



Original Article

The Financial Impact on Reimbursement of Moderately Hypofractionated Postoperative Radiation Therapy for Breast Cancer: An International Consortium Report



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Abstract

Aims: Moderately hypofractionated breast irradiation has been evaluated in several prospective studies, resulting in wide acceptance of shorter treatment protocols for postoperative breast irradiation. Reimbursement for radiation therapy varies between private and public systems and between countries, impacting variably financial considerations in the use of hypofractionation. The aim of this study was to evaluate the financial impact of moderately hypofractionated breast irradiation by reimbursement system in different countries.

Materials and methods: The study was designed by an international group of radiation oncologists. A web-questionnaire was distributed to representatives from each country. The participants were asked to involve the financial consultant at their institution.

Results: Data from 13 countries from all populated continents were collected (Europe: Denmark, France, Italy, the Netherlands, Spain, UK; North America: Canada, USA; South America: Brazil; Africa: South Africa; Oceania: Australia; Asia: Israel, Taiwan). Clinicians and/or departments in most of the countries surveyed (77%) receive remuneration based on the number of fractions delivered to the patient. The financial loss per patient estimated resulting from applying moderately hypofractionated breast irradiation instead of conventional fractionation ranged from 5–10% to 30–40%, depending on the healthcare provider.

Conclusion: Although a generalised adoption of moderately hypofractionated breast irradiation would allow for a considerable reduction in social and economic burden, the financial loss for the healthcare providers induced by fee-for-service remuneration may be a factor in the slow uptake of these regimens. Therefore,

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fee-for-service reimbursement may not be preferable for radiation oncology. We propose that an alternative system of remuneration, such as bundled payments based on stage and diagnosis, may provide more value for all stakeholders.

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Key words: Breast cancer; health economics; hypofractionation; radiation therapy; reimbursement

Introduction

The burden of cancer is increasing as a result of several factors, including an aging population. Even though there is international variation in breast cancer incidence and mortality between countries, breast cancer remains the most frequent cancer and the most common cause of cancer death in women internationally [1].

Breast cancer accounts for the highest healthcare expenses in the European Union [2]. Expenses are mostly from breast cancer medication costs. However, screening programmes, diagnostic procedures, other treatments modalities and other care costs, together with the productivity lost (e.g. time lost to the patient from work in order to receive treatments), significantly contribute to the economic burden posed by breast cancer [3].

In the curative setting, postoperative radiation therapy for breast cancer has been shown in systematic reviews and meta-analyses of prospective trials to reduce the locoregional relapse rate and to increase survival rates [4,5]. Previously, postoperative breast radiation therapy was given over a period of 5–6 weeks (total radiation therapy dose of 50–50.4 Gy in 1.8–2 Gy per fraction). In recent decades, moderately hypofractionated breast radiation therapy regimens have used slightly larger daily radiation therapy fraction sizes (e.g. 2.5–3.0 Gy), with reduced total dose and over a shorter period of time (e.g. 3 weeks), designed to achieving similar clinical outcomes to conventionally fractionated regimens [6,7]. Long-term follow-up in large randomised phase III trials supported the safety and efficacy of the hypofractionation protocols compared with 1.8–2 Gy fractionations [8,9]. Adoption of hypofractionation for breast cancer can reduce the burden of treatment, with significant implications for health economics and services. Shorter treatment protocols reduce the case load at radiation therapy units and of the treating teams, thus freeing up resources for more patients. It can also decrease indirect costs associated with patient's daily travelling and work disruptions (loss of productivity) and reduce other unaccounted for treatment-related costs [10].

Despite there being high-level evidence to support the use of hypofractionation-based radiation therapy for breast cancer, together with significant financial benefits for health economics, it has not been adopted in many countries [11]. This might be explained because the adoption of shorter treatment regimens in the proportionally important breast cancer patient population substantially reduces radiation therapy activity, which could result in a financial loss depending on the reimbursement system. On the other hand, the adoption of shorter treatment regimens may have a

significant beneficial impact on health economics by creating space for other treatments and decreasing waiting times.

The aim of this study was to calculate the financial impact of adopting moderately hypofractionated breast radiation therapy in different reimbursement systems and to provide data and proposals on how to overcome financial barriers to adopting hypofractionated radiation therapy for breast cancer patients.

