

Acknowledgements

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Conflict of Interest Statement

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List of Publications

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Palma D, Lagerwaard F, Rodrigues G, Haasbeek C, Senan S. Curative treatment of stage I non-small cell lung cancer in patients with severe COPD: Stereotactic radiotherapy outcomes and systematic review. *International Journal of Radiation Oncology, Biology, Physics*, in press.

Louie AV, Rodrigues G, Hannouf M, Lagerwaard F, **Palma DA**, Zaric GS, Haasbeek C, Senan S. Withholding Stereotactic Radiotherapy in Elderly patients with stage I Non-small Cell Lung Cancer and co-existing COPD is not justified: Outcomes of a Markov model analysis. *Radiotherapy and Oncology*, in press.

Palma D, Senan S. Stereotactic radiation therapy: changing treatment paradigms for stage I nonsmall cell lung cancer. *Curr Opin Oncol*. 2011 Mar;23(2):133-9.

Senan S, **Palma D**. Stereotactic lung radiotherapy: Do we need fiducial markers? *Annals of Thoracic Surgery*, 2011 Jan;91(1):335-6.

Palma DA, van Sörnsen de Koste JR, Verbakel WF, Senan S. A new approach to quantifying lung damage after stereotactic body radiation therapy. *Acta Oncol*. 2010 Dec 21. [Epub ahead of print]

Palma D, Visser O, Lagerwaard F, Belderbos J, Slotman B, Senan S. The impact of introducing stereotactic lung radiotherapy for elderly patients with Stage I NSCLC: A population-based time-trend analysis. *Journal of Clinical Oncology*, 2010 Dec 10;28(35):5153-9

Ong CL, **Palma D**, Verbakel WF, Slotman BJ, Senan S. Treatment of large stage I-II lung tumors using stereotactic body radiotherapy (SBRT): Planning considerations and early toxicity. *Radiother Oncol*. 2010 Dec;97(3):431-6.

Palma D, van Sornsen de Koste J, Verbakel W, Vincent A, Senan S. Lung density changes after stereotactic radiotherapy: A quantitative analysis in 50 patients. *International Journal of Radiation Oncology, Biology, Physics*, 2010 Oct 5. [Epub ahead of print]

Louie AV, Rodrigues GB, Hannouf M, Zaric GS, **Palma D**, Cao JQ, Yaremko BP, Malthaner R, Mocanu JD. Stereotactic Body Radiotherapy Versus Surgery for Medically Operable Stage I NSCLC: a Markov Model Based Decision Analysis. *International Journal of Radiation Oncology, Biology, Physics*, accepted, 2010 Oct 5. [Epub ahead of print].

Smith S, **Palma D**, Parhar T, Alexander C, Wai E. Inoperable Early Stage Non-Small Cell Lung Cancer: Comorbidity, Patterns of Care and Survival. *Lung Cancer*, 2010 Aug 27 [epub ahead of print]

Palma D, Senan S, Verbakel W, Vincent A, Lagerwaard F. Radiological and clinical pneumonitis after stereotactic lung radiotherapy: A matched analysis of 3D-conformal and volumetric modulated arc therapy techniques, *International Journal of Radiation Oncology, Biology, Physics*, 2010 June 26

Palma D, Tyldesley S, Sheehan F, Mohamed I, Wai E, Smith S, Senan S. Stage I non-small cell lung cancer (NSCLC) in patients aged 75 years and above: Does age determine survival after radical treatment? *Journal of Thoracic Oncology* 2010 April 28.

