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Readers of the UWOMJ will likely have noticed the absence of new issues of the journal over the last two years. The reason, as I often had the opportunity to explain to my fellow students, was the sad imbalance between our production costs and quickly-shrinking budget. The dissolution of our previous advertising partner – and principal financial source – in mid-production left the journal short on funds and scrambling to find alternative sources of income. Without sufficient resources, the printing and distribution process could not move forward.

Yet this apparent dormancy on the part of journal publication belies the enormous amount of activity and change which have taken place “behind the scenes” during this period. The past year saw the launch of a new updated website featuring a number of issues published exclusively online. While perhaps less satisfying than seeing the journal in hard copy, going online allowed us to clear the backlog of issues which had been long completed but arrested at the printing stage. The editing process was also improved with the reintroduction of the faculty-review process, whereby student submissions were reviewed by faculty experts before coming to print. This has helped to enhance the quality of articles, something which I am confident will be evident to our readers. Most important, perhaps, has been the renewed interest in the journal among first- and second-year medical students, many of whom have contributed either through submissions or by serving as editorial staff. Their hard work and creativity have ensured the continuation of the journal as a viable, high-quality publication.

It is this point which I especially hope to impress upon our readers. The efforts of our editorial staff, in particular our Junior Associate Editors, Wendy Ng and Amber Menezes, have reworked the production process and allowed this issue to be printed. Yet the lack of committed funds means that the journal remains in a precarious situation and that future financial difficulties may once again put a halt to production. It remains to our readers and the Faculty of Medicine at UWO to determine the degree of support which the journal should receive.

On that note, I would sincerely like to thank the Department of Paediatrics at the Schulich School of Medicine and Dentistry for their financial donation to the journal, which helped to offset the cost of our “Pediatrics” issue. I am also grateful for the support of our numerous faculty reviewers who have contributed their time and expertise. Finally, I would like to give special mention to Dr. Ronald Wexler, whose continued interest in the UWOMJ since his own days as Editor during medical school is truly a source of inspiration.

Sordid monetary matters aside, it has been a great pleasure and privilege for me to serve as Editor-in-Chief of the UWOMJ. I am happy and excited to give you the “Oncology” issue, and I hope that it may be the beginning of a revived journal for many issues to come.

Sincerely,

Eisar Al-Sukhni
Editor-in-Chief
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Editorial

Oncology is a far-reaching specialty encompassing medicine and surgery. In such a broad field, the issues that can be explored are limitless. We would like to thank our authors and editors for their research into the many different facets in this fascinating area. Their hard work is reflected in the diversity and the depth of the articles presented in this edition of the University of Western Ontario Medical Journal. We would also like to thank the faculty reviewers who have taken the time to offer feedback and mentorship to our authors. Finally, we would also like to thank CU Advertising for their assistance and support. This Oncology edition features articles ranging from research to reviews to commentary and reflection. We look forward to hearing your thoughts, suggestions and comments for continual improvement.

After a brief hiatus from regular publications, we are extremely proud to introduce our new Faculty Advisory Board. Furthermore, we have established a new panel of faculty reviewers to aid us in maintaining the high standards of the journal. It has been an honour to work with and learn from faculty, as well as our fellow students and future colleagues.

With these new changes in place, we are excited for the future and we look forward to bringing you more stimulating and thought-provoking pieces. The University of Western Ontario Medical Journal’s future has never looked better!

Please write to us at uwomj@meds.uwo.ca with your feedback.

Sincerely,

Wendy Ng and Amber Menezes
Junior Associate Editors

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Diagnostic Review

Examining the Efficacy of Positron Emission Tomography (PET) in Cancer Diagnosis

Mark Kirchhof, Meds 2009
Jaron Jia Rong Chong, Meds 2010

Diagnostic imaging has become the cornerstone of cancer diagnosis. Over the past twenty years, computed tomography (CT) has become the most widely adopted imaging method for detection and staging of a variety of cancers. However, there are many limitations to the use of CT in the diagnosis of cancer. For example, CT does not have the ability to distinguish between malignant and benign lesions. As such, functional imaging methods, such as positron emission tomography (PET), has gained an increased following in the medical community. PET allows clinicians to evaluate the functional characteristics of tumours and is superior to CT in the staging of a variety of cancers. Despite these benefits, the regulatory boards that govern the healthcare system in Canada have been slow to adopt PET as a standard of care due to some of the inherent limitations of the technology. New technology, such as multi-modal imaging involving PET in combination with CT, will undoubtedly address some of these inherent limitations. These developments will continue to increase the pressure on healthcare administrators to re-evaluate their positions on PET use in cancer care. Herein, we discuss some of the benefits and limitations of PET use in cancer diagnosis.

This article has been reviewed by Dr. Jean-Luc Urbain.

Introduction

Positron Emission Tomography (PET) is playing an increasing role in the diagnosis and staging of cancers since its development in 1973. However, the rate of adoption has not been equal throughout all nations and technology uptake has been limited by the approval of funding authorities. In Canada, as of June 2005, there is an installed base of 12 PET scanners, only 3 of which are available for clinical usage. This situation has created a dilemma for public health officials, nuclear medicine diagnosticians, and cancer patients alike as the debate continues over the clinical utility of PET scanning. This review describes the role of PET in oncology.

Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a medical imaging technique whereby a radioactive tracing compound is administered to a patient and the resulting radiation emissions detected by a detection array. These emissions are then analysed and reassembled into a three dimensional image of the target body region. The radioactive tracing agents all emit positrons (positively-charged electrons). When this emitted positron collides with a regular negatively-charged electron, two gamma rays are released at 180 degrees apart from each other. The PET detector array surrounds the patient in the shape of a ring. When two gamma rays are simultaneously detected on opposite sides of the ring, the trajectory of the rays can be traced back to their origin. A single trajectory is insufficient to compile an image. However, over the course of an acquisition, enough trajectories are detected to be analysed and compiled into an image. When these radioactive tracing agents are manufactured, they usually come in the form of modified molecules commonly found in the body. The most commonly used agent, $^{18}$F fluorodeoxyglucose (FDG), is an analog of glucose that cannot be metabolized by the body. FDG tends to accumulate in tumour cells with higher metabolic rates, which uptake greater amounts of glucose. This allows for high-contrast differentiation between tumours and normal tissues as well as more accurate diagnosis and staging, especially with regards to metastasis.
Clinical and Economic Evidence Supporting Usage

The effectiveness of PET scanning in the diagnosis and staging of tumours has been strongly established for several types of cancer, namely lung cancer, breast cancer, and colorectal cancer. Research from Brink et al. found significant increases in the sensitivity of FDG-PET in detecting and staging small-cell lung cancer over conventional imaging methods. In breast cancer patients, FDG-PET was able to find distant metastases in “30% of patients who were thought only to have local-regional recurrence” ultimately suggesting that PET may be useful for patients suspected of having tumour recurrence as well as identifying distant sites of metastases. Also important in the treatment of breast cancer is axillary lymph node staging, identified as a key factor in patient survival. While the majority of Stage I/II Canadian breast cancer patients currently undergo axillary lymph node dissection as a diagnostic methodology, it has been suggested that PET could offer a less invasive option. Similar results have been found using PET in the initial diagnosis of colorectal cancers. Although PET performed similarly to X-Ray Computed Tomography (CT) in the diagnosis of local lymph node involvement, PET was found to be superior to CT in the detection of hepatic metastases, with significantly greater sensitivity (88% vs. 38%).

Equally important to the usage of PET are issues of expense and cost-effectiveness. In an article by Valk et al., the cost-effectiveness of whole-body PET staging of multiple cancers was determined with the main finding being that surgical procedures averted through PET use resulted in savings ratios of 2:1 to 4:1. An economic analysis using PET for the work-up of pulmonary nodules and small-cell lung cancer in Italy found an overall cost savings using PET with very high sensitivity (89% - 94%) and specificity (80% - 100%). Canadian economic analysis confirms the cost-effectiveness of PET for staging for cancers. In an Alberta study, the cost per scan was found to range from $1,231 if 3200 annual scans were performed to $7,869 if 400 annual scans were performed, with a large portion of the cost coming from regulatory requirements. These per scan costs represent a significant savings over current rates from the United States. Research from Newfoundland found an estimated cost per PET study of $2,195 and that each PET device would only require 740 cases per year to break even.

Limitations of FDG-PET in Oncology

The major drawback in the use of PET is the prevalence of false-positives. The stomach, colon and small intestine are capable of FDG uptake making it difficult to distinguish normal tissue from neoplasms. In addition, since FDG is excreted via the urinary tract, intense accumulations of FDG can be found in the kidney and bladder which can limit PET use in the evaluation of gynecologic malignancies as well as exclude its use for detecting tumours of the bladder, local pelvic lymph nodes and prostate.

Inflammation is another confounding process in the use of FDG-PET. This becomes particular important in cancer patients that have been treated with chemotherapy or radiotherapy in which tissue damage has occurred, and the possibility of inflammation is high which sometimes requires weeks to months for healing before PET-FDG can be used. Related to the inflammation-based false-positives, infections, such as tuberculosis, can result in elevated FDG uptake in local lymph nodes making it difficult to differentiate between a lymph node neoplasm and immune cell proliferation. Other forms of healing, such as bone and joint processes, can also give false-positives. Healing bone can show FDG uptake for up to 6 months after sustaining an injury. Degenerative joint disease can also show elevated FDG uptake resulting in an intense, asymmetric signal that could be misdiagnosed as an osseous neoplasm.

Another major problem area, in the use of PET in an oncology setting, relates to FDG-PET use in endocrine tumours. Gastropancreatic neuroendocrine tumours have had limited detection success rates such that only tumours that have very high proliferative rates and a low stage of differentiation have been identified using FDG-PET. Hyperglycemia is another major limitation in the use of FDG-PET. This is particularly prevalent in pancreatic tumours or small pancreatic masses in patients with diabetes mellitus. Finally, in patients with pheochromocytoma, a neuroendocrine tumour of the adrenal gland, FDG-PET is incapable of distinguishing between the malignant form and the benign forms of the disease.

The Future of PET

While FDG uptake is substantially higher in most types of tumours, there are many exceptions, some of which have already been mentioned. Another drawback in the use of FDG as a tumour detecting tracer is that it does not differentiate between specific types of cancer. As such, a variety of alternative tracers are currently being investigated for their application in cancer therapy. These alternative tracers are based on DNA analogs to detect rapidly proliferating cells, amino acid analogs that detect cells producing higher levels of proteins and receptor agonists that allow for the identification of tumours expressing...
specific markers. A good example of this, is $^{18}$F-fluoro-$\beta$-estradiol which binds to estrogen-receptor positive breast cancer cells which, in this case, would alter the course of treatment for the cancer.

Paralleling the development of these new tracers is the use of supplemental imaging technologies, such as CT, in conjunction with PET. PET/CT produces better body maps in less time and as such the higher initial equipment costs are offset by increased throughput. The improved anatomical localization achieved using PET/CT can lead to improved diagnostic certainty, better biopsy guidance and ultimately better treatment for the patient. The only major drawback of PET/CT is the increased dosage of radiation the patient receives. Researchers have started to experiment with the possibility of PET/MRI since MRI provides better anatomical information and excellent soft tissue contrast over CT with far less radiation exposure. However, currently the detection technology used in PET scanners does not function well within the magnetic field of the MRI machinery.

Conclusion

The use of PET in the diagnosis of cancer has been a controversial topic among the medical community in Canada. This review has touched upon some of the major arguments in this continuing debate. It is apparent that PET usage in lung, breast and colorectal cancer has clear clinical advantages over current imaging technologies. Combined with many studies that show the diagnostic value of PET in these cancers actually decreases medical expenses, it becomes evident that the provincial governments across Canada should adopt PET scans as a standard in patient care in these situations. Conversely, it should be noted that PET is not an imaging panacea as there are many limitations in a variety of cancers. With new tracers and new technologies, like PET/CT, it is expected that the breadth of diagnoses that can be made with PET will increase. This will provide further impetus to examine the adoption of PET in more medical centres across the country.
Dr. Fei-Fei Liu obtained her medical degree from the University of Toronto and subsequently completed a fellowship at Stanford University. She returned to Toronto to begin clinical work at Princess Margaret Hospital but found herself delving into basic science research in her spare time. Over the years, her research expanded and she became the principal investigator of her own laboratory. Whether seeing patients on her clinic days, focusing on her research, or spending time with her family, Dr. Fei-Fei Liu’s optimism and sense of humor carry her through the challenges of balancing her multi-faceted career with her home life.

This article has been reviewed by Dr. Ken Harris.

Born in Taiwan, Dr. Fei-Fei Liu moved to Canada with her parents at the age of 8 and has been in Toronto for most of her life. Her post-secondary education began with two years of undergraduate coursework at the University of Toronto (U of T), followed by four years of medical school, also at the U of T. She started her training in internal medicine and then further refined her interests by specializing in radiation oncology.