Materials and Methods

This study was designed by an international consortium of radiation oncology experts. Data regarding costs and reimbursement issues related to moderately hypofractionated postoperative radiation therapy for breast cancer patients were collected from countries in all continents. A summary of these data was distributed to all experts in breast cancer care to facilitate a discussion about the use of hypofractionation for different curative settings of postoperative breast radiation. Thereafter, a web-questionnaire was designed to collect specific and relevant data to assess current reimbursement systems per country. This instrument included several variables that could be related to reimbursement calculation. If a variable was not applicable for the reimbursement calculation, it was described as 'not applicable'.

Data concerning reimbursement systems as applied in the contributors' countries were collected. Depending on the organisation of healthcare per country, the information is in general valid for a healthcare region or an entire country.

The reimbursement systems and the influence of hypofractionation-based radiation schedules on revenue were evaluated from both public and private (when applicable) practice perspectives. Basically, the two mainstream reimbursement systems are 'fee-for-service' (most systems are based on payment per fraction of radiation therapy) and the 'global (lump sum/fixed fee)' method. Therefore, we divided the observed worldwide variance of reimbursement systems into two groups: separate fees per activity (fee-for-service) or lumpsum for the entire treatment (fixed fee).

In the case of per fee-for-service, information about reimbursement fees was collected for two-dimensional (radiation therapy) treatment planning, three-dimensional conformal radiation therapy planning, intensity-modulated radiation therapy (IMRT) planning, per fractionation, per treatment week and for on-treatment physician visits. Information was provided by the authors of this study in collaboration with their local institutional financial departments or national policies. As the relative value of euro and dollar varies by only 10%, we did not recalculate into one single currency and assume this as unity.

Results

In total, data from 13 countries were collected (Europe: Denmark, France, Italy, the Netherlands, Spain, UK; North America: Canada, USA; South America: Brazil; Africa: South Africa; Oceania: Australia; Asia: Israel, Taiwan). Within Canada and Italy, where healthcare is managed on a provincial level, the provinces of Nova Scotia and Quebec, and Tuscany and Lombardy reported data separately. The number of fractions influenced reimbursement in most countries (77%). The corresponding revenue loss generated by the reduction in per-patient income from applying a hypofractionation-based schedule ranged from 5–10% to

30–40% (Table 1). When a revenue loss occurred, most countries (60%) reported a loss of 30–40% (Figure 1).

A variety of reimbursement systems exist in the evaluated countries. From the public sector perspective, in most countries (Australia, Canada – Quebec, Israel, Italy, Spain, Taiwan, UK and USA), reimbursement differs based on treatment planning technique; only three countries do not differentiate between IMRT planning and three-dimensional conformal radiation therapy planning (Denmark, Canada – Nova Scotia and France). Similarly, for all countries that have private practice, IMRT planning is related to higher reimbursement. Tables 2 and 3 summarise the reimbursement practice (per activity separately and per

Table 1

Basis of reimbursement and the potential influence of moderately hypofractionated radiation schedules on revenue

Country	Perspective	Base of reimbursement	Is there an influence of the total number of fractions on reimbursement?	Economic deficit generated by the reduction in income per-patient from applying a hypofractionation-based schedule
Australia	Public practice	Separate fees per activity	No	NA
	Private Practice	Separate fees per activity	No	NA
Brazil	Public practice	Lump sum for the entire treatment (fixed fee)	No	NA
	Private practice	Lump sum for the entire treatment (fixed fee)	No	NA
	Private practice	Separate fees per activity	Yes	10–20%
Canada (Quebec)	Public practice	Separate fees per activity	Yes	5–10%
	Private Practice	NA	NA	NA
Canada (Nova Scotia)	Public practice	Lump sum for the entire treatment (fixed fee)	No	NA
	Private Practice	NA	NA	NA
Denmark	Public practice	Separate fees per activity	Yes	30–40%
	Private Practice	NA	NA	NA
France	Public practice	Separate fees per activity	Yes	30–40%
	Private Practice	Separate fees per activity	Yes	30–40%
Israel	Public practice	Separate fees per activity	Yes	30–40%
	Private practice	Separate fees per activity	Yes	NA
Italy (Tuscany Region)	Public practice	Separate fees per activity	Yes	30–40%
	Private Practice	Separate fees per activity	Yes	30–40%
Italy (Lombardy)	Public practice	Separate fees per activity	Yes	30–40%
	Private Practice	Separate fees per activity	Yes	30–40%
The Netherlands	Public practice	Lump sum for the entire treatment (fixed fee)	No	No
	Private Practice	NA	NA	NA
South Africa	Public practice	Lump sum for the entire treatment (fixed fee)	No	NA
	Private Practice	Separate fees per activity	Yes	30–40%
Spain	Public practice	Lump sum for the entire treatment (fixed fee)	No	NA
	Private practice	Lump sum for the entire treatment (fixed fee)	No	NA
Taiwan	Public practice	Separate fees per activity	Yes	20–30%
	Private Practice	Separate fees per activity	Yes	20–30%
UK	Public practice	Separate fees per activity	Yes	30–40%
	Private Practice	Separate fees per activity	Yes	30–40%
USA	Public practice	Separate fees per activity	Yes	20–30%
	Private Practice	Separate fees per activity	Yes	20–30%

