Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Targeted intraoperative radiotherapy at the time of lumpectomy for patients with early breast cancer as an alternative to conventional 3-6 weeks of postoperative radiotherapy

1. Summary of the impact (indicative maximum 100 words)

Research from UCL Division of Surgery has transformed the breast cancer treatment paradigm so women can complete their local treatment intraoperatively (~30 min), with reduced toxicity. Our work has challenged the dogma of giving several weeks of whole breast radiotherapy (EBRT) after lumpectomy for breast cancer with our idea of irradiating only the tumour bed in selected cases; we have developed and evaluated new technology called TARGeted Intraoperative radioTherapy (TARGIT) within the novel approach of risk-adapted radiotherapy. To date, TARGIT has saved 180,000 hospital visits and could save £60M(UK)/ $280M(USA)/year.

2. Underpinning research (indicative maximum 500 words)

Radiotherapy for breast cancer remains an integral part of treatment and reduces the risk of local recurrence of cancer after breast-conserving surgery. However, many patients have limited access to radiotherapy and are unable to attend daily for 3-6 weeks for post-operative radiotherapy. Such patients will choose mastectomy, sacrificing the breast for the convenience of avoiding a lengthy and expensive course of radiotherapy. This problem is prevalent in many parts of the developing world, but also affects women in Europe and the USA who live far from a radiotherapy centre.

The initial impetus for "single-shot" intra-operative radiotherapy for breast cancer arose from observations by Professor Jayant S Vaidya at Tata Memorial Hospital, Mumbai during the early 1990s that although two-thirds of mastectomy specimens for small breast cancers harbour occult cancers distributed throughout the breast, well over 90% of breast recurrences in the conserved breast appear in the original tumour bed. Professor Vaidya moved to UCL in 1998 and, in collaboration with Professors Michael Baum and Jeff Tobias, developed a hypothesis for a novel treatment: we proposed that radiotherapy be limited to the tumour bed and administered as a "one-off" radiation treatment at the time of surgery, avoiding the expensive 15- to 30-day course of EBRT and sparing many an unnecessary mastectomy. This became the TARGeted Intraoperative radioTherapy (TARGIT) technique **[1, 2]**.

Through translational research in 2004-8 on the immediate effects of radiation on a fresh wound, in collaboration with Dr Samuele Massarut and Dr Gustavo Baldassare, we found for the first time that the fluid that collects in the wound after a lumpectomy is highly favourable to cancer cells, stimulating them to multiply and invade. This could partly explain the propensity of recurrence to occur in the tumour bed. We also found that giving TARGIT immediately after a lumpectomy nullifies such effects and creates a beneficial micro-environment that is not conducive to tumour growth and invasion **[3]**.

We conducted an international randomised clinical trial (TARGIT-A trial) (2000-2012) comparing single-dose TARGIT with standard 3-6 weeks' radiotherapy in 3,451 patients. We found that cancer control rates using TARGIT were similar to EBRT **[4]**. Updated results were presented at the San Antonio Breast Cancer Conference (6 Dec 2012, General Session 4, http://goo.gl/4E10l) confirming that, in selected cases, TARGIT given at the time of lumpectomy within a risk-adaptive approach gives similar cancer control as EBRT. In addition we showed that it also results in significantly fewer non-breast cancer deaths mainly from cardiovascular causes and other cancers. Long-term results of our phase 2 studies suggest that if TARGIT is given *in addition* to EBRT as a tumour bed boost, the local recurrence of cancer appears to be halved **[5]**. We have now launched the TARGIT-B randomised trial to test this in young / high-risk patients.

Our discovery that abolition of the tumour stimulating effect of surgical wound fluid by

intraoperative radiotherapy has opened up a new avenue of intervention for disease. This effect due to significant changes in wound proteins might spill over systemically and may explain some of the reduced non-breast cancer mortality that we have seen in our randomised trial. The HTA funded TARGIT-B trial will test this formally and begin a novel strategy for drug discovery, potentially benefiting future patients.

3. References to the research (indicative maximum of six references)

[1] Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, Metaxas M, Harte KJ, Sliski AP, Thomson E. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. Ann Oncol. 2001 Aug;12(8):1075-80. http://annonc.oxfordjournals.org/content/12/8/1075.long

[2] Vaidya JS, Baum M, Tobias JS, Morgan S, D'Souza D. The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. Eur J Surg Oncol. 2002 Jun;28(4):447-54. http://dx.doi.org/10.1053/ejso.2002.1275

[3] Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F, Berton S, Perin T, Candiani E, Reccanello S, Veronesi A, Canzonieri V, Trovò MG, Zaenker KS, Colombatti A, Baldassarre G, Massarut S. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. Clin Cancer Res. 2008 Mar 1;14(5):1325-32. http://dx.doi.org/10.1158/1078-0432.CCR-07-4453.

