Global adoption of single-shot targeted intraoperative radiotherapy (TARGIT-IORT) to improve breast cancer treatment – 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

Annually, 2 million women are given the diagnosis of breast cancer and 600,000 die from their disease[1]. It has been long established that a large proportion of patients with small cancers can be effectively treated by a lumpectomy, rather than a mastectomy. Such breast conserving therapy traditionally includes radiotherapy to the whole breast.

In the mid '90s, TARGeted Intraoperative radioTherapy (TARGIT-IORT) was proposed as a radical new approach to the treatment of breast cancer. TARGIT-IORT delivers radiotherapy targeted to the fresh tumour bed exposed immediately after lumpectomy[2 3]. This could potentially provide a rapid form of tumour-bed irradiation, while sparing nearby tissues and 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 confirmed[4-6], and a randomised trial was proposed in 1999[7] comparing TARGIT-IORT with conventional whole breast external beam radiotherapy (EBRT). Previously, a patient series[8], and randomised trial[9] exploring partial breast irradiation had been published. The initial results of this TARGIT-A trial were published in 2010 and 2013[7 10 11]. Long-term outcomes of the TARGIT-A trial have recently been published and have found that risk-adapted TARGIT-IORT given during lumpectomy is as effective as conventional whole breast radiotherapy and leads to fewer deaths from other causes[12].

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. If after repeated attempts, there was no response from a centre, we included the centre without the number of cases. The total number of patients treated in Germany was available from the National Database (https://www.destatis.de/) using the codes 8.52d, 8-523.6 and 8-521. Then, 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 previously[13]. A previously published study[13] 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. In order to have the most conservative estimate, we assumed that two thirds of patients treated were in urban areas (UN estimated that 55% of the world population lived in urban areas in 2018 https://ourworldindata.org/how-urban-is-the-world#un-estimates-55-of-people-live-in-urban-areas), saving 305 miles each and one third of patients saved 753 miles each. The total miles saved were used to calculate the amount of CO_2 saved.

We prepared an interactive web application that could be used by an individual patient who is considering this treatment to estimate their savings, using Google Maps to calculate the actual travel distance (by road) between the patient's home and the radiotherapy facility and yields both the travel distance, estimated time required to drive by car and CO_2 savings (by using the value of 0.3kg CO_2 emission per mile[13]). The tool should also show the centres where TARGIT-IORT may be available, nearest to their home.

Patients have been involved in dissemination of results of the TARGIT-A trial. We requested patients to test the two interactive tools and used their feedback for making improvements.

Long-term results of the TARGIT-A trial[12] as seen in figure 1 found that there was no difference in breast cancer specific mortality, but there was a significant reduction in non-breast cancer mortality when using TARGIT-IORT (HR 0.59, 95%CI 0.40 to 0.86, P=0.005). The Kaplan-Meier estimates of non-breast cancer mortality at 12 years were 5.4% for TARGIT-IORT and 9.9% for EBRT. The difference is 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 total for the remaining 34 (n=7853) was taken from the national database.

The first patient of 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. TARGIT-IORT has been used in 35 countries and at least 44752 breast cancer patients have been treated (Table 1). The total number of patients known to have been treated are approximately 30000 in Europe, 9000 in North America, 3000 in Asia Pacific, 2000 in South/Latin America, 500 in the Middle East and 200 in Africa. Figure 2 shows show centres which have offered TARGIT-IORT for breast cancer in an interactive Google map; it also shows when the first case was done 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 (Figure 2a and 2b). An interactive map (figure 3) showing the number of centres in each country is available at https://targit.org.uk/travel . Figure 4 shows how the number

of centres offering TARGIT-IORT increased worldwide from 1998 to 2020.

Scaling up the saved journeys to the 44752 patients, we found that 20,134,909 miles of travel may have already been saved, representing a carbon footprint reduction of 5.6 million kg of CO_2 emissions. Figure 5 shows the interactive tool that can be used to find the closest centre that could offer TARGIT-IORT as well as to assess how much an individual patient would save by using TARGIT-IORT in terms of travel distance, time, and carbon footprint. The interactive map and tools described can be seen at https://targit.org.uk/travel .

If we scale 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), then we can estimate that 1987 (95%CI 1129 to 2845) non-breast cancer deaths might be prevented.

