Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Transforming breast cancer patient care with a novel single-dose intraoperative radiotherapy (TARGIT-IORT) to replace several weeks of conventional radiotherapy

Period when the underpinning research was undertaken: **2000 - 2020**

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Jayant S. Vaidya	**Professor of Surgery and Oncology**	**1996 – 2004; 2009- present (Honorary 2004-2008)**

Period when the claimed impact occurred: 2013 - 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Investigators at UCL have developed and validated "single-shot" targeted intraoperative radiotherapy (TARGIT-IORT) for breast cancer. The innovation means radiotherapy to prevent cancer recurrence is completed in 15-40 minutes during surgery to remove the tumour and under the same anaesthetic, instead of 15-30 separate hospital visits for post-operative whole-breast radiotherapy. Patients undergoing TARGIT-IORT experience less pain, fewer side effects, and improved quality of life. In addition, deaths from radiation-induced cardiovascular and lung diseases and other cancers are reduced. TARGIT-IORT is recommended in national and international clinical guidelines. Globally, 45,000 patients (37,000 since 2014) have benefited in 38 countries, saving approximately GBP30,000,000 in healthcare costs and 20,000,000 miles in unnecessary travel to clinics, and avoiding 2,000 deaths from non-breast cancer causes.

2. Underpinning research

Radiotherapy following breast-conserving surgery reduces the risk of cancer recurrence. Traditional radiotherapy is given to the whole breast from outside the body (external beam radiotherapy, EBRT) requiring daily hospital visits for three to six weeks, starting several weeks after surgery. This prolonged course requires daily travel to the radiotherapy centre, often many miles away from the patient's home. Women may choose mastectomy over lumpectomy purely to avoid these multiple visits for radiotherapy. EBRT also exposes vital organs such as the heart and lungs to harmful scattered irradiation. This can lead to deaths from cardiovascular causes and other cancers. This harmful exposure is particularly pertinent to women being treated with early-stage breast cancer and when patients have other risk factors such as smoking.

The research team at UCL was the first to develop the technique of "single-shot" targeted intra-operative radiotherapy (TARGIT-IORT). TARGIT-IORT is given from *within* the breast, during surgical lumpectomy, whilst the patient is still under anaesthetic. This low-energy radiation procedure can be performed in a standard operating theatre. Depending on the size of the tumour cavity, different size spherical applicators, 1.5 – 5cm in diameter, are inserted in the tumour bed to deliver the treatment in 15-40 minutes (**R1, R2**).

Vaidya, in collaboration with the Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy (2004-2008) showed the fluid collecting in the wound after lumpectomy stimulates cancer cells to multiply and invade. However, applying TARGIT-IORT immediately after lumpectomy dramatically improves the tumour bed micro-environment and its cytokine profile, making it less conducive to cancer cell growth (**R3**).

The UCL team designed, implemented and administered the large randomised TARGIT-A trial between 2000 and 2012, including 2298 women from 32 centres in 10 countries, with close follow-up monitoring to the present day. The TARGIT-A trial compared 'risk-adapted' TARGIT-IORT with the standard treatment of three to six weeks of whole-breast radiotherapy (EBRT). The 'risk-adapted' approach meant that all patients in the experimental arm received TARGIT-IORT during lumpectomy, and about 20% also received whole breast radiotherapy if they were found to have specific factors. Factors include positive margins or unsuspected invasive lobular cancer post-operatively that could increase the risk of recurrence in other parts of the breast. Crucially, 8 out of 10 patients did not need any EBRT at all (**R4**).

Long-term follow up analysis (median 8.6 years, maximum 18.9 years, interquartile range 7.0-10.6) confirmed the efficacy of TARGIT-IORT at lower toxicity and cost. There was no difference in control of breast cancer, breast preservation and breast cancer mortality with TARGIT-IORT compared with whole breast radiotherapy. In addition, deaths from other causes were reduced by 41% (HR 0.59, p=0.005), which in absolute terms was a substantial reduction from 9.85% to 5.41%, at 12 years follow-up (**R5**, **R6**).

