

**DOCTOR OF MEDICINE THESIS**

**“RADIOTHERAPY FOR BONE METASTASES AND  
NEUROPATHIC BONE PAIN”**

**Dr Daniel Roos BSc (Hons), FRANZCR**

**Submitted under the auspices of the University of Adelaide  
Faculty of Health Sciences**

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## 1. CURRICULUM VITAE

**NAME:** Dr Daniel Edward Roos

**MAILING ADDRESS:** Department of Radiation Oncology  
Royal Adelaide Hospital  
North Terrace  
Adelaide  
South Australia 5000 Australia

Phone: + 61 (0)8 8222 4000  
Fax: + 61 (0)8 8222 2016  
Email: [droos@mail.rah.sa.gov.au](mailto:droos@mail.rah.sa.gov.au)

**DATE OF BIRTH:** 12 April 1953

**NATIONALITY:** Australian

**PERSONAL ACTIVITIES:** Piano, volleyball, tennis, gardening

**QUALIFICATIONS:**

1970	Matriculation, South Australian Public Examinations Board
1974	A Mus A, Australian Music Examinations Board (piano).
1975	BSc (Hons), University of Adelaide.
1976	Dip Ed, University of Adelaide.
1986	MB BS, University of Adelaide.
1992	FRANZCR, Royal Australian and New Zealand College of Radiologists.

**APPOINTMENTS:**

1976-80	Secondary teacher (mathematics/physics), Norwood High School, South Australia.
1986-92	Intern, Resident Medical Officer, Registrar in Radiation Oncology, Royal Adelaide Hospital.
1993	Senior Visiting Clinical Oncology Registrar, Mt Vernon Hospital, U.K.
1994 -	Consultant Radiation Oncologist, Royal Adelaide Hospital. Supervisor of Registrar Training (until 1998). Radiation Oncologist to Radiosurgery Unit. Chairman of Lymphoma Clinic.
1997 -	Senior Consultant Radiation Oncologist. Radiotherapy Intern Term Supervisor (from 1998).

**HONOURS & AWARDS:**

1970	Daws Road High School, South Australia, Dennis Gamblin Memorial Award for
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1993 academic and extra-curricular achievements (dux of school, head prefect, captain of A-grade football team).  
Inaugural Windeyer Fellow in Radiation Oncology, Royal Australian and New Zealand College of Radiologists.

### **PROFESSIONAL MEMBERSHIPS:**

- 1992 - Fellow Royal Australian and New Zealand College of Radiologists (RANZCR).
- 1994 - Member Trans-Tasman Radiation Oncology Group (TROG), Board Member 1996-, Secretary 1999-.  
Member Australasian Radiation Oncology Lymphoma Group (AROLG).
- 1995 - Member European Society for Therapeutic Radiology and Oncology (ESTRO).
- 1998 Assessor National Ranking of Cancer Research Grant Applications, Anti-Cancer Council of Victoria.
- 1998 - Member International Stereotactic Radiosurgery Society (ISRS).
- 1998 - 00 Member South Australian Anti-Cancer Foundation Cancer Research Advisory Committee.
- 1999 Member National Assessors Panel for Cancer Research Grants, Anti-Cancer Council of Victoria.
- 2000 - Reviewer for "Radiotherapy & Oncology"
- 2001 - Member American Society for Therapeutic Radiology and Oncology (ASTRO).
- 2002 - Member International Extra-nodal Lymphoma Study Group (IELSG).

### **NATIONAL & INTERNATIONAL CONFERENCE ORAL PRESENTATIONS:**

1. RANZCR Scientific Meeting, Adelaide, Oct 1991. Subdiaphragmatic Hodgkin's disease: the Royal Adelaide Hospital experience.
2. Royal Australasian College of Surgeons Section of Colon and Rectal Surgery Continuing Education Meeting, Adelaide, Sep 1994. Rectal carcinoma - radiation oncologist viewpoint. Invited lecture.
3. RANZCR Scientific Meeting, Brisbane, Oct 1998. Fractionation regimens for metastatic bone pain. Invited lecture.
4. RANZCR Scientific Meeting, Brisbane, Oct 1998. Radiosurgery at the RAH: the first 4½ years' experience.
5. Urological Society of Australasia Annual Scientific Meeting, Adelaide, Mar 1999. Trends in external beam radiotherapy for clinically localised prostate cancer. Invited lecture.
6. Royal College of Radiologists Second Consensus Workshop in Palliative Radiotherapy and Symptom Control, London, Apr 2000. Neuropathic pain and bone metastases. Invited lecture.
7. International Congress of Radiation Oncology, Melbourne, Feb 2001. Radiotherapy for neuropathic bone pain: TROG 96.05 update. Symposium on Palliation in Advanced Disease. Invited lecture.
8. Australian Society of Head and Neck Surgeons Annual Meeting, Adelaide, Mar 2001. The role of radiotherapy for early SCC of the larynx. Invited lecture.
9. Royal Australasian College of Surgeons Annual Scientific Congress, Adelaide, May 2002. Radiation and the Eye. Head & Neck/Ophthalmology session. Invited lecture.