Discussion

This paper describes the worldwide adoption of TARGIT-IORT for treatment of early breast cancer over the past two decades as a result of the outcomes described in the TARGIT-A trial[7 10-12]. It should be noted that a substantial absolute number of patients in TARGIT-A were at 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. Furthermore, most patients in the TARGIT-A trial who had high-risk features did *not* receive supplemental EBRT after TARGIT-IORT as part of the risk-adapted approach. For example, supplemental EBRT was *not* given to 78% of Grade 3, *not* given to 82% of ER negative and *not* given to 63% of node positive patients[14]. Rather, the decision regarding use of supplemental EBRT was made for the individual patient by the treating multidisciplinary team, particularly bearing in mind the main indications of unexpected lobular cancer and positive margins. Therefore, the TARGIT-A trial comprised a medium-risk population, and its results would be widely applicable to patients with breast cancer suitable for breast conserving surgery[12 14].

We could confirm that TARGIT-IORT has been used in 242 centres in 35 countries and about 45,000 patients 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 long term TARGIT-A trial results solely to the patients already treated suggest that use of TARGIT-IORT could already lead to 2000 fewer deaths from causes other than breast cancer such as cardiovascular and lung problems and other cancers.

One of the strengths of this study is that the data have been provided by the physicians and staff from the centre, by direct contact. Furthermore, we were able to get the data from 93% of centres. In addition, we provide interactive links (http://targit.org.uk/travel) for use by clinicians and patients. The Google map and the interactive tool can shows the readers which centre giving TARGIT-IORT is close to their home and how to get to the closest centre. They can also calculate the amount of travel they will save if they take TARGIT-IORT. One weakness is that a few centres' data return was before 2020, so the real numbers are likely to be higher than our estimate. The other obvious weakness is 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 prospective TARGIT-A randomised trial[12], data from several centres who have published their own experience of using TARGIT-IORT and well registry studies (http://bit.ly/TARGIT-IORT-Bibliography)[15-26]. In the process of collecting data for this paper, the network and communication pathways have been greatly strengthened. Therefore, now a proposal for a unified collection of outcome data from the whole world will become more feasible and more likely to succeed in the future.

Many benefits of TARGIT-IORT in suitably selected breast cancer patients have been previously described. By having TARGIT-IORT during their lumpectomy, 8 out of every 10 patients complete their radiotherapy right away, and entirely avoid the need for the repeated daily hospital visits over 3-6 weeks that are generally recommended[13]. The local radiation related toxicity is lower [20 27-33]. Quality of life including patient-reported outcomes (PROMS) such as cosmetic appearance and breast pain, are superior with TARGIT-IORT[33-38] (compared with external beam radiotherapy) and preferred by patients[39-43].

Many breast cancer patients across the world inevitably live a considerable distance from the radiotherapy centre[13 44 45], especially in low-medium resource countries, where all the above benefits would be even more pronounced. As noted above, the TARGIT-A trial eligibility was wide, so its results would indeed be applicable to a substantial proportion of patients even in the low-medium income communities. A recent study from South Africa[43] demonstrates how their patients have greatly welcomed this innovative opportunity. 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 conservation[46]. TARGIT-IORT is an effective and much more convenient option as per the report in rural USA[47]. Importantly, TARGIT-IORT can also reduce the cost of providing treatment[15 48-52] which is especially relevant when the resources are limited.

TARGIT-IORT enables some patients to have breast conservation when they would otherwise reluctantly choose mastectomy[53] or simply do not want to have conventional radiotherapy[24] because of their personal circumstances. Use of TARGIT-IORT in certain specific situations has also been described, e.g., in conjunction with oncoplastic surgery[54], for DCIS[55 56], or when external beam radiotherapy cannot be used or preferably avoided (such as in the presence of a pacemaker[57], previous radiotherapy to the breast[58-61], or breast implants[62]).

TARGIT-IORT is now included in several national and international guidelines[63-76] (https://www.targit.org.uk/targit-iort-in-guidelines). 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 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.

