

Global adoption of single-shot targeted intraoperative radiotherapy (TARGIT-IORT) for breast cancer – better for patients, better for health care systems

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Abstract

Introduction TARGeted Intraoperative radioTherapy (TARGIT-IORT), developed in the late 1990s, delivers radiotherapy targeted to the fresh tumour bed exposed immediately after lumpectomy for breast cancer. Long-term results of the TARGIT-A trial found TARGIT-IORT during lumpectomy as effective as whole breast radiotherapy along with significantly fewer deaths from causes other than breast cancer. This paper documents its worldwide use and impact.

Method Each centre provided the number of patients treated using TARGIT-IORT. These data were plotted on an interactive ‘My Google Map’. We also created an interactive web-based tool. Using the long-term outcomes from the TARGIT-A trial, we estimated the total savings in travel miles, time, carbon footprint, and the number of deaths from other causes that might be prevented.

Results Data from 242 (93%) of the 260 centres treating patients from 38 countries were available. The first was treated in 1998 at University College London. As of early 2020, at least 44752 women with breast cancer have been treated with TARGIT-IORT. <https://targit.org.uk/travel> displays the Google-map of centres with number of cases and the interactive tool that enables patients to find the nearest centre offering TARGIT-IORT and their travel savings. Scaling the main benefits up to the already treated patients, >20 million miles of travel would have been saved, and about 2000 non-breast cancer deaths might be prevented.

Discussion This paper demonstrates one can ascertain the number of patients who have been treated with a novel treatment. It shows how widely TARGIT-IORT has now been adopted and gives an indication of its beneficial world-wide impact on a large number of women with breast cancer.

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Introduction

A large proportion of patients with small breast cancers can be effectively treated by a lumpectomy and radiotherapy, rather than a mastectomy. Radiotherapy is traditionally given to the whole breast.

In the mid '90s, TARGeted Intraoperative radioTherapy (TARGIT-IORT)¹⁻³ was proposed as a radical new approach. This treatment delivers effective radiotherapy targeted to the fresh tumour bed exposed immediately after lumpectomy^{4,5}, while sparing nearby tissues and nearby vital organs such as the heart and lung.

In pilot studies starting from 2 July 1998, the safety and feasibility of this novel approach combining surgery and radiotherapy were confirmed¹⁻³, and the TARGIT-A randomised trial was proposed in 1999⁶ comparing risk-adapted single-dose TARGIT-IORT during lumpectomy vs. conventional fractionated whole breast external beam radiotherapy (EBRT) given daily for several weeks⁶⁻⁸.

Long-term outcomes of the TARGIT-A trial found TARGIT-IORT to be as effective in terms of breast cancer outcomes and that it led to fewer deaths from other causes⁹. Other benefits included lower radiation related toxicity¹⁰⁻¹⁷, reduced pain, better quality of life^{16,18-22}. When given a choice, TARGIT-IORT is preferred by patients over other methods of radiotherapy or 'no-radiotherapy'²³⁻²⁸.

The adoption of TARGIT-IORT for standard clinical practice has grown considerably over the last 20 years. In this short paper, to assess the worldwide impact of TARGIT-IORT, we aimed to count the number of patients treated with TARGIT-IORT around the world, as well as estimate the total benefits to the patient, in terms of the saving of travel distance, time, and reduction of transport-related carbon footprint and reduced deaths from other causes.

Method

Since the first case was performed in London in 1998, an international network has been developed between centres using TARGIT-IORT. Therefore, the contact details of a large proportion of the centres were available. Using Google forms and electronic communication, we requested the date when the first breast cancer patient was treated with TARGIT-IORT at their centre, and how many such patients were treated by their centre in total. We did not restrict this to those centres that had participated in the TARGIT trials. If after repeated attempts, there was no response from a centre, we included the name of the centre without the number of cases. We also queried the German National Database (<https://www.destatis.de/>) using the codes 8.52d, 8-523.6 and 8-521. Such databases were not available for other countries. Using My Google Maps, each hospital was displayed on an interactive map showing the date of the first case and the total number of cases performed at the centre, along with directions to a chosen hospital.