Palma D. Epidermal growth factor receptor (EGFR)-inhibitors, rashes, and survival: Is doxycycline the missing link? *Oral Oncology* 2010 Feb 25 [Epub ahead of print]

Palma D, Verbakel WF, Otto K, Senan S. New Developments in Arc Radiation Therapy – A review. *Cancer Treatment Reviews* 2010 Feb 22 [Epub ahead of print]

Thompson A, Keyes M, Pickles T, **Palma D**, Morovan V, Spadinger I, Lapointe V. Evaluating the Phoenix definition of biochemical failure after I-125 prostate brachytherapy: Can PSA kinetics distinguish PSA failures

from PSA bounces? *International Journal of Radiation Oncology, Biology, Physics*; 2010 Feb 2 [epub ahead of print]

Louie AV, Rodrigues G, Olsthoorn J, **Palma D**, Yu E, Yaremko B, Ahmad B, Aivas I, Gaede S. Inter-observer and intra-observer reliability for lung cancer target volume delineation in the 4D-CT era. *Radiotherapy and Oncology*. 2010 Jan 30. [Epub ahead of print]

Palma D, Pickles T, Keyes M, Morris WJ. Author reply. *Urology*; 2009 Apr;73(4):865

Morris WJ, Keyes M, **Palma D**, McKenzie M, Spadinger I, Agranovich A, et al. A population based study of biochemical and survival outcomes following permanent 125-iodine brachytherapy for low- and intermediate-risk prostate cancer. *Urology*; 2009 Apr;73(4):860-5

Morris WJ, Keyes M, **Palma D**, McKenzie M, Spadinger I, Agranovich A, et al. Evaluation of dosimetric parameters and disease response after ¹²⁵Iodine transperineal brachytherapy for low- and intermediate-risk prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2009 Apr 1;73(5):1432-8.

Palma D, Moiseenko V, Vollans E, McKenzie M, Morris J, Otto K. Author reply to Ost et al. *International Journal of Radiation Oncology, Biology, Physics*, 2009 Mar 15;73(4):1286.

Palma D, Vollans E, James K, Nakano S, Moiseenko V, Shaffer R, et al. Volumetric Modulated Arc Therapy (VMAT) for delivery of prostate radiotherapy: comparison with Intensity Modulated Radiotherapy (IMRT) and 3-Dimensional Conformal Radiotherapy (3D-CRT). *International Journal of Radiation Oncology, Biology, Physics*, 2008 Nov 15;72(4):996-1001.

Palma D, Pickles T. Prostate Cancer and Host Metabolic Factors. *Lancet Oncology*; 2008 Nov;9(11):1022-3.

Palma D, Pickles T. Duration of testosterone suppression and the risk of death from prostate cancer in men treated with radiation and 6 months of hormone therapy. *Cancer*; 2008 May 15;112(10):2322-3

Palma D, Tyldesley S, Pickles T, Prostate Cohort Outcomes Initiative. Pretreatment PSA velocity is associated with development of distant metastases and prostate cancer mortality in men treated with radiotherapy and androgen deprivation therapy. *Cancer*; 2008 May 1;112(9):1941-8.

Palma D, Pickles T, Tyldesley S, Prostate Cohort Outcomes Initiative. Obesity as a predictor of biochemical recurrence and survival after radiation therapy for prostate cancer. *BJU International*. 2007 Aug;100(2):315-9.

Palma D, Tyldesley S, Blood P, Liu M, Morris J, Pickles T; Prostate Cohort Outcomes Initiative. Pretreatment PSA velocity as a predictor of disease outcome following radical radiation therapy. *International Journal of Radiation Oncology, Biology, Physics*. 2007 Apr 1;67(5):1425-9.

Moulin DE, **Palma D**, Watling C, Schulz V. Methadone in the management of intractable neuropathic pain. *Canadian Journal of Neurological Sciences*, 2005;32:340-3.

Palma D, Dar AR, Millington S, Smits C, Rizkalla K, Incullet R. Castleman's Disease in Children: Report of 2 Cases and Clinicopathological Review. *Journal of Pediatric Hematology/Oncology*, 2004 Apr;26(4):264-6

Palma D, Blumwald E, Plaxton WC. Upregulation of vacuolar H⁺-translocating pyrophosphatase by phosphate starvation of *Brassica napus* (rapeseed) suspension cell cultures. *FEBS Letters* 2000 Dec; 486(2):155-158.