NA, not available.

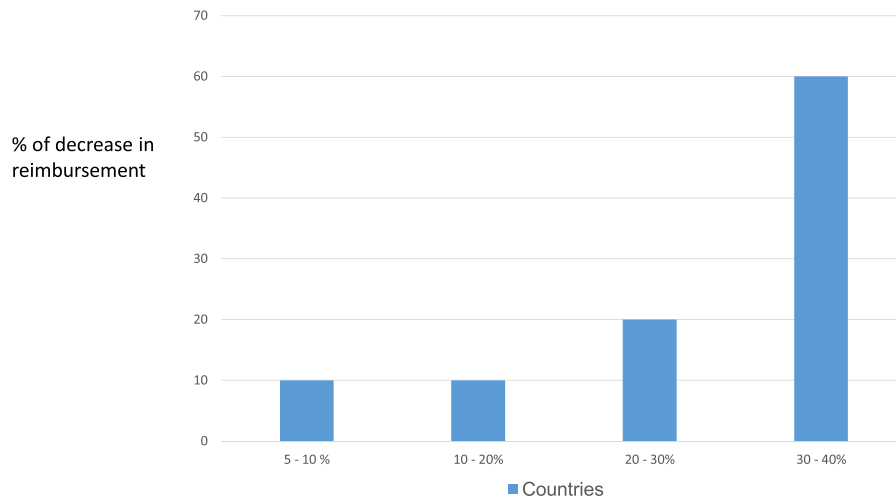


Fig 1. Decrease in remuneration generated by the reduction in per-patient reimbursement from applying a hypofractionation-based schedule compared with conventional fractionation.

lumpsum for the entire treatment) from the public and private perspective, respectively.

Discussion

To the best of our knowledge, this is the first study reporting the financial impact of worldwide radiation therapy reimbursement systems on the use of moderately hypofractionated postoperative radiation therapy for breast cancer patients. As breast cancer treatment makes up about 25% of the activities of most radiation oncology departments, a relative financial loss by introducing moderate hypofractionation for breast cancer immediately translates into a major reduction of overall revenues.

In general, a radiation therapy budget is expected to make up just 5% of yearly cancer care costs and therefore denotes less than 1% of the total healthcare budget [3,12]. To achieve the all-purpose aims of healthcare, there are several methods and tools that can be considered, such as quality, availability, acceptability and accessibility and, based on these, legislation and organisational models are created [13]. The definition of healthcare reimbursement systems involves the concept of the mode by which money is given to the care provider by healthcare customers [14]; suppliers can be institutional (e.g. hospitals), individual (e.g. physicians) or both combined. Although treatment costs and reimbursement are frequently used interchangeably to arrange the background for financial platforms and upcoming assets, it is essential to differentiate reimbursement, which is the consequence of compromises between payers and healthcare suppliers, from costs, which are related to real resource consumption [15,16]. The form of reimbursement implemented in a nation provides insight into how the healthcare system offers remuneration for particular treatments [14].