Her love of basic sciences research was sparked during her fellowship at Stanford University in 1987 with the study of clinical hyperthermia. By 1988, Dr. Liu was on staff at Princess Margaret Hospital (PMH) and was expected to devote all of her working hours to her clinical assignment. Nevertheless, she arranged to pursue her new-found fascination with laboratory research on evenings and on weekends. Given the lack of a model for a clinician-scientist at the time, the support of her mentors proved invaluable. Because she did not pursue a Ph.D., Dr. Liu had to learn through experience the science and the art of presenting meaningful data and of writing grants and manuscripts to secure peer-reviewed funding. Ultimately, Dr. Liu’s hard work allowed her to diminish her clinical commitment to 20%, with the remaining 80% of her intense work schedule being devoted to research. This mixture has proven fulfilling for Dr. Liu, who values the creativity and the problem-solving aspects of research and the ability to eventually translate the research findings into new ways of treating her patients. As the director of the U of T’s Department of Radiation Oncology Fellowship Program, Dr. Liu has been able to use the knowledge that she gained as a researcher and a physician to design a two-year, transdisciplinary, clinician-scientist program of international stature for radiation medicine training.

From her career, Dr. Liu has learned that scientific accomplishments are mostly achieved through hard work, passion, organization, and a competitive spirit, with luck also playing a role, albeit a minor one. Recognizing opportunities and networking within the scientific community are also essential. Flexibility and communication are likewise useful tools. Although Dr. Liu’s research began with the study of clinical hyperthermia, she began to explore new avenues upon re-evaluation of the data. Therefore, it is important to recognize the difference between perseverance and obstinacy. This distinction can mean the difference between steadfastly pursuing a futile research path for the sake of not giving up versus believing in a project that shows signs of long-term rewards.

Women often face unique challenges when pursuing an academic career in the basic sciences. At the Department of Medical Biophysics, with which Dr. Liu is affiliated, she has observed that although approximately half of all registered graduate students are female, this number declines as one progresses from a Master’s degree to the Ph.D. stream. Further up in the hierarchy, there are only 12 female principal investigators at the Ontario Cancer Institute (the research arm of the PMH) out of a total faculty of 68. Dr. Liu speculates that the research environment tends not to be friendly towards women as they are often more collaborative and conciliatory in nature, thereby focusing on a team-building approach. Meanwhile, men, in general, focus more on individual accomplishments, which better complements the merit system in academia. Because women are still the predominant caregivers in a family, those who begin to focus more
time on their children may see career advancement opportunities evaporate as research productivity declines. Clinical work appears to offer more flexibility for women—as possibly reflected in there being a majority of female medical students at the U of T—because private practice offers the convenience of control over hours devoted towards work versus family life.

In spite of these external forces, Dr. Liu is proof that building a career in research is not impossible for women. She stresses the importance of finding a spousal partner who can support you and your career choices and of being able to reciprocate this support, which involves continual work to build and to maintain a strong marital relationship. Time management is the key to balancing the demands that come from many different directions and to doing one’s best in all aspects of life. She believes that family life provides the anchor for satisfying work. At the end of a stressful time at work, family is what provides the strength to embrace a new day.
Clinical Procedures

The Role of Gastrectomies in the Management of Gastric Cancer: an Overview

Brent Mollon, Meds 2010

This article has been reviewed by Dr. Neil Parry.

Introduction

Cancer of the stomach is considered to be a major cause of cancer death worldwide, and is most prevalent in Japan, China, Korea, Central Europe and Central/South America.\(^1\) In Canada, the projected number of new cases and deaths in 2006 is estimated as 2800 and 1850, respectively.\(^2\) Thus, gastric cancer is the 8\(^{th}\) leading cause of cancer deaths in this country.\(^2\)

The difference in prevalence of this disease between Canada and other countries is believed to be partly due to diet. Foods high in carcinogenic compounds, like benzopyrene and N-nitroso compounds found in smoked or preserved foods, are believed to be one of the causative factors of gastric cancers.\(^1\) Indeed, gastric cancer incidence in the United States has decreased fourfold since 1930, and has been attributed to improved storage of food with decreased use of preservatives.\(^1\)

Early gastric cancers are often asymptomatic, leading to late diagnosis in many cases.\(^3\) Symptoms, once they develop, include weight loss, vomiting, an abdominal mass, indigestion, anorexia, and vague epigastric pain.\(^1\) Endoscopic studies with biopsy are considered to be the gold standard procedure to diagnose gastric cancers, although an upper-gastrointestinal X-ray series using a double contrast of air and barium has been noted to detect 86.9% of lesions.\(^1;3;4\)

Once the diagnosis of stomach cancer is made, the stage of the tumour should be established through physical examination, computed tomography, and possibly laparoscopy.\(^5\) While the correct approach to tumour staging is beyond the scope of this paper [see Reference 5 for summary of this information], tumour stage is the primary determinant of therapy. For example, the location of the tumour, the extent of lymph node involvement and the presence of metastatic sites all modify the operation which will be undertaken.\(^6\) As a gastrectomy is believed to be the only curative treatment for this cancer\(^7\), this article will focus on this procedure.

Gastric Cancer Resection

Gastrectomy

A curative gastrectomy refers to the removal of the stomach, which may be either partial (subtotal) or complete (total), followed by reestablishment of the GI tract.\(^6\) Tissues are removed to allow for at least 5 cm margins from the tumour in order to ensure complete excision of the cancer. Intra-operative pathology to prove cancer free margins is essential. The lymph nodes around the splenic artery are also removed and attempts are undertaken to preserve the spleen. While the pancreas is not often removed, the greater omentum along with the left gastric, celiac and common hepatic nodes are.\(^6\)

Multiple reconstructive methods can be used to establish GI continuity, although the type of gastrectomy (subtotal vs. total) will influence which one is performed. Sub-total gastrectomies, for example, can be followed by either Billroth I, Billroth II, or Roux-en-Y gastrojejunostomy (see Figure 1).\(^6\) A Billroth II reconstruction is advantageous over as Billroth I as it removes the stomach (and anastomosis) from the gastric bed, while a Roux-en-Y gastrojejunostomy prevents bile reflux. However, the Roux-en-Y procedure will expose the intestinal mucosa to gastric secretions produced by the proximal stomach, requiring the surgeon to either perform a truncal vagotomy or have the patient take proton-pump inhibitors for life to prevent ulcerations. Total gastrectomies are classically followed by a Roux-en-Y esophagojejunostomy reconstruction to connect the esophagus to the intestinal tract. Nonetheless, the higher mortality associated with total gastrectomies compared to the subtotal procedure has lead to surgeons proposing several modifications to the total gastrectomy in hopes of improved outcomes.\(^6\)

Palliative gastrectomies are also performed to relieve symptoms, such as gastric outlet obstruction or bleeding, of a patient with end-stage disease.\(^8\) While distally-located tumours may be resected, the poor prognosis associated with surgery for advanced proximal tumours suggests that other measures, such as bypass or venting gastrostomy tubes, should be undertaken for palliation.\(^9\)
**Pre-Operative Considerations**

Before undertaking a gastrectomy, a surgeon must first determine if a patient is able to tolerate the operation and if the tumour is resectable. Pre-operative investigations should include a full pulmonary and cardiovascular work-up. Computed tomography (CT scan) of the chest and abdomen are necessary to determine the size and location of the tumour as well as any metastatic disease. One should also obtain routine pre-operative blood work such as a complete blood count (to identify anemia), electrolyte panel, BUN, creatinine, coagulation profile, and liver function tests. The following measures should enable a surgeon to determine if an individual can tolerate surgery.

**Post-Operative Considerations**

Once the procedure is complete, a surgeon should take steps to ensure that a patient achieves adequate oral caloric intake while also evaluating the need for B12 injections due to the loss of intrinsic factor. Lastly, the need for annual physical examination, blood work and imaging to identify any metastases should be stressed to the patient as well as their family physician.

**Lymphadenectomies during Gastrectomies**

When surgically resecting a tumour, it is also important to remove the lymph node drainage of the tumour to limit metastatic spread. Lymphadenectomies for gastric cancers are classified as either D1, D2 or D3. D1 lymphadenectomies include the removal of the perigastric lymph nodes only. D2 lymphadenectomies remove the lymph nodes along left gastric, hepatic, celiac and splenic arteries in addition to those in the splenic hilum and the perigastric regions, and D3 lymphadenectomies remove the aforementioned nodes in addition to those within the porta hepatitis and periaortic regions. Numerically, D2 lymphadenectomies remove an average of 27 nodes (range of 17-44), while the D3 procedures remove an average of 43 (range of 25 to 64).

How aggressive surgeons should be while conducting lymphadenectomies is an area of much debate. Supporters of extensive lymphadenectomies note that these procedures should improve patient outcomes by helping to ensure no positive lymph nodes are left in after the operation, while also enabling physicians to more accurately stage the disease. This improved benefit has been noted in respective reports. However, other researchers have noted that large randomized controlled trials have failed to show any improvements in survival rates between D1 and D2, or D2 and D3 procedures.

Despite such discrepancies in the literature, most researchers and organizations in North America prefer D2 lymphadenectomies over D1 procedures. However, as surgeon experience is related to...
complications, it has been suggested that aggressive node dissection only be undertaken by surgeons who have demonstrated sufficiently low patient morbidity and mortality rates. This would help ensure that the benefits of extensive lymphadenectomies, if any, would not be overshadowed by an increased risk of surgical complications.8

Conclusion
While the incidence of gastric cancers has decreased dramatically, it still remains the 8th leading cause of death due to cancer in this country. This article explores what is considered to be the only known curative treatment for this form of cancer, a gastrectomy, while also noting preoperative and postoperative clinical considerations. While the debate about how extensive lymphadenectomies should be continues, the size/location of the lesion in addition to surgeon experience appear to be the main determinants of whether a D2 or D3 approach is most appropriate so as to limit surgical complications while maximizing clinical benefit.

References
Computing for Cancer: the role of distributed computing in cancer research

Samuel Krausz, Meds 2009
Jordan Glicksman, Meds 2010

Computers have always been used in medicine for patient management, personal research and communication. Recently, the utilization of massively parallel processing, brought about by distributed computing grids, has allowed for cancer researchers to develop drugs and test therapies at speeds never before available. The use of distributed computing in testing molecules for their cancer protein binding potential, automated tissue microarray analysis and tumour growth modeling are all currently promising research areas. Despite some inherent challenges, distributed computing may one day be used extensively in all areas of medical research.

The Internet may be synonymous with browsing and email, but its utility is much greater. The Internet is often used to garner information, be it a patient searching for facts regarding a recent diagnosis, or a physician trying to find the latest published research on treatment for an obscure disease. A conceptual link which is not immediately made, however, is the applicability of computers and the Internet in producing potential breakthroughs in cancer research.

Cancer research has traditionally focused on exploring epidemiology, practical experiments in molecular biology, clinical trials of potential medications or therapies and, more recently, an exploration of immunotherapy and gene therapy. It is a direct extension of cancer research’s foray into molecular biology and genetics which has ushered in the use of computers in the oncological arena.

History of distributed computing

Since the birth of computers over fifty years ago, the raw speed of computation has increased by a factor of over one million.\(^1\) Despite this increase in computational power, personal computers are still considered extremely slow in terms of requirements for solving highly complex scientific problems.\(^ 1\) Cancer research is one such area where the complexity of molecular and biological interactions practically precludes the use of even modern personal computers in any but the simplest experiments.

One method of solving this problem emerged in the 1980’s, and involved clustering multiple individual computers to form what was termed a ‘supercomputer’.\(^ 1\) While these combined computers have powers greatly exceeding those of individual units, the supercomputer must remain in a dedicated location, and both physical and economical constraints limit the system’s size.\(^ 1\) This static model of a supercomputer eventually evolved with the proliferation of the personal computer to ordinary individuals. With the subsequent advent of the Internet, a means of connecting individual computers located thousands of kilometers apart was feasible, and the birth of ‘distributed computing’ or ‘GRID computing’, was made. Before long, it was realized that most of the current 400 million computers’ processors sit idle for long periods of time, thus providing a potentially enormous computational resource. With the use of distributed computing, the formation of a supercomputer consisting of thousands or millions of individual computers was possible and finally ushered the way towards truly useful cancer research using computers.

Current implementations of distributed computing projects involve both a central server and client software downloaded by individual users.\(^ 2\) A simplified explanation of the system revolves around the server breaking apart a complex project and distributing chunks to individual clients. The client computers process these chunks, during idle processor time or when a screensaver is running, and the forward the completed work to the central server. The server combines these with other completed chunks and distributes further work to the clients.\(^ 3\)
While many scientific projects attempted to make use of distributed computing, cancer researchers quickly discovered the value this system could have in solving some previously insurmountable molecular biology problems.

