

AT LAST – AN IMPROVEMENT IN THE MANAGEMENT OF ADVANCED MELANOMA

For more than 15 years, since the first publication of the use of interferon in the adjuvant therapy of stage II melanoma, there have been no real advances in this disease which calls Queensland its breeding ground.

For many years both surgeons and radiation oncologists have questioned the value of adjuvant radiation therapy following nodal dissection for patients with high risk features on pathology. Radiation has been reported as having no value in the management of melanoma, apart from palliation.

Until recently the only randomised trial looking at this question was published in 1978. It was poorly designed, had little power and addressed the wrong endpoint. Since that time major units dealing with melanoma continued to use adjuvant radiation following nodal dissection in those patients considered at high risk of regional recurrence¹.

In 1992 at the Melanoma Clinic at Princess Alexandra Hospital, work began on studying the side-effects of adjuvant radiation in selected patients following nodal dissection. An in-house review of patients having surgery alone suggested a regional recurrence rate of up to 30% which was consistent with other published data. A series of 26 patients was subsequently treated with adjuvant radiation using a new schedule (48 Gy in 20 fractions over four weeks). A publication in 1995 reported a regional control rate of 88% and little in the way of increased side-effects².

The results of this phase I study prompted a much larger trial involving multiple centres under the auspices of the Trans Tasman Radiation Oncology Group (TROG). The study, known as TROG 96.06 recruited 234 patients from eight centres in Australia and New Zealand and was published in 2006³. A regional control rate of 87.5% at five years was confirmed, again with acceptable toxicity.

The outcomes of this study prompted the design of a phase III trial to be lead by TROG but ably supported by the Australian and New Zealand Melanoma Trials Group (ANZMTG). Following the accrual of 250 patients from 16 centres in four countries over 5.5 years, this study has had its first analysis of the major endpoint. A significant improvement in regional control following lymphadenectomy results from giving postoperative adjuvant radiation therapy. At one year, 31% of patients in the observation arm had relapsed in the nodal basin compared to 19% in those who received adjuvant radiation.

The study has been reported at both ASCO (American Society of Clinical Oncology) and ASTRO (American Society of Radiation Oncology) annual meetings in 2009⁴.

This finding will almost certainly change the management practice for nodal melanoma in those patients at high risk of regional recurrence.

Professor Bryan Burmeister
Director of Radiation Oncology, Princess Alexandra Hospital

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LATEST REPORT ON CHILDREN AND CANCER IN AUSTRALIA

Cancer Council Queensland has recently published a report on the incidence of childhood cancer in Australia from 1983 to 2006. Produced by the Viertel Centre for Research in Cancer Control, the report is based on the most recent information available from the Australian Paediatric Cancer Registry (APCR).

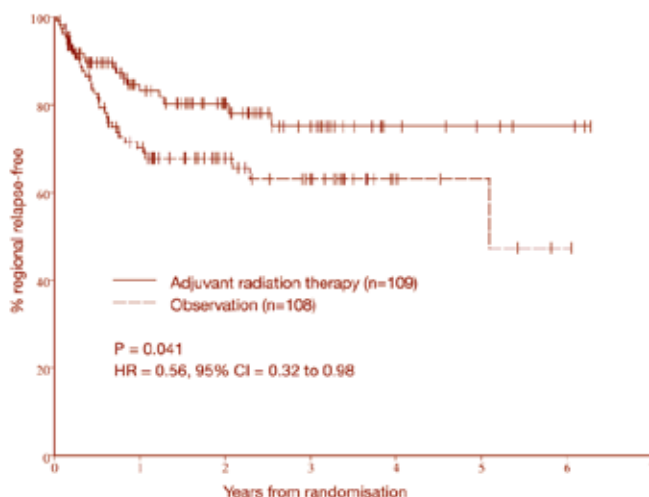


The APCR is one of the few national registries of childhood cancer in the world. All Australian State and Territory cancer registries and major paediatric oncology hospitals contribute to the registry to provide comprehensive information on cancer diagnosis, stage, treatment and survival for the Australian population aged 0-14 years. Detailed and verified data is currently available for the period 1983-2006.