In addition to avoiding the hospital visit required to plan radiotherapy, the large majority of patients (8 out of every 10) who received TARGIT-IORT would avoid 15 to 30 daily trips to the hospital they would have taken for conventional whole breast radiotherapy. Therefore, we made an estimate of the total savings by the patient – in terms of travel miles, travel time, and carbon footprint, using the methodology described previously²⁹. Our previous work²⁹ had found that patients in the TARGIT-A trial, mostly from urban areas in

the UK, saved on average 305 miles of travel, while those in semi-urban areas saved 753 miles. This estimate takes into account the additional travel required in the 20% of patients who are recommended whole breast external beam radiotherapy. It has been estimated that 55% of the world population lived in urban areas in 2018³⁰. For this paper we used the UK figures for travel savings and assumed a larger proportion of patients (66% rather than 55%) will be urban dwellers. The total miles saved were used to calculate the amount of CO₂ saved.

We prepared an interactive web application to make individual estimates. These tools were tested by patients, and their feedback was used for making improvements.

Long-term results of the TARGIT-A trial⁹ (e-figure 1) found no difference any breast cancer outcome or breast cancer specific mortality, but a significant reduction in non-breast cancer mortality (HR 0.59, 95% CI 0.40 to 0.86, P=0.005) such that it was 5.41% for TARGIT-IORT and 9.85% for EBRT. The difference was 4.44% (95%CI of the difference being 2.5% to 6.4%). We scaled up this difference to the total number of patients treated to estimate the number of non-breast cancer deaths that might be prevented.

We used STATA 16 for statistical analysis.

Results

Data from 242 (93%) of the 260 centres were available. Data from 31 of 64 centres (n=8212) in Germany were available directly from investigators and the remaining 33 (n=7853) from the German national database.

The first patient with breast cancer was treated with TARGIT-IORT on 2 July 1998 at the Middlesex hospital (now part of University College London Hospitals), University College London. Since then, we found that TARGIT-IORT has been used in 35 countries and at least 44,752 breast cancer patients have been treated (Table 1). The total number of patients known to have been treated are approximately 30,000 in Europe, 9,000 in North America, 3,000 in Asia Pacific, 2,000 in South/Central America, 500 in the Middle East and 200 in Africa.

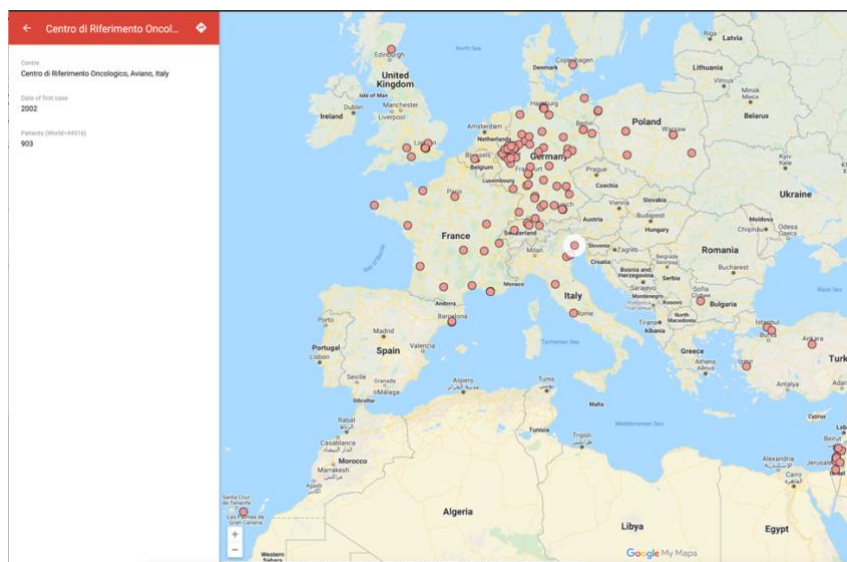
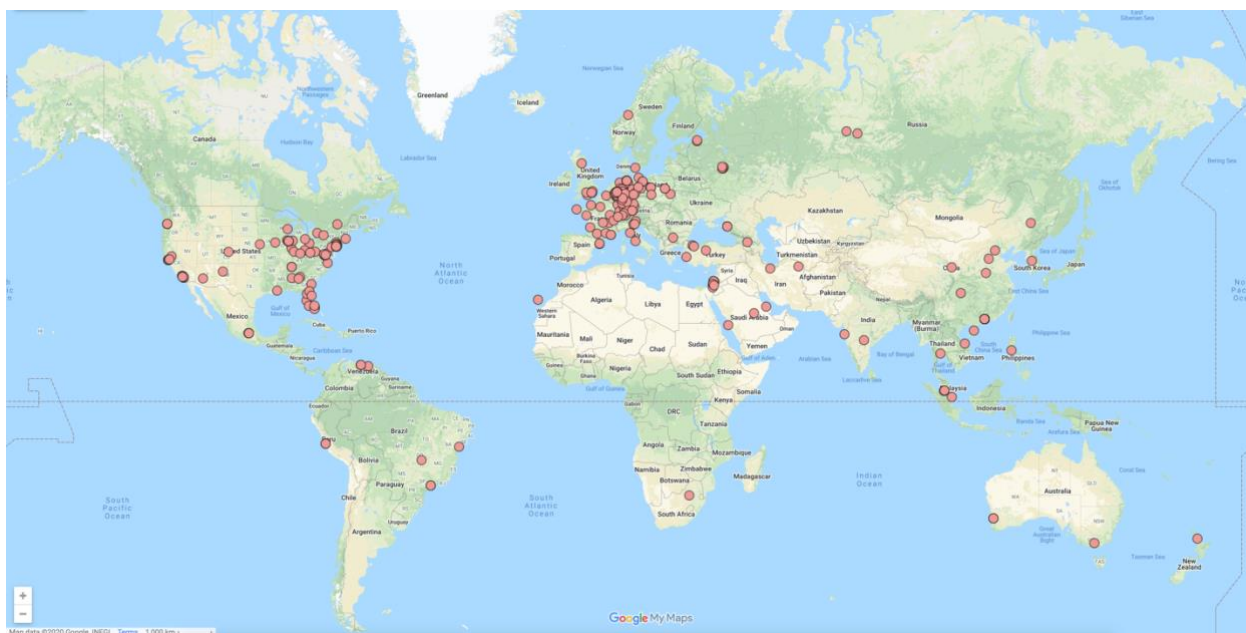
Figure 1 is the screenshot of an interactive Google map that shows the centres which have offered TARGIT-IORT for breast cancer, the year of their first case, and the number of cases performed as of August 2020. Once the reader clicks on a particular centre, they can get directions to the centre by clicking on the direction arrow on top left corner, next to the name of the centre. The interactive efigure 2 shows the number of centres in each country. eFigure 3 shows how they have increased since 1998.