Number of centres per country and region			
Region	*Country*	*Number of centres*	*Centres from where number of patients* **is available**
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/Latin America	Brazil	4	4
	Mexico	3	3
	Peru	2	2
	Venezuela	3	3
South/Latin 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**

Figure 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)

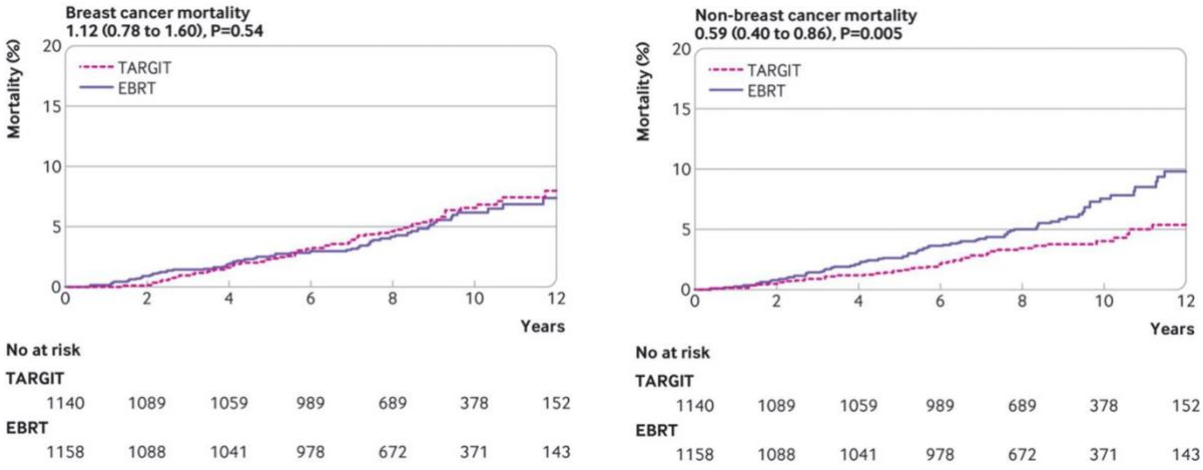


Figure 2: 1a: A screenshot of the map of the world with each dot representing a centre that has treated breast cancer with TARGIT-IORT. The name of the centre and number of cases treated by the centre (if available) is seen in the left-hand pane when you click on the centre in 1b below (the map can be zoomed in). This map is interactive and available at https://targit.org.uk/travel

