ELSEVIER

## Contents lists available at ScienceDirect

## **IPEM-Translation**

journal homepage: www.elsevier.com/locate/ipemt



## Communication

## Could building more satellite centres reduce the carbon footprint of external beam radiotherapy?

Robert Chuter a, b, \*

- a Christie Medical Physics and Engineering (CMPE), The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, United Kingdom
- b Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PL, United Kingdom

## ARTICLE INFO

Keywords: Carbon footprint Sustainability Satellite centres Service provision Hospital building Emissions

## ABSTRACT

Climate change is increasingly a health emergency. This has been recognised by the NHS which aims to be carbon net zero by 2040. Most of the carbon footprint of radiotherapy is due to patient travel. Here we investigate if satellite centres can help reduce this impact.

The carbon footprint of construction was estimated using two different methods. The post codes for 49 patients and 21 staff were collected and the distance to the satellite centre and main centre determined. The carbon footprint from each of these aspects was combined to determine how many years it would take for the reduced patient travel to offset the construction of the satellite centre.

The mean carbon footprint of travel to the satellite centre and main centre were  $116.0 \text{ kgCO}_2\text{e}$  and  $176.2 \text{ kgCO}_2\text{e}$  respectively. The carbon footprint of building the satellite centre was between  $1103 \text{ tCO}_2\text{e}$  and  $618 \text{ tCO}_2\text{e}$ , meaning it would take 5.6 - 10.0 years to offset the embedded carbon footprint of the new building.

For the first time this study has estimated the carbon footprint of building a satellite radiotherapy centre and how this, through reducing patient travel can lower the carbon footprint of the service within a decade. This work may help those wishing to sustainably improve service provision.

## 1. Introduction

The impacts of climate change are becoming increasingly apparent through a variety of extreme weather events, including severe flooding, wildfires, and heatwaves [1]. For example, a recent study has shown that about 60,000 deaths were caused in Europe alone, due to the extreme heatwave experienced there in 2022 [2]. These events highlight that lowering our carbon footprint is of key importance. However, in 2019 the National Health Service (NHS) in the United Kingdom (UK) was responsible for approximately 25 million metric tonnes  $\rm CO_2$  equivalent emissions ( $\rm CO_2e$ ), which is equivalent to roughly 5 % of the UK's entire carbon footprint [3]. Acknowledging these health threats and the environmental impact of healthcare, the NHS has committed to becoming carbon net zero, including its supply chain by 2045 [4]. This is a huge task and requires all parts of healthcare in the UK to be examined.

In the UK external beam radiotherapy (EBRT) treats approximately 120,000 cancer patients annually [5], 50 % of all cancer patients [6]. Previous work has shown that a large proportion (over 70 %) of the carbon footprint of radiotherapy is from patient travel [7,8]. This could

potentially be reduced in a number of ways including increased use of hypofractionation [9], better public transport and potentially by building a larger number of smaller, satellite centres. Increasing the number of satellite centres would mean that a patient's nearest centre would be nearer, reducing the carbon footprint of patient travel. However, building a centre also has a large associated carbon footprint [10, 11].

Here for an example satellite centre the carbon footprint of travel is determined and is compared to the embedded carbon footprint from building the centre itself. If there is a carbon footprint saving due to reduced travel from building a satellite centre, then over time the footprint from building the centre would be offset; this timescale is also estimated.

## 2. Methodology

To provide an initial estimate of the effect of building more satellite centres on the carbon footprint of treatments, three main considerations are needed: patient and staff travel to the satellite centre compared to a

E-mail address: robert.chuter@nhs.net.

https://doi.org/10.1016/j.ipemt.2023.100021

Received 10 November 2023; Received in revised form 12 December 2023; Accepted 12 December 2023 Available online 13 December 2023

2667-2588/© 2023 The Author(s). Published by Elsevier Ltd on behalf of Institute of Physics and Engineering in Medicine (IPEM). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

<sup>\*</sup> Corresponding author at: Christie Medical Physics and Engineering (CMPE), The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, United Kingdom.

main centre and the carbon footprint of building the centre. This example is based on the Salford satellite centre which is part of The Christie NHS Foundation Trust whose main centre in Withington, a suburb of Manchester (Greater Manchester, England, UK) and is about 12–13 km driving distance from the Salford satellite centre (Salford, England, UK) (see map in Fig. 1).

