



Cancer Genetics Gazette



A newsletter for specialist clinicians from the Familial Cancer Unit
July 2006 | Issue 1

Welcome to the first issue of the Cancer Genetics Gazette for 2006. Our articles for this issue are by Dr Graeme Suthers of the Familial Cancer Unit.

Radiotherapy in NF1 and NF2: call for caution

The treatment of neoplasia by radiotherapy usually represents an acceptable compromise. Although the treatment itself is mutagenic and increases the subsequent risk of another cancer, the benefit in managing the extant malignancy is much greater than the potential of another neoplasm arising.

The trade-off of risk and benefit may not be as clear cut if either the benefit is limited, or the risk is increased (or both). For example, patients with the autosomal recessive disorder, ataxia telangiectasia, are at high risk of developing lymphoma and are exquisitely sensitive to radiation in both normal and malignant tissue, necessitating modification of treatment protocols. The autosomal dominant disorders, Li-Fraumeni syndrome and familial retinoblastoma, are both characterised by multiple malignancies and a high risk of radiation-induced cancers. Patients presenting with multiple basal cell carcinomas or with medulloblastoma may have Gorlin syndrome, another disorder characterised by unusual sensitivity to radiation in normal and malignant tissue.

In recent years there has been growing interest in the use of radiation to treat benign lesions located in areas that may be difficult to reach surgically e.g. vestibular schwannomas, pituitary adenomas, and meningiomas. Radiation may well be beneficial for patients with sporadic benign lesions such as these. However, the risks appear to be substantially increased in patients with a familial predisposition to develop such lesions, even though such disorders are not typically associated with radiation sensitivity.

A recent review in the *Journal of Medical Genetics* noted that radiation treatment for sporadic benign neurological tumours is associated with a small finite risk of either malignant transformation in the benign lesion or new primary tumours arising in the radiation field. These risks are small, with there being only seven reports of malignant transformation in sporadic vestibular schwannomas in the medical literature. Radiotherapy for sporadic meningiomas and schwannomas is associated with no more than 3% increased risk of a second primary in the radiation bed after 30 years.

In contrast, the situation is dramatically different in patients with neurofibromatosis Type 1 (NF1) or Type 2 (NF2). Children with NF1 frequently develop an optic glioma. These are usually indolent lesions that do not necessarily require intervention. It is now clear that radiotherapy to such lesions in children with NF1

is associated with a three-fold increase in the risk of malignant transformation of the glioma. The risk of a second glioma (a new primary) is also markedly increased.

In patients with NF2, irradiation of a vestibular schwannoma is associated with a 10-fold increased risk of malignant transformation compared with the risk in patients with sporadic disease. Stereotactic radiosurgery ("gamma knife") for such lesions is appealing because of the potential for reduced morbidity, especially in patients at high risk of contralateral disease, but must be weighed up against this risk of malignant transformation. The authors note that many reports of radiation treatment for schwannomas have limited follow-up and may not reflect the true morbidity associated with radiotherapy in NF2.

NF1 and NF2 are not associated with cytologically evident chromosome fragility. There were no a priori data to suggest that these patients would be more susceptible to adverse effects of radiotherapy. Such concerns may extend to other familial tumour syndromes. There is indirect evidence to suggest that patients with von Hippel-Lindau syndrome are also more likely to develop adverse long-term outcomes from radiotherapy to haemangioblastomas.

The observations do not necessarily mean that radiotherapy is an inappropriate treatment for a specific patient with one of these disorders. But the study highlights that the trade-off of risks and benefits in treating histologically benign lesions in patients with a familial tumour syndrome may not be as clearly defined as in patients with sporadic lesions.

References

Evans DGR, Birch JM, Ramsden RT, Sharif S, Baser ME. Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes. *J Med Genet* 2006; 43:289-294.

Sharif S, Ferner R, Birch J, Gillespie JE, Gattamaneni HR, Baser ME, Evans DGR. Second primary tumours in Neurofibromatosis 1 patients treated for optic glioma: substantial risks after radiotherapy. *J Clin Oncol* 2006; 24 (16): 2570-2575.

Research snapshot

Methylation, genes, and families.

Most of the genetic errors that cause familial cancer are disruptions of the DNA sequence of the gene. The disruption may be loss of one or more nucleotides, or replacing one nucleotide with another. These genetic errors are determined by sequencing the gene and identifying the abnormality. However, a gene can also be inactivated by a process does not change the

gene sequence. The addition of methyl groups to nucleotides in the regulatory region of a gene renders the gene inactive, with the underlying DNA sequence remaining intact.