10. European Cancer Congress, Copenhagen, Sep 2003. Final results of a randomized fractionation trial on radiotherapy for neuropathic pain due to bone metastases (TROG 96.05).
11. Australian & New Zealand College of Anaesthetists Intercollegiate Pain Medicine Forum, Melbourne, July 2004. Radiotherapy for palliation of pain. Invited lecture.

## PUBLICATIONS:

\*Papers relevant to this thesis are asterisked.

1. **Roos DE**, O'Brien PC, Crompton JL. Ocular involvement in primary central nervous system lymphoma: an increasing clinical problem? *Australas Radiol* 1993;37:372-4.
2. **Roos DE**, Wigg DR. Skin infiltration within a radiotherapy portal for metastatic bladder cancer: case report and review of the clinical literature. *Acta Oncologica* 1993;32:689-93.
3. **Roos DE**, O'Brien PC, Wright J, Willson K. Treatment of subdiaphragmatic Hodgkin's Disease: is radiotherapy alone appropriate only for inguino-femoral presentations? *Int J Radiat Oncol Biol Phys* 1994;28:683-92.
4. O'Brien PC, **Roos DE**, Willson K. Radiotherapy alone for early stage Hodgkin's disease: a 16 year experience at the Royal Adelaide Hospital. *Australas Radiol* 1994;38:305-9.
5. Barton M, Boyages J, Crennan E, Davis S, Fisher RJ, Hook C, Johnson N, Joseph D, Khoo V, Liew KH, Morgan G, O'Brien P, Pendlebury S, Pratt G, Quong G, **Roos DE**, Thornton D, Trotter G, Walker Q, Wallington M. Radiotherapy for early infradiaphragmatic Hodgkin's disease: the Australasian experience. *Radiother Oncol* 1996;39:1-7.
6. **Roos DE**. Hypertrophic pulmonary osteoarthropathy: is there a role for radiotherapy to symptomatic sites? Case report and literature review. *Acta Oncologica* 1996;35:101-5.
7. **Roos DE**, Dische S, Saunders MI. The dental problems of patients with head and neck cancer treated with CHART. *Oral Oncol, Eur J Cancer* 1996;32B:176-81.
8. O'Brien PC, **Roos DE**, Liew KH, Trotter G, Barton M, Walker Q, Poulsen M, Olver I. Preliminary results of combined modality therapy for non-AIDS primary CNS lymphoma. *Trans-Tasman Radiation Oncology Group (TROG)*. *Med J Aust* 1996;165:424-7.
9. Zavgorodni S, Beckham W, **Roos DE**. A method for producing uniform dose distributions in the junction regions of large hinge angle electron fields. *Int J Radiat Oncol Biol Phys* 1996;35:765-70.
10. **Roos DE**, O'Brien PC. Combined modality therapy for early Hodgkin's disease: heterogeneity in Australasian clinical practice. *Australas Radiol* 1997;41:281-7.
11. Yeoh EK, **Roos DE**. Radiation Oncology training in Adelaide. Letter to the Editor. *Australas Radiol* 1997;41:408-9.
12. Yeoh E, Russo A, Botten R, Fraser R, **Roos DE**, Penniment M, Borg M, Sun WM. Acute effects of therapeutic irradiation for prostatic carcinoma on anorectal function. *Gut* 1998;43:123-7.
- 13.\***Roos DE**. Neuropathic back pain: discordance between the level of the involved spine/rib and the associated dermatome. *Clin Oncol* 1998;10:337-8.
14. **Roos DE**, Francis JW, Newnham WJ. A simple technique for treating age related macular degeneration with external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;43:1071-4.
15. Zavgorodni SF, Quach KY, **Roos DE**. Comparison of three simple radiosurgery techniques for treating elongated lesions. *Physica Medica* 1999;15:57-62.
16. **Roos DE**, Smith JG. Randomised trials on radio-iodine ablation of thyroid remnants for thyroid carcinoma – a critique. *Int J Radiat Oncol Biol Phys* 1999;44:493-5.