Patient and staff travel data in the form of postcodes were recorded. Construction plans for the centre were used to determine the size of the building and size of the linear accelerator (linac) bunkers. A summary of the activity data that were extracted is shown in Table 1.

## 2.1. Carbon footprint of patient travel

The postcodes for a total of 49 patients treated on both of the linacs at the Salford satellite centre of The Christie were extracted for one day (3rd March 2023) for this study. Three patients treated for Brain with Stereotactic Radiosurgery were excluded as this is a national service, meaning that the distances travelled would be higher. This comprised of 14 breast, 10 prostate, 8 lung, 7 brain, 2 pelvis, 2 skin, 1 rectum, 1 bladder, 1 head and neck, 1 lymphoma, 1 oesophagus and 1 cord compression patient. The number of fractions that each of them were being treated with was also recorded.

A route planning tool (The AA Ltd, Basingstoke, England, UK) was used to estimate a realistic road travel route, based on average off-peak driving conditions. Patient notes/schedules were used to identify the number of fractions attended by each patient to calculate the total distance travelled. The Department of Business, Energy, and Industrial Strategy (BEIS) conversion factor data [12] were then used to convert this distance into emissions, making the assumption that all patients travelled in an 'average' fuel economy car. The total number of patients treated at the satellite centre between 1st April 2022 and 31st March 2023 was 1736.

**Table 1**Summary of activity data, conversion factors and sources used in estimations of carbon footprint.

Activity	Activity data	Source	Conversion Factors used
Patient travel	Kilometres travelled	Post codes from the Medical Oncology software package MOSAIQ® <sup>1</sup>	Average petrol car, 0.1708 kgCO <sub>2</sub> e/km. [12]
Staff travel	Kilometres travelled	Post codes from staff survey via email	Average petrol car, 0.1708 kgCO <sub>2</sub> e/mile, plug in hybrid, 0.09349 kgCO <sub>2</sub> e/km, local bus, 0.1078 kgCO <sub>2</sub> e/km, light rail/tram, 0.0286 kgCO <sub>2</sub> e/km [12]. Bike & walk: 0.095 kgCO <sub>2</sub> e/km [13]
Concrete	$m^2$	Site architectural plans	Concrete, 131.75 kgCO <sub>2</sub> e per tonne. [12]
Building (Method 1)	m <sup>2</sup>	Site architectural plans	53 tCO <sub>2</sub> e for building a 4- bed detached house [13]
Building (Method 2)	m <sup>2</sup>	Site architectural plans	Average construction material, 80.34 kgCO <sub>2</sub> e per tonne [12]

<sup>&</sup>lt;sup>1</sup> MOSAIQ® https://www.elekta.com/products/oncology-informatics/elekta-one/oncology-care/medical-oncology/.

## 2.2. Carbon footprint of staff travel

Estimating the carbon footprint of staff travel is important as some staff, in particular physicists and clinicians, do not work at the satellite centre regularly so are likely to live nearer the main centre. This could potentially increase the carbon footprint of overall travel to the satellite centre. To estimate emissions resulting from staff travel an email was sent out to staff with 5 questions to be answered. These were:

## 1. How often on average do you work onsite at Salford per week?;

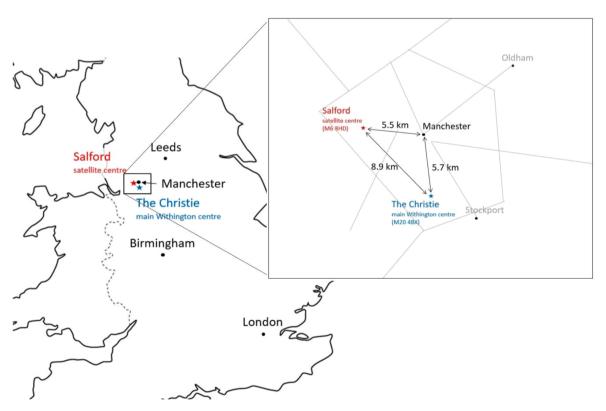


Fig. 1. A schematic showing the location of the main Christie hospital and the Salford satellite centre. The straight-line distances are shown in km.

- 2. How often on average do you work onsite at Withington per week?:
- 3. What is your post code;
- 4. On a typical day what mode of transport do you use to travel to Salford and:
- 5. On a typical day what mode of transport do you use to travel to Withington?.