Assessing the costs of radiation therapy is not a simple task and the features and structures available in each country should be considered [16–19]. In the Health

Economics in Radiation Oncology (HERO) - European Society for Radiotherapy and Oncology (ESTRO) study, 52 articles were analysed regarding the type and quality of radiation therapy cost, revealing that cost-calculation studies from the healthcare provider's standpoint still need a robust instrument for measuring radiation therapy costs. The results of methodologically all-encompassing cost studies indicate that the inadequate use of conventional cost-evaluation methods combined with the unsatisfactory data on resource inputs, has hampered comparability across published papers [16].

The cost of radiation therapy is often associated with the necessary investments in infrastructure and high-priced equipment. Radiation therapy equipment capable of more complex treatments such as IMRT require a higher capital expenditure related to both investment and maintenance than those capable of more basic treatments, and this cost is reflected in the higher remuneration to providers for using these techniques. Nevertheless, due to the labour-intensive task of technical planning and radiation therapy treatment delivery, the models of cost estimation show that the costs of salaries noticeably exceed those of equipment [10,12,20,21]. When radiation therapy complexity increases, additional costs are incurred to allow for treatment preparation, contemplation of delivery time and quality assurance [22]. It is not surprising, therefore, that radiation therapy costs are also determined by the total treatment period, such that reducing the number of fractions can have a meaningful impact [3,23].

The total cost of radiation therapy includes various components, including the costs of treatment-related activities, hospital overheads and social costs (Figure 2). For breast cancer patients, some cost components are the same for all treatments; for instance, the same radiation therapy technique is generally applied for the entire duration of the treatment regardless of the dose schedule. It is important to highlight that the time freed up can be used to increase the throughput of patients and reduce waiting lists. The time

Table 2

Public practice. Reimbursement practice – per activity separately and per lump sum for the entire treatment

Country	Per activity separately						Lump sum for the entire treatment		
	2D treatment planning	3D-CRT planning	IMRT planning	Per fraction	Per treatment week	For on-treatment physician visits	Whole treatment series all-in	Treatment series only radiation therapy fractions	Treatment series treatment planning
Australia (dollar)	66.55 –564.15	591.65 –1055.30	3283.45	224.20 (per IMRT fraction)	638.50 (simulation)	NA	NA	NA	NA
Brazil (dollar)	NA	NA	NA	NA	NA	NA	1512	NA	NA
Canada – Quebec (dollar)	NA	508.75	839.8	NA	18.15	20.15	NA	NA	NA
Canada – Nova Scotia (dollar)	530	530	530	294	1470	404	8070	2430	530
Denmark (euro)	NA	1620	1620	413	NA	NA	NA	NA	NA
France (euro)	450	1028	1128	186 395 (‘dedicated’ machine)	NA	NA	NA	NA	NA
Israel (dollar)	NA	7710	21 923	434 (3D) 1046 (IMRT)	2168 (3D) 5232 (IMRT)	NA	NA	NA	NA
Italy – Tuscany region (euro)	194	608	877	1500 (HF-WBI) 2250 (C-WBI)	375	22 (each)	2108 (HF-WBI) 2258 (C-WBI)	1500 (HF-WBI) 2250 (C-WBI)	608
Italy – Lombardy region (euro)	72.85	306.60	586.52	72.52 (3D) 154.32 (IMRT)	362.60 (3D) 771.6 (IMRT)	17.90 (each)	2088	1440	600
The Netherlands (euro)	NA	NA	NA	NA	NA	NA	NA	6954.87 10 122.34 (with respiratory control)	1163.82
South Africa (euro)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Spain (euro)	861.31	2430.20 –3679.16	3679.16	NA	NA	NA	2430.2 (3D) 3679.16 (IMRT)	NA	NA
Taiwan (dollar)	NA	300	600	200	1000	8	5000	4000	1000
UK (pound)	410.38	794.64	1383.93	158.93	NA	100	NA	NA	NA
USA (dollar)	NA	6150	8160	226 (3D) 524 (IMRT)	NA	199 per five fractions	NA	NA	NA

2D, two dimensional; 3D-CRT, three-dimensional conformal radiation therapy; C-WBI, conventional whole-breast irradiation; HF-WBI, hypofractionated whole-breast irradiation; IMRT, intensity-modulated radiation therapy; NA, not applicable.

made available could be invested in innovative and more time-consuming treatment approaches, including radical treatment for oligometastases. Thereby, the total cost diminishes with a reduction of the number of fractions. From an Australian perspective [24], the financial impact of using hypofractionated post-mastectomy radiation therapy is a cost reduction of over \$2000 per patient. Similarly, in a US assessment, the per-case marginal reduction of the hypofractionated schedule was \$4297 for breast cancer patients