17. **Roos DE**, Smith JG. Regarding two papers from the same group on radiotherapy for macular degeneration. Letter to the Editor. *Int J Radiat Oncol Biol Phys* 1999;44:737.
18. Christie D, Barton M, Bryant G, Cheuk R, Gebiski V, Hornsey J, Lonergan D, MacLeod C, Pratt G, **Roos DE**, Shannon J, Thornton D, Wirth A. Osteolymphoma (primary bone lymphoma): an Australian review. *ANZJ Med* 1999;29:214-9.
19. O'Brien P, **Roos DE**, Pratt G, Liew K, Barton M, Poulsen M, Olver I, Trotter G. A phase 2 multi-centre study of brief single agent methotrexate followed by irradiation in primary CNS lymphoma. *JCO* 2000;18:519-26.
- 20.\*Bentzen S, Hoskin D, **Roos D**, Nielsen O. Fractionated radiotherapy for metastatic bone pain: evidence-based medicine or . . . ? Letter to the Editor. *Int J Radiat Oncol Biol Phys* 2000;46:681-2.
- 21.\***Roos DE**, Davis SR, O'Brien PC, Hoskin PJ, Spry NA, Burmeister BH, Turner SL, Bernshaw DM. Eligibility audits for the neuropathic bone pain trial (TROG 96.05). *Australas Radiol* 2000;44:303-7.
22. **Roos DE**, Brophy BP, Zavgarodni SF, Francis JW. Radiosurgery at the Royal Adelaide Hospital: the first 4½ years' clinical experience. *Australas Radiol* 2000;44:185-92.
- 23.\***Roos DE**, O'Brien PC, Smith JG, Spry NA, Hoskin PJ, Burmeister BH, Turner SL, Bernshaw DM. A role for radiotherapy in neuropathic bone pain: preliminary response rates from a prospective trial (TROG 96.05). *Int J Radiat Oncol Biol Phys* 2000;46:975-81. Erratum 2000;47:545.
- 24.\***Roos DE**. Continuing reluctance to use single fractions of radiotherapy for metastatic bone pain: an Australian and New Zealand practice survey and literature review. *Radiother Oncol* 2000;56:315-22.
25. Yeoh E, Botten R, Russo A, McGowan R, Fraser R, **Roos DE**, Penniment M, Borg M, Sun W-M. Chronic effects of therapeutic irradiation for localised prostatic carcinoma on anorectal function. *Int J Radiat Oncol Biol Phys* 2000;47:915-24.
26. **Roos DE**. Radiotherapy for subfoveal neovascular membranes: delaying rather than preventing blindness? Letter to the Editor. *Australas Radiol* 2000;44:359-61.
- 27.\*Hoskin PJ, Yarnold JR, **Roos DE**, Bentzen S. Consensus statement: radiotherapy and bone metastases (Second Consensus Workshop in Palliative Radiotherapy and Symptom Control, London, 2000). *Clin Oncol* 2001;13:88-90.
28. Yeoh E, Botten R, McGowan R, **Roos DE**, Penniment M, Borg M, Russo A, Fraser R, Sun W-M. In response to Dr D. Vordermark (Is there more than one radiation-induced fecal incontinence syndrome?). *Int J Radiat Oncol Biol Phys* 2001;49:280-1.
29. Lamb D, Denham J, **Roos DE**, Kovacev O. TROG - goals for the second decade. *Radiother Oncol* 2001;58 (Suppl 1): Abstr 3.
- 30.\***Roos DE**. Radiotherapy for neuropathic bone pain: TROG 96.05 update. *Radiother Oncol* 2001;58 (Suppl 1): Abstr 177.
31. Wirth A, Wolf M, Prince M, MacCleod C, Gibson J, **Roos DE**, Dart G, Davis S, Schwarzer A, Grigg A. Optimal timing of involved-field radiotherapy with transplantation for Hodgkin's disease and non-Hodgkin's lymphoma: an Australasian Leukaemia and Lymphoma Group Pilot Study. *Radiother Oncol* 2001;58 (Suppl 1): Abstr 154.
32. Ryan G, **Roos DE**, Fisher R, Seymour J. Primary breast lymphoma. *Australas Radiol* 2002;46: Abstr A40.
33. **Roos DE**. Radiation and the Eye. *ANZ J Surg* 2002;72 (Suppl): Abstr HN14.
34. **Roos DE**, Brophy BP, Zavgorodni SF, Katsilis ES. Radiosurgery for brain metastases at the Royal Adelaide Hospital: are we treating the right patients? *Australas Radiol* 2002;46:402-8.
35. **Roos DE**, Reid CM. Benign familial pemphigus: little benefit from superficial radiotherapy. *Australas J Dermatol* 2002;43:305-8.
36. Bydder S, Spry NA, Christie DRH, **Roos DE**, Burmeister BH, Krawitz H, Davis S, Joseph DJ, Poulsen M, Berry M. A prospective trial of short fractionation radiotherapy for liver metastases. *Australas Radiol* 2003;47:284-8.

