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Adjuvant breast radiotherapy: How to trade-off cost and effectiveness?

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ABSTRACT

Introduction: A series of health economic evaluations (HEE) has analysed the efficiency of new fractionation schedules and techniques for adjuvant breast radiotherapy. This overview assembles the available evidence and evaluates to what extent HEE-results can be compared.

Methods: Based on a systematic literature review of HEEs from 1/1/2000 to 30/10/2016, all cost comparison (CC) and cost-effectiveness analyses (CEA) comparing different adjuvant breast radiotherapy approaches were analysed. Costs were extracted and converted to Euro 2016 and costs per QALY were summarized in cost-effectiveness planes.

Results: Twenty-four publications are withheld, comparing different fractionation schedules and/or irradiation techniques or evaluating the value of adding radiotherapy. Normofractionation and intensity-modulated, interstitial or intraluminal techniques are important cost-drivers. Highest reimbursements are observed in the US, but may overestimate the real cost. Hypofractionation is cost-effective compared to normofractionation, the results of partial breast irradiation are less unequivocal. Intra-operative and external beam approaches seem the most cost-effective for favourable risk groups, but whole breast irradiation is superior in terms of health effect and omission of radiotherapy in terms of costs.

Conclusion: Hypofractionation may be considered the most relevant comparator for new strategies in adjuvant breast radiotherapy, with omission of radiotherapy as an interesting alternative in the very favourable subcategories, especially for partial breast techniques. Although comparison of CC and CEA is hampered by the variability in clinical and economic settings, HEE-based evidence can guide decision-making to tailor-made strategies, allocating the optimal treatment in terms of effectiveness as well as efficiency to the right indication.

Excellent survival results in early and locally advanced breast cancer allowed to change the treatment paradigm in breast cancer therapy from maximizing cure to awareness for long-term toxicity, quality of life and treatment burden [1].

An evolution from normofractionation to shorter, hypofractionated schedules was made possible through growing evidence on the radio-biologic aspects of breast cancer, indicating a higher sensitivity to fraction dose than originally assumed [2–5]. These schedules have further evolved into extremely accelerated schedules [6,7], and in combination with knowledge on the recurrence patterns of breast cancer and new technological capabilities, have paved the way for accelerated partial breast irradiation (APBI) [8–17].

In healthcare, the development of evidence is built on three core questions, evaluating efficacy, effectivity and efficiency of new approaches.

Efficacy research (can it work?) is confined to the rules of a trial, with strict intake criteria, follow up of compliance and complications and quality check of the providers' interventions. This question has been answered for most of the above-mentioned approaches, although for APBI, be it with post-operative external, intra-operative or peri-operative dose delivery, longer follow up is still awaited [13–15,17,18].

The question on effectivity (does it work?) evaluates if results can be repeated in a real-world setting, under less ideal circumstances. This can be provided by observational research, based on large-scale databases [19]. As an example, a Medicare-based analysis compared brachytherapy-based APBI with standard whole breast irradiation (WBI) for overall survival, complications and mastectomy rates. It found equivalence for survival, but an increase in complications and subsequent mastectomies [20].

But even if a new approach proves effective, additional expenses in healthcare must be worthwhile from the perspective of healthcare payers. This evaluation of efficiency is explored in health economic evaluations (HEE), cost comparisons (CC) inventorying the cost difference of new strategies versus the gold

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standard, and cost-effectiveness evaluations (CEA) comparing the incremental cost to incremental health effects. In HEE, health effects are expressed in natural units, ideally 'life years gained' (LYG) or 'quality adjusted life years' (QALY), factoring in the importance that individuals assign to purely clinical gains. Whereas CCs give a mere representation of the cost, be it resource costs, reimbursement figures or charges, CEAs provide a more complete analysis with the ultimate aim to define whether implementing a new intervention is financially acceptable from a societal perspective. Such societal acceptance can be translated into a 'willingness-to-pay' (WTP), indicating how much a society is prepared to pay per LYG or QALY. This can be a fixed amount, depending on the economic status of a country, or variable, depending on factors such as the societal impact, the illness burden or the innovative nature of the technology [21].

Even with reassuring and robust evidence, implementation of new approaches can be slow, as is observed for hypofractionation [22–27] or on the contrary, can anticipate the evidence, as for APBI, where the need for reassuring long-term results on intra-operative and balloon-based APBI has not impeded its widespread application, within but also outside of clinical trials [28,29]. The answer to this paradox may at least to some extent be ascribed to the conflicting economic impact of these techniques between different stakeholders.

This paper aims at providing a comprehensive overview of the published literature on costs and cost-effectiveness of hypofractionated and accelerated breast radiotherapy, based on a systematic review of the literature. Comparability of data is ascertained by applying monetary conversions, categorization is performed for different radiation techniques and fractionation schedules.

