

Institution: Cardiff University
Unit of Assessment: UoA1
Title of case study: A New Standard of Care for Locally Advanced Prostate Cancer
1. Summary of the impact <p>Locally advanced prostate cancer (where a tumour has extended outside the prostate gland to surrounding tissues) will affect around 20,000 men per year in the US, and 4,000 men per year in the UK. Prior to the underpinning research, there was no consensus on the standard of care, with hormone therapy often being given alone. The International randomised clinical trial, led by Cardiff researchers showed that treating locally advanced disease with a combination of radiotherapy and hormone therapy halved the risks of dying of prostate cancer. Consequently, it is now a standard of care, enshrined in European and North American guidelines, that all such patients who are fit enough to receive it, should now be offered combined modality radiotherapy plus hormone therapy.</p>
2. Underpinning research <p>Prior to this underpinning research, the UK Medical Research Council conducted a randomised trial in patients with localised and locally advanced prostate cancer, comparing hormone therapy alone, radiotherapy alone, and hormone therapy plus radiotherapy. The trial failed to accrue sufficient patients to show any differences in outcomes, and the result was uncertainty about the role of radiotherapy in such patients. Surveys conducted by the Medical Research Council in the UK and the National Cancer Institute of Canada (NCIC) in Canada, indicated that almost half of clinicians would treat patients with locally advanced disease with hormone therapy alone. On the other hand, previous randomised trials had also indicated that, if such a patient was to be treated with radiotherapy, overall survival was improved if hormone therapy was added. This added to the confusion, since these latter trials could not differentiate between benefits due to hormone therapy per se, or to the combination of hormone therapy plus radiotherapy.</p> <p>This was the background to the Intergroup Study (MRC PR07/NCIC PR3), which was designed to test the efficacy of radiotherapy in patients being treated with hormone therapy and led for the Medical Research Council by Professor Malcolm Mason in Cardiff (Head of Department, Section of Oncology and Palliative Medicine since 1997). Patients with locally advanced disease were randomised to lifelong hormone therapy alone, or to the same plus radiotherapy to the prostate and pelvis^{3.1}. The trial recruited patients from 1995-2005, with 1205 patients recruited, the majority of them by the Medical Research Council group. There were two pre-planned interim analyses, and after the second of these in August 2009, the independent Data Monitoring and Safety Committee recommended disclosure of the results. The results showed that radiotherapy reduced the chances of dying from any cause by 23%, and reduced the chances of dying from prostate cancer by 46%^{3.2}.</p> <p>The final analysis was presented at the American Society for Clinical Oncology in June 2012^{3.3}. This confirmed, and strengthened the beneficial effects of radiotherapy, with a 30% reduction in the chances of death from any cause, and a 54% reduction in the chances of dying of prostate cancer. The toxicity and adverse effects of radiotherapy were reported to be modest, and acceptable, and there was no demonstrable long-term adverse impact of radiotherapy on quality of life.</p> <p>The results of this trial are comparable with two other studies: a Scandinavian Prostate Cancer Group (published in 2009), and a French randomised trial (published in 2012) of similar design. The French study is smaller (and therefore less powerful) than the present study, and in addition has insufficient length of follow up data to be able to measure the effect of radiotherapy on survival. The Scandinavian study was limited by its use of non-standard hormone therapy (flutamide, which is never used in the UK or USA in this context, and may be inferior to the hormone therapy used in the present study), and its patient population was comprised of men with a better prognosis than in the present study. A survey of UK and Canadian clinicians conducted by the Medical Research</p>

Council (see below) has shown that 97% of respondents were aware of the PR07 trial, compared with 79% being aware of the Scandinavian trial. For these reasons, the present study is considered the most influential.

The distinct roles of Prof Mason (Cardiff University) in this trial are:

1. Chief Investigator for the UK MRC group.
2. Led the UK input into the design and modification of the study.
3. Oversight of the trial conduct for the UK patients (the majority of the patients in this study), and overseas patients recruited through the MRC (Russia, South Africa).
4. Led the UK input into the analysis and publication of the interim analysis.
5. Gave the first presentation of the results of the final analysis.