37. Yeoh EK, Fraser RJ, McGowen RE, Botten RJ, Di Matteo AC, **Roos DE**, Penniment MG, Borg MF. Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2003;55:943-55.
- 38.\***Roos DE**, Davis SR, Turner SL, O'Brien PC, Spry NA, Burmeister BH, Hoskin PH, Ball DL. Quality assurance experience with the randomized neuropathic bone pain trial (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol* 2003;67:207-12.
39. **Roos DE**. Radiotherapy for benign familial pemphigus. Letter to the Editor. *Int J Radiat Oncol Biol Phys* 2003;56:908.
- 40.\***Roos DE**, Fisher RJ. Radiotherapy for painful bone metastases: an overview of the overviews. Editorial. *Clin Oncol* 2003;15:342-4. Erratum 2003;15:509.
- 41.\***Roos DE**, Turner S, Burmeister B, Smith J, Hoskin P, Spry N, O'Brien P, Ball D. Final results of a randomized fractionation trial on radiotherapy for neuropathic bone pain (TROG 96.05). *Eur J Cancer* 2003;1:S13 (Abstr).
42. Wirth A, Prince HM, Wolf M, Stone JM, Matthews J, Gibson J, MacLeod C, Szer J, Grigg A, To B, **Roos DE**, Schwarzer AP, Davis S. Optimal scheduling to reduce morbidity of involved field radiotherapy with transplantation for lymphomas: a prospective Australasian Leukaemia and Lymphoma Group study. *Bone Marrow Transplantation* 2005;35:291-8.
- 43.\***Roos DE**, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH, Hoskin PJ, Ball DL. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (TROG 96.05). *Radiother Oncol* 2005;75:54-63.
44. Wirth A, Yuen K, Barton M, **Roos DE**, Gogna K, Pratt G, MacLeod C, Bydder S, Morgan G, Christie D. Long-term outcome following radiotherapy alone for lymphocyte predominant Hodgkin's lymphoma: a retrospective multicentre study of the Australasian Radiation Oncology Lymphoma Group. *Cancer* (in press).
45. Ryan GF, **Roos DE**, Seymour JF. Primary non-Hodgkin's lymphoma of the breast: retrospective analysis of prognosis and patterns of failure in two Australian centres. *Clinical Lymphoma* (in press).
46. **Roos DE**, Ball DL, Burmeister BH, Fischer RJ. RE: J Kiffer et al. – Letter to the Editor regarding F Schwarz et al. – Are single fractions of radiotherapy suitable for plantar fasciitis? *Australas Radiol* 2005;49:257.
- 47.\*Pollicino CA, Turner SL, **Roos DE**, O'Brien PC. Costing the components of pain management. Analysis of Trans-Tasman Radiation Oncology Group trial (TROG 96.05): one versus five fractions for neuropathic bone pain. Accepted by *Radiother Oncol* Mar 2005.
48. O'Brien PC, **Roos DE**, Pratt G, Liew K-H, Barton MB, Poulsen MG, Olver IN, Trotter G. Combined modality therapy for primary CNS lymphoma: Long-term data from a phase II multi-centre study (TROG 92.01). Accepted by *Int J Radiat Oncol Biol Phys* Apr 2005.

#### **BOOK CHAPTER:**

- 49.\***Roos DE**. Lung Cancer. In: Jasmin C, Coleman RE, Coia LR, Capanna R, Saillant G (eds). *Textbook of Bone Metastases*. John Wiley & Sons, London, 2005:523-31.