[4] Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sütterlin M, Esserman L, Holtveg HM, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010 Jul 10;376(9735):91-102. http://dx.doi.org/10.1016/S0140-6736(10)60837-9.

The Lancet fast-tracked our paper describing the first results of the TARGIT-A trial and published it with an independent editorial entitled “Partial breast irradiation: a new standard for selected patients”. Our conclusion was on their front masthead page: “For selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy (TARGIT) should be considered as an alternative to external beam radiotherapy delivered over several weeks”. It is a **‘Highly Cited Paper’** in the ISI database.

[5] Vaidya JS, Baum M, Tobias JS, Wenz F, Massarut S, Keshtgar M, Hilaris B, Saunders C, Williams NR, Brew-Graves C, Corica T, Roncadin M, Kraus-Tiefenbacher U, Sütterlin M, Bulsara M, Joseph D. Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery. Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):1091-7. http://dx.doi.org/10.1016/j.ijrobp.2010.07.1996.

Grants awarded by the Health Technology Assessment program of the National Institutes of Health Research:

- £694,143: TARGIT-A trial: Targeted intraoperative radiotherapy for breast cancer (2009)
- £1,540,174: TARGIT-Boost trial for young / high risk breast cancer (2012)

4. Details of the impact (indicative maximum 750 words)

Over 200 breast cancer teams world-wide now use TARGIT including: Cleveland Clinic; University of California San Francisco; University of Southern California; Cornell; Georgetown University; Advocathealth hospitals in Chicago; Moffit cancer centre, Florida; about two-thirds of breast centres in Germany; several centres in the rest of Europe. The busiest centre has treated over 500 cases and manufacturers Carl Zeiss report that in all, over 8,000 patients have been treated with TARGIT **[a]**.

Thus, this idea and resulting research from UCL has revolutionised the treatment paradigm from

radical radiotherapy to localised radiotherapy.

Impact on patients and their families: improvement in length and quality of life, at a reduced cost

Many women are obliged to choose a mastectomy when they are not able to take the prolonged postoperative course of radiotherapy because of geography, time or money constraints. Many receive suboptimal treatment. With TARGIT, such women can have a lumpectomy and preserve their breast. Even amongst those who have a lumpectomy, TARGIT causes less pain, higher level of patient satisfaction, and higher quality of life scores than those receiving conventional radiotherapy **[b]**. There is a significant improvement in a woman's cancer journey when the whole of local treatment is completed at the time of the cancer operation, rather than a daily 3-6-week commute to the cancer hospital. TARGIT patients also have half the risk of death from heart disease or other cancers by avoiding toxicity. From the numbers in the trial (13 fewer deaths amongst 1,140 patients who were randomised to receive TARGIT at the time of lumpectomy), one can extrapolate that out of 8,000 patients, 91 such deaths have already been prevented. In communities where the patients have to pay for their treatment, TARGIT is a fraction of the cost of conventional radiotherapy – leading to more equitable availability of treatment.

Impact on the routine treatment guidelines/recommendations for patients in the community

The TARGIT-A trial was the first proof of principle of 'partial breast irradiation' and other methods of giving partial breast irradiation have proliferated. TARGIT either as a tumour bed boost or as definitive treatment as well as other methods of partial breast irradiation are now included in guidelines issued by the European Society of Breast Cancer Specialists **[c]**, the European Society of Medical Oncology (which are also endorsed by the Japanese Society of Medical Oncology) **[d]** and in German national guidelines **[e]**.

In March 2011, at the biennial international "St Gallen consensus" conference, 52 world experts voted in favour of using intraoperative radiation in selected patients. At this time the only level 1 randomised evidence was from the TARGIT-A trial **[f]**. In December 2012, the newsletter at the largest breast cancer conference at St Gallen featured our late breaking paper **[g]**. Our research has also attracted significant media attention both in scientific periodicals as well as lay press **[h]**.

NICE is currently consulting on the use of TARGIT in routine practice **[i]**. The Marmot committee on screening has suggested that in patients whose cancers are found only on mammographic screening, if TARGIT is used rather than EBRT, this would minimise side effects due to the over-diagnosis and overtreatment that is known to occur with mammographic screening **[j]**. We have also demonstrated that TARGIT is a method of avoiding cardiac toxicity of EBRT **[k]**.