[11]. The social-cost perspective should also be part of this discussion. In the US context, Suh *et al.* [25] estimated the costs of transportation using the average number of miles moved per day, the average reimbursement rate per mile and the parking costs. Using the national average hourly wage for 55- to 64-year-old US women as a reference, the authors calculated the number of hours spent during treatment and displacement. Unsurprisingly, these non-direct medical costs were evidently associated with the

Table 3

Private practice. Reimbursement practice – per activity separately and per lump sum for the entire treatment

Country	Per activity separately						Lump sum for the entire treatment		
	2D treatment planning	3D-CRT planning	IMRT planning	Per fraction	Per treatment week	For on-treatment physician visits	Whole treatment series all-in	Treatment series only radiation therapy fractions	Treatment series treatment planning
Australia (dollar)	66.55 –564.15	591.65 –1055.30	3283.45	224.20 (per IMRT fraction)	638.50 (simulation)	NA	NA	NA	NA
Brazil (dollar)	NA	NA	NA	NA	NA	NA	5800 (3D) 7572 (IMRT)	NA	NA
Canada – Quebec (dollar)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Canada – Nova Scotia (dollar)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Denmark (euro)	NA	NA	NA	NA	NA	NA	NA	NA	NA
France (euro)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Israel (dollar)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Italy – Tuscany region (euro)	194	608	877	1500 (HF-WBI) 2250 (C-WBI)	375	22 (each)	2108 (HF-WBI) 2258 (C-WBI)	1500 (HF-WBI) 2250 (C-WBI)	608
Italy – Lombardy region (euro)	94.71	398.58	763.78	94.33 (3D) 200.62 (IMRT)	471.65 (3D) 1003.1 (IMRT)	23.27 (each)	2610	1800	810
The Netherlands (euro)	NA	NA	NA	NA	NA	NA	NA	NA	NA
South Africa (euro)	588	1265	2700	474	814	0	NA	NA	NA
Spain (euro)	1500	1500 –3600	5500	NA	NA	NA	1500–3600 (3D) 5500 (IMRT)	NA	NA
Taiwan (dollar)	NA	300	600	200	1000	8	5000	4000	1000
UK (pound)	2400	2700	3635	550	NA	NA	NA	NA	NA
USA (dollar)	NA	7380 –9225	9792 –12240	271–339 (3D) 629–786 (IMRT)	NA	239–298 per five fractions	NA	NA	NA

2D, two dimensional; 3D-CRT, three-dimensional conformal radiation therapy; C-WBI, conventional whole-breast irradiation; HF-WBI, hypofractionated whole-breast irradiation; IMRT, intensity-modulated radiation therapy; NA, not applicable.

total treatment period (i.e. the number of fractions) and shorter total treatment times were advantageous [25]. A study from Ontario, which has a socialised healthcare system, showed that for whole-breast irradiation, patients were bearing 37% of the treatment cost because of the daily commute to the hospital [26].

In addition to the evident benefit of hypofractionation on costs [3,27], it is important to review the reimbursement system in an overall evaluation of institutions before adopting shorter schedules as practice. Konski *et al.* [11] showed the consequences in terms of costs and reimbursement when a US radiation oncology department used hypofractionation for most common tumours, thus exploiting Medicaid- and Medicare-qualified unit values

and reimbursement rates. The relative value unit for 2015 was used to establish any alterations in reimbursements. The variation in the total number of fractions was adjusted to measure the consequences in terms of staff time, machine capacity and workforce predictions. The results indicated that if 100 breast cancer patients are treated with shorter schedules, hospital-based technical billing due to hypofractionation would be reduced by \$429 699.98. The per-case marginal reduction for each physician was 10.44 relative value units, representing a decrease of 1044 relative value units for each 100 breast cancer patients who receive hypofractionation. Hence, considering these US-based cost calculations, an increase in hypofractionation prescription over conventional fractionation