3. References to the research

3.1 **Mason MD**, Brewster S, Moffat LE, Kirkbride P, Cowan RA, Malone P, Sydes M, and Parmar MKB. Randomized trials in early prostate cancer. II Hormone therapy and radiotherapy for locally advanced disease: a question is still unanswered. *Clin Oncol* (2000) 12:215-216 DOI:10.1053/clon.2000.9156

3.2 Warde P, **Mason M**, (JOINT FIRST AUTHORS), Ding K, Kirkbride P, Brundage M, Cowan R, Gospodarowicz M, Sanders K, Kostashuk E, Swanson G, Barber J, Hiltz A, Parmar MKB, Sathya J, Anderson J, Hayter C, Hetherington J, Sydes M & Parulekar W. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet* (2011) 378 (9809):2104-2111 DOI: 10.1016/S0140-6736(11)61095-7

3.3 **Mason MD**, Parulekar W, Sydes MR, Parmar M, Anderson J, Barber J, Brundage MD, Cowan R, Gospodarowicz MK, Hayter C, Hetherington J, Hiltz AC, Kirkbride P, Kpostashuk E, Sanders K, Sathya J, Swanson GP, Chen B, Warde PR. Final analysis of intergroup randomized phase III study of androgen deprivation therapy (ADT) plus radiation therapy (RT) in locally advanced prostate cancer (CaP) (NCIC-CTG, SWOG, MRC-UK, INT: T94-0110). *J Clin Oncol* 30, 2012 (suppl; abstr 4509) (Copy available on request from HEI)

The resources at the Clinical trials Units to run this trial were supported by:

NCI-US Grant CA077202, awarded to the US South West Oncology Group 1993.

CCSRI Grants #14469 and # 015469, awarded to National Cancer Institute, 1993.

UK Medical Research Council Grant G9805643, awarded to MRC Clinical Trials Unit (Named grantholder Prof M Parmar; co-applicant M Mason).

UK National Cancer Research Network, provided infrastructure for follow up.

4. Details of the impact

Medical practice for locally advanced prostate cancer has changed. Prior to the underpinning research, hormone therapy alone was considered adequate treatment. Following the present study, hormone therapy alone is no longer considered sufficient treatment for such patients, and, according to the guidelines, 100% of patients suitable for radiotherapy must be offered it. In Western countries, cancer treatment policies in major treatment centres are governed by

guidelines, and therefore, while there are no data to measure the number of men receiving this treatment in comparison to earlier years, the changes to recognised guidelines can be measured. After the first UK presentation of the interim analysis, at the UK National Cancer Research Institute conference in 2010, Professor Sir Richard Peto (Professor of Medical Statistics and Epidemiology, University of Oxford) stated publicly that he expected to see the population mortality rates from prostate cancer to fall following the implementation of this study. Our estimates are that implementation of these study results will prevent up to around 1,000 deaths per year from prostate cancer in the UK, around 5,000 deaths per year in the USA, and of the order of 50,000 deaths per year worldwide.

Following the first presentation of the interim analysis in 2010, by Professor P Warde in the US and by Professor M Mason in the UK, there was intense, worldwide media interest. This was renewed when the formal publication of the interim analysis was released in 2011; a typical example being the statement from the UK Prostate Cancer Charity, reported in the Daily Telegraph, that radiotherapy should be made a standard treatment for this condition^{5.1}. This view is further endorsed by opinion leaders worldwide, for example, Professor W Shipley, Harvard University and Massachusetts General Hospital, Boston, who states, quoting the present study, that "...the combined use of [(RT) and (HT)] for patients with locally advanced prostate cancer should be the recognized standard of care throughout the world"^{5.2}.

