these patients would potentially benefit from early total androgen ablation.

3. Comparative Genomic Hybridisation Array and DNA Sequencing to Direct Treatment of Metastatic Breast Cancer: a Multicentre, Prospective Trial (SAFIR01/UNICANCER).

F Andre, T Bechelot, F Commo, et al.

Lancet Oncology 2014;15:267-274

Background

Breast cancer is characterised by genomic alterations. We did a multicentre molecular screening study to identify abnormalities in individual patients with the aim of providing targeted therapy matched to individuals' genomic alterations.

Methods

From June 16, 2011, to July 30, 2012, we recruited patients who had breast cancer with a metastasis accessible for biopsy in 18 centres in France. Comparative genomic hybridisation (CGH) array and Sanger sequencing on PIK3CA (exon 10 and 21) and AKT1 (exon 4) were used to assess metastatic biopsy samples in five centres. Therapeutic targets were decided on the basis of identified genomic alterations. The primary objective was to include 30% of patients in clinical trials testing a targeted therapy and, therefore, the primary outcome was the proportion of patients to whom a targeted therapy could be offered. For the primary endpoint, the analyses were done on the overall population registered for the trial. This trial is registered with ClinicalTrials.gov, number NCT01414933.

Findings

423 patients were included, and biopsy samples were obtained from 407 (metastatic breast cancer was not found in four). CGH array and Sanger sequencing were feasible in 283 (67%) and 297 (70%) patients, respectively. A targetable genomic alteration was identified in 195 (46%) patients, most frequently in PIK3CA (74 [25%] of 297 identified genomic alterations), CCND1 (53 [19%]), and FGFR1 (36 [13%]). 117 (39%) of 297 patients with genomic tests available presented with rare genomic alterations (defined as occurring in less than 5% of the general population), including AKT1 mutations, and EGFR, MDM2, FGFR2, AKT2, IGF1R, and MET high-level amplifications. Therapy could be personalised in 55 (13%) of 423 patients. Of the 43 patients who were assessable and received targeted therapy, four (9%) had an objective response, and nine others (21%) had stable disease
for more than 16 weeks. Serious (grade 3 or higher) adverse events related to biopsy were reported in four (1%) of enrolled patients, including pneumothorax (grade 3, one patient), pain (grade 3, one patient), haematoma (grade 3, one patient), and haemorrhagic shock (grade 3, one patient).

Interpretation

Personalisation of medicine for metastatic breast cancer is feasible, including for rare genomic alterations.


B A Thompson, A B Sprudle, J-P Plazzer, et al., on behalf of InSiGHT

Nature Genetics 2014;46:107-115

The clinical classification of hereditary sequence variants identified in disease-related genes directly affects clinical management of patients and their relatives. The International Society for Gastrointestinal Hereditary Tumours (InSiGHT) undertook a collaborative effort to develop, test and apply a standardized classification scheme to constitutional variants in the Lynch syndrome–associated genes MLH1, MSH2, MSH6 and PMS2. Unpublished data submission was encouraged to assist in variant classification and was recognized through microattribution. The scheme was refined by multidisciplinary expert committee review of the clinical and functional data available for variants, applied to 2,360 sequence alterations, and disseminated online. Assessment using validated criteria altered classifications for 66% of 12,006 database entries. Clinical recommendations based on transparent evaluation are now possible for 1,370 variants that were not obviously protein truncating from nomenclature. This large-scale endeavor will facilitate the consistent management of families suspected to have Lynch syndrome and demonstrates the value of multidisciplinary collaboration in the curation and classification of variants in public locus-specific databases.

5. Genome wide Association Study of Survival in Patients with Pancreatic Adenocarcinoma.

C Wu, P Kraft, R Stolzenberg -Solomon, et al.

Gut 2014;63:152-160

Background and objective

Survival of patients with pancreatic adenocarcinoma is limited and few prognostic factors are known. We conducted a two-stage genome-wide association study (GWAS) to identify germline variants associated with survival in patients with pancreatic adenocarcinoma.

Methods

We analysed overall survival in relation to single nucleotide polymorphisms (SNPs) among 1005 patients from two large GWAS datasets, PanScan I and ChinaPC. Cox proportional hazards regression was used in an additive genetic model with adjustment for age, sex, clinical stage and the top four principal components of population stratification. The first stage included 642 cases of European ancestry (PanScan), from which the top SNPs (p≤10−5) were advanced to a joint analysis with 363 additional patients from China (ChinaPC).

