How decades of clinical trials have transformed breast cancer radiotherapy

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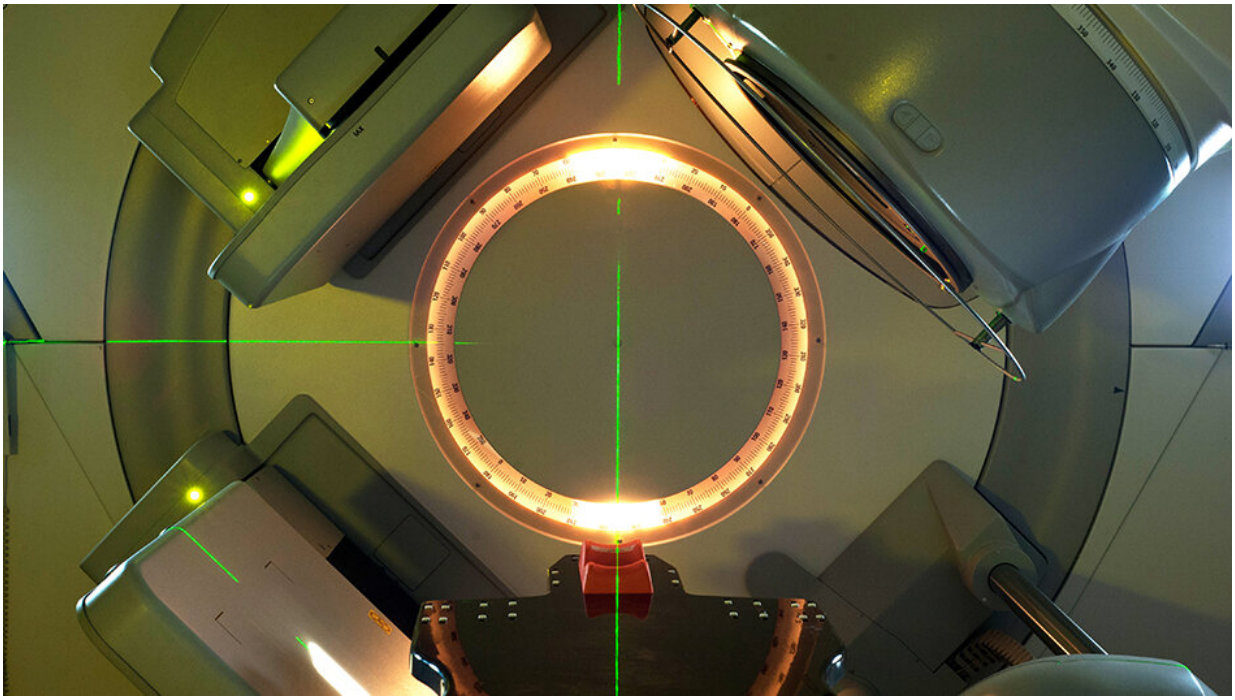

Radiotherapy machine at The Royal Marsden Hospital. Credit: Jan Chlebik, The ICR

After leading numerous practice-changing trials, Professor John Yarnold received a prestigious award at the 2021 ESTRO Congress. For Breast Cancer Awareness Month, Diana Cano looks back at the huge impact he has had in the field of breast cancer radiotherapy.

In the last few decades, researchers have developed and tested new radiotherapy treatment regimens that allow women with breast cancer to be treated with fewer daily doses of radiation, whilst minimizing side effects and the burden on patients, and without losing any effectiveness against cancers.

Professor John Yarnold has led many of these clinical trials—which involved more than 20,000 patients in total—including the START, FAST and FAST-Forward trials.

This year, during the European Society for Radiotherapy and Oncology (ESTRO) Congress held in Madrid, Professor Yarnold received the Claude Regaud Award for his translational research in breast radiotherapy. Regaud is known for describing the principles of 'fractionation'—the process of dividing a dose of radiation into multiple 'fractions.'

"It is an honor to receive this award in honor of Professor Claude Regaud, whose experimental work 100 years ago had such a profound influence on the development of radiotherapy," said Professor Yarnold.

Shorter treatment courses

The way in which fractions, or daily doses, of curative radiotherapy are divided has changed in recent years. The total dose of curative radiotherapy given to patients is conventionally divided into many small fractions spread over several weeks.

For decades fraction sizes, measured in gray (Gy), remained small (typically 2Gy) for all patients, allowing a high total dose (60Gy or more) to be delivered to the tumor over six weeks or more.

However, radiotherapy trials led by Professor Yarnold, in collaboration

with Professor Judith Bliss and colleagues at the ICR's Clinical Trials and Statistics Unit (ICR-CTSU), have shown in trials spanning almost 40 years that for early breast cancer, a lower total dose is as effective when delivered in fewer, larger fractions given over a shorter period of time.