Materials and methods

Publications on HEE of adjuvant breast radiotherapy, published between 1/1/2000 and 31/10/2016, were retrieved through systematic literature review in Medline, Embase and Cochrane databases. The methods are described in a previous publication [30]. From this series, only publications focusing on the cost and cost-effectiveness of adjuvant whole breast irradiation (WBI), post-mastectomy radiotherapy (PMRT) or partial breast irradiation (PBI) were withheld for comparison. Publications were excluded if results could not be related to the specific radiotherapy cost (e.g. if including surgery or systemic therapy cost) or to specific techniques or fractionation schedules (e.g. in large database evaluations, as SEER analyses, based on global charges over different techniques and fractionation schedules).

Comparison of treatment cost

Cost data were extracted from both CCs and CEAs. Direct radiotherapy costs per technique and fractionation schedule are presented, excluding non-medical and indirect costs. The published costs are inflated to the year 2016 (for one article that did not mention a reference year, 2015 was assumed, based on publication date), according to the country-specific Consumer Price Indices (http://fxtop.com/en/inflation-calculator.php) and then converted to Euro, using available conversion factors (www.xe.com/currencytables). Because monetary values are subject to fluctuations, the 31st January of 2016 was chosen as reference date.

Comparison of cost-effectiveness

Data were derived from the CEA publications. Incremental cost-effectiveness is defined as the incremental cost of a new intervention compared to the standard, and divided by the incremental health effect between both interventions, also referred to as incremental cost-effectiveness ratio (ICER) [31]. For the incremental costs, the same technique of inflation and conversion to Euro-2016 was applied as described above. For readability and comparability, only ICERs based on QALYs are presented in this publication, even if the original publication also provided incremental effects in LYG.

Results

Comparison of treatment cost

Twenty-four publications are withheld, 3 based on real-cost exercises [32–34] and 21 on reimbursement or both [24,35–54] (Table 1).

WBI or PMRT is delivered with external beam radiotherapy (EBRT) or more specifically, intensity-modulated radiotherapy (IMRT) and costs are available for normofractionated schedules, with or without a boost (25–35 fractions for EBRT; 28–33 for IMRT) and hypofractionated schedules (EBRT 11–20 fractions; IMRT 16 fractions).

APBI is delivered with EBRT (APBI-EBRT 4–10 fractions) or IMRT (APBI-IMRT 10 fractions), with single-fraction intra-operative radiotherapy (IORT), with post-operative interstitial brachytherapy (APBI-IS) or with balloon-based brachytherapy, applying a single- or a multi-lumen balloon-technique (APBI-balloon, further subdivided in either APBI-SL or APBI-ML). Postoperative intraluminal partial-breast techniques all apply 10 fractions. Two articles, included in the APBI-EBRT group, report the cost of EBRT in 5 fractions for WBI [33,52].

Overall, 81 radiotherapy costs are extracted from these publications, of which 69 are based on reimbursement and 12 on real costs. An overview of the published costs, expressed in €-2016, can be found in Table 1; aggregated data per treatment category (technique and fractionation schedule) and per cost type are presented in Fig. 1. Unsurprisingly, costs increase with the number of fractions, especially when IMRT is applied. Post-operative intraluminal strategies also lead to higher costs. In contrast, the cost of IORT remains low over different reimbursement systems (UK and US-data available), comparable to the cost of APBI-EBRT.

Regional and time-bound factors influence costs. On average, hypofractionated and normofractionated EBRT cost almost twice as much in the US than elsewhere (respectively 7609€ and 11,316€ versus 3649€ and 6670€). Large variability is also observed within the US healthcare system itself: the reimbursement of APBI-IS ranges from 11,709€ to 20,276€; the same goes for balloon-based brachytherapy, with APBI-ML ranging from 13,453€ to 24,141€. From 2011 on, reimbursements drop with almost 25%.

The number of real-cost calculations per radiotherapy technique is too low to draw firm conclusions. Overall, real-life costs seem lower than reimbursement, except for IORT, where reimbursement seems to align with real cost (Fig. 1). However, when costs and reimbursement are compared within the European setting, the opposite may apply, real-life costs exceeding the reimbursement in several countries (Table 1).

Comparison of cost-effectiveness

Fourteen publications were analysed on cost-effectiveness results (Table 2). A fifteenth CEA was not withheld, because aesthetic outcome was used as health effect, hampering comparison with the recommended effects of LYGs and QALYs [50]. Cost-effectiveness results are illustrated in Fig. 2, comparing the cost-effectiveness of radiotherapy versus no radiotherapy in different age- and risk-groups [32,35,37,38,40,49,51] and Fig. 3, comparing different fractionation schedules and radiotherapy techniques (either APBI compared to WBI or inter-comparison of different

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