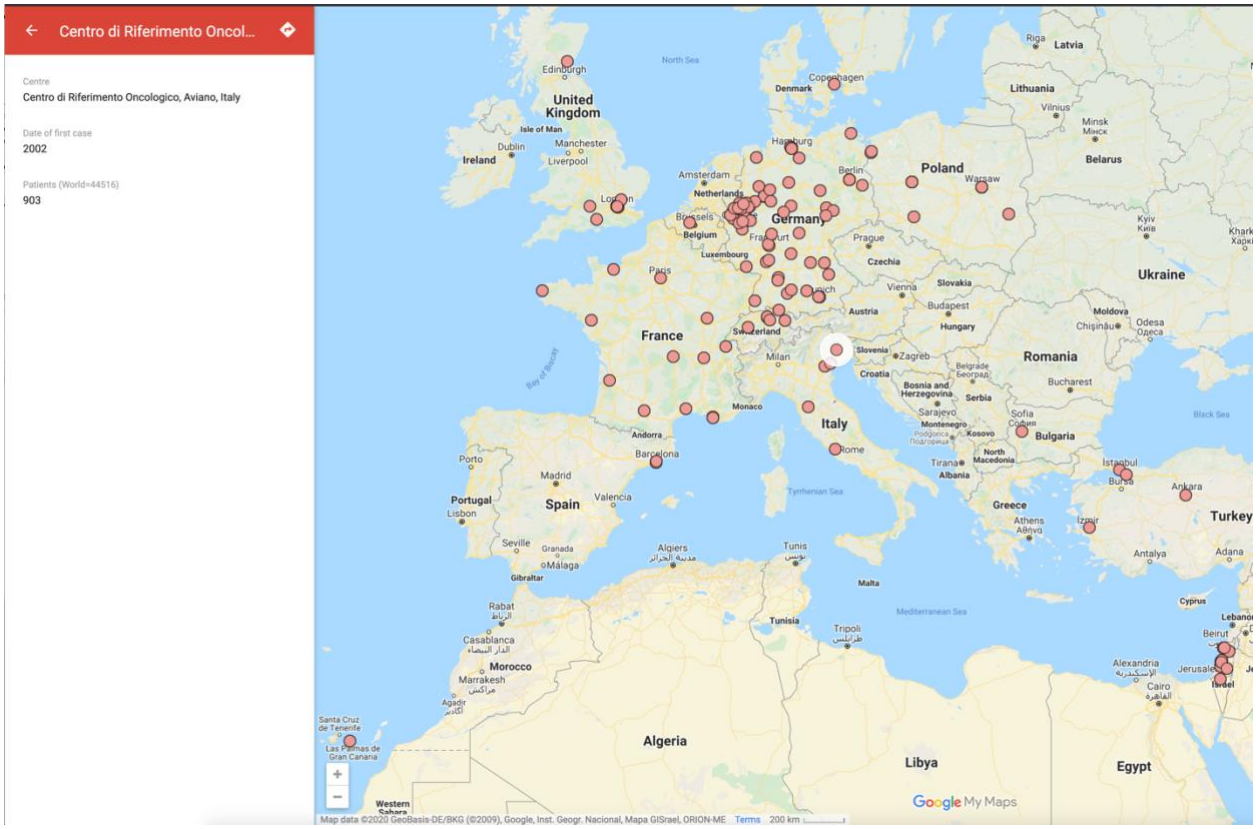


Figure 3 World map showing countries in which TARGIT-IORT is offered for breast cancer. The shading correlates with the number of centres in each country. For an interactive map see https://targit.org.uk/travel

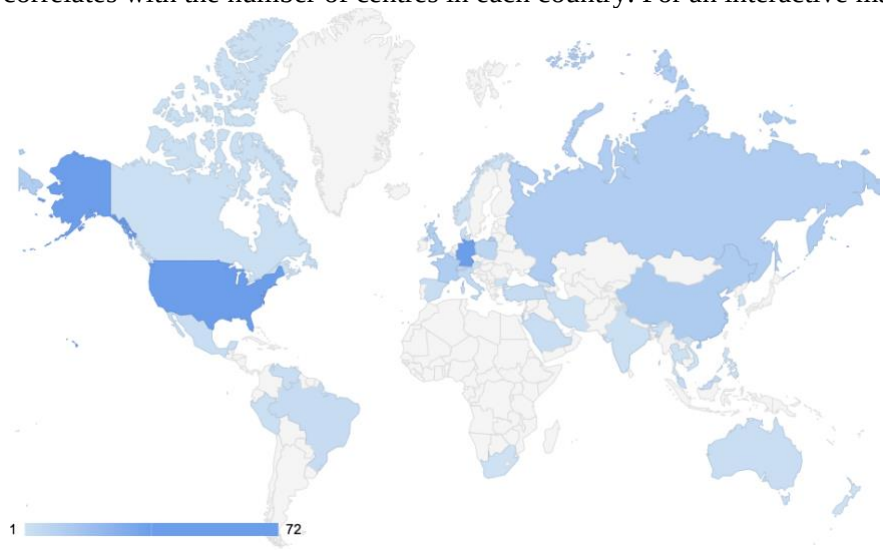


Figure 4 The number of centres offering TARGIT-IORT increased worldwide from 1998 onwards. The graph below includes only those centres from which the date of first case was returned to us.