Scaling up the saved journeys by avoiding EBRT, because of the use of TARGIT-IORT to the 44,752 patients, we estimate that over 20 million (20,134,909) miles of travel have already been saved, representing a carbon footprint reduction of 5.6 million kg of CO₂ emissions.

Figure 2 is the screenshot of the interactive tool with which one can find the centre offering TARGIT-IORT closest to one's home. It will also estimate how much an individual patient would save by using TARGIT-IORT in terms of travel distance, time, and carbon footprint.

These interactive maps and tools can be accessed at <https://targit.org.uk/travel>.

Figure 1: Screenshots of the map of the world with each dot representing a centre that has treated breast cancer with TARGIT-IORT. The name of the centre and number of cases treated by the centre (if available) is seen in the left-hand pane when you click on the centre in 1b below (the map can be zoomed in). This map is interactive and available at <https://targit.org.uk/travel>



Scaling up the 4.44% (95%CI 2.5% to 6.4%) reduction in non-breast cancer mortality to the 44752 patients treated to date (mid-2020), we estimate that 1987 (95%CI 1129 to 2845) non-breast cancer deaths from causes other than breast cancer such as cardiovascular and lung problems and other cancers might be prevented.

Discussion

This paper describes the worldwide adoption of TARGIT-IORT for treatment of early breast cancer over the past two decades. We could confirm that TARGIT-IORT has been used in 242 centres in 35 countries and about 45,000 patients in 6 continents have been treated. In the process, an estimated 20 million miles of journeys were avoided. Applying the reduction in non-breast cancer mortality, found in the TARGIT-A trial, to the patients already treated suggests that use of TARGIT-IORT could lead to 2000 fewer deaths from causes other than breast cancer.

Over the last decade there has been growing support for the use of partial breast irradiation (PBI) instead of whole breast

radiation therapy, and it is arguable that TARGIT-IORT is much better for patients than other methods of PBI³¹⁻³⁴. The TARGIT-A trial cohort comprised a medium-risk population, with a substantial number of patients at a higher risk of relapse: 1898(83%) were younger than 70 years, 366 (16%) had tumours >2cm in size, 443 (20%) patients had grade 3 cancers, 488 (22%) patients had involved nodes, and 426 (19%) had ER or PgR negative tumours. Therefore, its results would also be applicable to patients with breast cancer suitable for breast conserving surgery more widely than other methods of PB I^{9 33}.