This change is reflected in the addition to published cancer treatment guidelines. In the UK, the National Institute of Clinical Excellence (NICE) guidelines on prostate cancer^{5.3, 5.4} (update currently in draft – October 2013) will quote this trial as evidence for mandating the use of RT in these patients. Similarly, in the US, the NCCN guidelines^{5.5}, which are regarded as the cornerstone of approved forms of cancer treatment in the country, quote the Intergroup publication and recommend RT plus HT as a standard. In the US, like NICE guidance in the UK, healthcare providers are obliged to follow the recommended treatment pathways as published by the National Comprehensive Cancer Network (NCCN), and this is reflected in insurance re-imburement. The European Association of Urology (EAU) guidelines^{5.6} also quote the publication, but their status is not mandatory at the present time. The trial will be quoted in the 2013 update of the EAU guidelines, currently in preparation^{5.7}. In relation to the Lancet publication, Professor Patrick Walsh, Johns Hopkins', Baltimore, USA, states "The message is loud and clear. All patients with locally advanced prostate cancer (T3 or T4), organ confined disease with a PSA concentration of more than 40 ng/ml, or PSA greater than 20 in the presence of Gleason score 8 or higher should receive radiation in addition to androgen deprivation therapy"^{5.8}. The survey of clinicians in the UK and in Canada conducted by the Medical Research Council, and by the National Cancer Institute of Canada has been referred to earlier. Among the findings were that 91% of clinicians in Canada, and 88% in the UK regarded the evidence on hormone therapy plus radiotherapy to be sufficiently strong for this to be the standard of care^{5.9}.

In summary, and as discussed above, this study has triggered a change in medical practice, whose reach is international, covering at least the UK, Europe, and North America with recommendations extending to Asia^{5.2}.

5. Sources to corroborate the impact

- 5.1 <http://www.telegraph.co.uk/health/healthnews/8865230/Radiotherapy-helps-halve-prostate-cancer-deaths-Lancet.html> (An example to corroborate the media interest, saved as .pdf on 2nd July 2013 and available on request from HEI)

- 5.2 Gray, P & Shipley, WU. The importance of combined radiation and endocrine therapy in locally advanced prostate cancer. *Asian J Androl.*, 2011 14:245-246. DOI: 10.1038/aja.2011.177 (Quotes the present study shows that the combined use of RT and HT for patients with locally advanced prostate cancer should be the recognized standard of care throughout the world)
- 5.3 National Institute for Clinical Excellence. Guidelines for the management of prostate cancer. (. <http://guidance.nice.org.uk/CG58> shows updated guidance in preparation and due for publication in January 2014)
- 5.4 Director, NICE National Collaborating Centre for Cancer (will confirm that the 2014 National Institute of Clinical Excellence (NICE) guidelines on prostate cancer quote publication 3.2, and recommend treatment based on these findings).
- 5.5 NCCN Guidelines on prostate cancer.
http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (use username morgande@cardiff.ac.uk and password REF2014 to access. Quotes the intergroup publication and recommends RT and HT as a standard in the US. Also saved as .pdf on 22 July 2013 and available on request from HEI)
- 5.6 EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Treatment of Clinically Localised Disease. *Eur. Urol.* 2011 59:61-71 DOI: 10.1016/j.eururo.2010.10.039 (Backs up the claim that the study published as 3.2 is quoted in these guidelines. Is available on request from HEI)
- 5.7 Chairman of EAU Prostate Cancer Guidelines Committee, Department of Urology, St Etienne University Hospital, Paris (can corroborate that the trial will be quoted in the 2013 update of the EAU guidelines, currently in preparation).
- 5.8 Published commentary written by Professor Walsh giving his opinion on paper 3.2. Author: Walsh P.C. Title: "Re: Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: A randomised, phase 3 trial". *Journal of Urology*, Volume 188, Issue 3, September 2012, Page 810 DOI: 10.1016/j.juro.2012.05.065 (Backs up the quote from Professor Walsh regarding specific patient treatment and available from HEI on request)
- 5.9 Policy & Research Impact Co-ordinator, Medical Research Council Clinical Trials Unit (can provide full details and data for the survey of clinicians in the UK and Canada conducted by the Medical research Council and the National Cancer Institute of Canada)