**Searching for anti-cancer drugs**

One project, funded by the National Foundation for Cancer Research and run by Oxford University and United Devices, aims to discover drugs suitable for killing cancerous cells or retarding their growth. Normally, it takes between 12-15 years from a molecule’s discovery to go through the process of effectiveness and safety testing and regulatory approval to finally reach the consumer market. Almost half this time is spent screening potentially therapeutic compounds, a time which this project hopes to reduce significantly.²

In essence, the Cancer Project engages in a game of reduction and simplification. The project started with a list of over 1 billion compounds found in commercial catalogues and combinatorial chemical libraries. The list was reduced to compounds with drug-like properties, namely ones with suitable molecular masses and solubilities, which yielded a total of 35 million compounds. With this list, an exchange of various functional groups in each molecule produced 100 derivatives for each compound, producing a final collection of 3.5 billion potential anti-cancer drugs.² Twelve cancer-related proteins, with established active sites, were subsequently chosen for testing. Each of the 3.5 billion compound was to be tested against these active sites, in order to discover which would bind and potentially interfere with the given cancer protein’s method of action.²

Even with the small list of proteins being investigated, the vast number of potential molecules and bindings was daunting. Moreover, in order to reduce error and improve quality and reliability, each molecule needed to be tested multiple times and ranked in terms of binding potential and binding energies. The sheer scale of the project involved the largest computational chemistry project ever undertaken.² One year after the project’s launch however, over 1.5 million volunteer computers were recruited, in over 200 countries, producing a virtual supercomputer which had processed over 100,000 years worth of CPU time.² Calculations were proceeding at a rate of 15,000 molecules screened every second and eventually came up with a list of 800,000 potential molecules in 2002.²

While this ‘shortlist’ of molecules is only a fraction of the original 3.5 billion, it is still far from being a feasible amount testable against cancer. The project has since continued to a second phase, where distributed computing, together with software called LigandFit, will determine, and more accurately prioritize, the suitability of these molecules for actual drug development. As of this year, the second phase of the project has involved over 1.9 million volunteers and has computed almost 43 years worth of computational time, but is not yet complete.²

While this project’s progress seems highly encouraging, there are still many difficulties in the approach. First, the active site on target proteins may not always be previously known. While brute-force computational searches for binding sites based on ligand-protein energy of interaction can be attempted, this is not feasible. The amount of calculations necessary for this type of search far outnumbers the capabilities of even the largest of distributed computing systems.² An efficient automated method of discovering these active sites must be developed, or else searches must be limited to small parts of the molecule instead of complete ligands. A second problem does not involve computation power, but rather social aspects of the system. As distributed computing requires large amount of volunteer computers, a given computational power cannot be guaranteed. Individuals may lose interest and uninstall the program or competing research may foster greater support and thus eliminate potential participants from the available pool. Furthermore, questions of security and viruses, of paramount importance to today’s consumers, must be addressed before widespread acceptance is achievable. There are methods of combating these risks, but they must be used effectively and transparently to the end-user. Efforts at recruitment, either through appropriate advertisement or incentives, must be considered if distributed computing is to be used successfully for future projects. Also, this type of investigation is hypothesis generating and not hypothesis testing in nature. Thus, while research such as the Cancer Project may eventually narrow down a small list of drugs to be tested, drug company involvement, governmental regulation and most importantly, in vivo testing, must all be completed before successful drugs can be produced and used.
Other distributed computing cancer projects

Distributed computing, in its fight against cancer, is not simply limited to screening potential drugs. A novel use of this technology is being developed utilizing IBM’s World Community Grid (a distributed computing environment) together with a new tool called tissue microarrays (TMA). TMA’s allow researchers to determine the specific cancer type and stage of a given tissue sample and systematically determine which therapies may be effective. A specific treatment can then be utilized based on the presence of a given biomarker. While TMA’s are arguably quite useful, their major limitation revolves around the subjective interpretation of the array by observers. By digitizing the specimens, computers can be utilized for this assessment, although the analysis is computationally very complex. While few biomarkers have been examined to date, a large database of these markers, coupled with the power of a distributed system, could allow parallel analysis of hundreds of arrays together with simultaneous experiments on them. This increased speed in computation and analysis, which would not be possible on an individual computer, could allow for the discovery of minute changes in measurable factors and thus facilitate future research in cancer biology and drug discovery.

Other cancer-related research projects utilize distributed computing in various ways. Some, like Parabon’s Compute-against-Cancer, aim to analyze patient responses to chemotherapy and thereby mitigate potentially adverse effects. Others, like Integrative Biology (IB), started in 2004, aim to develop all-encompassing models for future research. IB is a project aiming to build a secure and resilient distributed infrastructure which will be used to develop complex models of cancerous tumour growth. Eventually, it is hoped this system will allow for the understanding of cancer’s biological mechanisms completely. This system will utilize high-performance computers, large databases and complex visualization systems to achieve this goal. While the technical methods of distributed computation are similar to those used in the Cancer Project, the computer network consists solely of researchers and super-computers at specific facilities, not necessarily volunteer computational cycles provided by individuals.

It is evident that distributed, or GRID, computing holds tremendous potential in the field of cancer research. It is important to note that this technology is not limited to oncology, and has prospective use in helping develop cures for many diseases ranging from AIDS, to Alzheimer’s. The ever-increasing speed of both personal computers and the Internet will undoubtedly benefit future research utilizing this technology and may, one day, make distributed computing a method of choice in developing better therapy for a wide variety of diseases.

References

The field of neuro-oncology has shown dramatic advancements over the past several years after a period of relative quiet throughout much of the late 20th century. We are at a pivotal turning point in the field as genotyping and further advances in the use of chemotherapy continue to push the borders of brain tumour therapy. Thus, it seems fitting at this point in history to have a brief look at the origins of neuro-oncology and the more recent developments that are advancing the field at a rapid pace. This article takes its readers through a tour of the origins of neurosurgery and then analyzes the more recent multimodal approach to neuro-oncology to give some perspective and appreciation of this rapidly evolving field.

Introduction

Despite having developed tremendously over the past several centuries, the field of neurology is one area in medicine that is continuing to show rapid growth in all facets even today. With improvements in imaging and genetic analysis, neurology is growing by leaps and bounds, transforming a specialty that was primarily diagnostic a few decades ago to one in which interventional procedures and curative treatments are becoming increasingly common.\(^1\)\(^,\)\(^3\)

Another field which has continued to improve, thanks in large part to the advent of radiotherapy over the past century and rapid developments in the field of chemotherapy, is that of oncology. Cancer research has plastered the pages of the lay press on a daily basis over the past decade and continues to make headlines within the scientific community as one of the fastest evolving fields in medicine today.

The field of neuro-oncology, in contrast, had a period of quiet in the last two decades of the 20th century as research and trials were unable to keep up with developments in other areas of medicine. The last decade, however, has seen progress in this blossoming field with the publication of several landmark trials. This article will place recent developments in a historical perspective, beginning with early neurosurgical work and concluding with a look at where current cutting-edge research is leading us today.

The beginnings and development of neurosurgery

Pre-1850: From trephining to anesthetics

Some form of neurosurgery existed in ancient societies, as evidence of trephining can be traced back over three thousand years to Ancient Egypt.\(^4\) However it was in 1573 that Giovanni Croce published *Chirurgiae*, a book which has the first depictions of a neurosurgical operation taking place.\(^5\) It was not until 1846 when William Morton discovered the usefulness of sulphuric ether, the first modern anesthetic, on the 16th of October at Massachusetts General Hospital\(^6\), that the field of neurosurgery began to flourish.

1850-1900: Removing tumours

These developments caused a flurry of activity on the surgical front and it was in 1879 that Scottish surgeon William Macewen described what is believed to be the first removal of a dural based tumour.\(^7\) It was a few years later in 1884 when British physician Alexander Bennett diagnosed a cerebral tumour in a patient of his and decided that surgical intervention would be the best approach. He asked surgeon Richman Godlee to operate and it was Godlee who carefully removed the tumour from deep within the cortex. The patient died soon after of infection but autopsy results indicated that this was perhaps one of the first gliomas to have been successfully excised from a patient.\(^8\)
1900-1950: Cushing to the gamma-knife

Surgical developments continued gradually over the next several decades and it was in the early 1930s when Harvey Cushing, a Professor of Surgery at Harvard Medical School, reported a remarkable decrease in the mortality of neurosurgical patients over the previous decade. After statistically analyzing over two-thousand verified tumours, Cushing showed significant decreases in the mortality rates of neurosurgery used to treat acoustic neuromas (25.0 to 4.4%), gliomas (30.9 to 11.1%), meningiomas (21.0 to 7.7%), and many other cerebral tumour subtypes. These advancements are simply one example of Cushing’s many significant contributions to the field of neurosurgery in the first half of the 20th century.

The next major development in the field of neurosurgery was the development of stereotaxic surgery by Ernest Spiegel in 1947 as he used a stereotaxic frame to accurately localize sites for the biopsy and treatment of neurological lesions. In 1950, Lars Leskell developed Spiegel’s apparatus to create the concept of stereotaxic radiosurgery using the ‘gamma knife’. Leskell thus became the first physician to be able to deliver radiation in a focused manner to localizable tumours within the brain.

Post-1950: Microsurgery and beyond

Neurosurgical developments continued over the next several years and it was in the late 1960s that Gazi Yagarsil, proclaimed “Man of the Century 1950-1999” by the well-respected scientific journal Neurosurgery, developed the concept of microsurgery. He developed the idea of performing surgery on small and delicate tissues with the aid of an operating microscope. This advancement in the field was unparalleled in its significance over the second half of the 20th century as it allowed surgeons to operate much more efficiently on the very fine and delicate structures within the brain.

Thus, in just over a century since the advent of modern anesthetics and the beginnings of surgery as we know it today, the field of neurosurgery developed significantly, allowing a safer and more precise approach to brain tumour resection. Advances in the field have continued over the past several decades but this serves as an introduction to the origins of the field of neuro-oncology as it is known today.

Beyond neurosurgery

The first step: Combining surgery and radiation therapy

In 1978 a landmark study by the Brain Tumor Study Group and the National Cancer Institute (NCI) reported on a prospective, randomized-controlled study which analyzed the use of a chemotherapeutic agent, 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU), and/or radiation therapy in surgical patients who were found to have anaplastic glioma. The results of this pivotal trial provided clear evidence for the benefit of radiotherapy as it prolonged survival from 14 to 36 weeks versus controls. The addition of BCNU alone produced a statistically insignificant increase in survival and the use of adjuvant BCNU to radiotherapy also yielded unimpressive results. This study paved the road for treatment over the next quarter century as postoperative cranial radiation became standard treatment for patients with malignant gliomas, but the use of chemotherapy remained on the sidelines for the time-being.

A side-step: Genotyping and brain tumours

It would be at the University of Western Ontario in London, Canada that the next major development in neuro-oncology would occur, over 20 years after the last milestone. In research that began a decade earlier, it was reported in 1998 that anaplastic oligodendrogliomas with coincident loss of chromosome 1p and 19q had increased susceptibility to chemotherapeutic intervention. The results were monumental and led to a flurry of activity within the neuro-oncological field in attempts to more carefully delineate genetic factors predictive of treatment response or prognosis. The use of genotyping and other forms of cutting-edge medical technology are thus serving an important role in the development and progression of neuro-oncology.

The second step: Surgery and chemotherapy... the relationship begins

Almost 25 years after the landmark Brain Tumor Study Group and NCI trial implicated that BCNU had a minimal role in the treatment for malignant glioma, the results a multinational randomized placebo-controlled trial that used BCNU wafers (Gliadel wafers) to complement surgery were published in April of 2003. The results indicated that the insertion of a small biodegradable polymer containing BCNU into the resection cavity at the time of surgery for malignant glioma increased median survival from 11.4 to 13.1 months versus the placebo group. Although the results may seem insignificant to most, this was the single largest increase in survival of malignant gliomas post-surgery in over 25 years.
The third step: Surgery, chemotherapy, and radiation therapy – finally united

In March 2005, Stupp and colleagues published the results in a multicentre international randomized-controlled trial addressing treatment of glioblastoma multiforme. In this study, patients were randomized, following maximum possible surgical resection, to receive either radiation with concurrent chemotherapy with Temozolomide followed by six cycles of adjuvant Temozolomide or radiation alone. Median survival in the radiation plus Temozolomide group was 14.6 months compared with 12.1 months in those receiving radiation alone. However the research made waves among the neuro-oncological community as it also indicated that combined treatment with radiation plus temozolomide led to two-year survival rates of 26.5% versus only 10.4% in those given radiation alone. This near tripling of 2-year survival rates was absolutely unheard of in the field of neuro-oncology.

Along with the publication of the landmark temozolomide trial came evidence by Monika Hegi that silencing of the DNA-repair gene O6-methylguanine-DNA methyltransferase (MGMT) is positively correlated to a significant survival advantage in those with glioblastoma multiforme. This finding illustrates the pivotal role that molecular analysis is playing in the advancement of brain tumour.

Future Directions: A rapidly evolving field

After nearly twenty years of largely unsuccessful efforts, the field of neuro-oncology has shown considerable developments over the past decade. With continued advancements in the fields of radiology, gene therapy, and cancer therapeutics in general, neuro-oncology has tremendous potential for development over the coming years. We are thus clearly at a frontier in the treatment and management of brain tumours and this brief look at past achievements in neuro-oncology provides perspective on future advancements.

References

Health Promotion

HPV Vaccination

Jennifer Clara Tang, Meds 2009
Jonathan Klein, Meds 2010

“One less daughter, one less sister, one less friend… whose life might be affected by cervical cancer. With Gardasil™, you could be one less.”

The young hip-looking teenager speaks this phrase with deep conviction as she stares out from the television. The North American approval of Gardasil™, a vaccine against the human papilloma virus (HPV) by Merck Frosst, has led to a media surge. As of July 10, 2006, Health Canada issued market authorization for sale and distribution of Gardasil™. The Society of Obstetricians and Gynecologists of Canada (SOGC) has been actively increasing its promotion of HPV awareness through radio spots and campus flyer distribution. Indeed, thanks to increasing media attention, HPV is the “disease de jour” that medical learners should understand. This review article hopes to provide a broad overview of HPV including current vaccines, guidelines surrounding these drugs, and challenges facing future vaccination programs.

