

# AUSTRALIAN SARCOMA STUDY GROUP: DEVELOPMENT AND OUTLOOK

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## Abstract

Sarcomas represent a small, diverse and high impact group of cancers that disproportionately affect the young. There is good data to link outcomes to clinical research participation for many cancers, including sarcomas. Historically neglected because of the rarity of these disorders, Australian clinicians first began to self-organise about a decade ago, to develop the Australian Sarcoma Group, a society designed to increase the focus on sarcomas in Australia. In December 2007, with Cancer Australia funding, the Australian Sarcoma Group took the next step towards establishing an effective clinical research co-operative group, by forming the Australian Sarcoma Study Group. This group has been in existence for only 12 months, but already has a keen multidisciplinary group and a portfolio of research.

## Sarcomas in Australia

Sarcomas are a small, complex and heterogeneous group of cancers that have been relatively neglected over the past 30 years. Although the numbers are small by comparison with more common cancer types, the impact upon the community is disproportionate to its incidence. There are about 800 new sarcoma cases in Australia each year, an increase of 40% over the previous decade according to Australian Institute of Health and Welfare data in 1998.<sup>1</sup> The community impact of sarcoma is frequently underestimated. On average, 17 life years per patient are lost due to sarcomas (three times greater than bowel, lung or breast cancer).<sup>2</sup> In 2003, the total burden of disease measured by disability adjusted life years (DALYs) due to sarcomas (5879) was comparable to cervical cancer (5231), eight times the impact of germ cell tumours (862) and more than twice that due to all cancers in children (2512).<sup>3</sup> Current treatment costs for sarcomas are very high. The per capita lifetime cost to the community of bone and connective tissue tumours (\$29,593) is the 6th highest for any cancer type, or equivalent to the cost of colorectal cancer (\$18,246) and breast cancer (\$11,897) combined.<sup>4</sup>

In part this community cost is because of the relatively young age of onset of many sarcomas, and the lethality of these disorders. Sarcomas comprise 10-20% of cancer in the young and the overall mortality is about 50%,<sup>5</sup> among the worst for any cancer type in adolescent and young adult patients (AYAs). Cancer in AYAs is an important public health issue in the United States, because there have been no improvements in survival over the past 30 years.<sup>6</sup> The onTrac@Petermac program studies in over 14,000 Australian AYAs with cancer indicate that AYA with sarcomas do substantially worse than children. The five year survival for both osteosarcoma and Ewing sarcoma in AYAs between 1983-2003 is about 45%, compared to 76% for children under 15 years. Despite increasing numbers, according to Australian Institute of Health and Welfare data, public expenditure on cancer in the 15-25

year-old group actually fell by 13% between the years 1993-2001 (the only group in which this occurred).<sup>7</sup>

Survival rates are equally poor for older patients with sarcoma. Response rates for the most active current chemotherapies are disappointing, and there remains no clear role for the adjuvant use of chemotherapies despite almost 30 years of clinical trials. However, as for many rare cancer types, this is changing. The new class of molecularly targeted therapeutics have made impressive proof-of-principle impact in sarcomas (for example, GIST, dermatofibrosarcoma protuberans, giant cell tumour of bone, tenosynovial giant cell tumours, Ewing sarcoma, and others). The impact of these breakthroughs has extended far beyond this smaller patient population, providing important insights into treating more common cancers. A significant proportion of sarcomas are characterised by signature molecular defects, which holds promise for the rational development of molecularly targeted therapies. Indeed the contribution of sarcomas to the current understanding of tumour suppressor gene biology is particularly impressive, and includes the roles of the retinoblastoma cell cycle checkpoint, and the p53 DNA damage checkpoint.

Outcomes for AYA with sarcoma correlate significantly with poor participation in clinical trials in both the US<sup>6</sup> and Australia.<sup>8</sup> Participation rates in clinical trials for Australian AYA sarcoma patients are particularly low (<4%) compared to children with sarcomas (13-46%) or AYA with haematologic cancers (about 10%). Paediatric research groups have failed to recruit AYA patients, because 90% are treated at adult institutions. Of the 14 sarcoma-specific trials registered at the NCI with Australian sites,<sup>9</sup> one (GIST) was open at adult centres; the remainder are only open at paediatric hospitals. The GIST study is supported by the Australasian Gastro-Intestinal Trials Group.<sup>10</sup> As of July 2007, there were literally no multi-institutional clinical trials for adult sarcoma patients in Australia, compared with seven trials in prostate cancer,

37 trials in breast cancer, 16 for lung cancer, six for renal cancer and bladder cancer, and 15 for melanoma. The lack of clinical trials infrastructure is the major barrier to trials access for adult Australian sarcoma patients.