#### **RESEARCH GRANTS:**

1. As Chair of “A prospective randomised trial of single fraction versus fractionated radiotherapy for neuropathic pain due to bone metastases (TROG 96.05)”:

- (1) RAH Special Purposes Fund Grant-in-Aid – Sep 1996, \$11,400.
  - (2) National Health and Medical Research Council Project Grant 981871 – 1998-2000, \$172,000.
2. As Chair of “A randomised trial of surgery plus whole brain radiotherapy (WBRT) versus radiosurgery plus WBRT for solitary brain metastases”:
- (1) RAH Cancer Centre Equipment Fund – Aug/Sep 2002, \$12,200.
  - (2) Royal Australian and New Zealand College of Radiologists Research Grant – July 2003, \$12,000.
3. As Australasian Co-Chair of “A phase III international randomized trial of single versus multiple fractions for re-irradiation of painful bone metastases (NCIC CTG SC.20)”:
- (1) RAH Special Purposes Fund – July 2003, \$10,000.
  - (2) RAH Cancer Research (Tied) Fund 1005 – Sep 2003, \$15,000.
  - (3) Cancer Council Australia, International Research Infrastructure Support – Feb 2004, \$40,000.

## 2. SUMMARY

I have a background of active research in Radiation Oncology since passing the final examination of the Royal Australian and New Zealand College of Radiologists (RANZCR) at the first attempt in 1992. My first two papers were published the following year [1,2 – see curriculum vitae], and there are currently 49 publications (26 first authorships).

My primary research interest has involved the use of radiotherapy (RT) for palliation of painful bone metastases. This interest originated from a year at Mt Vernon Hospital, UK, as the inaugural RANZCR Windeyer Fellow in Clinical Oncology (1993). I worked with Dr Peter Hoskin, a leading figure in the British Bone Pain Trial Working Party responsible for three randomised fractionation trials on this subject. These and many other previous and subsequent studies have demonstrated (counter-intuitively) that low dose single fraction RT is as effective as higher dose fractionated schedules in relieving bone pain, with intention-to-treat overall response rates (RRs) of about 60%. However, the studies provided virtually no data on the efficacy of RT specifically for bone pain with a neuropathic component (NBP), a scenario occurring in perhaps as many as 20% of patients with bone metastases during the course of their disease.

On returning to Australia as a consultant radiation oncologist at the Royal Adelaide Hospital in 1994, I joined the Trans-Tasman Radiation Oncology Group (TROG), the major radiotherapy clinical trials group in Australasia. During the following year, I developed a protocol for a randomised controlled trial comparing one with five fractions of RT for NBP (TROG 96.05). The first patient was registered in February 1996, and a total of 15 centres in Australia (11), New Zealand (3) and UK (1) took part. A National Health and Medical Research Council Project Grant of \$172,000 was awarded for the study (1998-2000). Preliminary findings (blinded to trial arm) were published in 2000 [23], and extensive quality assurance activities for the trial were summarised in two further publications [21,38]. The accrual target was met in December 2002 ( $n = 272$ ) and the final analysis was reported as an oral presentation at the 12th European Cancer Congress, Copenhagen, September 2003. The essential findings were that NBP responds similarly to localised pain (overall intention-to-treat RR 57%) with no statistically significant difference in RR or time to treatment failure between randomisation arms [43]. A subsequent cost analysis quantified the relative cost to the Australian healthcare system for the two fractionation schedules [47].

During the conduct of the trial, I undertook and published a survey confirming the reluctance of Australasian radiation oncologists to use single fractions for painful bone metastases despite the emerging randomised trial results [24]. I also contributed to the international debate on this controversial subject as co-author with three high profile researchers in a Letter-to-the-Editor [20], and was a member of an International Consensus Panel on palliative radiotherapy endpoints for future bone metastases trials [Chow E et al. *Radiother Oncol* 2002;64:275-80].

I presented invited lectures entitled: Fractionation regimens for metastatic bone pain (RANZCR Scientific Meeting, Brisbane, 1998); Neuropathic pain and bone metastases (Royal College of Radiologists Second Consensus Workshop in Palliative Radiotherapy and Symptom Control, London, 2000) [27]; Radiotherapy for neuropathic bone pain: TROG 96.05 update (International Congress of Radiation Oncology, Melbourne, 2001) [30]. My recognised expertise in this field also led to invitations to write an Editorial on the published overviews of bone pain studies [40], and a book chapter on bone metastases from lung cancer [49].

My active role in bone pain research continues. The abovementioned International Consensus Panel collaboration led to the development of the first randomised trial on re-treatment of

bone metastases with RT. This National Cancer Institute of Canada sponsored international Intergroup trial (NCIC SC.20/TROG 03.08) has an accrual target of 650 patients and was activated in January 2004. I am the Australasian Co-Chair, securing \$40,000 funding for local capitation from Cancer Council Australia in February 2004.

I believe this body of work constitutes a significant contribution to the literature on RT for bone metastases, and NBP in particular. My research on the latter constitutes the first prospective data ever obtained on RT for this clinical problem, enabling informed selection of single or multiple fraction treatment schedules.