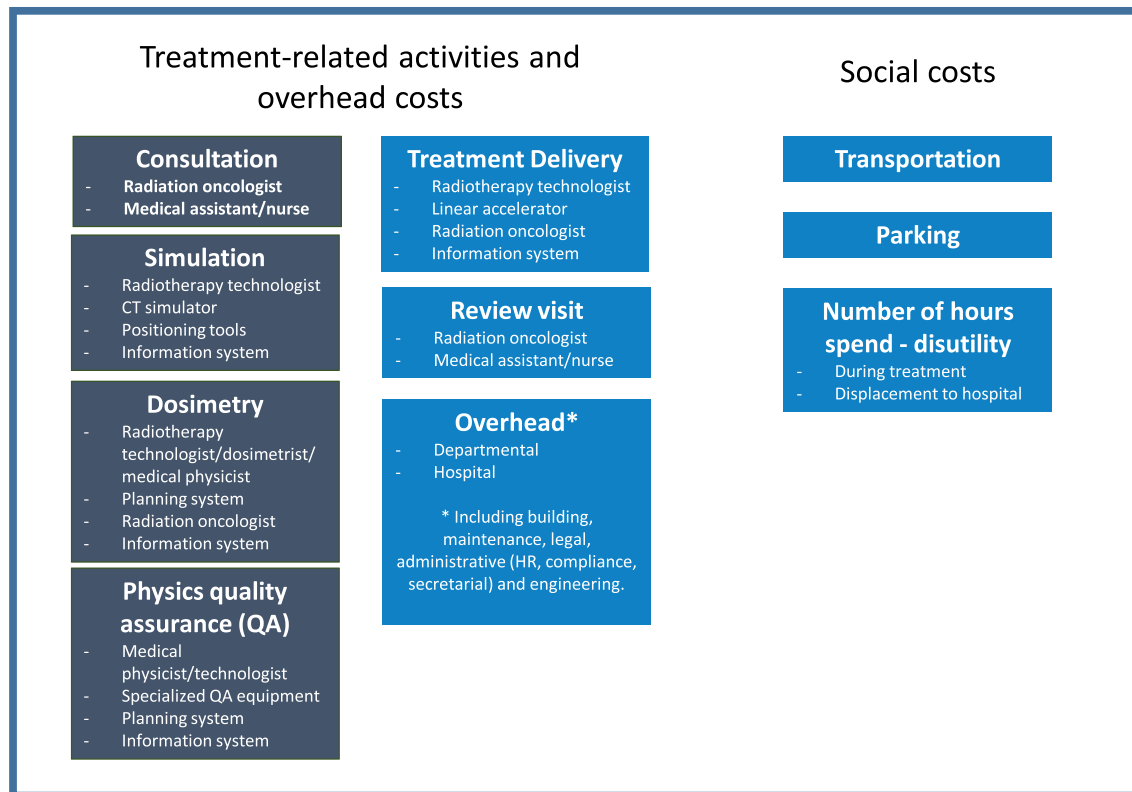


Fig 2. Costs of treatment-related activities, hospital overheads and social costs.

will decrease the demand on radiation oncology departments, which will then have to deal, at least on the short to intermediate term, with financial losses resulting from a reduction in per-patient income in fractionation-based reimbursement arrangements.

This study shows that although reimbursement practices differ across public and private institutions and between countries, the financial loss from a reduction in per-patient income due to the use of a hypofractionation-based schedule is substantial and quite similar across payment systems and countries (Table 2, Figure 1). It is important to highlight that the reimbursement information was provided by the authors of this study. Although there may be even more variation when also taking not-evaluated medical services into account, the retrieved data serve as the basis for an overview of reimbursement amounts for each country across public and private practices in Europe, the Americas, Africa, Asia and Oceania. Moreover, the results of this study are in agreement with a recent report from the HERO-ESTRO group that analysed the reimbursement of public health radiation therapy services in Europe [15]. Moreover, as illustrated in Tables 2 and 3, reimbursement is not only based on the number of fractions but also on the complexity of the technique used, wherein complex treatment planning is generally associated with higher reimbursement fees.

Reimbursement of treatment planning and treatment delivery may depend on a number of other factors that vary between countries: complexity of delivery, image guidance,

respiratory control, etc. The introduction of new techniques and/or modalities in radiation oncology is most often translated into the 'level of complexity'. With fractionation being the main factor in most fee-for-service systems and other co-variables adding up to a huge number of possible combinations, we focused solely on the effect of hypofractionation. Healthcare reimbursement is adapted, depending on the country, at intervals varying between annually up to exceeding a decade.