The observations applying to clinical therapeutics into sarcomas also apply to psychosocial and quality of life outcomes research, clinical genetics and molecular research. Sarcomas are over-represented in inherited cancer predisposition syndromes. Australia has outstanding resources for undertaking internationally competitive clinical genetic studies, provided the clinical 'front end' facilitates access for patients. Australia has a vigorous basic and translational research community in sarcomas, with basic research programs in all states. In order to leverage bench resources by systematically improving access to clinically annotated biospecimens, a national infrastructure for patient recruitment, data and biospecimen collection, and storage is needed.

### **Australian Sarcoma Group – a coalition of the willing**

To meet these needs, in December 2007, with funding from Cancer Australia, and under the auspices of Clinical Oncology Society of Australia, the Australasian Sarcoma Study Group (ASSG) established itself as a national Cooperative Cancer Clinical Trial Group and commenced operation in January 2008. The ASSG had historic antecedents. The first recognised musculoskeletal oncology group began in 1998 with the formation of the Orthopaedic Oncology Society of Australia (OOSA). This was a special interest group created under the auspices of the Australian Orthopaedic Association. At that time, the specialty of orthopaedic oncology was a recognised field abroad and the Australian pioneers of the discipline (Professor William Marsden (deceased), Mr Ian Dickinson and Professor Peter Choong) had returned from the United Kingdom, United States and Europe with the knowledge, skills and interest that led to the development of OOSA.

Recognising the importance of establishing a standard of practice, the key orthopaedic oncology surgeons from each state at that time (Ian Dickinson – Brisbane; William Marsden and Paul Stalley – Sydney; Peter Choong – Melbourne; David Wood – Perth) agreed to meet on a regular basis to share their experiences and knowledge with each other and to create a network by which the discipline could be expanded in Australia. It was clear from the outset that surgeons alone could not develop the field without the participation of their multidisciplinary groups, and so OOSA was borne. Through OOSA, the main orthopaedic oncology units in Australia were able to identify themselves to other members and also any special interest that they may have had. Soon other surgeons joined the group and with them pathologists, radiologists, nuclear physicians, medical oncologists and radiation oncologists.

Meeting once a year, OOSA provided a forum by which difficult cases could be discussed, registrars could be educated and themes related to musculoskeletal pathology explored. It was a trend from the start to select a single tumour and to "do it to death" over a day and a half. With the contribution of overseas participants, a number of very

successful meetings were held covering both primary and secondary bone and soft tissue tumours.

In 2000, members of OOSA agreed that the name of the group should be changed to the Australian Sarcoma Group (ASG) to highlight the special interest the group had in sarcomas, and to dispel the notion that this group was primarily orthopaedic in nature. Ian Dickinson, orthopaedic surgeon, became the inaugural president of ASG from 2001 to 2002; Peter Choong orthopaedic surgeon (Victoria) followed for 2003-2004; Mark Clayer orthopaedic surgeon (South Australia) from 2005-2006; and David Thomas medical oncologist (Victoria) from 2007-2008. The present incumbent for the 2009-2010 period is Sandro Porceddu, a radiation oncologist (Queensland), attesting to the multidisciplinary nature of the group and the combined influence that the different specialties are bringing to the practice of sarcoma management around Australia.

Through the ASG, there is now a consensus about the manner in which patients with suspected sarcomas are investigated, exposed to neoadjuvant or adjuvant therapy and their sarcomas resected. Regular interaction among the group has allowed consolidation of practice philosophy, and in latter years the focus of ASG has broadened to include collaborations to support clinical and basic research. All saw the newly created Australian Sarcoma Study Group (ASSG) as the paramilitary wing of the ASG, a vehicle to take sarcoma practice in Australia to a new level where clinical practice was not only integrated with basic and clinical research, but that this research should also cross international boundaries in seeking partnerships with other major centres around the globe. In this regard, over the past two years major strides have been made to foster clinical trials research between Australia and umbrella groups in Europe and North America.