3. References to the research

R1. Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, Metaxas M, Harte KJ, Sliski AP, Thomson E (2001). Targeted intra-operative radiotherapy (TARGIT): an innovative method of treatment for early breast cancer. *Annals of Oncology* : official journal of the European Society for Medical Oncology / ESMO; 12(8): 1075-80. DOI: 10.1023/a:1011609401132

R2. Vaidya JS, Baum M, Tobias JS, Morgan S, D'Souza D. (2002) The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. *European Journal of Surgical Oncology* : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology;28(4):447-54. DOI: 10.1053/ejso.2002.1275

R3. 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. (2008) Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. *Clinical Cancer Research* : an official journal of the American Association for Cancer Research; 14(5): 1325-32. DOI: 10.1158/1078-0432.CCR-07-4453

R4. 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 HMR, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M (2010) Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 376: (8735):91-102. DOI: 10.1016/S0140-6736(10)60837-9

R5. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Saunders C, Brew-Graves C, Potyka I, Morris S, Vaidya HJ, Williams NR, Baum M. (2016) An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial) *Health Technology Assessment* Volume: 20, Issue: 73, doi.org/10.3310/hta20730

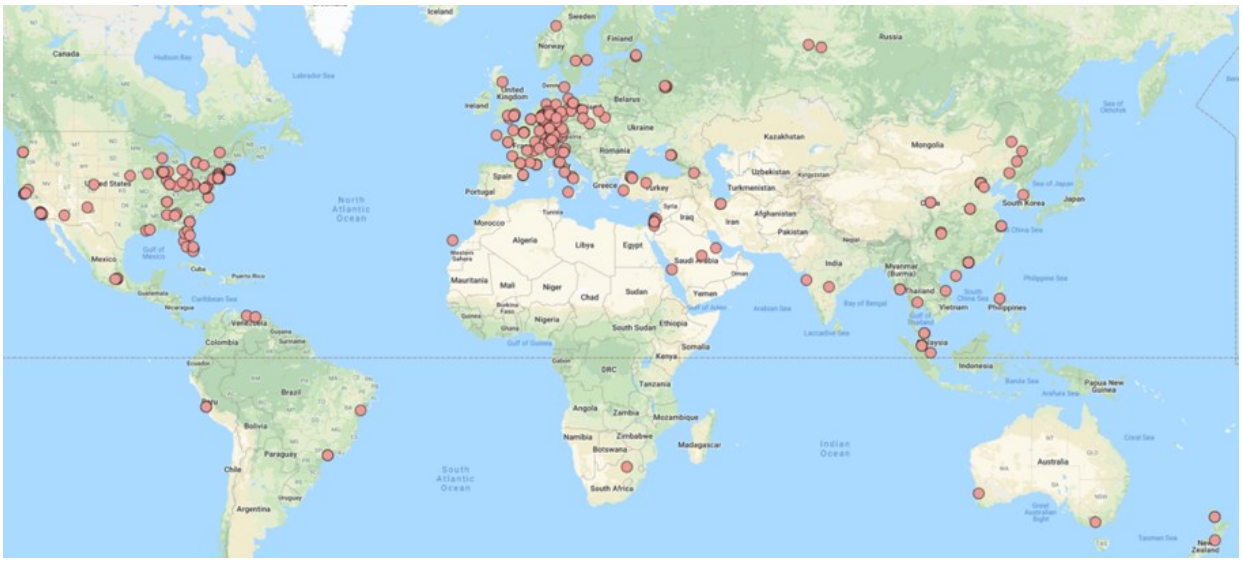
R6 Vaidya JS, Bulsara M, Baum M, (35 more authors) Tobias JS (2020) Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. *BMJ* ; 370: m2836. doi: https://doi.org/10.1136/bmj.m2836

4. Details of the impact

One in eight women will be diagnosed with breast cancer during their lifetime. Over 90 percent will have surgery to remove the tumour and over 60 percent will also have external beam

radiotherapy (EBRT) to help prevent recurrence. Most commonly, EBRT is delivered via 15 consecutive doses at a specialist centre. This involves multiple clinic appointments, which disrupt patients' lives and delays recovery from the trauma of having breast cancer. *Single-dose* TARGIT-IORT given during lumpectomy, developed and validated at UCL, significantly reduces the impact of breast cancer treatment on patients' lives as well as reducing unnecessary travel and healthcare costs. It also reduces the chance of death from non-breast cancer related causes. National and international clinical guidelines now recommend its use and, since 2014, the number of patients treated has increased from 8,000 to 45,000 by October 2020 (**S1**).