In many countries, patients live a considerable distance from the radiotherapy centre^{29 35 36} and are more likely to receive a mastectomy than breast conservation³⁷. Even in the USA as recently as 2015, patients who lived farther away from the radiation facility (> 9.2 miles/ 19 minutes away by road) were 36-44% more likely to receive a mastectomy than breast conservation³⁷. TARGIT-IORT is a much more convenient option^{27 38}.

Figure 2. A screenshot of the interactive tool to assess how much an individual patient would save by using TARGIT-IORT in terms of travel distance, time and carbon footprint. This example is for someone living in Berkeley, California, USA, for example, and going for radiotherapy at the University of California San Francisco UCSF hospital, the closest radiotherapy centre from this house. This interactive tool can be accessed at <https://targit.org.uk/travel>

The tool can be used to find a TARGIT-IORT centre near you and also find how much travel and time you will save*.

TARGIT-IORT

Your Address:

Conventional Radiotherapy Center Address:

Planned number of Radiotherapy Treatments:

Compare Travel

Travel, time and environmental cost-savings by having TARGIT-IORT for breast cancer instead of whole breast Radiotherapy

For the 80% of patients who are treated with TARGIT-IORT and don't need whole breast radiotherapy,

You will save	Per Trip	In Total
Travel Distance Saved (miles)	--	--
Time Saved (hh:mm)	--	--

You would avoid travelling ___ miles per trip, ___ miles in total.

You would save ___ hours (including time spent travelling to the hospital and time in hospital).

You would also reduce your carbon footprint by ___ Kg CO2 emissions.

NB. Distance and time are for a car journey and time includes 1h in the hospital per trip; the carbon footprint assumes 300 g CO2 / mile of travel by a diesel car. Estimates using the method described in <https://bmjopen.bmj.com/content/6/5/e010703>

powered by Google

The tool can be used to find a TARGIT-IORT centre near you and also find how much travel and time you will save*.

TARGIT-IORT

Your Address:

Conventional Radiotherapy Center Address:

Planned number of Radiotherapy Treatments:

Compare Travel

Nearby centres where TARGIT-IORT for breast cancer has been offered

TARGIT-IORT Centre	Team Members	Distance (miles)	
Bay Area Cancer Physicians at Summit Medical Center, Oakland, CA, USA	Valery Uhl	3	Get Directions
California Pacific Medical Center, San Francisco, CA, USA	John Lee, Terry Pierce	14	Get Directions
UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA	Michael Alvarado, Jane Wei	15	Get Directions
Sutter Medical Center, Sacramento, USA	Jeannine Graves	79	Get Directions
Beverly Hill Cancer Centre (Helen Rey), California 90210, USA	Dennis Holmes	372	Get Directions

Travel, time and environmental cost-savings by having TARGIT-IORT for breast cancer instead of whole breast Radiotherapy

For the 80% of patients who are treated with TARGIT-IORT and don't need whole breast radiotherapy,

You will save	Per Trip	In Total
Travel Distance Saved (miles)	33	851
Time Saved (hh:mm)	0:59	51:51

You would avoid travelling **33** miles per trip, **851** miles in total.

You would save **51:51** hours (including time spent travelling to the hospital and time in hospital).

You would also reduce your carbon footprint by **511** Kg CO2 emissions.

NB. Distance and time are for a car journey and time includes 1h in the hospital per trip; the carbon footprint assumes 300 g CO2 / mile of travel by a diesel car. Estimates using the method described in <https://bmjopen.bmj.com/content/6/5/e010703>

powered by Google

*This comparison does not take into account other benefits of TARGIT-IORT such as reduced personal cost, better cosmetic outcome, better quality of life or fewer deaths from non-breast-cancer deaths (9.85% vs 5.41% at 12 years)

We believe that wider availability and applicability of TARGIT-IORT should enable many more women to have the choice of having breast conservation when they would otherwise have a mastectomy because they are not able to have conventional radiotherapy³⁹⁻⁴⁸. TARGIT-IORT also reduces the cost of providing treatment⁴⁹⁻⁵⁴.

Importantly, TARGIT-IORT lowers the toxicity and reduces deaths from cardiovascular causes and other cancers by a substantial amount (4.4% by 12 years)³³, which has become increasingly important with the rising rates of survival with modern breast cancer treatment.

