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Recent Developments in Radiation Therapy Decision Making in Early Invasive Breast Cancer

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Abstract

Adjuvant whole-breast irradiation following breast-conserving surgery is a well-established treatment standard for early invasive breast cancer. Screening, early diagnosis, surgical technique refinement, knowledge of new and specific molecular prognostic factors, and now the standard use of more effective neo/adjuvant systemic therapies have all played a role in lowering the rates of locoregional relapses. This highlights the importance of reliably identifying women with such low-risk disease burdens in whom removing radiation from the treatment plan would not jeopardise oncological safety. This review summarises the current evidence for radiation de-intensification strategies and details ongoing prospective clinical trials investigating the omission of adjuvant whole breast irradiation in molecularly defined low-risk breast cancers, as well as related evidence supporting the potential for radiation de-escalation in triple-negative clinical subtypes.

Keywords: Breast cancer • Biomaterials • Prognosis • Radiation

Introduction

For more than three decades, breast-conserving surgery combined with adjuvant radiation has been the well-established standard of care for women diagnosed with early invasive breast cancer. The early breast cancer trialists' collaborative group patient level meta-analysis of 17 randomised trials involving over 10,000 women found compelling evidence favouring adjuvant radiotherapy over no radiotherapy after breast-conserving surgery for a 10-year absolute risk reduction of 15.7% for any recurrence and a moderate absolute reduction in breast cancer mortality by 3.8% at 15 years. In high-risk patients, adding a tumour bed radiation boost reduces the relative risk of local recurrence by 50%.Screening, early diagnosis, imaging refinements, surgical techniques, pathological evaluation, and a better understanding of tumour biology have all improved over the last few decades.

When compared to traditional radiotherapy modalities for early breast cancer, modern radiotherapy techniques incorporating hypofractionation schedules have improved quality of life, decreased hospital stay, and reduced side effects. Furthermore, despite the lack of proven survival benefits in some cases, optimal locoregional control undoubtedly contributes to improved quality of life. To avoid over-treatment for early invasive breast cancer, radiotherapy decisions should be made in the same way that systemic therapy decisions are. This need has prompted a rethinking of radiotherapy indications and the launch of investigations to identify any subset of low-risk women with such a negligible burden of residual locoregional disease risk following breast-conserving surgery who could be safely spared radiation therapy. Recently, much attention has been focused on elderly early-stage breast cancer patients with favorable prognostic factors [1].

Literature Review

Despite its undeniable benefits, radiation therapy is associated with a significant morbidity risk. Radiation dermatitis is the most common early complication of adjuvant radiation after breast-conserving surgery, and it can potentially disrupt the radiation schedule if severe. Furthermore, while the risk of acute radiation toxicity is significantly lower with partial breast radiation compared to whole breast radiation, some studies have shown that the risk of delayed dermal toxicities, such as telangiectasia, fat necrosis, and subcutaneous fibrosis, is increased. Furthermore, both early and delayed arm lymphedema remain debilitating morbidities that affect every fifth breast cancer survivor, lowering their quality of life and putting a strain on the health-care system.

Despite these recommendations, the use of radiation therapy among elderly women has continued, with the decision largely influenced by patients' age and physicians' preferences. Furthermore, achieving higher locoregional control with radiation may be the preferred choice of women to avoid the deterioration in quality of life and financial costs associated with locoregional recurrence, particularly in the presence of poor prognostic factors such as grade 3 histology and positive surgical margins. It has also been reported that elderly women may prefer radiation therapy to adjuvant endocrine therapy. Beyond the omission of adjuvant radiation in select indolent tumours in elderly patients, de-intensification strategies have evolved over the last two decades and have positively contributed to patient convenience and compliance by reducing radiation.

Discussion

Until about a decade ago, the standard of care for whole breast irradiation was 45-50 delivered in 25 fractions of 1.8-2.0 once a day for 5 weeks, with or without a tumour bed boost. This prolonged treatment period has been linked to acute and late radiation-induced toxicities, poor quality of life, low compliance, increased workload, and high healthcare costs. Furthermore, several factors, including patient age, co-morbidities, income, ethnicity, education attainment, distance to the treatment facility, and the availability of radiation oncologists, have been linked to disparities in radiotherapy receipt. These impediments contribute to a higher rate of mastectomy among women who would otherwise have chosen breast-conserving surgery with adjuvant radiation [2-6]. Given that the majority of in-breast recurrences occur in the index quadrant, Accelerated Partial Breast Irradiation is an alternative approach to hypofractionation that delivers targeted radiation to the lumpectomy site over a 2-5 day period and has shown promising results for oncological safety and cosmetic outcomes while reducing treatment time to 2-5 days. Single or multiple catheter brachytherapy, intraoperative radiotherapy, and the use of external beam radiation therapy techniques such as three-dimensional conformal radiation therapy and intensity-modulated radiation therapy are all methods of APBI delivery.

Intraoperative radiotherapy, which delivers a single fraction of electrons

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or soft X-rays intraoperatively immediately after tumour resection, is another strategy that has been evaluated in two randomised controlled trials. At a median follow-up of 12.4 years, the European Institute of Oncology's ELIOT trial found increased local and regional relapse rates associated with intraoperative radiotherapy compared to conventional whole breast radiation, despite no significant difference in overall survival rate between the two groups. Several factors were found to be significantly associated with a significantly increased risk of ipsilateral breast tumour recurrence in the exploratory analysis. However, for a subset of patients with extremely favourable tumour biology, intraoperative radiotherapy as currently administered may still be an appropriate option [5].

Disseminated tumour cells are cancer cells that escape the circulation after physical detachment from the primary tumor, extravasate into distant sites such as bone marrow, and are capable of survival in a hostile host niche, reversible quiescence, and therapeutic resistance. DTCs are found in approximately 40% of women with breast cancer who do not have clinical or histological evidence of overt metastatic disease at the time of diagnosis. A substantial body of evidence from clinical studies has shown that patients with DTC positivity have aggressive tumour biology, such as larger tumour size, higher grade, axillary lymph node metastasis, and oestrogen/progesterone receptor negativity and positivity.

Conclusion

Adjuvant radiotherapy is an important part of early breast cancer management because of its proven efficacy in preventing locoregional and distant failures. Traditional whole breast irradiation approaches have evolved significantly over the years, to the point where the less intensive option of whole breast hypofractionated radiation is now the preferred standard, yielding improved compliance, cosmetic outcomes, and quality of life. More recent data show that an ultra-hypofractionation regimen delivered in five fractions in less than a week has comparable efficacy and safety. The equivalence of accelerated partial breast radiation delivered by external beam has been demonstrated in several clinical trials and endorsed for women with tumours with favourable biology, and may be an appealing option in resource-constrained areas when combined with ultra-hypofractionation.

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Conflict of Interest

There are no conflicts of interest by author.

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