Location of 260 centres now offering TARGIT-IORT for patients with breast cancer



This map and an interactive web tool (https://targit.org.uk/travel) can locate the nearest TARGIT-IORT centre, as well as travel and CO2 emission savings by using TARGIT-IORT instead of EBRT

Benefits to patients

- **Better quality of life and reduced treatment burden**

TARGIT-IORT allows all women with appropriate clinical indication to choose lumpectomy over mastectomy and preserve their breast, regardless of their location and economic status. Compared to lumpectomy followed by postoperative traditional radiotherapy, TARGIT-IORT causes less pain and results in a higher level of patient satisfaction and quality of life scores (**S2**)**.** In 2017, Radio presenter Kirsty Lang had the treatment and said: "My operation went so smoothly that I felt like a bit of a fraud. I went under the knife at lunchtime and by late afternoon I was told the tumour had been successfully removed and there was no sign of the cancer having spread. I didn't even stay overnight and I was back presenting Front Row on Radio 4 six days later. For the next couple of weeks, I walked around with a spring in my step." (**S3**). The novel treatment can dramatically improve a woman's cancer journey as the local treatment is completed at the time of tumour removal, rather than via a daily commute for three to six weeks to the cancer hospital (**S4**). Each patient also saves approximately 45 hours of their time (travel, waiting and clinic appointments) and enjoys fewer interrupted days during their breast cancer treatment.

- **Reduced travel and carbon footprint**

The WHO estimates that two thirds of the world's population live in urban areas, while a third live in rural areas. Based on distances travelled to breast cancer clinics in the UK, two thirds of patients treated to date have saved 305 miles travel, and a third of patients saved 753 miles. Scaled up to the 45,000 women treated to date, this translates into a saving of 5.6 million kg of CO_2 emissions (4.6 million kg since 2014); this is a conservative estimate as many women in other countries may have to travel significantly further (**S4**).

- **Reduced risk of death from serious radiation induced diseases**

Patients who receive the single-shot TARGIT-IORT also have nearly half the risk of death from heart disease or other cancers by avoiding toxicity of several weeks' radiotherapy treatment (**S5**). In the TARGIT-A trial, there were 13 fewer deaths amongst 1,140 patients who were randomised to receive TARGIT at the time of lumpectomy, compared to the group who received EBRT. Extrapolating this to 45,000 patients, 513 such deaths have been prevented by five years after diagnosis, increasing to 2,000 by the time the 4.4% difference accumulates at 12 years.

- **Less pain, better cosmetic outcome, better quality of life and patient preference**

Patients undergoing TARGIT-IORT therapy have been shown to have less pain, better cosmetic outcomes, and better breast-related quality of life, compared to those treated with EBRT, based on several international studies. Patients and doctors (as potential patients) also preferentially choose TARGIT-IORT over EBRT (**R5**).

The benefits to patients of TARGIT-IORT are widely recognised among potential patients and healthcare professionals. The technology was included in the Forbes list of top 10 medical innovations for 2015 (**S6**) and continues to be discussed in mainstream media and on social media. The most recent follow up data published in August 2020 has already generated an Altmetric attention score of over 1000 (**R4**). As a result, women are increasingly seeking out centres that can provide the treatment.

TARGIT-IORT included in guidelines/recommendations for breast cancer treatment

TARGIT-IORT, delivered either as a tumour bed boost followed by standard EBRT, or as definitive treatment are now included in several guidelines including the European Society of Medical Oncology (which are also endorsed by the Japanese Society of Medical Oncology), in German national guidelines and the St Gallen Consensus (**S7**). The Marmot committee on screening recommended TARGIT-IORT in those patients whose cancers are found only on mammographic screening, as it minimises side-effects due to over-diagnosis and overtreatment] (**S8**). In 2015, Australia's MSAC (the equivalent to the UK's National Institute for Health and Clinical Excellence (NICE)) recommended TARGIT-IORT and in 2018, NICE recommended TARGIT-IORT in centres that have the expertise and equipment to deliver it on the NHS (**S9**).

During the 2020 COVID-19 pandemic, TARGIT-IORT was recommended in at least seven "COVID-19" national and international guidelines in UK, USA, Europe, Germany, Singapore, allowing vulnerable cancer patients to avoid unnecessary viral exposure during hospitals visits for radiotherapy treatment (**S10**).