Results
In the first stage of cases of European descent, the top-ranked loci were at chromosomes 11p15.4, 18p11.21 and 1p36.13, tagged by rs12362504 (p=1.63×10−7), rs981621 (p=1.65×10−7) and rs16861827 (p=3.75×10−7), respectively. 131 SNPs with ps10−5 were advanced to a joint analysis with cases from the ChinaPC study. In the joint analysis, the top-ranked SNP was rs10500715 (minor allele frequency, 0.37; p=1.72×10−7) on chromosome 11p15.4, which is intronic to the SET binding factor 2 (SBF2) gene. The HR (95% CI) for death was 0.74 (0.66 to 0.84) in PanScan I, 0.79 (0.65 to 0.97) in ChinaPC and 0.76 (0.68 to 0.84) in the joint analysis.

Conclusions

Germline genetic variation in the SBF2 locus was associated with overall survival in patients with pancreatic adenocarcinoma of European and Asian ancestry. This association should be investigated in additional large patient cohorts.

6. Cancer and Systemic Inflammation: Treat the Tumour and Treat the Host.

C S D Roxburgh and D C McMillan

British Journal of Cancer 2014;110:1409–1412

Determinants of cancer progression and survival are multifactorial and host responses are increasingly appreciated to have a major role. Indeed, the development and maintenance of a systemic inflammatory response has been consistently observed to confer poorer outcome, in both early and advanced stage disease. For patients, cancer-associated symptoms are of particular importance resulting in a marked impact on day-to-day quality of life and are also associated with poorer outcome. These symptoms are now recognised to cluster with one another with anorexia, weight loss and physical function forming a recognised cluster whereas fatigue, pain and depression forming another. Importantly, it has become apparent that these symptom clusters are associated with presence of a systemic inflammatory response in the patient with cancer. Given the understanding of the above, there is now a need to intervene to moderate systemic inflammatory responses, where present.

In this context the rationale for therapeutic intervention using nonselective anti-inflammatory agents is clear and compelling and likely to become a part of routine clinical practice in the near future. The published literature on therapeutic intervention using anti-inflammatory agents for cancer-associated symptoms was reviewed. There are important parallels with the development of useful treatments for the systemic inflammatory response in patients with rheumatological disease and cardiovascular disease.

7. Multitarget Stool DNA Testing for Colorectal-Cancer Screening.

T F Imperiale, D F Ransohoff, S H Itzkowitz, et al.

NEJM March 19, 2014DOI: 10.1056/oa1311194

Background

An accurate, noninvasive test could improve the effectiveness of colorectal-cancer screening.

Methods

We compared a noninvasive, multitarget stool DNA test with a fecal immunochemical test (FIT) in persons at average risk for colorectal cancer. The DNA test includes quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and β-actin, plus a hemoglobin immunoassay. Results were generated with the use of a logistic-regression algorithm, with values of 183 or more considered to be positive. FIT
values of more than 100 ng of hemoglobin per milliliter of buffer were considered to be positive. Tests were processed independently of colonoscopic findings.

Results

Of the 9989 participants who could be evaluated, 65 (0.7%) had colorectal cancer and 757 (7.6%) had advanced precancerous lesions (advanced adenomas or sessile serrated polyps measuring ≥1 cm in the greatest dimension) on colonoscopy. The sensitivity for detecting colorectal cancer was 92.3% with DNA testing and 73.8% with FIT (P=0.002). The sensitivity for detecting advanced precancerous lesions was 42.4% with DNA testing and 23.8% with FIT (P<0.001). The rate of detection of polyps with high-grade dysplasia was 69.2% with DNA testing and 46.2% with FIT (P=0.004); the rates of detection of serrated sessile polyps measuring 1 cm or more were 42.4% and 5.1%, respectively (P<0.001). Specificities with DNA testing and FIT were 86.6% and 94.9%, respectively, among participants with nonadvanced or negative findings (P<0.001) and 89.8% and 96.4%, respectively, among those with negative results on colonoscopy (P<0.001). The numbers of persons who would need to be screened to detect one cancer were 154 with colonoscopy, 166 with DNA testing, and 208 with FIT.