In total 9 clinicians, 35 radiographer, 10 physics and 1 admin staff were emailed the questions. As with patient travel, the AA route planning tool was used to estimate the distance of a realistic road travel route [14] and the BEIS conversion factors [12] were used to convert this distance into emissions for the mode of transport that they specified.

## 2.3. Carbon footprint of the building

Due to the complexity with determining an accurate figure for the carbon footprint of building the satellite centre, two methods for estimating for the carbon footprint of the building were used:

**Method 1**. To determine a rough estimate for the centre, the carbon footprint for a four-bedroom detached house of 53 tCO $_2$ e [13] was scaled up using building plans for the satellite centre for the 1-floor (plus plant room above) building and assuming that the average UK house was 76 m<sup>2</sup> [15]. In addition to this, the carbon footprint of the 2 linac bunkers was determined by calculating the size of the bunkers, and therefore volume of concrete, from the building plans and using the conversion factor for concrete (see Table 1).

**Method 2.** The same building plans for the satellite centre were used to estimate the volume of construction material that would have been needed. The plans did not include what the external and internal walls and floors were made of, so a value of  $80.35~\rm kgCO_2e$  per tonne for average construction materials was used [12], an average density of  $2000~\rm kg/m^3$  was also assumed. Again, the carbon footprint of the 2 linac bunkers was added to this value, as with Method 1.

It is assumed in this study that the linacs themselves would be needed whether at the main centre or the satellite and are therefore not included in the assessment. The same may be true of the bunkers that house them. However, provision of a satellite building will necessarily involve some duplication of construction, which may include additional bunkers due to necessary redundancy due to needing a back-up linac in case of services, down time or linac replacement, and by including these estimates for the  $\mathrm{CO}_2\mathrm{e}$  of the satellite bunkers, a "worst case" building figure is generated.

## Battellite Centre Main Centre

# Satellite Centre Main Centre

Fig. 2. (a) The distance patients (N = 49) travelled to treatment at the satellite centre and the distance they would have travelled if they had been treated at the main centre. b) The carbon footprint in kgCO<sub>2</sub>e per patient of travel to and from the satellite centre and main centre. The boxes mark the 5th and 95th percentiles, the band marks the median, stars mark the mean and the whiskers mark the maximum and minimum values.

## 3. Results

## 3.1. Carbon footprint of patient travel

The average distance between patients' homes and the Salford centre was 19.8 km (range 2.2-48.1 km), whereas for Withington the average was 30.9 km (range 7.1-61.1 km) (see Fig. 2). Once multiplied by the number of fractions, which ranged between 5 and 33 and the conversion factor for an average petrol car, this gave a mean (and min to max) carbon footprint of  $116~kgCO_2e$  ( $7.9~to~491.6~kgCO_2e$ ) for travel to Salford and  $176.2~kgCO_2e$  ( $17.8~to~624.7~kgCO_2e$ ) for Withington. This gave a mean saving of  $60.2~kgCO_2e$  per patient from patient travel between the two centres. As the total number of patients treated at the satellite centre a year was 1736, over a year about  $103~tCO_2e$  was saved due to reduced travel to/from the satellite centre compared with the main centre.

This result can be tested for resilience to changed circumstances. For example, if everyone had travelled in an average battery electric car (0.0514 kgCO<sub>2</sub>e per km) instead of an average petrol car the saving would be 31 tCO<sub>2</sub>e per year. At the other end, if everyone had travelled in a  $4 \times 4$  (0.202 kgCO<sub>2</sub>e per km) the saving would be 123 tCO<sub>2</sub>e per year. If we still assume that all patients travel in an average petrol car but the total number of patients drops by 20 % from 1736 to 1389, the total saved per year drops to 82.3 tCO<sub>2</sub>e per year, if it were to increase by 20 % to 2082 the saving would be 123.5 tCO2e per year. Combining these scenarios so we have the lowest scenarios (20 % less patients and all travel by electric car) and highest scenarios (20 % more patients and all travel by  $4 \times 4$ ). The lowest scenario would give a saving per year of 25 tCO<sub>2</sub>e and the highest scenario would give a saving of 147 tCO<sub>2</sub>e per year. A potentially more realistic scenario whereby 5 % of people travel by electric car [16] and there was a 5 % increase in patient numbers [17] would put the value nearer 104 tCO2e per year, which is very close to the original value.