Cost savings to health care services

TARGIT-IORT is cost-saving and cost-effective, and 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 access to treatment. The UCL team also estimated that TARGIT-IORT costs less to deliver than EBRT (GBP1700 vs GBP2385, saving approximately GBP685 per patient). Assuming 13,300 patients a year in the UK would be suitable for TARGIT-IORT, the estimated cost saving of is GBP9,100,000 each year, rising to GBP21,000,000 including patient and societal costs (**R6**).

Breast cancer constitutes approximately a third of the workload of a typical radiotherapy department and in many areas there can be long waiting lists. The time saved by completing radiotherapy during surgery rather than patients having daily post-surgical radiotherapy for several weeks can be used to treat other cancers in a timely manner.

Assuming each of the 45,000 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 to four EBRT sessions (10 minutes per session), this is a saving of up to 1.2 million radiotherapy sessions to date (984,000 session since 2014). Assuming each session costs a conservative GBP200, the saving of 1.2 million sessions has already saved GBP250,000,000 worldwide (GBP205,000,000 since 2014). Adoption of TARGIT by the NHS would save approximately GBP9,000,000 per year. A more formal model predicts a saving of USD280,000,000 in the US (**S11**).

5. Sources to corroborate the impact

S1 Vaidya JS. An interactive world map showing centres that offer TARGIT-IORT. 2020. http://bit.ly/35BwojG (accessed 23 Mar 2020). https://targit.org.uk/travel
S2 Corica T, Nowak AK, Saunders CM, et al. (2016) Cosmesis and Breast-Related Quality of Life Outcomes After Intraoperative Radiation Therapy for Early Breast Cancer: A Substudy of the TARGIT-A Trial. *International journal of radiation oncology, biology, physics*; 96(1): 55-64.
S3 Kirsty Lang interviewed in the Mail on Sunday February 2017: https://www.dailymail.co.uk/health/article-4166950/Radiotherapy-new-breast-cancer-blaster.html
S4 Coombs NJ, Coombs JM, Vaidya UJ, et al. (2016) Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. *BMJ open* ; 6(5): e010703.
S5 Vaidya JS, Bulsara M, Wenz F, et al. (2016) Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials. *International journal of radiation oncology, biology, physics* ; 96(2): 259-65.
S6 Szczerba RJ. Cleveland Clinic Announces Top 10 Medical Innovations For 2015. https://www.forbes.com/sites/robertszczerba/2014/10/29/cleveland-clinic-announces-top-10-medical-innovations-for-2015/#32a501713a72.
S7 TARGIT-IORT is used in over 250 centres in 35 countries, and included in most national and international guidelines summarised here: www.targit.org.uk/targit-iort-in-guidelines
S8 Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. (2013)The benefits and harms of breast cancer screening: an independent review. *British journal of cancer* ; 108(11): 2205-40.
S9 (NICE) NIfHaCE. Intrabeam radiotherapy system for adjuvant treatment of early breast cancer: Technology appraisal guidance [TA501]. 2018. https://www.nice.org.uk/guidance/ta501 (accessed 23 Mar 2020).
S10 UK and US International Guidelines
i) Global radiation oncology's targeted preparedness for COVID-19 https://www.sciencedirect.com/science/article/pii/S2405630820300227
ii) British Association of Cancer Surgery (BASO~ACS): https://baso.org.uk/media/98159/covid_19_and_breast_cancer_march_2020.pdf
iii) German University Hospitals: https://ro-journal.biomedcentral.com/articles/10.1186/s13014-020-01527-1
iv) Italian Association of Radiotherapy and Clinical Oncology https://www.thegreenjournal.com/article/S0167-8140(20)30221-8/fulltext
v) Implementation of breast cancer continuum of care in low- and middle-income countries during the COVID-19 pandemic: https://www.futuremedicine.com/doi/10.2217/fon-2020-0574
vi) Adapting care for older cancer patients during the COVID-19 pandemic: Recommendations from the International Society of Geriatric Oncology (SIOG) COVID-19 Working Group https://www.geriatriconcology.net/article/S1879-4068(20)30366-0/fulltext
vi) The impact of COVID-19 on and recommendations for breast cancer care: the Singapore experience https://erc.bioscientifica.com/view/journals/erc/27/9/ERC-20-0157.xml
S11 Vaidya JS, Wenz F, Bulsara M, et al. (2016) An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health technology assessment* ; **20**(73): 1-188.