### **Aims of the Australian Sarcoma Study Group**

Today, the ASSG is a thriving association of clinicians, nurses and researchers numbering over 70 members, in stark contrast to its first foray as OOSA where there were fewer than 15 members. Through the ASG and its state led groups, the future of ASSG will be to develop guidelines for the early management of patients with suspected sarcoma at the primary care level, and also for the tertiary level management of this disease. Through a coordinated approach with the ASG, the ASSG aspires to provide a leadership role in the management of primary bone and soft tissue tumours in the Asia-Pacific region and to contribute strongly and meaningfully in a global setting.

The broad aim of the ASSG is to improve outcomes for sarcoma and related tumours in the Australian community by undertaking outstanding international basic, translational, clinical and supportive care research. The foundation goals include:

- taking a leadership role nationally and internationally in basic, translational, clinical and supportive care research;
- identifying unique strengths and opportunities in the Australian environment;

- developing a particular focus on adolescents and young adults; and
- building bridges with local, national and international communities.

The ASSG secretariat was enabled with the appointment of an Executive Officer (Dr Sally Whyte) in March. Since that time, the group has established a constitution, a board with representation from the major states and disciplines relevant to sarcoma care, a scientific advisory committee and a Community and Philanthropy Advisory Committee. These committees have called upon individuals representing most of the clinical and allied health disciplines relevant to treatment of sarcomas, and also with diverse geographical representation. Two groups deserve specific mention. A small but committed group of clinicians from New Zealand are also members of the group, as well as strong paediatric representation at both the board and scientific advisory committee levels. In addition to clinical skill sets, the group has attracted the support of basic and translational scientists from many states, who have an interest in sarcomas.

## Research and development

The group's research program was initiated in July 2008 and has three studies in various stages of development. These include a world-first, philanthropically supported kindred study of inherited cancer risk in adult-onset sarcomas, the Australian Sarcoma Kindred Study (ASKS). The ASKS aims to recruit over 600 consecutive cases of sarcoma presenting to adult cancer institutions to better define the spectrum of familial risk, outside the well-known Li-Fraumeni and neurofibromatoses. It will also form a resource for the impending revolution in cancer genetics that is currently being driven by massively parallel sequencing platforms. A second study which has commenced recruitment in November 2008, is the neoadjuvant sunitinib and radiotherapy study in resectable soft-tissue sarcomas (SUNXRT). This world-first study is a single site, phase Ib/II design, and aims to test the Jain hypothesis. The Jain hypothesis states that tumour vasculature is inherently abnormal, and that angiogenesis inhibitors may act to partially 'normalise' the neoplastic vascular tree.<sup>11</sup> It is predicted that this will result in increased oxygenation to tumours which are otherwise hypoxic, and that this will increase the efficacy of radiotherapy. It is known that sarcomas are frequently hypoxic,<sup>12,13</sup> and the SUNXRT study builds on recent Australian research that confirms that hypoxia is associated with bad biologic behaviour in these tumour types (K Khamly and D Thomas; unpublished data). Finally, the ASSG is undertaking a study to investigate the reasons for poor survival in AYA with osteosarcoma and Ewing sarcoma, compared to children with the same diseases. Initial data strongly suggests that much of the excess mortality in AYA populations occurs in males with these diseases, as well as in Hodgkin's lymphoma. This research also showed that a key difference between males and females is that females experience greater toxicity associated with chemotherapy for these cancers, as well as apparently greater benefit. The study aims to formally examine the pharmacologic handling of a key cytotoxic, doxorubicin, in both children and AYA populations with these cancer types. Excitingly, this study will recruit from

both paediatric and adult centres, with plans to open the study in multiple states.

A major achievement has been the contribution of the CPAC. In the first eight months, CPAC has already attracted major philanthropic funding, through linkages to community groups with a focus on sarcomas, including Rainbows for Kate and the Ross Trust. More importantly, these funds are based on community partnerships, with commitment to mutual support and cross-representation between the ASSG and the funding partners. This substantial support will significantly leverage government funds, and accelerate the development of research into this devastating disease.

