



# Radiotherapy in breast cancer through a value-based perspective

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The standard local therapy for early-stage breast cancer is breast conserving surgery (BCS) followed by whole breast adjuvant irradiation (WBI), eventually associated to a boost dose to lumpectomy cavity (1-4). This approach provides high rates of local control and survival with the possibility of breast conservation (1). Traditionally, adjuvant WBI has been delivered employing conventional fractionation (1.8–2 Gy/die), entailing 5–7 weeks of treatment. This approach is time-consuming and hence represents a logistic burden, for both the patient (working issues, prolonged anxiety, costs) and healthcare providers (costs and workload) (5). In this sense, it is noteworthy that several studies showed that up to 50% of patients requiring radiotherapy do not undergo treatment mainly due to its duration (6). The past two decades brought important treatment changes and new radiation regimens have been developed to overcome these issues. The use of hypofractionated radiotherapy, which employs fewer fractions given using higher dose per fraction over a shorter overall treatment time, has been validated within prospective clinical trials and new approaches were introduced such as accelerated partial breast irradiation (APBI) together with new techniques such as intra-operative radiotherapy (IORT), which are also based on hypofractionation (7-12). While hypofractionated WBI requires the irradiation of the whole breast gland, APBI is based on a reduction in treatment volumes, since most disease relapses are located within the lumpectomy cavity. If selection criteria are appropriate, APBI delivered with IORT provides rates of local control similar to conventional treatments (11-14). Given the high incidence and

prevalence of breast cancer and the frequent need for radiotherapy, an evolution toward shorter treatments will inherently have an impact on healthcare budgets. These new radiation regimens are more convenient for patients, reducing the number of hospital visits, but also for health services in general, since they allow for a decrease in radiotherapy department workload and human resources need (15,16). Generally, increasing possibilities come with increasing costs and put healthcare budgets under strain. In order to support decision-making for different therapeutic options, evidence on cost and cost-effectiveness of new interventions and technologies needs to be reliable and to come with high quality. Deshmukh *et al.* recently reported on a cost-effectiveness analysis which compared different adjuvant radiotherapy approaches in early-stage breast cancer patients after lumpectomy: conventionally fractionated whole breast irradiation (CF-WBI), hypofractionated whole breast irradiation (HF-WBI) and APBI given with IORT (17). A decision-analytic model was designed to simulate the clinical course of women aged 45–75 and treated with BCS for stage I/II breast cancer. Data on recurrence and complication rates, mortality and utilities (5-year radiation-associated quality of life scores) were collected from several randomized clinical trials (7,8,11,12,18). Medical care costs were obtained from Medicare reimbursement charts. Cost-effectiveness analysis was performed according to the guidelines provided by the Second Panel on Cost-effectiveness in Health and Medicine (19). Cost-effectiveness analysis was estimated assuming both societal and healthcare sector perspectives. The comparative assessment was performed looking at

cost-effectiveness ratio, the ratio of expected costs and expected quality-adjusted life years (QALYs). Two scenarios were considered: (I) radiation-associated disutility or side effects persisting after five years and (II) radiation-associated disutility discontinued after 5 years. Deshmukh *et al.* also performed a sensitivity analysis looking at the likelihood of cost-effectiveness at USD 50,000 per QALY and USD 100,000 QALY. Incremental cost-effectiveness ratios (ICERs) were used to analyse lifetime outcomes. Deterministic and probabilistic sensitivity analyses evaluated the robustness of the results. HF-WBI was found to be superior to CF-WBI for all parameters, because CF-WBI was associated to increased cost and decreased QALYs in all scenarios. Moreover, HF-WBI was found to be more cost-effective than IORT in most settings, ranging from 75–80% of probability to be cost-effective. The results were comparable when considering both social and health care perspectives. The ICER, an index sensitive to treatment cost, age and disease relapse probability, which normally increases with age, showed that HF-WBI was the most cost-effective option in all scenarios. Nevertheless, supposing a lower price point for IORT, this option becomes a convenient high value intervention for elderly patients at low risk of relapse. It is important to notice that the comparative value of HF-WBI is strictly correlated to the cost of therapy as well as on the relative recurrence rate. Supposing a different relative cost between IORT and HF-WBI, this may tilt the cost-effectiveness calculation in favour of IORT, particularly for older women. Moreover, proper allocation to IORT treatment of (low-risk) breast cancer patients may increase the cost-effectiveness of IORT (with local relapse rates down to 1.5%) (11). This is confirmed by the data reported in a recent study which found IORT having less costs and higher QALYs compared to WBI (20). Even when considering the capital investment for the equipment which could be recouped after 3–4 years, these results support IORT as a potential cost-effective option in this setting. It is worth to further analyse the opportunity of IORT use for elderly patients, where the difference of cost-effectiveness is low between HF-WBI and IORT. In this subset of patients, the total cost of IORT is lower than HF-WBI, with a negligible difference of QALY. Conversely, the likelihood of HF-WBI to be more cost-effective than IORT increases rapidly with the decrease in patient age. One of the drawbacks of the study is not having considered the increase in QALY, for an elderly population, derived from the reduction in overall treatment time and costs. The available clinical evidence

and data on treatment costs both seems to prefer HF-WBI, but some economic questions remain unanswered. The most important one is whether we expect the potential long term side effects to be of such a magnitude to still justify the adherence to conventional fractionation and to justify the consequent higher societal investments (16). Answers will be available in the coming years based on formal cost-effectiveness evaluations driven by considerations related to tumor profile, patient specificity and country characteristics. In a recent systematic review of 24 publications, Monten *et al.* compared different fractionations schedules and/or irradiation techniques in term of health-economic parameters to evaluate the value of adding radiotherapy (21). HF-WBI was shown to be more cost-effective compared to CF-WBI, while the results of APBI were less unequivocal. HF-WBI is thought to be the most relevant comparator for new radiotherapy strategies, with omission of radiotherapy as an interesting alternative in low-risk breast cancer patients (22,23). Although the comparison of cost-effectiveness is hampered by the variability in clinical and economic settings, health-economic evaluations based on the clinical evidence can guide the decision-making process toward tailor-made strategies, allocating the optimal treatment to the right patient. Breast cancer involves a plurality of life dimensions affecting both the individual and the surrounding family and community. The costs that breast cancer generates are manifold and plural. They include those strictly related to healthcare, but also those having a socio-economic nature, such as the impact on working life and the ability to produce income, and those related to more intangible costs pertinent to psychological domains and the inner human nature. Therefore, socio-economic costs have a multidimensional profile and refer to different fields. A robust analysis and processing of data and indicators derived from different sources is needed to evaluate these types of costs (24). The data obtained must be considered as a whole and harmonized in order to obtain a more holistic value that represents the overall cost of the disease. The selection of the most appropriate adjuvant treatment for breast cancer patients after BCS should take into account not only clinical endpoints such as the risk for local relapse or survival and treatment-related toxicity profile, but also patient reported outcomes including quality of life and psycho-social evaluation (25). Cost-effectiveness is also a major determinant. In this sense HF-WBI is the preferable choice compared to CF-WBI, but APBI delivered with IORT is a reasonable option for low-risk elderly breast cancer patients.

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