## 3.2. Carbon footprint of staff travel

In total 21 staff members responded, including 10 radiographers, 7 physicists, 3 clinicians and 1 admin staff member. The distance between staffs' homes and the Salford centre ranged between 2.3 and 44.2 km, whereas for Withington this ranged between 1.0 and 57.8 km. The mode of transport was broken down such that 66 % used a car, 9.5 % used either a bike, electric car or tram/train, with 1 person (4.7 %) walking to the satellite centre. The values were similar for the main centre; 62 % by car, 14 % walked, 9.5 % used either an electric car or bike and 1 person took the bus. Once the number of days working at the satellite centre per week were included the mean carbon footprint from staff travel due to

the satellite was  $13 \text{ kgCO}_2\text{e}$  (0.2 to  $47.7 \text{ kgCO}_2\text{e}$ ) per week. If all these staff were to work those days at the main site instead the mean carbon footprint would be  $20.6 \text{ kgCO}_2\text{e}$  (0.07 to  $59.1 \text{ kgCO}_2\text{e}$ ) per week.

Looking at just the staff that work at the satellite 3 or more days a week shows that the total distance all the staff that responded travelled was 101.8 km to the satellite centre which would have been 163.7 miles if they had worked at the main centre.

## 3.3. Carbon footprint of the building

The results of the two methods for estimating for the carbon footprint of the building are show below.

Method 1

The main part of the satellite centre is  $54.3 \text{ m} \times 25.8 \text{ m}$ , equivalent to  $37.4 \text{ m}^2$ , whereas the average house is  $8.7 \text{ m}^2$ . Scaling up from a house to the centre gives a factor of 18.6. As the carbon footprint for a house is  $53 \text{ tCO}_2$ e the gives a value of  $975.8 \text{ tCO}_2$ e for the main body of the satellite centre. The two linac bunkers have a volume of about  $333 \text{ m}^3$ , if the density of concrete is  $2400 \text{ kg/m}^3$  the mass of concrete in the bunkers would be 798,720 kg, giving a carbon footprint of  $127.3 \text{ tCO}_2$ e in the linac bunkers. This gives a total for the building of  $1103.2 \text{ tCO}_2$ e using method 1. As the average amount of carbon footprint saved per year due to reduced patient travel is  $103 \text{ tCO}_2$ e (9.3 % a year), this means that the carbon footprint of building the centre would offset within 10 years. Using the lowest and highest scenarios from Section 3.1, this would give a range of between 44 and 7.5 years, 10.6 years for the more realistic scenario.

Method 2

The total volume of construction material was estimated to be  $3156.6~\mathrm{m}^3$ , giving a total mass of 6213.6 tonnes. Multiplying this by the conversion factor for average construction material gives a carbon footprint of  $491.3~\mathrm{tCO_{2}e}$  for the main body of the satellite centre. As before the two linac bunkers have a carbon footprint of  $127.3~\mathrm{tCO_{2}e}$  in the linac bunkers. This gives a total for the building of  $618.7~\mathrm{tCO_{2}e}$  using Method 2. As the average amount of carbon footprint saved per year due to reduced patient travel is  $103~\mathrm{tCO_{2}e}$  (16.6~% a year), this means that the carbon footprint of building the centre would offset within  $5.6~\mathrm{years}$ . Using the lowest and highest scenarios from Section 3.1, this would give a range of between  $24.7~\mathrm{and}~4.2~\mathrm{years}$ ,  $5.9~\mathrm{years}$  for the more realistic scenario.

## 4. Discussion

For the first time this study has estimated the carbon footprint of building a satellite centre and how this, through reducing patient travel, can lower the carbon footprint of the service within a decade or two. The need for work like this has been highlighted in several articles calling for action within radiation oncology [18,19].

Previous work has shown that patient travel is the dominating factor when estimating the carbon footprint of radiotherapy [7–9]. It has also been shown that an increase in the use of hypofractionation during the first stages of the COVID pandemic was responsible for a 32 % reduction in the carbon footprint of patient travel, with virtual care making up the rest [9]. The results here show that there is between a 7–13 % saving due to reduced travel. Unlike a move to hypofractionation, however, this requires a large investment and large initial carbon footprint, which takes around 7–13 years to offset with the reduction in patient travel.