## The future

Work is progressing on the development of a national, consensus clinical dataset, and establishing the mechanisms for data collection across all states. This resource will be linked to biospecimen collection, which is already in train in most centres. The purpose of this project is to be able to undertake a detailed analysis of outcomes for Australian sarcoma patients, using well-annotated datasets, and to facilitate derivation of clinically important correlates of molecular studies. The aim is to implement this database, which has already been piloted in Victoria, across at least three states by early 2009.\*

\* ASSG welcomes new members. The best way to make contact if you have an interest is via the website, which will go live in early 2009 ([www.australiansarcomagroup.org](http://www.australiansarcomagroup.org)). For more information contact the ASSG executive officer, Dr Sally Whyte (+61 3 9656 1111).

## References

1. Australian Institute of Health and Welfare; Australasian Association of Cancer Registries. Cancer in Australia 1998: Incidence and mortality data for 1998. Cancer series no. 17. AIHW cat. no. CAN 12, 2001 [cited 2008 Dec 12]. Available from: [www.aihw.gov.au/publications/can/ca98/](http://www.aihw.gov.au/publications/can/ca98/).
2. Giles G, Thursfield V, editors. Canstat: Cancer in Victoria 2001. Melbourne: The Cancer Council Victoria Epidemiology Centre; 2003.
3. Begg S, Vos T, Barker B, Stevenson C, Stanley L, Lopez AD. The burden of disease and injury in Australia 2003. Canberra: Australian Institute of Health and Welfare; 2007 [cited 2007 Nov 14]. Available from: <http://www.aihw.gov.au/publications/hwe/bodaia03/bodaia03-c00.pdf>
4. Australian Institute of Health and Welfare. Health and Welfare Expenditure Series Number 22: Health system expenditures on cancer and other neoplasms in Australia, 2000-01. Canberra: Australian Institute of Health and Welfare; 2005 [cited 2007 Nov 14]. Available from: <http://www.aihw.gov.au/publications/hwe/hsecna00-01/hsecna00-01.pdf>.
5. [cdc.gov/nchs/](http://www.cdc.gov/nchs/) [homepage on the Internet]. Atlanta, Georgia: Centers for Disease Control and Prevention. [updated 2008 Dec 11; cited 2008 Dec 12]. Available from: <http://www.cdc.gov/nchs/>.
6. Bleyer A, Montello M, Budd T, Saxman S. National survival trends of young adults with sarcoma: lack of progress is associated with lack of clinical trial participation. *Cancer*. 2005;103:1891-7.
7. Australian Institute of Health and Welfare. Health and Welfare Expenditure Series Number 22: Health system expenditures on cancer and other neoplasms in Australia, 2000-01. Canberra: Australian Institute of Health and Welfare; 2005 [cited 2007 Nov 14]. Available from: <http://www.aihw.gov.au/publications/hwe/hsecna00-01/hsecna00-01.pdf>.
8. Mitchell AE, Scarcella DL, Rigutto GL, Thursfield VJ, Giles GG, Sexton M, et al. Cancer in adolescents and young adults: treatment and outcome in Victoria. *Med J Aust*. 2004;180:59-62.
9. National Cancer Institute. Soft Tissue Sarcoma. Bethesda (United States): National Cancer Institute; no date [cited 2008 June 12]. Available from: [www.cancer.gov/cancertopics/types/soft-tissue-sarcoma/](http://www.cancer.gov/cancertopics/types/soft-tissue-sarcoma/).
10. [gicancer.org.au](http://www.gicancer.org.au) [homepage on the Internet]. Sydney: Australasian Gastro-Intestinal Trials Group; 2008 [cited 2008 Dec 12]. Available from: <http://www.gicancer.org.au/trials/index.html>
11. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*. 2005 Jan 7;307(5706):58-62.
12. Brizel DM, Rosner GL, Harrelson J, Prosnitz LR, Dewhirst MW. Pretreatment oxygenation profiles of human soft tissue sarcomas. *Int J Radiat Oncol Biol Phys*. 1994;30:635-42.
13. Evans SM, Hahn SM, Magarelli DP, Zhang PJ, Jenkins WT, Fraker DL, et al. Hypoxia in human intraperitoneal and extremity sarcomas. *Int J Radiat Oncol Biol Phys*. 2001;49:587-96.