Impact on the healthcare delivery and budget

Breast cancer constitutes 1/3 of the workload of a typical radiotherapy department and in many areas there can be long waiting lists. When a significant proportion of this time is freed up by using TARGIT in the operation theatre, it can be used to treat other cancers in a timely manner.

Assuming that each of the 8,000 patients who had TARGIT during their lumpectomy would have required 30 conventional radiotherapy sessions rather than the single session at the time of surgery, and that TARGIT takes the time equivalent of 4 routine radiotherapy sessions, this is a saving of 208,000 radiotherapy sessions to date. Assuming each session costs a conservative £200, the saving of 208,000 sessions has already saved £41.6m world-wide. It is estimated that adoption of TARGIT in the UK will save about £60m per year from manpower costs alone. A more formal model has predicted this amount to be $280m in the US **[l]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[a] Correspondence from the Head, Medical and Health Economy, Carl Zeiss detailing number of patients treated is available on request.

[b] Welzel G, Boch A, Sperk E, et al. Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A. Radiat Oncol. 2013 Jan 7;8(1):9. http://doi.org/n2v

[c] Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012 Apr;13(4):e148-60. http://doi.org/n2w. *See reference 41.*

[d] Senkus E, Kyriakides S, Penault-Llorca F, et al.; on behalf of the ESMO Guidelines Working Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Aug 22. http://doi.org/n2x. *See reference 46*.

[e] German National Guidelines, "Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms", 2012. See pages 138/139 http://www.krebsgesellschaft.de/download/S3_Brustkrebs_Update_2012_OL_Langversion.pdf

[f] Goldhirsch A, Wood WC, Coates AS, et al.; Panel members. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011 Aug;22(8):1736-47. http://doi.org/cpc9t4.

[g] 2012 **San Antonio Breast Cancer Symposium Highlights**: TARGIT vs Conventional Radiotherapy: 10 Years On. 6 December 2012 2012;3:3. Available on request.

[h] Selected news coverage in scientific periodicals and lay press – copies of articles without URLs are available on request

- Charlie Schmidt Early Breast Cancer: Single Dose of Radiation During Surgery Gains Support. **JNCI Journal of the National Cancer Institute** 2010;102(17):1304-09
- Partial Breast Irradiation safe for some women with invasive breast cancer. **NCI News Bulletin** 15 June 2010; 7:12
- Helwick C, Goodman A, Cavallo J. Research Roundup from San Antonio: Intraoperative Radiotherapy vs. External-beam Radiotherapy. **The ASCO Post**. 2013;4(3):41.
- **BBC News**, 2010: One-shot radiotherapy 'success against breast cancer.' http://bbc.in/p3SCnh
- **Independent**, 2010: Dramatic advance in treatment of breast cancer. http://ind.pn/9teYZP
- **Times of India**, 2010: Soon, one-shot radiotherapy for breast cancer? http://bit.ly/15DATUo
- **NY Times**, 2010: Findings may alter care for early breast cancer.
- **LA times**, 2010: New Treatment for breast cancer.
- **Daily Mail**, 2012: Me and my operation: Targeted intraoperative radiotherapy blasted my breast tumour. http://dailym.ai/fqgOaR

[i] NICE appraisal (in progress) 'Intrabeam targeted intraoperative radiotherapy for the treatment of early or locally advanced breast cancer' [ID618] To appraise the clinical and cost effectiveness of the INTRABEAM Photon Radiosurgery System for the adjuvant treatment of early or locally advanced breast cancer during surgical removal of the tumour. http://www.nice.org.uk/nicemedia/live/14150/63573/63573.pdf

[j] Marmot M, Altman G, Cameron DA, et al. Independent UK Panel on Breast Cancer Screening replies to Michael Baum. BMJ. 2013 Feb 13;346:f873. http://doi.org/n2z. *See reference 5.*

[k] Vaidya JS, Bulsara M, Wenz F. Ischemic heart disease after breast cancer radiotherapy. N Engl J Med. 2013 Jun 27;368(26):2526-7. http://doi.org/n22

[l] Alvarado M, Ozanne E, Mohan A, Esserman L. Cost-effectiveness of intraoperative radiation therapy for breast conservation. **Journal of Clinical Oncology** 2011;29(15_suppl):abstr 6081.