This article has been reviewed by Dr. Osman Tarabain.

Background

In the past, HPV was overshadowed by other sexually transmitted infections like HIV, chlamydia, and gonorrhea. Many patients are oblivious to the fact that HPV is the most commonly sexually transmitted infection in the world. There are over 96 different strains of HPV, 30-40 which infect the genital tract. This group can be further subdivided into low risk HPV (which, at worst may cause ano-genital warts) and high risk HPV (associated with cancer). Condoms provide little protection, as HPV is transmitted through affected skin to skin contact. In most healthy individuals, HPV can be cleared by the immune system, leaving the patient no indication that they ever contracted the virus. However, if left untreated, certain strains of HPV, may lead to the second deadliest global cancer in women: cervical cancer. Anal, vaginal, vulvar and oral cancer may also result. Health Canada estimates that 75 percent of Canadians will have at least one HPV infection in their lifetime. A vaccine for HPV would hold great promise for developing nations, as they carry 80% of worldwide cervical cancer incidence and mortality.

Mechanism of Infection

HPV is a double-stranded non-encapsulated DNA virus with an 8 kb circular genome. Its viral capsid is formed by structural proteins L1 and L2, which play an important role in the vaccination. The virus is introduced through erosion or microtrauma of the epithelial layers, then proceeding to infect basal squamous epithelium. In a worst case scenario, a high risk strain of the virus will hijack basal keratinocytes, amplify itself, and slowly cause dysplasia, carcinoma in situ and finally, invasive carcinoma (fig 1). As mentioned previously, most patients affected with HPV will clear the virus. The time from viral infection to noticeable cauliflower-like lesion on affected skin can range from weeks to months. The time span from infection to development of invasive carcinoma, is roughly 10 years. This long time span explains why the incidence of cervical cancer rises over age 25 and is highest for women over the age of 40 years. Early identification of any dysplasia through the pap smears has helped to drastically reduce mortality due to cervical cancer (reduction in incidence rates from 21.6 per 100,000 in 1969 to 10.4 per 100,000 in 1990). Yet despite these screening efforts, every year cervical cancer continues to claim the lives of 273,500 women worldwide. An effective vaccination for HPV has the potential to eliminate associated cancers.
HPV Vaccination

Merck Frosst and GlaxoSmithKline have both developed HPV vaccinations, (Gardasil™ and Cervarix, respectively) though at the time of this publication, only Gardasil™ is available in Canada and the USA. The current formulation of Cervarix only protects against HPV 16 and 18. Gardasil™ is a quadrivalent vaccine derived from yeast cells which protects against the two most common high risk strains of HPV (16 and 18, associated with 70% of cases of cervical cancer) as well as the low risk strains (HPV 6 and 11, associated with genital warts). Gardasil™ requires 3 intramuscular injections of 0.5 mL; the second dose is given 2 months after the first, and the third dose is given 6 months after the first. The current cost of Gardasil™ is $135.00. Currently it is available for women, ages 9-26 years, though Merck advises inoculation prior to sexual debut. It is not currently recommended for use in men or women over age 26 years as not enough research has been performed in these groups. If administered to women who already have HPV, it cannot alter the course of that strain, however, it will protect against the other 3 strains. The vaccine does not protect against all oncogenic strains of HPV, thus women who are vaccinated should continue to be screened with pap smear.

Both vaccinations work by exposing the body to subunits of selected strains of HPV in order to elicit an immune response (production of serum antibodies). The L1 viral protein is the major component of the vaccine; clinical trials have shown its ability to self assemble into virus-like particles that successfully induce high levels of neutralizing antibodies in subjects. The vaccine would enable the body to identify and eliminate certain strains of HPV before they have a chance to hijack epithelial cells and cause cancer. Thus far, L1 viral proteins have demonstrated strain specificity (i.e. if vaccinated against HPV 16 with its L1 VLP, the patient is only immune to this strain; they do not have cross immunity against other strains of HPV).

Gardasil™ has proven to be very successful in reducing the incidence of a “cervical cancer” endpoint as defined by the FDA Vaccines and Related Biologicals Advisory Committee. Since it would be unethical to use cervical cancer as an endpoint to determine success of vaccines, the FDA designated development of histologically determined CIN (cervical intraepithelial neoplasia) grade 2 or higher on pap smear as a surrogate endpoint. The original cohort of subjects inoculated with Gardasil™ (n=468) has been followed for 1.5 years; to date, the vaccine has been 100% effective in preventing CIN 2 or higher associated with HPV 16 and 18, as well as any genital warts associated with HPV 6 or 11. One major limitation to Gardasil™ is unproven duration of immunity. Studies looking at HPV 16 specific vaccination have demonstrated efficacy at 3.5 years post inoculation, however, more research needs to be done to establish duration. Gardasil™ has not been associated with any serious side effects, but as with duration of immunity, more time must pass before it can be declared free of any serious long term effects.

Challenges

While the development of a vaccination for HPV holds tremendous potential, there are several hurdles that stand in the way of worldwide distribution. Cost and ease of delivery are important issues, especially when considering use of the vaccine in developing countries. The stigma associated with vaccination for an exclusively sexually transmitted infection is another hurdle that must be overcome.

As mentioned previously, developing nations carry 80% of worldwide incidence of cervical cancer. The HPV vaccine has the potential to save countless lives, yet when statistics indicate that 40% of children from developing nations are not vaccinated for life-threatening diseases like measles, it is difficult to imagine how an expensive and labour intensive (3 injections) vaccine like Gardasil™ might be administered. Identifying a cost-effective form of the HPV vaccine is one of the areas of research supported by a $28 million dollar grant from the Bill and Melinda Gates Foundation. Possible HPV vaccination programs are limited by temperature sensitive nature of the vaccine as well as the requirement for multiple injections over 6 months. Research has been done to explore the option of a one-time intranasal delivery of vaccine. Future HPV vaccines must be inexpensive, easy to administer and require little commitment from the patient. Although not as major a factor in developed countries, cost is still an issue. At $135.00 for a course of three injections, the cost is prohibitive for some lower-income women. Critics fear that the expense of the vaccine will turn HPV and cervical cancer into diseases of the poor. Prince Edward Island is considering coverage of the HPV vaccine under its provincial health plan. As of January 2007, New Hampshire will be the first state to offer free HPV vaccine to girls aged 11 to 18 years. From a purely economic standpoint, it is not clear that provincial funding of the HPV vaccine will reduce overall costs associated with cervical cancer. The vaccine will not eliminate pap smears, as current vaccines only guard against 2 strains of HPV and other strains might still cause cervical cancer.
Stigma associated with vaccination against sexually transmitted infections is a problem faced in both developing and developed nations. Some lobby groups fear that vaccination will encourage promiscuity. Others fear that the vaccination may provide a false sense of security to the patient. Attitudes of both the physician and the patient play a major role in the success of vaccine programs. An American study of opinions of adolescents and adults found that “recommendation by physicians was one of the most important factors that would most influence their decision to be vaccinated against HPV” 18. A Mexican study reported that “perception of cervical cancer risk and knowledge of the benefits of the HPV vaccine were the 2 important factors that mothers said would influence them to allow their teenage daughters to get vaccinated”. 19 Not surprisingly, a study of American pediatricians found that good knowledge of HPV was a primary factor influencing their likelihood of recommending the vaccination to adolescents in their practice. 20 A survey by the SOGC indicated that 87% of Toronto, Ontario high school students had not heard of HPV. 3 Public education through initiatives like the SOGC’s award winning sexual and reproductive health website (www.sexualityandu.org) is essential to overcoming stigma. 21

Conclusion

The development of an HPV vaccine is an important step towards eradicating cervical cancer. Further research needs to be done to clarify the following issues: i) duration of immunity provided by the vaccine, ii) use of the vaccine in men and women older than 26 years, iii) cost of the vaccine and iv) development of a single injection vaccine (as opposed to 3 separate injections). Both physicians and the public should be educated about HPV so as to overcome stigma surrounding vaccination. There is great optimism that in Canada, stigma over vaccination for HPV may not be an insurmountable obstacle. The path has already been blazed with the introduction of the hepatitis B vaccination in the early 1990s. 22 Like HPV, Hepatitis B is an oncogenic virus that is sexually transmitted. Today, vaccination for hepatitis B takes place routinely in elementary schools nationwide. With continued efforts, school age HPV vaccination may be routine in the next 10 years.

References


Medicine and the Law

BRCA Genetic Testing: Ethical, Legal and Policy Considerations

Christian Fortin, Meds 2009
Michael Slatnik, Meds 2010

There is a concern that life insurance companies will use genetic tests to deny coverage or charge increased premiums to patients with mutations for genetic disorders. Those in favour of restricting an insurer’s ability to use genetic information suggest that the fear of genetic discrimination will deter patients from pursuing important genetic testing. Others argue that restriction will disrupt the insurance industry because it will allow high-risk patients to purchase life insurance policies at rates that underestimate the true risk of mortality. This essay focuses on the BRCA genes and reviews the literature to evaluate the possibility that (1) mutation positive individuals will purchase additional insurance to the detriment of other insured individuals, or that (2) women will avoid genetic testing and therefore forego the opportunity to benefit from prophylactic therapies. The paper discusses the current state of the law, possible policy directions, and the need for lawmakers and insurers to develop appropriate measures before emerging genetic technologies can calculate genetic risks with greater certainty.

This article has been reviewed by Dr. Lois Champion.

Introduction

One of the most important ethical debates of the Human Genome Project arises from the possibility of ‘genetic discrimination’. Many people are concerned that one’s genetic status, as revealed by genetic testing, could serve as a basis for wrongful discrimination relating to the provision of consumer services. There is a particular concern that life insurers could charge increased premiums to those predisposed to genetic disorders. It is controversial as to whether the use of genetic information by insurance companies would be an acceptable business practice or conduct akin to racial discrimination.

The BRCA genes, which are more fully described below, are particularly relevant in evaluating the potential role of genetic information in the insurance underwriting process as mutated BRCA genes confer a calculable risk of breast and ovarian cancer in women. Moreover, prophylactic therapies are available to affected women. The BRCA genes will thus serve as a model in the following discussion of the ethical, legal, and policy considerations related to the use of genetic information by life insurers.

The BRCA genes

Breast-cancer associated genes 1 and 2 (BRCA1 and BRCA2) were discovered in 1994 after extensive studies and molecular testing of women in hereditary breast and ovarian cancer (HBOC) families. Both BRCA1 and BRCA2 are tumor-suppressor genes which, when mutated or defective, result in some loss of cell-cycle regulation and a 50-80% risk for developing breast cancer, along with increased susceptibility to ovarian cancer. The BRCA genetic test involves direct nucleotide sequencing of the BRCA1 and BRCA2 genes and costs thousands of dollars in a US laboratory. Interventions available to affected women include chemoprevention, and bilateral prophylactic mastectomy and oophorectomy.

Evidence to guide policy direction

Policy relating to genetic testing should be guided by a thorough understanding of the tests and their implications, as well as evidence regarding decisions pre- and post-testing. With genetic tests such as BRCA, an issue relating to the business of life insurance is the information asymmetry that results after a genetic test, resulting in the consumer having more information about their health if they choose not to disclose their test results to a prospective insurer. The tendency of high-risk individuals to purchase insurance at rates that underestimate risk is termed ‘adverse selection’ and is recognized as an undesirable
consequence of restricting an insurer’s ability to utilize a prospective customer’s genetic test results.\(^3\) Insurance companies seek mandatory disclosure in order to accurately value insurance plans, whereas genetic interest groups argue that mandatory disclosure results in discrimination and public reluctance to be tested, and that voluntary disclosure is the best method.\(^4\)

The decision to be tested for a BRCA mutation is one that has important repercussions and all testing must be accompanied by proper genetic counseling. A study of women in a high prior-risk clinic in Michigan showed that out of 184 candidates for testing, only 106 (58\%) underwent testing and of those who declined, 48/78 (62\%) cited concerns about cost and insurance discrimination as the reasons for not undergoing the test.\(^5\) This same study estimated that half of patients declining testing for insurance concerns would be positive, and in high prior-risk clinics, approximately 25\% of patients will decline testing for reasons of cost, confidentiality and insurance concerns. Fear of genetic discrimination are prevalent even in those highly educated in health policy; in a survey of the Special Interest Group in Cancer of the National Society of Genetic Counselors (USA), 68\% undergoing genetic testing would not attempt reimbursement from their insurance company for the test for fear of later discrimination, and 26\% claim they would use an alias for the test.\(^6\) Policy must be in place to clarify confidentiality issues and the use of genetic testing in insurance and healthcare settings in order to prevent public reluctance to be tested, which would decrease the positive benefits of testing.