The objective to provide reliable, safe and high-quality radiation therapy while minimising both acute and late side-effects is related to optimal treatment planning and delivery, independent of the fractionation schedule used. By contrast, the antiquated system of paying by fraction number is nonsensical and counterintuitive, hampering the introduction of evidence-based shorter therapy schedules. Very recently, the first tumour outcome-related end point evaluation from the FAST Forward trial was published [28,29], which proposed a schedule of just five fractions in 1 week. If a moderately hypofractionated schedule is replaced for many patients in the coming years by a 5 fractions in 1 week schedule, it will demand much more robustness of RT treatment planning and delivery. These few fractions could hence cost more per fraction (due to the more complex verification) than conventional fractionation and moderate hypofractionation to plan and deliver. Thus, it is important to propose a better remuneration system based on complexity rather than one so heavily influenced by fraction number.

The best solution to this impasse is probably to introduce improved and optimised reimbursement and healthcare delivery systems. Recently, scholars worldwide have examined various delivery and payment models, including those that are evolutions of the fee-for-service system [30]. Optimal alternative payment systems aim at enhancing clinical outcomes and decreasing both consumption and costs. To maximise outcomes, the model (value-based) intervention ought to be focused on improving the equilibrium between cost and healthcare quality. The value-based payment concept — in which healthcare consumers and payers maintain the distribution system that is largely responsible for both costs and quality of care — is one of the most studied models, and it promises to have a positive impact in this framework. However, it is important to recognise that, notwithstanding the advances of alternative payment systems, there is still limited evidence regarding the efficacy of these reimbursement models; this issue requires further debate before practical implementation [31,32].

The financial discussion of the viability of widespread adoption of moderate hypofractionation in breast cancer patients has special importance for countries with limited resources [33–35]. Khan *et al.* [36] evaluated the impact of shorter schedules for breast cancer patients from countries with emerging economies and restricted radiation therapy assets. The implementation of hypofractionation in these emerging economies is not merely an issue of increased cost-effectiveness but also one of improved access to quality healthcare and enhanced patient survivorship. A shift from a conventional schedule to hypofractionation could thereby decrease waiting times and allow more patients to be treated, particularly in systems with restricted funds [37,38].

Finally, the importance of hypofractionation has perhaps never before been clearer than in the current pandemic. The reduction in the number of patient visits to the radiation oncology department by using hypofractionation is particularly important, insofar as this approach limits the risk for disease transmission for both patients and personnel, while at the same time preventing jeopardising the outcomes of cancer intervention [39,40]. Although our study was conducted before the worldwide COVID-19 pandemic, its insights are even more relevant now and for the future. Finally, it is unethical to deny any patient access to evidenced-based moderate breast hypofractionation based on a potential loss of income. Out-dated reimbursement systems need to be re-designed to facilitate implementation of high-quality randomised trial results and reflect complex and quality-assured modern radiation therapy.

Conclusions

Moderately hypofractionated radiation therapy schedules are preferable for breast cancer patients, by decreasing the daily burden linked to travel and disutility following a lower number of treatment fractions, but similar rates of local relapse and often reduced side-effects. Moreover, its widespread adoption will also be beneficial for healthcare systems,

by reducing the workload for both healthcare providers and infrastructure, especially when resources are limited. The possible financial loss induced by the reduction in per-patient income due to fractionation-based reimbursement should be compensated by an evolution of the reimbursement model from a fee-for-service system to a bundled payment system. In this context, the reimbursement systems should be more adaptable based on progress in both knowledge and techniques, and not remain so inert over time. We therefore favour a change in the current fee-for-service model prevalent worldwide, to one which allows for better compensation for increased quality in treatment planning and delivery. The reimbursement amount could then be based on average cost data collected from patients receiving optimal breast radiation therapy. As reimbursement in such a model should be independent of the type of radiation therapy planning and the number of fractions, clinicians may be more inclined to favour moderately hypofractionated treatment schedules and their associated radiation therapy planning. This would improve value for all stakeholders, including doctors, payers and the country's healthcare system, but above all improve the patient experience, which is paramount.

Conflicts of interest

The authors declare no conflict of interest.

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