Although the number of children diagnosed with cancer each year represents only 0.6% of all cancers diagnosed, the consequences of

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Fig 1: Time to regional relapse following lymphadenectomy in patients with nodal metastatic melanoma⁽⁴⁾



LATEST REPORT ON CHILDREN AND CANCER IN AUSTRALIA *continued*

childhood cancer are far-reaching. Cancer was responsible for 19% of all deaths recorded among Australian children aged 1-4 years during 2004 which was the second most common cause of death behind accidents and drowning. Beyond the loss of young lives, childhood cancer is associated with long-term adverse health outcomes for a large proportion of survivors due to either the cancer itself or the consequences of treatment.

How many children are diagnosed with cancer in Australia?

In the 10 years from 1997-2006, an average of 618 children under the age of 15 were diagnosed with cancer each year in Australia, corresponding to a rate of 156 per million children per year. The overall incidence of childhood cancer was significantly higher among boys, with 337 cases per year compared to girls with 282 cases per year.

Almost half of all childhood cancers were diagnosed among children aged 0-4 years, with 285 cases per year or a rate of 223 per million, compared to an average of 156 cases per year (or 117 per million) among children aged 5-9 years and 177 cases per year (or 131 per million) in the 10-14 age group.

Leukaemias were the most common type of cancer diagnosed among Australian children, accounting for around one third of all cases (or an average of 207 cases per year). The next most common types of cancer were tumours of the central nervous system, with 141 cases per year or 23% of all childhood cancers, followed by lymphomas with 62 cases per year or 10% of the total.

The report presents data on average annual incidence by sex, age group and State/Territory for each of the main childhood cancer diagnostic groups. Trends in incidence rates were also calculated by sex and by age group to examine if there were any significant changes in cancer incidence over time.

How have rates of childhood cancer incidence changed over time?

The trend in incidence rates for all childhood cancers combined increased significantly by an average of 1.7% per year between 1983-1994, but has subsequently remained stable.

Incidence rates have also been stable among boys since 1994, following a significant increase of 1.7% per year between 1983-1994, while for girls, an ongoing significant increase of 0.9% per year was observed in incidence rates between 1983-2006.

Trends by age group were mixed. Among children aged 0-4 years, incidence rates increased significantly by an average of 0.7% per year between 1983-2006, while incidence rates remained stable among children aged 5-9 years. However, within the 10-14 age group, a significant increase of 2.7% per year was recorded between 1983-1996, with evidence of a possible decrease between 1996-2006, although the latter trend was not statistically significant.

Significant increases in incidence rates over the period 1983-2006 were observed for hepatic tumours (3.3% per year), germ cell tumours (2.2% per year), leukaemias (0.9% per year) and lymphomas (0.7% per year). In contrast, incidence rates for other malignant epithelial tumours and melanomas significantly decreased by 5.8% per year between 1996-2006. There was also some evidence of a possible decrease in the trend for tumours of the central nervous system from 1998 onwards, although the annual percentage change was not statistically significant.

This comprehensive report will be a useful resource for clinicians, health managers and their supporters who are working towards improving outcomes for children with cancer.

The full report is available at http://www.cancerqld.org.au/page/Research_statistics/VCRCC/Statistical_reports or contact research@cancerqld.org.au to arrange for a copy of the report to be mailed out.

ARE DELAYS IN ETHICS APPROVAL IMPACTING ON CLINICAL TRIAL PROJECTS?

Each year QCOG undertakes a review of cancer clinical trial activity in Queensland and these results showed that the rate of patient recruitment to cancer clinical trials had declined during the previous 12 month period (2008). One possible reason for this decline is that the number of active clinical trials available for recruitment has also decreased. There are a number of new studies planned to commence however anecdotal feedback from QCOG members suggests that considerable delays are being experienced with obtaining Human Research Ethics Committee (HREC) approval for protocols.

It was proposed to undertake a survey to determine if the delays in obtaining HREC approval experienced by some centres were consistent throughout Queensland Institutes and to quantify the times being taken to obtain approval.

Method

A written survey was distributed to centres in Queensland identified as sites where cancer clinical research is undertaken; both public and private. Surveys were addressed to the Data Manager and were posted in February 2009. Respondents were requested to complete a single page survey and to record details of the time periods involved in obtaining approval for cancer trial protocols submitted in the previous 12 month period -Dec 2007 to Dec 2008.