As described above, insurance companies fear that those with the informational advantage of positive genetic tests will purchase additional policies, and cite this possibility of adverse selection as a reason for mandatory disclosure of tests. In a one year follow-up of a group of Utah women who underwent BRCA1 testing, it was found that consumers do not exploit the information asymmetry caused by genetic testing: none of family history, testing status or participation in early BRCA1 research seemed to be indicators of demand for life insurance, and the only factors found to influence insurance policy purchase were socioeconomic ones.\(^7\) The women who tested positive were found to have statistically similar amounts of life insurance in comparison to those who tested negative. Conversely, another study of women undergoing BRCA testing or counseling revealed that the decision to increase life insurance coverage was associated with a positive BRCA test.\(^8\) The paucity of empirical research, along with conflicting results of studies described above, suggests that much more research is need to determine if restricting insurers’ ability to use genetic information for actuarial calculation will result in adverse selection.

### The Concept of Genetic Discrimination

The precise meaning of discrimination is often confused in the context of risk calculation based on genetic status in the life insurance industry. Insurers intentionally use the word ‘discrimination’ in the sense of merely drawing distinctions among individuals based on generally accepted principles of actuarial science. Discrimination utilized in this neutral sense must be distinguished from the kind of discrimination that is deemed illegal and wrongful under human rights legislation. In Ontario, the *Human Rights Code* prohibits discrimination relating to such areas as services, accommodation, and employment on a discreet number of enumerated grounds including race, ethnic origin, sexual orientation and age.\(^9\) However, one who discriminates on one of these or other enumerated grounds can often justify discriminatory behaviour by demonstrating that a distinction was drawn on *bona fide* and reasonable grounds. The Supreme Court of Canada has acknowledged that the calculation of insurance premiums does not fit easily with concepts of human rights norms, but has justified the practice of differential treatment that is based on sound and accepted underwriting procedures and if there are no practical alternatives.\(^10\)

Some leading Canadian commentators on this topic suggest that discrimination on the basis of genetic status, as revealed by a predictive genetic test, will be wrongful in the insurance industry only if there is no actuarial basis for concluding that a customer is at increased risk.\(^11\) These critics often call attention to the fact that family history—which often serves as a proxy for genetic risk—plays a valid role in life insurance premium calculation. Other critics highlight the fact that some patients oppose the practice of drawing distinctions on genetic status, even if genetic tests can accurately predict the risk of mortality. In discussing BRCA predicting genetic testing, one scholar notes that “the public may believe differential pricing based on breast cancer risk would be socially intolerable, even though actuarially fair.”\(^12\) It has been noted that Canadian human rights law is evolving and might place restrictions on the ability of insurers to use genetic information when calculating premiums.\(^12\) There is a good probability, however, that differential premiums based on genetic status will be justified if based on sound scientific principles and in the absence of alternatives.
Policy Alternatives

Potential strategies at addressing the inevitable problems created by life insurers’ use of genetic information include legislative prohibition, the establishment of moratoria upon insurers, and maintenance of the status quo. Many European Countries including Austria, Belgium, and Denmark have embraced the first option and have enacted legislation that places an outright restriction on a life insurer’s ability to request or use genetic testing in calculating premiums.\(^1\) The Netherlands has adopted a similar approach but only to policies below a predetermined monetary figure, thereby ensuring that all individuals can purchase a basic amount of life insurance.\(^1\) Moratoria are usually established by the insurance industry but often at the behest of governments. Insurers within the United Kingdom utilized the moratorium method in the past, but reserved the right to use genetic information when approved by a governmental committee and when the insurance contract was over a specified amount. The rationale of this moratorium was to give the industry and the relevant authorities more time to converse and possibly develop a framework for the use of genetic information in life insurance premium calculation.\(^1\) Finally, the status quo approach leaves it to the life insurance industry to decide for itself how to use genetic information. Canada appears to have opted for the status quo; there did not exist any provincial or federal legislation regulating life insurers’ use of genetic information or a self-imposed industry moratorium during the preparation of this article.

In 2004, insurers, patient advocates, and researchers knowledgeable in genetics policy established the Canadian Genetics and Life Insurance Task Force to suggest policy options relating to life insurance and genetics.\(^1\) The task force urged policy-makers, insurers and physicians to debate the merits of either (1) imposing a temporary moratorium on the use of genetic information for life insurance policies below a specified amount, or (2) creating an independent standing body that would oversee the use of genetic information by life insurers. It is not clear whether stakeholders took up this challenge.

Concluding Comments

Reports of actual discrimination on the basis of predictive genetic test results have hitherto been scarce.\(^1\) Policy makers, therefore, have some time to debate the benefits and drawbacks of regulating a life insurers’ ability to use a customer’s genetic status in their underwriting activities. On the other hand, the number of diseases for which there are genetic tests increased 600% from 1997 to 2006.\(^1\) It is therefore crucial to have policy directing the use of genetic testing which strikes an appropriate balance between encouraging patients to access beneficial genetic testing and promoting a fair and effective life insurance regime.

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Microcystic adnexal carcinoma (MAC) or sclerosing sweat duct carcinoma is a rare slowly growing but locally aggressive malignant skin tumour displaying sweat duct and pilar (follicular) differentiation. It typically occurs on the face of middle aged adults. MAC is frequently misdiagnosed because of its asymptomatic clinical presentation and bland histology on superficial small punch or shave biopsy. Because of its deeply infiltrating nature, the optimal biopsy for MAC is incisional or excisional biopsy. Lack of early diagnosis can lead to an aggressive neoplasm with high rate of recurrence, and rarely regional and distant metastasis. Micrographic Mohs surgery is the preferred treatment of choice for MAC. A case history of a recent patient with MAC treated at London Health Sciences Centre is reviewed.

This article has been reviewed by Dr. Mariamma Joseph and Dr. Dao Nguyen.

Introduction

First defined by Goldstein and colleagues in 1982, there have been only approximately 150 cases of MAC described in the English medical literature.  MAC is a slow-growing albeit locally aggressive adnexal carcinoma with a high tendency to recur despite excision. Its aggressive nature is often due to delay in diagnosis, inadequate tissue sampling and thus, detection at an advanced stage of disease with invasion beyond skin into underlying tissue. Thus, a high index of suspicion is necessary in assessing these tumours and adequate deep biopsy for diagnosis are essential. Surgical excision with clear margins are crucial in prevention of local recurrence and distant metastasis. We review the clinicopathologic features of MAC and present a recent aggressive case of MAC involving the scalp of a 58 year old woman.

Clinical Presentation

MAC typically presents as a slowly-growing flesh-coloured, yellow or erythematous firm plaque or nodule in the head and neck region. Caucasians are affected most frequently and there does not appear to be a gender predisposition. The tumour presents in a wide age group (11-90 years) although the majority of those affected are between the ages of 40 and 60 years. The patient often presents with a lesion which has been present for several years and has grown slowly.

At diagnosis, most tumours measure between 0.5 cm and 2.0 cm in diameter but occasionally can be very large measuring up to 12 cm. The skin surface of MAC is usually smooth and non-ulcerated, unlike other cutaneous carcinomas. It is almost always unilateral and predominantly left-sided in North Americans, a fact that has been suggestively attributed to greater sun exposure of the left side of North American drivers. MAC has mostly been found on the cheek, lips, nasolabial fold and in the periorbital area and is less common in the nose, scalp, eyelid and eyebrow. Typical clinical presentation of MAC can be seen in Figure 1.
Generally, the tumour is asymptomatic, until invasion into underlying tissue develops, causing symptoms which may include pain, stinging, change in sensation or functional motor loss due to perineural invasion.\textsuperscript{3} Metastasis of MAC is rare, with only four described cases in the literature. One recent case described MAC in the axilla metastasizing to the axillary lymph nodes.\textsuperscript{3} Haematogenous metastasis of MAC to liver and bone with intracranial spread along optic nerve into the cranium has also been discovered on autopsy of a 73 year old woman.\textsuperscript{3}

**Diagnosis**

The diagnosis of MAC is made by full-thickness tissue biopsy. CT or MRI may be necessary for tumour staging and treatment planning.\textsuperscript{1}

Histologically, MAC is a poorly circumscribed deeply invasive tumour composed of variable portions of keratocysts, basaloid or squamoid nests and infiltrating cords and ductular structures set in a paucicellular desmoplastic stroma. Keratocysts are usually present in the superficial portion and cords of cells and perineural invasion characterize the deepest portion, thus inadequate depth of tissue biopsy may result in failure to diagnose this malignancy. The nuclei of all these cells are rather uniform with only minimal pleomorphism or atypia. Mitotic figures are very rare. MAC is mostly located in the dermis but can infiltrate to subcutaneous fat, skeletal muscle, perichondrium, periosteum or perineurium. The histology of a typical case of MAC is presented in Figures 2A-D.
Deep incisional or excisional biopsy would demonstrate deep infiltration of MAC and possible perineural invasion allowing accurate diagnosis. A small superficial punch or shave biopsy that includes only keratocysts and bland basaloid cells may lead to an erroneous benign diagnosis of syringoma or trichoepithelioma. The area of the biopsy could also lead to an incorrect diagnosis of squamous cell carcinoma if the sample contains high levels of keratinised cells with few tubules.

Immunohistochemistry of MAC supports ductal differentiation, with positivity for Epithelial Membrane Antigen (EMA) and Carcino Embryonic Antigen (CEA), features common to many adnexal tumours with ductular differentiation.

**Histogenesis**

The histogenesis of MAC remains uncertain, but Goldstein considered origin from pleuripotential adnexal epithelial cells capable of pilar (hair) and eccrine (sweat) gland differentiation. Mostly scientists have postulated that MAC solely shows eccrine differentiation. Sub-clinical spread of the tumour beyond clinical margins may be explained by invasion through shelving or conduit spread.

**Management and Outcome**

The tumour does not generally respond to radiation treatment, and in those cases where response is evident, there is a high rate of recurrence. Therefore, surgical excision is currently the best method of treatment. Because of the tumour's infiltrative nature, planned surgical excision margins are designed widely, beyond the clinically evident margins of the tumour. Surgical treatment options for MAC include wide local excision and micrographic Mohs surgery (MMS). MMS is currently the most widely accepted surgical treatment. Although there are only few studies in the literature comparing the recurrence rates in lesions treated with wide excision versus MMS, it appears that MMS provides the least morbidity and the best chance for cure. The reported rates of recurrence with wide excision are 40-60%, and the technique of MMS allows complete histologic examination of 100% of all margins while sparing maximal amount of tissue in comparison to standard “bread-loafing” techniques which permit examination of only 1-2% of specimen margins. The recurrence rate following MMS ranges from 0% to 12%. The prognosis is good if local recurrence can be prevented. Only 1 case of death due to MAC metastasis has been reported.

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*Figure 2.* MAC, histology. 2A) The dermis is widely infiltrated by tumour showing superficial keratocysts (arrow) and deep narrow epithelial strands. 2B) Note the bland uniform cytology of epithelial cells. 2C) Ductular differentiation is present (arrow). 2D) Perineural invasion is present (Hematoxylin-Eosin stain).
Case Report

A 58-year-old woman presented with a large pruritic hairless growth on the left side of her scalp which had been present for over a decade and had previously been punch biopsied twice with diagnosis of benign alopecia. She gave a recent history of paralysis of left side of face with drooping of left upper eyelid and eyebrow and ulceration of the lesion. On examination, she had a large firm, indurated skin tumour (9.5 x 5.5 cm) with irregular borders surrounded by alopecia involving the left parietal region of the scalp (Figure 3). A large elliptical skin biopsy confirmed the diagnosis of MAC. A CT scan of the head revealed invasion of the tumour through the skull into the underlying dura and leptomeninges.

The tumour was widely excised by a plastic surgeon using a modified Mohs procedure with negative circumferential peripheral skin margins, confirmed by frozen section examination intraoperatively. Classic MMS technique was not feasible in this case due to the substantial size, location and infiltrative nature of the tumour. The resected specimen included full-thickness scalp and portions of the skull and dura. Pathologic examination showed classic features of MAC (Figure 2A-D). The skin and bone margins were found to be clear on permanent section, and the patient subsequently underwent reconstruction of her cranial defect. Adjuvant radiotherapy was instituted, however, aggressive local tumour recurrence developed with brain metastasis. The patient expired 18 months following diagnosis.

Conclusion

Although rare, a high index of suspicion for MAC should maintained in the differential diagnosis of slow-growing tumours in the head and neck region, particularly on the face. Prompt diagnosis and treatment are crucial to prevent local recurrence and distant metastasis. Our case demonstrates a very rare, aggressive form of MAC of scalp with invasion into bone and meninges, leading to brain metastasis and death despite attempted wide surgical resection and radiotherapy.

Acknowledgements

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A Look at Acute Lymphoblastic Leukemia in Children

Wendy Ng, Meds 2009

Acute lymphoblastic leukemia (ALL) is the most common malignancy found in the pediatric population. This type of cancer occurs in children in 2/3 of cases, with a current cure rate of almost 80% in children. In comparison, only 30 to 40 percent of adults with ALL are cured, likely due to the higher association of infavourable genetic abnormalities in adults’ leukemic lymphoblasts.¹ Usually occurring at approximately 2 to 9 years of age (Sather), ALL presents with fever, fatigue, pallor and pain. At least half of patients with ALL present with fever, often induced by pyrogenic cytokines released from leukemic cells or due to infection.¹ In contrast, acute myeloid leukemia (AML) is less common than ALL, with an unclear etiology and similar presentation. A discussion of the diagnosis, treatment and outcomes for ALL is presented, with a particular emphasis on childhood ALL.