Conclusions

In asymptomatic persons at average risk for colorectal cancer, multitarget stool DNA testing detected significantly more cancers than did FIT but had more false positive results.

Dr. Loukas Kaklamanis

Meetings and Congresses in 2014

Belgrade Edition 2014 April
Update in Dermatopathology
For information and registration:
lole@med.bg.ac.rs

Craiova Edition 2014 April
Update in Soft Tissue Tumours
For information and registration:
http://escop.umfcv.ro/2014/Welcome-both.html

Craiova Edition 2014 September
Update in Malignant Lymphomas
For information and registration:
http://escop.umfcv.ro/2014/Welcome-both.html

Zagreb Edition 2014 October
Update in the Pancreas and the Bile Duct System Pathology
For information and registration: lbrcic@mef.hr
2014 Dermpedia Comprehensive Review of Cutaneous Hematopathology and Dermatopathology Update
10-12 April 2014
Scottsdale, Arizona, USA
http://www.dermpedia.org/event/scottsdale2014

European Society of Pathology Masterclass
Breast Pathology with Radiological Correlation
30 May 2014
Brussels, Belgium
admin@esp-pathology.org

7th British Association of Urological Pathologists
kidney and bladder pathology course
28–29 April 2014
London, U.K.
www.baup.org.uk

Criminal Justice Residential Training Course for Pathologists
2–6 June 2014,
Durham, U.K.
pathology@homeoffice.gsi.gov.uk

Spanish-Spanish Pathologist Meeting
Spanish Society of Anatomical Pathology and
Spanish Division of the IAP
1-4 May 2014
Valencia, Spain
http://www.iap-bonn.de

International Renal Pathology Conference 2014
Renal Pathology Society
5-7 June 2104
Ljubljana, Slovenia

3rd Pannonia Congress of Pathology
Slovenian Society of Pathology and Forensic Medicine
15-17 May 2014
Bled, Slovenia
http://www.klinika-golnik.si/pannonia/

19th Congress of the European Hematology Society
12-15 June 2014
Milano, Italy
http://www.ehaweb.org/news/1

15th World Congress of Cervical Pathology and Colposcopy
26-30 May 2014
London, U.K.
http://www.asccp.org/Education/Meetings-and-Courses

London Uropathology Conference
19-20 June 2014,
London, U.K.
www.utopathologyuk.com

Practical pulmonary pathology
30 June–2 July 2014
London, U.K.
a.nicholson@rbht.nhs.uk
Some Recently Published Books

Molecular Pathology and Diagnostics of Cancer
By Domenico Coppola
2014 (1st ed), 450 pages, ~EUR150

Molecular pathology is based on the emergence of new techniques that greatly enhance the diagnostic accuracy when facing challenging differential diagnoses. In addition, new molecular techniques are entering the clinical arena for their value in predicting therapy response and tumor prognosis. This book provides a guide for the practicing pathologist and for both pathology residents and fellows during the daily sign-out of
challenging cases. The book is organized by anatomical systems and provides a detailed description of molecular tests that may help in the diagnosis. Furthermore, a description of the current molecular tests required to identify patients for treatment is offered. The application of molecular pathology techniques to the clinical practice has already shown its usefulness and the number of such tests is growing exponentially as more molecular targets are discovered. Molecular Pathology and Diagnostics of Cancer will give practicing and training pathologists an up-to-date resource to guide the correct management of pathology cases requiring molecular testing.

**Medical Writing: A Prescription for Clarity**
By Neville Goodman, Martin Edwards, Andy Black
2014 (3rd ed), 356 pages, ~EUR40

Effective communication is the ultimate, but often daunting, purpose of any medical research or review. This book provides the practical information necessary to turn first drafts into concise, unambiguous text, without loss of individuality. Written by a consultant anaesthetist and two experienced medical editors, all sympathetic to the problems and needs of medical writers, the book deals with the basic craft of writing, from choosing the best word or phrase to essential grammar. This expanded fourth edition includes many more words better replaced, and deals explicitly with the problems of writers whose first language is not English. Whether you are writing a simple clinical report or a thesis, supervising others, running a course on medical or scientific writing, or just want to develop your skills in written communication, this book is the ideal guide and reference. Clear, simple and precise, and illustrated with apt cartoons, this is an invaluable handbook.