Results

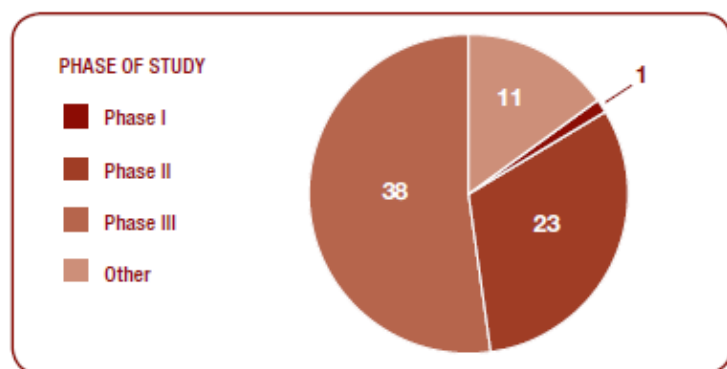
Sixteen responses to the survey were received representing 80% of the survey recipients.

ARE DELAYS IN ETHICS APPROVAL IMPACTING ON CLINICAL TRIAL PROJECTS *continued*

Fourteen respondents indicated that they had submitted a total of 122 cancer clinical trial protocols for HREC approval in the previous 12 month period (range 1-48 per institute). Two institutions had not submitted any new protocols for HREC approval in the previous 12 month period. Survey forms were completed in relation to 73 protocols.

12/16 respondents were Queensland Health facilities.

Type of cancer clinical trial protocols submitted for approval from Dec 2007 to Dec 2008:



25/73 protocols were industry sponsored studies.

70/73 protocols were multicentre studies and 65 of these has been previously approved by another HREC.

54/73 protocols were submitted to HREC's using the National Ethics Application Form (NEAF).

Time lines for approval of protocols:

On average centres submitted protocols 30 days prior to the scheduled HREC meeting.

HREC approval at first meeting	Time taken to advise of decision *	Time to final approval date*	Time to activation of trial*
Yes (n=34)	-	-	88 days (5-241)
No (n=39)	6 days	54 days (8-297)	129 days (8-359)

**Time calculations determined from date of HREC meeting*

For those protocols which received initial HREC approval, there were still additional steps/processes to be completed before the trial was able to commence. These included:

- Site initiation meeting
- District Exec approval
- Director General approval
- CTN submission and approval by TGA
- CaSS approval
- Contract negotiation

Nine protocols were still pending activation more than three months after HREC approval.

The reasons cited for non- approval of protocols by HREC included:

- Request for further information (n=11)
- Changes to participant information and consent form (PCIF) (n=28)

The average time taken to respond to the HREC requests for further information was 26 days (range 1 – 161 days).

Of the 39 protocols that were reconsidered by the HREC, 26 trials were eventually approved and activated.

Eleven studies were approved and await activation. Reasons for the delay in activation include:

- Ongoing negotiation of contract and indemnity issues (n=9)
- Sponsor delays eg. supply of drug, site meetings (n=2)

Two studies are still pending approval.

Discussion

The results from this survey provide a snapshot of the experiences associated with obtaining HREC approval for cancer clinical trial protocols in Queensland. The results appear to be consistent across most centres and there does not appear to be any difference between private and public institutes.

Less than 50% of protocols submitted to HREC's were approved at the first meeting. The main reasons cited for non-approval of protocols was the need for additional information or changes to the patient consent and information form (PCIF). On average centres took 26 days to provide this additional information to the HREC.

For protocols that received initial HREC approval, 88 days elapsed since the date of the HREC meeting before the trial was ready for activation.

Studies which did not receive initial approval and required further information to be submitted to the HREC took an average 129 days to reach activation. This difference can be attributed in part to the delay in providing additional information to the HREC.

Based on these results a two – four month time frame for obtaining HREC approval and associated approvals to enable trial activation is usual.

There are some noticeable cases of extensive delays experienced by some centres. One centre reported that only one of nine trial submissions received HREC approval at the initial meeting. Seven studies did eventually receive HREC approval but only three of these had been activated. The remaining five approved trials were still awaiting activation and one study was still pending approval; a success rate of only 33%.

The delays being experienced by centres to obtain approval for trial activation are not due to the HREC and the provision of Ethical and Scientific approval for the study but primarily as a result of complying with research governance requirements (site specific assessment).

In the past two years Queensland Health has introduced a two step process for approval of clinical research. Step one is the scientific and ethical review of a protocol undertaken by a designated HREC. Step two is completion of the research governance requirements. Step two can happen in parallel with step one but normally takes place after the HREC have given their approval. The survey did not seek to address specific questions regarding the research governance requirements however the majority of survey respondents were very critical of the delays associated with obtaining research governance approval. In particular the legal or contractual arrangements for the study were one of the main issues.