This article has been reviewed by Dr. Sam Yoshida.

Introduction, Characterization and Diagnosis

ALL can result from the blockage of any lymphoid cell at a point of development, and a diagnosis of ALL is dependent on immunophenotyping.¹ The diagnosis of ALL can be obtained by a bone marrow aspiration.

The French-American-British (FAB) classification is based on morphology and simple cytochemical stains. There are three major subgroups. By this system, FAB L1 is the most common, with small cells, small nucleoli, and little cytoplasm. FAB L2 includes large cells, a clefted nucleus, large nucleoli, and abundant cytoplasm. FAB L3 includes large cells, a homogenous nucleus, many nucleoli, abundant cytoplasm, and prominent vacuoles. This system is effective, although cytogenetics and immunophenotyping have been suggested to add further to diagnostic accuracy in some cases.²

Immunoflow cytometry determines the B cell expression of CD19 or CD10 or cALLa (common/childhood ALL antigen), a historical marker that is obsolete. TdT (terminal deoxynucleotidyl transferase) is a marker for B cell leukemia, as well, but has been suggested to have both a low sensitivity and specificity for prediction of relapse.³ T cell markers such as CD7, CD2, CD4 and CD8 can assist in determining different treatments and survivals. On the basis of such immunophenotypic analyses alone, firm diagnoses can be made in virtually all cases.¹

Cytogenetic analyses look for hyperdiploidy and translocations. Patients with hyperdiploidy with more than 50 chromosomes often have other clinical features that suggest a good prognosis.⁴ B cell translocations include t(4,11)⁴, t(9,22)⁴, t(8,14)⁴, and t(1,19)⁶ which give poor prognoses. In contrast, patients with t(12,21) generally have a favourable prognosis.⁷

T cell translocations, for example, include t(11,14).⁵ These patients are often young males, often with associated unfavourable clinical characteristics. In addition, children with Philadelphia chromosome-positive ALL have been found to have a poor prognosis, with no consensus on the best treatment for this variant.⁹

Associated Clinical Features, Treatments and Outcomes

The primary goal of therapy is to induce complete remission and to restore normal haematopoiesis. Therapy for ALL is based on risk, wherein factors such as age, white blood cell count, patient gender and cytogenetics must be accounted for.¹⁰,¹¹ The presence of a mediastinal mass or central nervous system leukemia also predicts a relatively poor prognosis.¹¹ The inclusion of race or ethnicity as a part of race-adapted therapy, thereby allocating black and Hispanic children to more aggressive protocols, remains debatable.¹² Differences in clinically determined prognostic indicators are likely a result of the presence or absence of genetic abnormalities.¹
Patients between the ages of 2 to 9 years with a white blood count of less than 50,000 microL are considered to be at standard risk, with a high 4-year event-free survival of 80%. In turn, patients greater than 10 years of age with a white blood count of greater than 50,000 microL are considered to be at high risk, with a 4-year event-free survival of approximately 65%. However, patients at less than 1 year of age with a white blood count of over 100,000 microL and with associated poor cytogenetics – such as the unfavourable MLL translocations – are at very high risk. These patients have a reported survival of up to 50% with a sibling-donated bone marrow transplant and less than 30% survival with a matched unrelated donor. With such a poor prognosis, infants with ALL are treated with multiple drugs at high dosages and with no cranial irradiation.

As therapy for ALL improves, reported survival rates have increased over the years – with a cure rate from less than 30% overall to 80% overall since 1970. Most standard risk and high-risk patients should receive chemotherapy alone. Intensive chemotherapy includes fractionated high-dose cyclophosphamide, high-dose methotrexate and cytarabine.

Furthermore, male patients require a longer duration of therapy compared to female patients, as a result of sanctuary sites. It has been reported that female patients have a better event free survival period even when treated with less therapy. High risk patients with sanctuary site involvement, such as in the central nervous system or testicles, should also receive radiation. However, since cranial irradiation can result in significant neurotoxicity and predisposes to a risk of brain tumours, as well as to neuropsychological deficits and endocrinopathy leading to short stature, obesity, precocious puberty and osteoporosis, many physicians choose to administer intensive systemic chemotherapy early on, and ultimately give patients growth hormone therapy to avoid negative endocrine-related effects. In addition, high risk patients receive chemotherapy and consideration for bone marrow transplants. Flow cytometry can be used as a prognostic indicator, as children with ALL who achieve a profound clearance of leukemic cells after 2 to 3 weeks of remission-induction chemotherapy have been reported to have excellent outcomes. It is an important challenge to integrate new data in the literature with modern methods of assigning risk-based therapy.

Supportive care for patients with ALL includes the administration of broad-spectrum antibiotic therapy for patients presenting with fever. At most centres, patients are treated prophylactically for Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole at 3 days per week. Since hyperuricemia, hyperkalemia and hyperphosphatemia with secondary hypocalcemia are common in patients with a great burden of leukemic cells, patients should also be hydrated intravenously and treated for these associated conditions.

It should be noted that the third most common malignancy in children is relapsed ALL. For these patients, therapy remains controversial, with debates over the benefits and risks of chemotherapy alone, sibling bone marrow transplants, matched unrelated donor bone marrow transplants, with respect to the optimal timing of bone marrow transplants, and the suggestion of no therapy at all. Conventional intensive chemotherapy can cure up to 30% of children who have relapsed, and similar results have been reported with autologous bone marrow transplantation.

Conclusion

ALL is a serious disease, often occurring in children, and should be treated according to risk stratification. However, despite major improvements in risk-assignment in recent decades, unknown mechanisms still account for the successes and failures of therapy in individual patients. Efforts are underway to identify new drugs and therapeutic approaches which may lead to options that are more specific and less toxic compared to standard chemotherapy. It is promising to note that in the past few decades, remarkable advances have been made in the cure rates of childhood ALL, and novel strategies of treatment may ultimately result in better treatment options.

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Liver resections have historically been associated with high morbidity and considerable mortality, directly linked to excessive hemorrhaging. To this day, control of blood loss remains one of the key challenges in liver surgery. A number of approaches can be applied to successfully reduce blood loss. These include selective vascular control (SVC), continuous and intermittent portal triad clamping (PTC), hepatic vascular exclusion with preservation of caval flow (HVEPCF), and total hepatic vascular exclusion (THVE). For resection of peripheral small lesions SVC is preferable since ischemic insult to the remnant of liver is minimized. For more extensive lesions SVC results in unacceptable bleeding and open approach with continuous or intermittent PTC is preferred. Continuous PTC is associated with lower blood loss; with intermittent PTC longer ischemic time is tolerated. Prolonged resections of massive tumors may be best approached by HVEPCF with continuous or intermittent occlusion of hepatic venous drainage. An alternative approach uses inflow occlusion with occlusion of hepatic vein draining the segments being resected. Finally, tumors invading hepatic veins or IVC are best approached using THVE, which allows resection of venous confluence with adequate margins. The drawbacks include significant hemodynamic disturbance and portal hypertension with bowel engorgement. Increasingly complex and extensive hepatic resections necessitate increasingly aggressive methods of vascular control. Under appropriate circumstances each of these methods has a role in liver resections.

Selective Vascular Clamping (SVC)

The ligation of vascular pedicle to the segment of the liver being resected is the only method that avoids ischemia and reperfusion injury to the remnant of the liver, which can decrease its ability to hypertrophy and compensate postoperatively. Furthermore, SVC allows a clear demarcation of the boundary between the hepatic segments with intact and disrupted blood supply. Portal hypertension, a major drawback of PTC, is avoided or significantly reduced. The main concern with SVC is the potential for profuse hemorrhage from the cut liver surface. Nonetheless good results have been reported, making SVC an alternative to be considered. A randomized controlled trial by Figueras et al compared standard PTC to SVC in liver resections involving two or less liver segments, finding no significant differences in intraoperative blood loss. Wu et al describe several limitations of the hemihepatic SVC: additional 20 to 30 min are required for dissection of hepatic hilum, the technique is not suitable when the malignant tumor invades the hilar plate, and in patients with dense adhesions of the hilum secondary to previous hepatic artery embolization clamping may be especially challenging. Gotoh et al compare selective ligation of vascular pedicles after intraparenchymal dissection to hilar lobar clamping and to PTC in patients with cirrhosis and hepatocellular carcinoma. The lobar clamping group was found to have significantly shorter operation time and intraoperative blood loss than the other two groups. On the basis of these results Gotoh recommended lobar clamping as a method of vascular control, especially in cirrhotics. These results show that under appropriate circumstances SVC can be used with low risk of excessive hemorrhage, while ischemic injury to the liver is minimized. The role of SVC remains mainly in minor liver resections of peripheral lesions, where severe hemorrhage is less likely to occur.

Portal Triad Clamping (PTC)

Hepatic inflow occlusion is simple to perform, involving placement of a vascular clamp over the hepatoduodenal ligament. Care must be taken to identify the presence of any accessory hepatic arteries and the numerous collaterals present in cirrhotics. In the only randomized controlled trial to demonstrate
effectiveness of PTC in controlling blood loss, Man et al report that PTC was associated with lower blood loss per resection area, shorter operative times, and improved postoperative liver function compared to liver resections without extrahepatic vascular control. Overall PTC is well tolerated: liver with unimpaired parenchyma can be safely exposed up to 60 min of normothermic ischemia. If longer time is required, PTC can be used intermittently with 15-20 min ischemic intervals separated by 5 min reperfusion intervals. The hemodynamic disturbance during PTC is tolerated by most patients. However, PTC allows backbleeding from the hepatic veins that can contribute to blood loss. A common way to minimize this involves using low central venous pressure (CVP) anesthesia; this is accomplished with restriction of IV fluids and, if necessary, infusion of intravenous nitroglycerin. The danger of low CVP is the increased possibility of potentially lethal air embolism during resection. Another drawback of PTC is portal hypertension and venous stasis. King et al report significant ischemic changes in the bowel following 60 min of PTC. Finally, since PTC alone does not control the hepatic veins, in resections of tumors encroaching on the hepatic venous confluence or directly involving intrahepatic vascular structures more extensive methods of vascular control are preferred.

Figure 1. The Pringle maneuver, or portal triad clamping (PTC): portal triad is isolated and controlled with umbilical tape or vascular clamp.

Hepatic Vascular Exclusion with Preservation of Caval Flow (HVEPCF)

Historically, retrohepatic control of hepatic veins was considered dangerous because of the possibility of massive hemorrhage and air embolism with injury to these vital structures. If control of hepatic veins could be established, it offers several key advantages. Surgery can be done in a bloodless field, the danger of air embolism is eliminated, and preservation of caval flow avoids significant hemodynamic disturbance of THVE. The technique of intermittent vascular exclusion can be applied, extending the total ischemic time if needed. The dissection, however, requires difficult exposure and is technically challenging. Smyrniotis et al compare hepatectomy with THVE or HVEPCF, and report that the THVE group required more intravenous fluids and blood and demonstrated greater postoperative hepatic, pancreatic, and renal function impairment. There was no difference in intra-operative blood loss. Comparing PTC to HVEPCF revealed that HVEPCF group was found to have significantly lower blood loss, lower transfusion requirements, and shorter hospital stay than PTC group. On the other hand, the incidence of postoperative complications was similar between the two groups and the postoperative bleeding rate was higher in the HVEPCF group. Another approach is to clamp only the hepatic vein draining the segments being resected. This reduces the length and complexity of dissection, while providing very good control of hepatic venous blood loss. With these advances, many surgeons use HVEPCF as the preferred method of vascular control in major liver resections.
Total Hepatic Vascular Exclusion (THVE)

Total exclusion of the liver from the circulation involves applying clamps to hepatoduodenal ligament, infrahepatic IVC, and suprahepatic IVC. The main advantages of THVE are operating in bloodless field and prevention of air embolism with injury to hepatic veins. It is particularly valuable in resection of tumors that lie in close proximity to major hepatic veins and where resection is technically challenging. A major drawback of IVC occlusion in THVE is the severe hemodynamic disturbance associated with a drop in preload and increase in total peripheral resistance.13, 16 Most patients can tolerate these changes without hemodynamic instability, provided aggressive infusion of intravenous fluids is used. Between 20% and 30% cannot tolerate the instability.14 A trial of IVC clamping of 3 to 5 minutes is usually undertaken to assess the change in hemodynamic parameters. The length of ischemia that could be safely tolerated during THVE is proven to exceed 60 min, and can probably be safely extended to 150 min.17 However, the advantages of THVE over PTC have been controversial. A randomized controlled trial, by Belghiti et al, compared patients undergoing major liver resections using PTC or THVE and found no significant differences in intraoperative blood losses or postoperative liver enzymes.18 Other major downside of THVE is associated portal hypertension with bowel edema, exacerbated by disruption of portosystemic shunts with occlusion of IVC. The ischemic time limit of THVE cannot be overcome by intermittent clamping, which results in unacceptable hemodynamic instability. Blood loss with THVE is minimized during the actual resection, but can be profound after the unclamping.17, 19 Potential causes of technical failure with THVE include incomplete clamping, unrecognized anomalous origin of left hepatic artery, or unrecognized venous inflow into excluded segment of the IVC from right adrenal vein or other sources. If the exclusion is not complete, profound hemorrhage can ensue, with blood unable to drain to the heart filling the liver towards the surgical field.