Curriculum Vitae

David Anthony Palma was born August 5, 1978 in London, Ontario, Canada. He attended Jean Vanier Elementary School and Catholic Central High School, and after graduation in 1997 moved to Kingston, Canada where he earned a Bachelor's Degree in Life Sciences from Queen's University. In 2000 he returned to London, Ontario to study Medicine at the University of Western Ontario, where he first became interested in Radiation Oncology and cancer research.

After graduation from medicine, David began his Radiation Oncology residency program at the British Columbia Cancer Agency in Vancouver. During this time his research focused on patient outcomes and new radiotherapy techniques. He was the chief resident in Radiation Oncology in 2008. In 2009 he completed his Radiation Oncology exams to become a Fellow of the Royal College of Physicians of Canada. In 2009-2010, David completed a Master's Degree in Epidemiology from the Harvard School of Public Health and a research fellowship in SBRT at the VU University in Amsterdam.

In 2001, when David was a second-year medical student, he met a first-year medical student named Cheryl Smits on her very first day at school. Four years later they married. David and Cheryl have two children: Kiara, born in August 2008 (whose favourite song is *Hansje Pansje Kevertje*), and Adam, born in August 2010. They are now living in London, Ontario, where Cheryl has a Family Medicine/Obstetrics practice, and David is a Radiation Oncologist and Clinician-Scientist at the London Regional Cancer Program.

Selected List of Abbreviations

3D-CRT	Three-dimensional conformal radiotherapy
4D-CT	Four-dimensional computed tomography
BED	Biologically effective dose
CBCT	Cone-beam CT
CCI	Charlson comorbidity index
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CSS	Cause-specific survival (synonym: disease-specific survival)
CT	Computed tomography
CTC-AE	Common terminology criteria for adverse events
CTV	Clinical target volume
CurRT	Curative-intent radiotherapy (synonym: radical intent) (often considered as 45 Gy in 15 fractions or higher doses)
DVH	Dose-volume histogram
ECOG	Eastern Cooperative Oncology Group
FDG	18-fluorodeoxyglucose
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GGO	Ground glass opacification
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GTV	Gross tumor volume
Gy	Gray; the SI unit of radiation dose
HR	Hazard ratio
HU	Hounsfield unit
IMRT	Intensity modulated radiation therapy

MLD	Mean lung dose
NSCLC	Non-small-cell lung cancer
OAR	Organ at risk
OS	Overall survival
PallRT	Palliative-intent radiotherapy (often considered as 40 Gy in 15 fractions or lower doses)
PET	Positron emission tomography
ppo-FEV1	Predicted post-operative forced expiratory volume in 1 second
PTV	Planning target volume
RP	Radiation pneumonitis
RT	Radiotherapy
SBRT	Stereotactic body radiation therapy
VATS	Video-assisted thoracoscopic surgery
VMAT	Volumetric modulated arc therapy
V _x (e.g. V ₅)	Volume of lung (in percent) receiving <i>x</i> Gray or more (e.g. volume of lung receiving 5 Gray or more)

Definitions of Statistical Terms and Outcomes

Confidence Interval	A range of values likely to contain the true population parameter with a specified precision (usually 95%). For normally-distributed data, the boundaries of a 95% confidence interval are the mean \pm 1.96 x standard error
Disease-specific survival	Time until death due to a specified disease (e.g. lung cancer) (synonym: cause specific survival)
Distant metastasis	Progression of disease at sites of the body beyond the primary tumor or regional nodes, usually via hematogenous spread
Hazard ratio	The effect of a variable (e.g. treatment) on the hazard or risk of an event (e.g. death); similar to a relative risk
Local control	Absence of disease progression at the primary tumor site
Locoregional control	Absence of disease progression at the primary site and the regional lymph nodes
Overall survival	Time until death from any cause
Palliative intent	Treatment with the goal of reducing the symptoms of disease, without curing the disease
Radical intent	Treatment with a goal of eradicating known cancer
Regional control	Absence of disease progression in the regional lymph nodes