Conclusions

Scientific and ethical review of research protocols by Human Research Ethics Committees in Queensland is conducted within a reasonable timeframe and complies with Queensland Health benchmark of 60 calendar days.

The time frame from HREC approval to trial activation varies significantly between centres and can lead to extended delays in trials commencing. The main reasons cited for delays are due to research governance processes associated with finalising contracts and indemnity issues. The benchmark of 25 days for completion of these processes is rarely achieved.

Actions to address the delays in obtaining approval for research proposals need to address the research governance requirements and is vital for ensuring that Queensland can maintain and improve its participation in cancer clinical trial research.

ATTITUDES AND KNOWLEDGE OF RANDOMISED CANCER CLINICAL TRIALS AND BARRIERS TO PARTICIPATION AMONG RURAL AND REMOTE PATIENTS.

The best treatment option for most cancers is participation in clinical trials¹. Participation in trials is generally low and among rural patients it is likely to be even lower for several reasons. A study was conducted to assess the knowledge of randomised clinical trials among rural, remote and regional cancer patients of north Queensland, their willingness to participate in them and factors affecting their participation.

The survey was conducted in medical oncology outpatient clinics at the Townsville Cancer Centre and Mt Isa Hospital. All patients with cancer were eligible to participate and were required to provide informed consent. The questionnaire addressed the following areas:

- 1 Demographics; including level of education, prior cancers, history of their cancer therapy, stage of their disease and previous experience or knowledge of clinical trials.
- 2 Knowledge of clinical trials using an eight item knowledge scale.
- 3 Willingness to participate.
- 4 Reasons for participation or non-participation in clinical trials.
- 5 Rural factors.
- 6 Preferred number of visits for clinics and treatment, preferred number of visits for blood tests and reviews as part of the trial protocol.

Rural patients were identified using the Australian Standard Geographical Classification (ASGC) which groups geographic areas into five classes. These classes are based on Census Collection Districts (CDs) and are defined using the Accessibility / Remoteness Index for Australia (ARIA)². Chi-square, t-tests, Wilcoxon and linear regression were used for analysis.

178 patients participated in the survey – a response rate of 90%. Median

distance to the trial centre (Townsville) for rural participants was 180km (range 80 - 1300km). 45.4% lived in rural / remote areas. When asked if they would take part in a randomised controlled trial, 13.2% of participants said no, 56.3% said yes and 30.5% were unsure. When adjusted for level of education, there was no difference between rural/remote patients and regional patients ($p=0.206$). For randomised controlled trials, there were no significant relationship between willingness to participate and rurality or education level ($p=0.6$). For the majority of patients, the maximum number of clinic visits and blood tests did not matter. Cost of travel (41.1% rural/remote; 23.5% regional; $p < 0.001$) and the need for family or friends to accompany (38.9% rural/remote; 24.1% regional; $p=0.021$) were more important for rural/remote than regional patients as factors affecting participation.

In conclusion, rural and remote patients are as interested in participating in randomised clinical trials as regional patients and therefore they should not be excluded because of rurality. Knowledge of trials is poor and there is a need for education earlier in the consultations. Cost of travel and need for family members to accompany may be barriers for participation among rural and remote patients and as such trial budgets should include cost of travel to encourage participation of patients from rural and remote areas.

Dr Sabe Sabesan, Dr Suresh Varma and Dr Zulfiqer Otty
Department of Medical Oncology, Townsville Cancer Centre

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2. Rural, Regional and Remote Health: A Guide to Remoteness www.aihw.gov.au/publications/phe/rrrh-gtrc/rrrh-gtrc-c01.pdf

QCOG BREAST GROUP DATE REMINDER

The next QCOG Breast Group Meeting will be held on Tuesday 20 April 2010 from 6pm.

A panel of interesting and varied speakers will present the latest news on breast cancer trials and clinical updates.
To ensure that you receive your invitation, please contact qcog@cancerqld.org.au.

**Queensland Co-operative
Oncology Group**



Have you joined QCOG?

For further information regarding membership of QCOG or to join the mailing list to receive further newsletters and updates, please contact:

Heather Day

QCOG Professional Officer
Cancer Council Queensland
PO Box 201
Spring Hill Qld 4004
Phone (07) 3634 5306
Fax (07) 3259 8527
qcog@cancerqld.org.au



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