The strengths of this study are that the data were provided directly by the physicians and staff from the centre, and the response rate was excellent 93%. In addition, we provide user-friendly interactive links (<https://targit.org.uk/travel>) for use by clinicians and patients. The obvious weakness is that this paper does not describe data about outcomes, but this is not the intention of this manuscript. Outcome data is best gained from comparative analysis within the randomised trials (e.g. TARGIT-A)⁹, as well as published data from several centres' experience of TARGIT-IORT, and from

registry studies (<https://targit.org.uk/publications>)^{17 27 38 54-64}. Also, as the list of centres using TARGIT-IORT was compiled using personal contacts, we may have missed some centres, underestimating the number of cases. The network of centres using this approach is now been greatly strengthened and will in due course provide the foundation for a unified collection of outcome data.

TARGIT-IORT is now included in several national and international guidelines⁶⁵⁻⁷⁸ (<https://www.targit.org.uk/targit-iort-in-guidelines>) for breast cancer treatment. Several of these guidelines specifically recommend using TARGIT-IORT during the COVID-19 pandemic caused by the SARS-CoV-2 virus to give the added advantage of reducing patient exposure to hospital environments and public places.

This paper we have described the impact of a new treatment proven in a randomised clinical trial over the worldwide breast cancer community. It demonstrates how widely this evidence-based approach has now been adopted, and how it has benefitted women with breast cancer around the world.

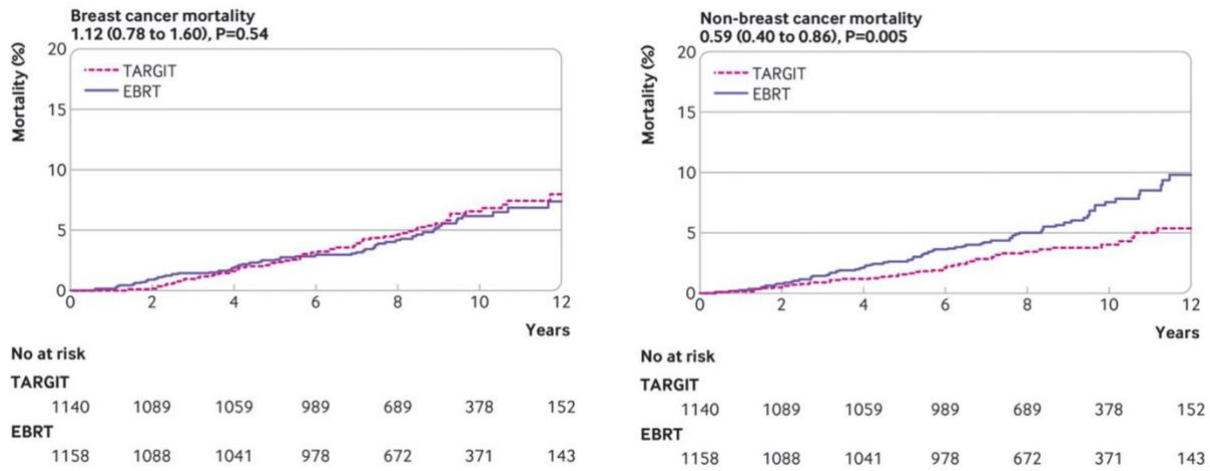
Table 1 Number of centres that have treated breast cancer patients with TARGIT-IORT around the world.

<i>Number of centres per country and region</i>			
<i>Region</i>	<i>Country</i>	<i>Number of centres</i>	<i>Centres from where number of patients is available</i>
Africa	South Africa	1	1
Africa Total		1	1
Asia & Pacific	Australia	3	3
	China	13	13
	India	2	2
	Malaysia	4	4
	New Zealand	1	1
	Philippines	1	1
	Singapore	1	1
	South Korea	1	1
	Thailand	1	1
	Vietnam	1	0
Asia & Pacific Total		28	27
Europe	Austria	1	1
	Belgium	1	1
	Bulgaria	1	1
	Denmark	1	1
	France	12	12
	Georgia	1	1
	Germany	63	65
	Israel	9	9
	Italy	5	5
	Norway	1	1
	Poland	8	2
	Russia	12	3
	Spain	3	3
	Switzerland	6	6
	Turkey	4	2
	United Kingdom	11	11
Europe Total		140	124
Middle East	Iran	2	2
	Saudi Arabia	3	3
Middle East Total		5	5
North America	Canada	2	2
	USA	72	71
North America Total		74	73
South/Central America	Brazil	4	4
	Mexico	3	3
	Peru	2	2
	Venezuela	3	3
South/Central America Total		12	12
Grand Total		260	242