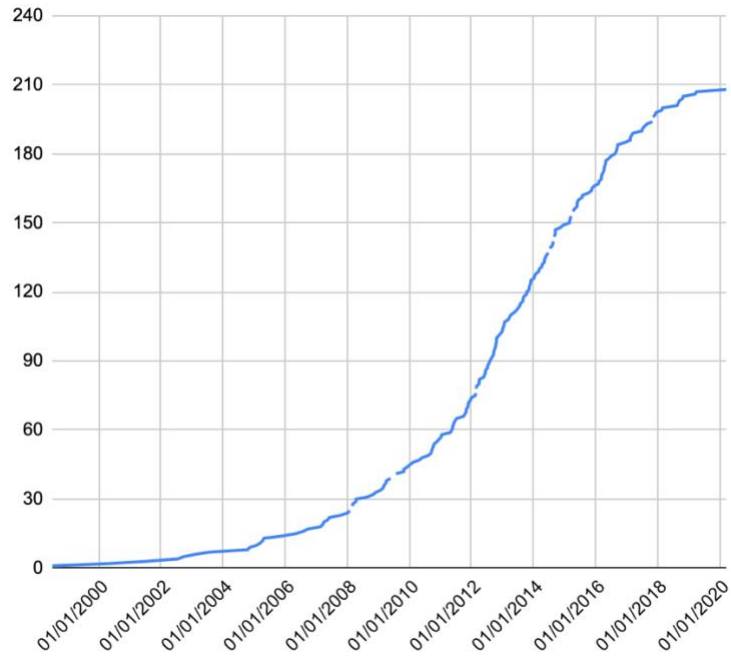
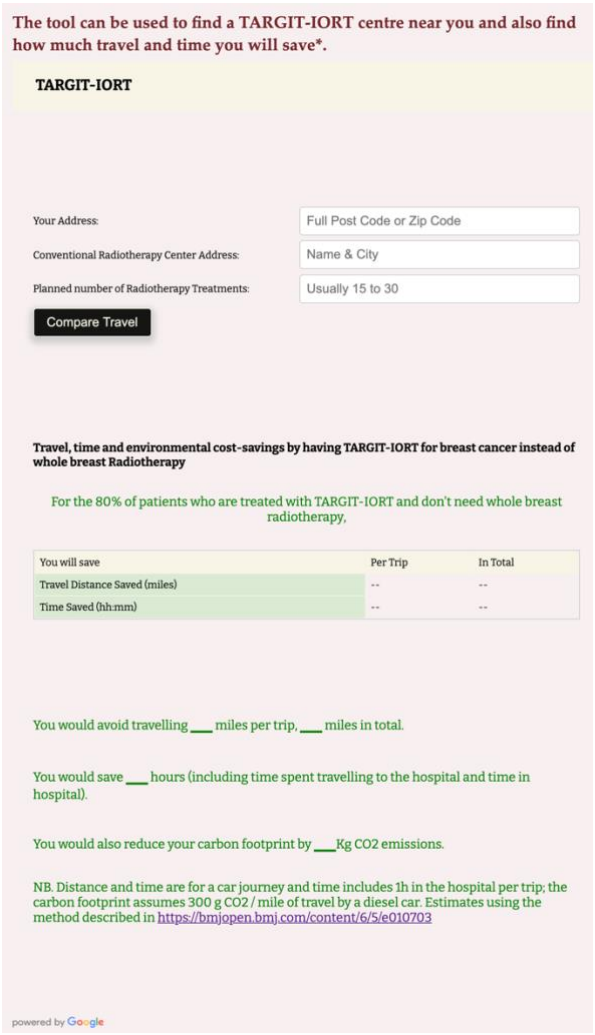
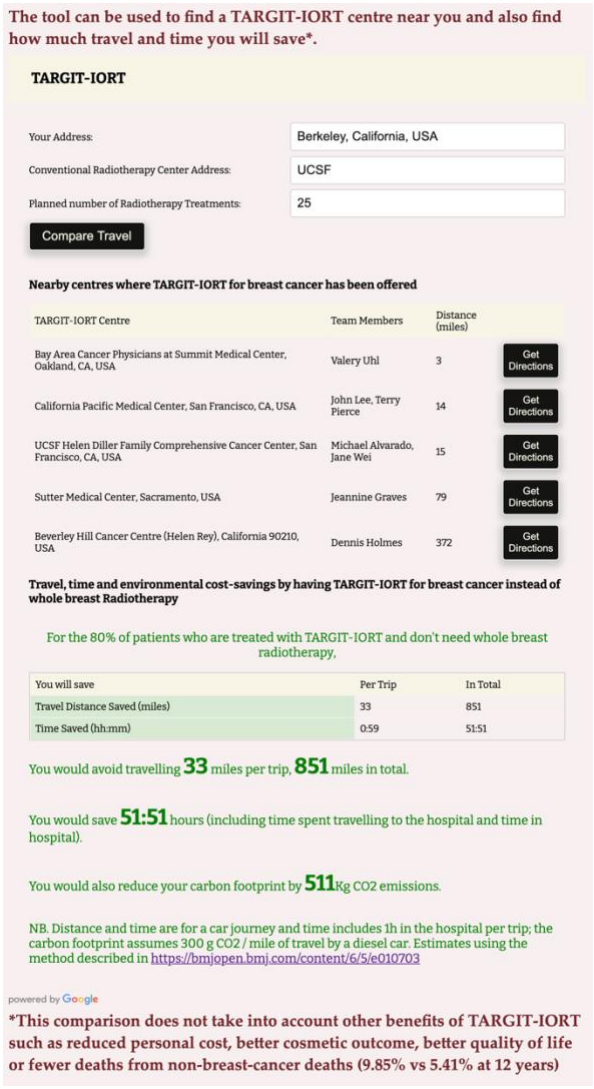


Figure 5. A screenshot of the interactive tool to assess how much an individual patient would save by using TARGIT-IORT in terms of travel distance, time and carbon footprint. This example is for someone living in Berkeley, California, USA, for example, and going for radiotherapy at the University of Califoria San Francisco UCSF hospital, the closest radiotherapy centre from this house. This interative tool can be accessed at https://targit.org.uk/travel





TARGIT-IORT Global Collaborators

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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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