It should also be noted that the carbon footprint estimates of the buildings include the carbon due to the provision of concrete linac bunkers at the satellite centres. It may also be argued that the bunkers would be needed even without using a satellite, but located at the main centre. While the carbon footprint of the bunkers is significant (more than  $100\ tCO_2e$ ), it is not the major component of the building footprint. In this scenario, the results constitute "worst case" (that is, longest) times to offset the building emissions for a satellite.

The estimation of the effect of changes in staff travel due to the new

satellite centre have potentially excluded roles such as cleaning staff and wider administrative staff as well as any staff moving between the two centres during the work day. In addition, this work does not make an estimate for the duplication of equipment at the satellite. It is possible that some facilities (patient reception, waiting areas, and clinic rooms) as well as some equipment (for example, mirrored servers) will be provided that would not be needed if the linac were instead built at the main centre. The impact of this is expected to be relatively small, and also will distort the results in the opposite direction to the possible overestimation of bunker construction emissions.

Potential scenarios have been modelled to show a range in the time it would take to offset the building of a new small centre with 2 linacs. However, the largest uncertainty is likely to be in the estimation of the carbon footprint of the building of the centre itself. Due to the complex nature of building a new centre and the many factors that go into it, for example new equipment, transport of the materials and construction staff, this is very much an initial estimate. More detailed work involving detailed lists of the quantity of each material used, where they were sourced from and how they were transported would be needed to give an exact value. This work is undoubtedly needed but by using two methods to estimate the carbon footprint of construction, it should provide a good initial estimate.

Due to variability in the size of centres, the patient catchment area and available modes of transport and similar concerns for staff travel, it is unlikely that this work will be accurately generalisable to other centres. However, once again, it will provide a reasonable initial value for most purposes, and provides a methodology which could be used to model equivalent scenarios for other centres which are considering the environmental aspects of a business case for a satellite centre.

Satellite centres are likely to have other benefits too, for example reduced patient travel is likely to benefit patients through reduced travel costs and less time spent travelling for treatment, potentially missing less work or leisure time. Even though this is only an initial investigation into the effect satellite centres could have on reducing the carbon footprint of EBRT, it may still provide enough additional motivation and information for centres thinking about building a satellite centre. It is important that careful planning for new centres be based on, for example, detailed cancer prevalence data and future predictions so that these centres are used to their full capacity, otherwise the estimated benefits of the new centre may not be met. It would also be important for this geographical location and distribution of new centres to be determined on a national level so that it can be fully optimised and new staff and patient distributions accounted for.

With an expected increase in cancer incidence in the coming decade [20] mostly due to a growing and ageing population, it is likely that more linacs, and associated bunkers and buildings will be required. If these are needed anyway then it makes sense to put them nearer patients and to a certain extent this negates the carbon footprint of building the bunker and acquiring the linac as it would have happened anyway, just at the main centre.

## 5. Conclusion

Due to reduced patient travel to a satellite centre rather than to the main centre, the construction of the satellite centre and associated carbon footprint can be offset, in this case within a decade. This may further motivate centres to build smaller centres nearer to hard-to-reach populations in their catchment area.

## **Funding**

None.

## **Ethical approval**

Not required.

## **Declaration of Competing Interest**

None declared.

## Acknowledgments

RC would like to thank the staff from The Christie satellite centre in Salford who responded to the staff travel email, and to Phill Cooper, Gerry Lowe and Shaun Atherton for additional information and help. RC would like to acknowledge the support of Cancer Research UK Manchester Centre award [CTRQQR-2021\100010].