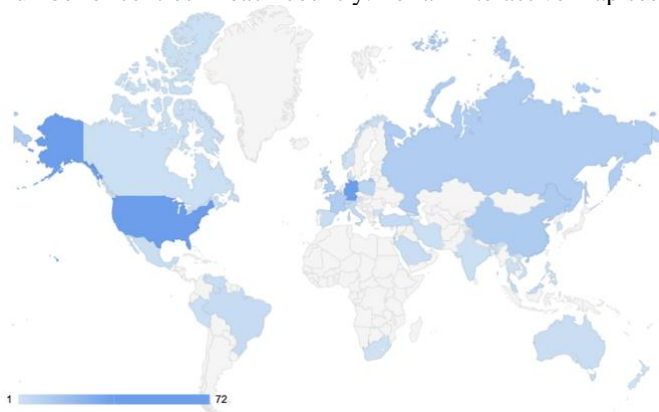
Region	Number of patients treated
Africa	179
Asia pacific	2785
Europe	29716
Middle East	1009
North America	9019
South America	2026
Total	44734

Supplementary figures

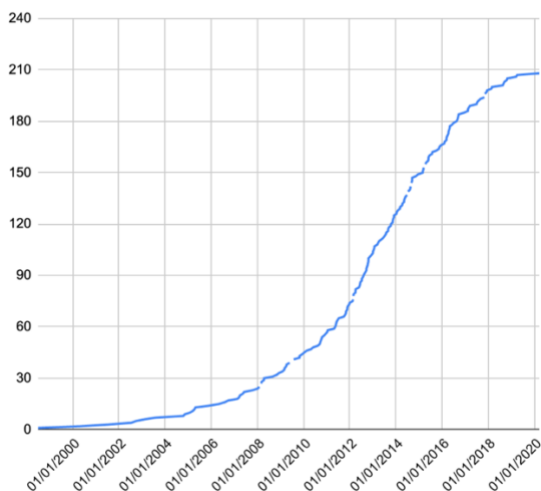
eFigure 1 Kaplan-Meier curves showing breast cancer mortality and non-breast cancer mortality for TARGIT-IORT v EBRT in the TARGIT-A trial. Figures under titles are hazard ratios (95% confidence intervals) and log rank test P values. EBRT=external beam radiotherapy; TARGIT = targeted intraoperative radiotherapy = TARGIT-IORT (taken from BMJ 2020;370:m2836 <https://www.bmj.com/content/370/bmj.m2836.full.pdf>)



eFigure 2 World map showing countries in which TARGIT-IORT is offered for breast cancer. The shading correlates with the number of centres in each country. For an interactive map see <https://targit.org.uk/travel>



eFigure 3 The number of centres offering TARGIT-IORT increased worldwide from 1998 onwards. The graph below includes only those centres from which the date of first case was returned to us.



TARGIT-IORT Global Collaborators

Jayant S Vaidya, Uma J Vaidya, Michael Baum, Max Bulsara, David Joseph, Jeffrey S Tobias, on behalf of the TARGIT-IORT Global Collaborators. The centres are listed in order when the first case was treated firstly within TARGIT-A trial, then TARGIT-B trial and then those outside these two trials. This table is not an exhaustive list and includes only those given by contributors who have responded to our emails for collaboration. We apologise for the omission of any names.

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Author contributions: JSV conceived the project and discussed it with UJV, MBa, JST and MBu, and wrote the first draft; UJV helped in making contacts, collecting data from centres and collating data, programming for creating the figures and tables, JSV, MBa, MBu, JST, DJ and UJV contributed to finalising the draft. All other authors and contributors/collaborators contributed by treating patients and returning their own data for the compilation and approving the manuscript for submission.

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Data sharing statement: UCL is supportive of data sharing and will endeavour to assist in requests for data sharing. All requests for data sharing will adhere to the UCL Surgical & Interventional Trials Unit (SITU) data sharing agreement policy. These data will be held at UCL on secure servers and cannot be released to any third parties. All requests for access to the data will be formally requested through the use of a SITU data request form which will state the purpose, analysis and publication plans together with the named collaborators. All requests are dealt with on a case by case basis. All requests will be logged and those successful will have a data transfer agreement which will specify appropriate security and privacy agreements, and acknowledgement of the TARGIT Trialists' Group, investigators, the sponsor, and funders.

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