Figure 2. Total hepatic vascular exclusion with cross clamping suprahepatic IVC, infrahepatic IVC, and portal triad clamping

To this day, control of blood loss remains one of the key challenges in liver surgery. A number of approaches can be applied to successfully reduce blood loss and transfusion requirements. These include selective vascular clamping, portal triad clamping, hepatic vascular exclusion with preservation of caval flow, and total hepatic vascular exclusion. Each method has its downsides and offers its unique advantages. For resection of peripheral small lesions SVC is preferable since ischemic insult to the remnant of liver is minimized and danger of profuse hemorrhage is low. For more extensive lesions SVC results in unacceptable bleeding and open approach with continuous or intermittent PTC is preferred. Prolonged resections of massive tumors may be best approached by HVEPCF with continuous or intermittent occlusion of hepatic venous drainage. Finally, tumors invading hepatic veins or IVC are best approached using THVE, which results in significant hemodynamic disturbance and potential ischemic injury, but allows resection of venous confluence with adequate margins. Thus increasingly complex and extensive hepatic resections necessitate increasingly aggressive methods of vascular control.
References
An overview of the screening and staging strategies for organ confined prostate cancer

David Horovitz, Meds 2009

Prostate cancer is the second most common cause of cancer death and the most frequently diagnosed cancer in North American men. Its behaviour is quite variable, ranging from microscopic, well differentiated and clinically unimportant to highly aggressive with extensive invasive and metastatic capability. Disease that is confined to the organ is usually curable, but capsule penetration, invasion of seminal vesicles, and metastases to lymph nodes usually precludes this aspiration; hence, the widely held believe that much effort should be directed at its early detection. Historically, this goal was met via digital rectal examination and enquiries of urinary symptoms. However, most PC diagnoses today are first discerned from elevated PSA levels, and thus, most present asymptomatically. Many advances have been made with regards to approaching this disease, and herein, an overview of the screening strategies used to detect PC and subsequent diagnostic and staging methods will be presented.

Prostate-specific antigen (PSA) is now routinely used as a prostate specific marker for the screening of prostate cancer (PC) and plays a major role in diagnosing the disease. After all, many studies have demonstrated that the likelihood of finding PC on biopsy increases with PSA levels, especially in higher ranges, and various others have demonstrated that the use of PSA detects PC and raises its incidence.

However, the viability of PC screening has been the focus of much controversy in recent years and the Laval University Prostate Cancer Screening Program (LUPCSP) conducted the first prospective, randomized trial in 1988 to try to resolve this issue. Here, 46,486 men aged 45-80 were randomized into either the screening (digital rectal exam (DRE) on first visit plus PSA measurements with 3.0 ng/ml being the upper limit of normal) or control group, and after 11 years of follow up, 10/7348 and 74/14231 deaths occurred in the two groups respectively, yielding a 62% reduction in cause-specific mortality.

The results of two larger international prospective RCTs are eagerly awaited by the oncologic community: the Prostate, Lung, Colorectum and Ovary (PLCO) Screening Trial and the European Randomized Screening Trial for Prostate Cancer (ERSPC). These were both established around 1994 and the final evaluation may take another 10 years.

Although the traditional cut-off for biopsy indication has been ≥4 ng/ml, the usefulness of this value has come into question by recent studies stemming from the Prostate Cancer Prevention Trial (PCPT). Here, 5754 men over the age of 55 were biopsied based on an indication of PSA ≥4 ng/ml or an abnormal digital rectal examination (DRE). These parameters only resulted in a 24.7% detection rate. Another group has demonstrated that as many 15% of men with PSA <4 ng/ml have PC and 15% of these are high grade. These same authors have since reported the receiver operating characteristic curve for PSA and have shown that there is no cut-off for healthy men that has both high sensitivity and specificity, but rather a continuum of PC risk at all values of PSA.

While it is generally accepted that the positive predictive value (PPV) of DRE increases with PSA levels, its usefulness at low PSA values remains another topic of much debate. For instance, while Carvalhal et al. concluded that “appreciable” PPVs for DREs could be obtained with low PSA levels, Schroder et al found that they were “poor” in a similar European study and thus recommended that under these circumstances, it should be replaced with a test of higher sensitivity.

Different molecular forms of PSA are evident in serum and this may be helpful in differentiating PC from benign prostatic hyperplasia (BPH), a condition that affects 25% of men above the age of 50.
While 10-30% of total PSA is not bound to any other serum proteins, approximately 70-90% of the total PSA is bound to α1-antichymotrypsin (a small amount is complexed with α1-antitrypsin, Protein C, and α1-macroglobulin). Several studies have demonstrated that patients with PC have a lower serum ratio of free PSA to total PSA than patients with BPH, and thus, fractionated PSA is an indicator that may allow for differentiation.

Suspicious screening results are usually followed up with a transrectal ultrasound (TRUS). Most lesions are hypoechoic and are frequently best seen when small. In a series of 960 patients, it was found that approximately 66% of cancers were hypoechoic while only 51% of these were actually cancer. Some cancers may show areas of increased echogenicity, probably as a result of dystrophic calcification. While 25% of carcinomas may be isoechoic and therefore not visible on gray scale sonography, they may be picked up on random biopsy. Colour Doppler may have a role to play in visualizing such tumours, but there is incongruity in the evidence.

Transcapsular invasion into the periprostatic fat may be difficult to detect with TRUS, especially if it is subtle. The sonographic signs range from obvious tissue invasion to bulging of the gland with slight compression. Involvement of the seminal vesicles may be seen as asymmetry in their shape, size, or sonographic characteristics. Detecting cancer spread through the apex is also very difficult to do with TRUS, and this is worrisome because a positive finding changes the treatment. Thus, in order to determine the likelihood of either seminal vesicle involvement or extracapsular extension in patients who are thought to have clinically localized PC, an MRI of the prostate gland using an endorectal probe can be obtained.

CT scans are unable to diagnose extracapsular extensions and seminal vesicle invasion accurately, and most are negative for metastasis, particular in those patients with lower PSA (<20) and Gleason Scores (<8). Specialized CT scans are invaluable, however, in the planning of radiation treatment fields for those men undergoing radiotherapy. Bone scans may also be utilized as a staging study, but like CT are infrequently positive among men with localized disease.

It has clearly been shown since the 1980’s that MRI has limited value in detecting lymph node metastases. Although it has a high specificity its sensitivity is quite low. However, the advent of Indium 111 capromab pendetine (ProstaScint®), a radiolabelled monoclonal antibody to prostate-specific membrane antigen, may offer a means to detect such soft tissue PC metastases. When used properly, it can be a valuable tool in staging the PC and in most studies thus far, its predictive ability before therapy was superior to and shown to enhance the specificity of CT and MRI. Furthermore, since CT and MRI can rarely detect disease upon relapse in low PSA settings (<1.0 ng/ml), this molecular imaging might offer the best method to assess relapse.

The recent development of three-dimensional magnetic resonance spectra imaging (3D-MRSI) has enhanced the diagnostic evaluation beyond the assessment of purely morphologic features. This method uses strong magnetic field and radio wave information to distinguish PC from healthy peripheral zone tissue using the spectra information of choline, creatinine, citrate and various polyamines. In one study of 53 patients, the authors used the 3D-MRSI and MRI to localize the cancer to a sextant of the prostate with a specificity of 91% and a sensitivity of up to 95%.

With all of this said, prostate biopsy is still the gold standard for the diagnosis of PC. Transrectal biopsy is a relatively simple office technique, usually performed without sedation or analgesia. In the ultrasound-guided sextant biopsy, a biopsy gun is used to take a specimen from suspicious areas followed by six tissue cores from the base, midzone, and apical areas of the right and left lobes of the gland. It is an imperfect test as a large proportion of men with a negative initial biopsy but persistently high serum PSA will have cancer diagnosed on subsequent biopsies. In one report, cancer was detected in 10% of second biopsies, and in another study, the risk of detecting a clinically unimportant cancer was found to be 4%.

Nevertheless, upon obtaining the biopsy, a pathologist will evaluate small suspicious areas and try to differentiate carcinoma from typical and atypical cells. A Gleason grade is made from this analysis to provide an index of prognosis and to guide local therapy. Primary and secondary scores are recorded and combined to form a final Gleason grade. Grades of 2,3 and 4 usually suggest low-grade cancers, grades of 5,6 and 7 usually represent moderately differentiated cancers, and grades of 8,9 and 10 usually signify high-grade cancers. Clinical staging often underestimates the extent of tumour actually found and the probability of upstaging at the time of surgery is directly related to the Gleason score.

One predictive model that utilizes a combination of Gleason grade, serum PSA and clinical stage to predict the presence of organ-confined cancer (and thus the highest likelihood of cure with radical prostatectomy or external beam radiation therapy) is the Partin model. Probability plots and nomograms have been designed from this model to assist urologists in preoperative prediction of final pathological
stage. They may be used to assess risk for metastasis and guide certain aspects of surgical management in organ-confined disease. However, they are specific for the diverse ethnic mix of the United States and their use has not been validated in most other countries despite the fact that they are still widely used.

In conclusion, the general approach used to detect PC has changed dramatically over the past few decades, particularly with the advent of PSA testing which has been highly accredited for use in high PSA ranges. However, while screening for the disease using PSA and DRE has significantly increased its early detection, these strategies may not actually decrease mortality. Transrectal ultrasound, MRI, CT, and bone scans can be used for further investigation, but the diagnosis of PC can only be made with a positive biopsy. Finally, preoperative predictions of pathological stage may be made using nomograms and probability plots derived from the Partin model.

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Human T-Lymphotropic Virus-I Infection and Adult T-cell Leukemia/Lymphoma: Pathogenesis and Clinical Considerations

Brent Mollon, Meds 2010

The Human T-Lymphotropic Virus type I (HTLV-I) was the first human retrovirus discovered and is implicated as the causative agent of Adult T-cell Leukemia/Lymphoma (ATLL). The oncogenic properties of this virus are believed to occur through the actions of the Tax protein, which has been shown to act through direct protein-protein interactions or alteration of signalling pathways to result in T-cell transformation, apoptosis inhibition and eventual clonal expansion of infected cells. Clinically, ATLL can present in one of four forms, termed acute, lymphomatous, chronic, and smoldering. Due to the range in symptoms, definitive diagnosis is often based on immunophenotypic, morphologic and serologic testing to note the characteristics of the cancerous tissue and test for the presence of HTLV-I. Once diagnosed with ATLL, the prognostic outlook of a patient may be influenced by many factors, such as the form of ATLL or the types of proteins expressed by the cancerous cells. While clinical trials are currently being conducted to determine the efficacy of new therapies, an optimal therapy with a high cure rate does not exist to effectively treat ATLL and HTLV-I infection.

Introduction

In July of 1977, a 28 year old male sought medical attention for the presence of nodules on his skin. A skin biopsy, lymph node biopsy, metatarsal bone biopsy, and examination of cells from the peripheral blood revealed malignant convoluted T-cells. A diagnosis of cutaneous T-cell lymphoma was made, and after treatment with concurrent whole-body electron-beam radiation therapy and combination chemotherapy the cancer appeared to go into complete remission. Unfortunately, the disease recurred 18 months later with widespread systematic involvement. The patient was treated with the combination of hydroxyldaunomycin, vincristine, the epipodophylotoxin VP-16, and cyclophosphamide. Once again, treatment resulted in a complete remission, but only a few months later, the patient presented with pulmonary infiltrates and brain lesions and soon after succumbed to the disease.

During the above ordeal, two T-lymphoblast cell lines were established from this patient. From these T-lymphoblast cell lines a type C primate virus (also known as a primate retrovirus) was isolated. This virus, known as the Human T-Lymphotropic Virus (HTLV-I), was the first human retrovirus to be discovered. After its identification as a retrovirus, HTLV-I was identified as the causative agents in two generally fatal diseases: HTLV-I associated myelopathy (HAM) and adult T cell leukemia/lymphoma (ATLL).

ATLL and HTLV-I

As noted in a review by Freedman & Harris, ATLL has been defined as “... a peripheral T-cell neoplasm associated with infection by the human T-lymphotrophic virus, type I” (para. I), by the Revised European-American Lymphoma and World Health Organization classifications. The terms leukemia and lymphoma are used to distinguish the source of cancerous tissue. Leukemia is the result of malignancies in hematopoietic stem cells which proliferate to replace regular stem cells within the bone marrow. On the other hand, Non-Hodgkin’s Lymphomas originate from the malignant transformation of lymphocytes that are differentiating within the peripheral lymphoid tissues.
Pathogenesis

ATLL manifests itself in only 2-5% of infected individuals, and usually becomes evident 20-30 years following initial infection.\textsuperscript{12} The virus has been reported to spread through sexual intercourse, blood transfusions and through lymphocytes present in breast milk.\textsuperscript{13-15} It is estimated that this virus has infected 10 to 20 million individuals worldwide and is endemic in the Caribbean Basin, Southern Japan, parts of Central and South America, Middle Eastern Asia, and Africa.\textsuperscript{16-17} Also, some regions in the United States also have endemic levels of HTLV-I, although it is found primarily in African-American individuals.\textsuperscript{18}

The transcriptional activator p40tax has been the focus of much research due to its implication as a major oncoprotein of HTLV-1.\textsuperscript{4,19,20} For example, this protein has been present in leukemic cells and in myelopathy.\textsuperscript{21-22} In addition, infection of CD4+ T-cells with retroviral vectors containing the Tax proteins have been shown to result in T lymphocyte immortalization.\textsuperscript{17}

The mechanisms by which Tax enables viral replication and latency are complex and are beyond the scope of this paper. Nonetheless, as stated by Scadden and colleagues,\textsuperscript{4} the ultimate result of the actions of the Tax protein is “… to promote cell proliferation, induce genetic instability, and inhibit apoptosis, leading to the persistent clonal expansion of infected cells and the promotion of oncogenesis.”.