### References

- [1] P. Stott, How climate change affects extreme weather events, Science 352 (2016) 1517–1518, https://doi.org/10.1126/science.aaf7271.
- [2] J. Ballester, M. Quijal-Zamorano, R. Fernando Méndez Turrubiates, F. Pegenaute, F.R. Herrmann, J.M. Robine, et al., Heat-related mortality in Europe during the summer of 2022, Nat. Med. 29 (2023) 1857–1866, https://doi.org/10.1038/ s41591-023-02419-z
- [3] I. Tennison, S. Roschnik, B. Ashby, R. Boyd, I. Hamilton, T. Oreszczyn, et al., Health care's response to climate change: a carbon footprint assessment of the NHS in England, Lancet Planet. Health 5 (2021) e84–e92, https://doi.org/10.1016/ s2542-5196(20)30271-0.
- [4] Greener N.H.S., https://www.england.nhs.uk/greenernhs/; 2022 [accessed 8th January 2022].
- [5] Cancer Research UK 2011 Radiotherapy—the Unsung Hero of Cancer Treatment, 2022. https://news.cancerresearchuk.org/2011/01/28/radiotherapy-the-uns ung-hero-of-cancer-treatment/ [accessed 16th March 2022].
- [6] G. Delaney, S. Jacob, C. Featherstone, M. Barton, The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines, Cancer 104 (6) (2005) 1129–1137, https://doi.org/10.1002/ cncr.21324.
- [7] R. Chuter, C. Stanford-Edwards, J. Cummings, C. Taylor, G. Lowe, E. Holden, et al., Towards estimating the carbon footprint of external beam radiotherapy, Phys. Med. (2023) 112, https://doi.org/10.1016/j.ejmp.2023.102652.
- [8] N.J. Coombs, J.M. Coombs, U.J. Vaidya, J. Singer, M. Bulsara, J.S. Tobias, et al., 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 (2016), e010703, https://doi.org/10.1136/bmicneg.2015.010703
- [9] R. Cheung, E. Ito, M. Lopez, E. Rubunstein, H. Keller, F. Cheung, et al., Evaluating the short-term environmental and clinical effects of a radiation oncology department's response to the COVID-19 pandemic, Int. J. Radiat. Oncol. Biol. Phys. 115 (2023) 39–47, https://doi.org/10.1016/ji.ijrobp.2022.04.054.
- [10] Myhre, G., D. Shindell, F.M. Bréon, W. Collins, J. Fuglestvedt, J. Huang, D. Koch, J. F. Lamarque, D. Lee, B. Mendoza, T. Nakajima, A. Robock, G. Stephens, T. Takemura and H. Zhang. Anthropogenic and natural radiative forcing supplementary material, p 29. In: Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel On Climate Change [Stocker, T.F., D. Qin, G.-K. Plattner et al. (eds.)]. Available from www.climatechange2013.org and www.ipcc.ch.
- [11] N.C. Onat, M. Kucukvar, Carbon footprint of construction industry: a global review and supply chain analysis, Renew. Sustain. Energy Rev. 1 (124) (2020), 109783, https://doi.org/10.1016/j.rser.2020.109783.
- [12] Department of Business, Energy and Industrial Strategy (2022). https://www.gov. uk/government/publications/greenhouse-gas-reporting-conversion-factors-2022. (Accessed 18 July 2023).
- [13] M. Berners-Lee. How Bad Are Bananas?: the Carbon Footprint of Everything, London: Profile Books, 2020.
- [14] The AA: Mileage Calculator https://www.theaa.com/route-planner/route . (Accessed 21 April 2023).
- [15] Shrink That Footprint, https://shrinkthatfootprint.com/how-big-is-a-house/. (Accessed 18 July 2023).
- [16] The Eco Experts, Electric Vehicle Statistics 2023, https://www.theecoexperts.co. uk/electric-vehicles/ev-statistics. (Accessed 6 October 2023).
- [17] Macmillan Cancer Support, https://www.macmillan.org.uk/dfsmedia/1a6f235 37f7f4519bb0cf14c45b2a629/9468-10061/2022-cancer-statistics-factsheet; October 2022. (Accessed 6 October 2023).
- [18] R. Chuter, G. Lowe, N. Dickinson, Curing a malignant climate, Clin. Oncol. 34 (2022) 148–150, https://doi.org/10.1016/j.clon.2021.12.018.
- [19] K.E. Lichter, K. Charbonneau, A. Sabbagh, A. Witztum, R. Chuter, C. Anand, et al., Evaluating the environmental impact of radiation therapy using life cycle assessments: a critical review, Int. J. Radiat. Oncol. Biol. Phys. 117 (2023) 554-567
- [20] C.R. Smittenaar, K.A. Petersen, K. Stewart, N. Moitt, Cancer incidence and mortality projections in the UK until 2035, Br. J. Cancer 115 (2016) 1147–1155, https://doi.org/10.1038/bjc.2016.304.