These kinds of dosing schedules are known as 'hypofractionated' radiotherapy and they deliver a lower total dose in fractions greater than 2Gy, thereby enabling much shorter treatment courses. These smarter treatment courses are kinder to patients too; keeping side effects low and reducing the number of times they have to travel to and from hospital.

Breast cancer trials looking at 'hypofractionation' like START, FAST and FAST-Forward, led by the ICR, often in partnership with The Royal Marsden where Professor Yarnold was an Honorary Consultant Clinical Oncologist, have established the current standards of care.

START trials

Historically, women received radiotherapy in 25 daily doses of 2Gy over five weeks after their breast surgery. The first practice-changing trials led by Professor Yarnold were the START-A and START-B trials, carried out between 1998 and 2002.

The START-A trial was based on results of the START-P pilot trial, which he led in the 1980's. This was the first trial run by the Clinical Trials and Statistics Unit.

The UK START trials showed that 15 fractions of 2.7Gy given over three weeks are at least as safe and effective as 25 fractions of 2Gy over five weeks—reducing the length of standard treatment by a fortnight. These two landmark trials led to hypofractionated radiotherapy becoming the standard treatment for women with early breast cancer in the UK in 2008.

"Our trial results offered doctors and patients high level evidence that shorter radiotherapy courses could be delivered with milder early and late side effects without compromising cancer cures," said Professor Yarnold.

"The unusual design of the START-P and -A trials controlled for effects of time and tested for two different levels of hypofractionated therapy. In fact, these features enabled the first direct measure of sensitivity to fraction size of any human cancer.

"It is extremely rewarding to know our work has contributed to improving the quality of life of many women with breast cancer over the years."

FAST trial

The next step was the FAST trial, which tested the safety of increasing the fraction size from around 3Gy to 6Gy and reducing reduce the number of fractions from 25 to five. The FAST trial compared late side effects—those appearing months or years after treatment—after hypofractionated radiotherapy with those that appeared after conventional radiotherapy.

FAST successfully showed that five larger fractions given as one fraction per week could be delivered safely, causing no more changes in the healthy tissues of the breast than 25 small fractions over five weeks.

The three-year results of the FAST trial were published in 2011 and showed that reducing the number of radiotherapy fractions to five was feasible and safe in the short term. Just over a year ago, the 10-year results from the FAST trial confirmed that the shorter treatment course is as safe in the long term too, since side-effects remained low a decade later.

FAST-Forward

The START and FAST trials laid the groundwork for the recent FAST-Forward trial, testing an even shorter treatment course of five fractions of breast radiotherapy delivered in a single week. This was recently found to be safe and effective, when compared to the three-week standard established by the START trial, and has become a UK standard for patients with early breast cancer—being incorporated into the UK Royal College of Radiologists national consensus guidelines in May 2021.

The five-dose schedule is increasingly being adopted internationally. The results of this trial were presented and published just as the global coronavirus pandemic hit, enabling safe delivery of breast radiotherapy to tens of thousands of women who would have otherwise faced delays or interruptions to their treatment.

"Beyond its immediate beneficial impact on patients, who find the treatment much easier, the research has strengthened interest in the study of hypofractionated radiotherapy in different cancers, not only in response to our trials but reflecting technological advances in radiotherapy and new insights into how the body's immune responses to cancer might be strengthened by hypofractionation," said Professor Yarnold.

Making a difference

Thanks to large, well-conducted clinical trials like START, FAST and FAST-Forward, coordinated by the ICR-CTSU, radiotherapy research continues to improve outcomes for many women out there.

Hypofractionation provides a clear example of how a better

understanding of biology, coupled with technological advances, can offer benefit for both patients with breast cancer and healthcare systems.

Frequent visits to hospital can be difficult for some women, especially older patients who live far away from hospital, so it is crucial that we carry out research that can give patients a better quality of life.

And, while shorter courses of radiotherapy with fewer visits to hospital give patients a better quality of life, irrespective of age or physical fitness, hypofractionated radiotherapy is also particularly relevant in low-to-middle-income countries where women may have to travel very long distances to access radiotherapy services.

Looking back

After being involved in so many practice-changing radiotherapy trials that have transformed treatment for countless patients, it is difficult to quantify Professor Yarnold's impact on the field of cancer research.

Not only was he involved in breast cancer trials, he also led many other trials, including the first-ever randomized trial at the ICR and The Royal Marsden. This was a randomized trial started in 1982, evaluating a single fraction of radiotherapy for patients with metastatic bone pain, which has long been a national and international standard of care.

In recognition of his outstanding achievements and contributions to the field of radiotherapy, Professor Yarnold was also made Emeritus Professor upon his retirement.

"Working with patients is always a privilege, but the most stimulating and enjoyable aspect of the last 40 years has been working with multidisciplinary groups of colleagues on clinical trials that have transformed radiotherapy treatment."

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