Cellular Morphology

Genetically, all clones of the malignant T cell contain an integrated HTLV-I provirus\textsuperscript{23}, with the T cell Receptors genes all being clonally rearranged.\textsuperscript{24} In addition, deletion of tumour suppressor regions like the p16 gene, or of a potential tumour suppressor gene located on 6q15-21, can be noted in some cell lines.\textsuperscript{25,26} Lastly, trisomy or partial trisomy of chromosomes 3q, 6q and 14q has also been noted.\textsuperscript{7,27} The form or extent of the genetic abnormalities present in these malignant cells may help dictate how aggressive these malignancies will be.\textsuperscript{7} The malignant cells of ATLL also present with several morphological abnormalities. For example, it is common to find cells with peculiar hyperlobated nuclei in a peripheral blood test in patients presenting with leukemia.\textsuperscript{28} In the bone marrow, patchy infiltrates may be noted, while infiltrates in the lymph nodes are more diffuse.\textsuperscript{7}

Clinical Manifestations

The above cellular changes will eventually manifest themselves in one of the four distinct clinical forms of ATLL.\textsuperscript{17} The symptoms of these forms, which are termed acute, lymphomatous, chronic or smoldering, have been summarized in Table 1. Of the above, the acute form is most prevalent, occurring in 60% of patients with ATLL.\textsuperscript{7} In addition, 25% of patients presenting with the smoldering or chronic form of the disease will eventually return to the acute form, perhaps the result of a genetic modification.\textsuperscript{29} Interestingly, the acute and lymphomatous forms of ATLL present with hypercalcemia, which is believed to be paraneoplastic in origin.\textsuperscript{7}

Diagnosis and Prognosis

Due to the numerous symptoms patients with ATLL may present with, correctly diagnosing this disorder usually involves the noting of morphological characteristics of infected T cells, immunophenotyping and the use of serologic tests to identify antibodies against HTLV-I.\textsuperscript{12} Serologic diagnostic tests include the enzyme linked immunosorbent assay (ELISA) or particle agglutination.\textsuperscript{30,31} Polymerase Chain Reaction (PCR) based testing may be used to make a diagnosis of ATLL. This test has the ability to distinguish between HTLV-I and HTLV-II, and can also quantify proviral load in the blood or tumour cells.\textsuperscript{12,32,33} In addition to PCR, Western Blotting may also be used to confirm the presence of HTLV-I or distinguish between HTLV type I and II.\textsuperscript{12,34}

Many different factors have been identified which might determine how aggressive the cancer will be. From a clinical point of view, one of the major factors dictating survival rate is the form of ATLL. As summarized in Table 2, patients with Acute ATLL have the worst prognostic outlook, with a median survival rate of 6.0 months and a 4 year survival rate of 5%.\textsuperscript{35} In addition to ATLL type, factors such as increased provirus load or deletion/suppression of tumour suppressor genes like p16 may also worsen prognostic outlook.\textsuperscript{7,17,25,36}
Table 1: Overview of the symptoms associated with the four clinical forms of ATLL. 7;12;17

<table>
<thead>
<tr>
<th>Form</th>
<th>% of Cases</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>60%</td>
<td>Lytic bone lesions, Hypercalcemia, Generalized lymphadenopathy (chronic lymph node enlargement), Cutaneous lesions, similar to those noted in mycosis fungoides, CNS involvement in 10% of cases, Hepatosplenomegaly (enlargement of the liver and spleen), Opportunistic Infections</td>
</tr>
<tr>
<td>Lymphomatous</td>
<td>20%</td>
<td>Prominent Lymphadenopathy, Frequent blood, skin and bone lesions, Hypercalcemia is common, Absence of circulating tumour cells, Note: this form is a T-cell non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Chronic</td>
<td>15%</td>
<td>Skin Lesions, Lymphocytosis (increased number of lymphocytes in the blood stream), Skin Lesions, Liver, lung and lymph node involvement, Absence of Hypercalcemia, No CNS or GI involvement</td>
</tr>
<tr>
<td>Smoldering</td>
<td>5%</td>
<td>Normal blood lymphocyte counts, &lt;5 percent circulating neoplastic cells, Absence of Hypercalcemia, Skin or Pulmonary Lesions</td>
</tr>
</tbody>
</table>

Table 2: Prognostic outlook for the four types of ATLL.35;37

<table>
<thead>
<tr>
<th>Form</th>
<th>Duration of Survival (Median)</th>
<th>4 Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>6.0 months</td>
<td>5</td>
</tr>
<tr>
<td>Lymphomatous</td>
<td>10.2 months</td>
<td>5.7</td>
</tr>
<tr>
<td>Chronic</td>
<td>24.3 months</td>
<td>26.9</td>
</tr>
<tr>
<td>Smoldering</td>
<td>not reached after 13.3 months</td>
<td>62.8</td>
</tr>
</tbody>
</table>

Treatment

Different therapies aimed at managing ATLL have been studied within the clinical setting, including: conventional chemotherapy for lymphoblastic leukemia or non-Hodgkin’s lymphoma, allogenic hematopoietic stem cell transplantation, anti-retroviral drugs, monoclonal antibodies and arsenic trioxide (for an overview of current therapies, see reference 35). While some therapies look promising, each form of therapy tested has a unique set of strengths and weaknesses. Acknowledging such limitations, researchers are now proposing a type-tailored approach to therapy.35 Using this protocol, patients would be given different regimens depending on which form of ATLL they present with (see Figure 1). Unfortunately, at this point in time, an affective treatment for ATLL, which essentially requires treatment for both the cancer and the HTLV-I infection, does not exist.35
Conclusion

There has been a fair amount of biochemical and therapeutic work directed towards understanding HTLV-I and treating the related ATLL. More research needs to be done in order to understand the factors that contribute to viral latency in patients currently in remission. No treatment protocols thus far have been effective in curing ATLL in a wide range of patients. Therefore, additional research should be conducted to uncover new treatment regiments, as well as to establish the optimal combinations of current therapies to treat each of the four forms of ATLL.

References


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- 29% of males 15-19 do not use condoms
- 44% of males 20-24 do not use condoms
- 51% of females 15-19 do not use condoms
- 53% of females 20-24 do not use condoms

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- In Canada, 30% of people with HIV don't know they have HIV

Chlamydia

- Close to 60,000 cases of Chlamydia were reported in 2004, the highest number of cases since the disease became reportable in 1990

Gonorrhea

- Reported cases have dropped from 14.9 per 100,000 in 1997 to 2.9 per 100,000 in 2004

Syphilis

- Syphilis is escalating in both males and females, but more so in males. 2004 rates for men were 15 times higher than in 1997

Social responsibility

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Feature Article

48 Years and Counting

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Emeritus, Department of Psychiatry and Pediatrics, Hospital for Sick Children and Department of Psychiatry and Pediatrics, University of Toronto

The purpose of this paper in writing a personal history is to help others define for themselves their direction, the value of a solid professional and personal life, ending up, regardless of the limitations in one’s life, with humility to find out that giving back ultimately is one of life’s greatest rewards.

This article has been reviewed by Wendy Ng, Meds 2009.

My life and career in medicine have been an interesting journey. As a child I was greatly influenced by a friend of my father who was a family doctor and who used to take me on with him when he made housecalls. Later, as a teenager I got to know another family doctor who allowed me to assist him in tonsillectomies. Then in high school I discovered that my greatest pleasure was talking and getting to know people, which laid the seeds for my going into psychiatry.

The big secret in our family was that my father was unable to read or write, and this was a source of pain for him. Probably for this reason, he wanted me to become a lawyer to help him grow his business. Dad did allow me to make my own decision and although he was sad, I greatly respect his giving me the right to do what I wanted to do. My development was also influenced by my mother, who was a voracious reader, and this has also been part of my life. One of my greatest memories is of reading to them both in the twilight of their lives, when my mother was virtually blind, a chapter of a book that I had written.

When I went to medical school I disliked biochemistry and physiology, although today I wish I had been more studious in these areas. Kreb’s cycle in my day was referred to as “crap’s” cycle. In disappearing from labs, I often went to the library and read psychiatry, which laid the groundwork for my belief in a talking cure.

Several events in my internship were very meaningful and, as I look back on them, seem to have helped shape my career. When I started out in obstetrics as part of my rotating internship at the Montreal General Hospital, I really enjoyed talking to the patients who had problems with their lives after delivery. I then went to the Montreal Children’s Hospital and while I was doing my in-patient work, I met a four-and-a-half-year-old boy named Jean Guy who had carcinoma. I taught Jean Guy to bounce a ball. Every morning he was waiting for me to play. When I left to do internal medicine in my rotating internship and came back at Christmas, I found out that Jean Guy had died. I left the big red ball that I had bought him at the hospital, feeling very sad for him. However, I felt lucky to have known him and still always think of his courage.

Another other experience I had at the hospital was when the son of family friends was dying of leukemia and I tried to be supportive to them. I still remember the son asking me, when I went into his room, how come his head was so big, which was a result of the medication. I learned then the importance of listening and learning from children.

Starting out in psychiatry, I did believe with a passion that the talking cure was the answer. Coming in the midst of the Kennedy era, I said to my friend, “We are going to change things.” Now that the black box has been opened, the combination of neurobiology and the environment has added to my understanding, although much is still to be learned.

In my career serendipity has played a large role. I moved from McGill to Toronto and started working part-time at the Hospital for Sick Children. I was very sad about leaving Montreal because of the changes that had occurred and stimulated by the FLQ crisis. Because of my training, I had, when asked, the opportunity to do research on fatal genetic disorders, the lipid storage disorders which allowed me to find a way to deal with my sadness and gain a commitment to move in this direction as well as clinical practice. I wish that I had planned to look for a direction doing research earlier, for it has been vital to my
growth in medicine. I also think a great gift would be for all to try and find a direction early, and consider doing research. Studies have shown that individuals doing some research have particularly enjoyed their careers in psychiatry.

Medicine is a labour-intensive career. When I was a resident the mantra of my teachers was always to work harder and read more, and excellence only was considered normal. I have no regrets about this mantra. However, the world is a big place and being a physician is not the only reality. It is the doctor’s subjective reality and does not include the big picture. I urge everyone to take time to smell the roses and find other interests to enlarge your view of this complex and interesting world.

Osler’s quote of treating the patient who has the illness is very important. It also applies to physicians who have to heal themselves. Don’t forget that your family at dinner is probably one of the most exciting activities for you. I have had the privilege of working with 3 medical families and seeing the tragedies of alcoholism, drug addiction, marital disharmony and financial ruin, to name a few, far too often.

I have discovered that a great source of my family tradition 4,5 through my grandchildren has been an excitement that I cannot put into words and provides hope in the succeeding generations. Being called Grampa and spoiling them, allowing my children to pick up the responsibility, is sheer joy.

I have contributed to medical organizations, including human rights, which has been my interest since my undergraduate days, where I was involved in World University Service. This has been stimulated by my commitment of coming from an immigrant family and enunciated by Dad, who insisted that you never forget where you came from. The problem with medical politics, although one makes a contribution, is that much of the time it is organizational and has the feeling that it is sometimes not real. So I have found another source to add to my reality which has been establishing a lecture in human rights at the University of Toronto and becoming involved in International Development Enterprises, 6 which is a non-profit organization that attempts to promote agriculture development through water in third world countries.

How I got started in this was good fortune. My classmate, Paul Polak, has been coming to Homecomings talking about his organization and at our last Homecoming, I said, “Paul, you have done it. I would like to contribute.” The richness of watching his creativity 7, hearing about his organization and his ability to see and plan and create has led to an enterprise which now has an annual budget of $10 million and hopefully will increase over the years.

As I sit writing in the airplane on my way to an International Development Enterprises board meeting, I think about many things in life that have been good to me. As I hope for all of you that you remember to look after yourselves, a steadying force for me has always tried to keep one foot on the ground. I will always remember THE professor at the University of Toronto, the late Robin Hunter, saying to me, “Schneiderman, when are you going to stop pushing water uphill?” I find that my growth has led to humility and my admission was very comforting. I don’t know everything about everything.

We are fortunate to have medicine as a career. The benefits of helping patients have been one of life’s greatest rewards.

References
2. Graduate of the University of Western Ontario Doctor of Medicine 1958.
Feature Photography

Left: “Amor” in Madrid, Spain
Photographer: Michael Slatnik, Meds 2010

Right: The Jewish Museum in Berlin
Photographer: Michael Slatnik, Meds 2010

Bottom: Homeless on the streets of Rome
Photographer: Michael Slatnik, Meds 2010