**Molecular Testing in Cancer**
By George M. Yousef, Serge Jothy
2014 (1st ed), 678 pages, 85 illus, ~EUR150

Molecular Testing in Cancer provides a state of the art review of clinically relevant molecular pathology in cancer. The book provides a brief, easy to read review of commonly employed diagnostic molecular techniques including recently developed "next generation" analytic tools, and offers a system-based run-through of the utility of molecular testing in individual cancer types, as well as reviewing current markers in cancer diagnosis, prognosis, and management. The volume also provides a prospective for the future which includes recently characterized and emerging biomarkers.

**Diagnostic Pathology: Gynecologic Pathology**
By Ester Oliva, Marisa Nucci
2014 (1st ed), 800 pages, ~EUR250

Designed as an easy-to-use and comprehensive reference for practicing pathologists and pathologists-in-training, Diagnostic Pathology: Gynecologic Pathology is a highly anticipated title in the Diagnostic Pathology series offered by Amirsys. This textbook is filled with bulleted, but highly detailed, text on common and uncommon entities involving the female genital tract including tumor and tumor-like lesions. It is filled with superior medical images, including gross and microscopic pathology, a wide range of supportive immunohistochemistry, and detailed medical illustrations with numerous examples of morphologic findings. For each site within the female genital tract, you’ll find reference to important anatomic, histologic, and specimen handling issues including those encountered at the time of frozen section. In addition, uncommonly discussed topics such as inflammatory diseases of the vulva are covered by experts in the field of dermatopathology. You’ll also find new information on classification of squamous lesions of the distal female genital tract. Moreover, each chapter will cover the role of immunohistochemistry as well as other ancillary techniques in the differential diagnosis in gynecologic pathology. This volume is intended to be a concise, user friendly, superior diagnostic textbook for the busy practicing pathologist as well as pathology residents and fellows in training.
Diagnostic Immunohistochemistry
By David Dabbs
2013 (4th ed), 960 pages, ~EUR320

Diagnostic Immunohistochemistry presents the latest information and most reliable guidance on immunohistological diagnoses in surgical pathology. David J. Dabbs, MD and other leading experts bring you state-of-the-art coverage on genomic and theranostic applications, molecular anatomic pathology, immunocytology, Non-Hodgkin’s lymphoma, and more. Additional features such as tables discussing antibody specifications, differential diagnosis boxes, ancillary anatomic molecular diagnostics, and full-color histological images ensure user-friendly coverage that makes key information easy to find and apply. The fully searchable text is also available online at expertconsult.com, along with a downloadable image bank and access to Path Consult. This concise and complete resource is today's indispensable guide to the effective use of immunohistochemical diagnosis.

Enzinger and Weiss's Soft Tissue Tumors
By John Goldblumb, Sharon W. Weiss and Andrew L. Folpe
2013 (6th ed), 1176 pages, 2000 illus, ~EUR320

Enzinger and Weiss's Soft Tissue Tumors is your essential medical reference on the diagnosis of tumors of the skeletal muscles, connective tissue, fat, and related structures. No other source matches Enzinger and Weiss's scope and depth of coverage in this complex and challenging area of surgical pathology, and no other text contains as much practical information on differential diagnosis. Microscopic findings are correlated with the latest developments in molecular biology, cytogenetics, and immunohistochemistry, providing you with a comprehensive and integrated approach to the evaluation of soft tissue specimens.

Intraoperative Frozen Sections
By Pedram Argani and Ashley Cimino-Mathews
2013 (1st ed), 288 pages, 500 illus, ~EUR120

Intraoperative Frozen Sections presents diagnostic challenges involved in the evaluation in the pathology lab of specimens obtained during surgery through the case experience of expert pathologists. Sixty three problems cover the wide range of approximately of problems encountered in intraoperative consultations. Each presentation provides the case information as presented to the consultant, the evaluation and analysis of the specimen, discussion of the results and teaching points observed in the case, and an overall comment providing additional context for the diagnostic problem that has been presented. This problem-oriented format makes the book a superb reference resource for the working diagnostician and an ideal teaching tool for the resident or fellow. Coverage includes pediatric specimen there is a section describing recognition of artifacts. Each case presentation is supported by several high-quality color photomicrographs with detailed explanations of each image, including images of the permanent sections and immunostains where applicable.

Prof. Gordan Vujanic