Methylation is a normal regulatory process for many genes, with methylation and de-methylation being used to turn genes off and on (respectively). Abnormal methylation of genes is also a common abnormality in cancer, and it almost always reflects non-heritable (somatic) mutations that have accumulated with age.

However, heritable abnormalities causing familial cancer have now been identified in small number of kindreds. Three South Australian patients have been identified with abnormal methylation of the MLH1 gene at conception, and each went on to develop hereditary non-polyposis colorectal cancer. The familial implications of these findings are being explored (manuscript submitted).

These studies have highlighted the dynamic nature of mutations and broadened the repertoire of methods necessary to clarify cancer risk in some of these families.

Reference

Hitchins et al. MLH1 germline epimutations as a factor in hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2005; 129:1392-9.

Staff changes

Familial Cancer Unit, Women's and Children's Hospital, SA

A second clinical geneticist has joined the Familial Cancer Unit. Dr Nicola Poplawski trained in New Zealand, Australia, and Canada. She has an MBChB and an MD from the University of Otago, New Zealand. Dr. Poplawski is working part-time with the SA Clinical Genetics Service, dividing her time between the Familial Cancer Unit and the Metabolic Unit.



The Cancer Council South Australia

Dr Carolyn Harrington has joined The Cancer Council as the Cancer Genetics Education Officer. Carolyn has a background in science and genetics, with a PhD in cancer research. Her role is to develop, implement and evaluate strategies for broadening cancer genetics education in public and professional communities, especially with individuals at risk of familial cancer.



Clara Tait has left the post of Cancer Genetics Education Officer to work with The Cancer Council among culturally and linguistically diverse communities (CALD). Clara's hard work and commitment to cancer genetics education, including being the inaugural editor of The Gene Pool, is gratefully acknowledged.

The Cancer Council South Australia

202 Greenhill Road
Eastwood SA 5063

t 08 8291 4111
f 08 8291 4122
Free 1800 188 070

www.cancersa.org.au
tcc@cancersa.org.au

The Familial Cancer Unit

Women's and Children's
Hospital
North Adelaide SA 5006

t 08 8161 6995 f 08 8161 7984

cywhs.famcancer@cywhs.sa.gov.au



Web watch

The aim of Web Watch is to connect specialist clinicians with relevant and informative links to web based resources, with particular emphasis on cancer genetics education.

<http://www.kconfab.org/>

The Kathleen Cunningham Foundation for research into Familial Breast Cancer (KconFab) expects to have accumulated data on approximately 1000 multigenerational, multi-case kindreds by 2007. This is an important resource for researchers in areas of clinical, epidemiological and genetic aspects of familial breast cancer.

<http://www.geneclinics.org/>

The GeneClinics website provides free online access to fully referenced expert reviews of (to date) 340 different genetic disorders (GeneReviews). New reviews are regularly added. Most entries include a clinical description, clinical and genetic diagnosis methods, important differential diagnoses, management guidelines, a review of genetic counselling issues and resource links for clinicians, researchers and families. Every entry is dated (initial posting and most recent review). [The site also links to a database of US-based genetic laboratories that provide testing for genetic diseases (GeneTests; www.genetests.org), but most relevant testing in relation to familial cancer is already available in South Australia]. Five cancer reviews are currently listed, including reviews of BRCA1 and BRCA2 hereditary breast/ovarian cancer and hereditary non-polyposis colon cancer (HNPCC). The reviews are generally excellent but have one important limitation; some of the clinical recommendations differ from the evidence based conclusions reached by Australasian experts and institutions, most often when the review authors practice in the USA where the litigation environment differs in significant way to that encountered in Australasia.

<http://www.nbcc.org.au/resources/newsletters.html>

Clinical Update is produced by the National Breast Cancer Centre for health professionals. It provides a brief abstract and key findings of relevant journal articles, with a commentary of study outcomes in context with the Australian healthcare system.

Do you wish to receive other cancer genetics newsletters?

The Gene Pool cancer genetics newsletter for general practitioners

Gene Trek newsletter for Familial Cancer Unit clients

If you wish to receive the Cancer Genetics Gazette electronically or the other newsletters, please contact:

Dr Carolyn Harrington, Cancer Genetics Education Project Officer
The Cancer Council South Australia
PO Box 929, Unley SA 5061
t 08 8291 4269 f 08 8291 4268
charrington@cancersa.org.au

Editorial responsibility for this Newsletter is taken by Dr Graeme Suthers of the Familial Cancer Unit. Printing and distribution of this newsletter is sponsored by the South Australian Familial Cancer Service and The Cancer Council South Australia.