Rethinking Radiotherapy: 5-Day Ultra-Hypofractionation for DCIS Shows Promising Results

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Professor Angel Montero-Luis and colleagues recently presented compelling data at the ESTRO Congress on a streamlined radiotherapy approach for ductal carcinoma in situ (DCIS). Their study evaluated the safety and efficacy of ultra-hypofractionated (UHF) irradiation delivered over just five treatment sessions. A total of 101 women with DCIS received 26 Gy in five fractions, with a simultaneous integrated boost (SIB) to the tumor bed delivering a total of 29–31 Gy.

Most patients (90%) were treated post–breast-conserving surgery, while 10 had undergone mastectomy. Additionally, adjuvant hormonal therapy was administered in 79% of cases. With a median follow-up of 37 months, the outcomes are excellent: no locoregional or distant recurrences and only mild acute and early-late toxicities.

Interestingly, patients with smaller planning target volumes (PTVs) showed a statistically significant reduction in both acute and late toxicities, highlighting the importance of personalized treatment planning.

In this interview, Professor Montero shares the motivation behind this study, how these results could reshape treatment for DCIS, and what lies ahead for ultra-short-course radiotherapy.

Professor Montero, What motivated your team to investigate ultra-hypofractionated radiotherapy for DCIS, and what unmet clinical needs did you hope to address with this study?

Ductal carcinoma in situ (DCIS) is a non-invasive breast lesion that may precede, but does not inevitably progress to, invasive breast cancer. Before the advent of population-based breast cancer screening programmes, DCIS accounted for fewer than 5% of all new breast cancer diagnoses. Its incidence rose markedly following the implementation of screening—rising in the United States from 1.87 per 100,000 women in 1973 to 32.5 per 100,000 in 2004, and in Europe from 4.9 per 100,000 in 1989 to 20.68 per 100,000 in 2011—before reaching a plateau.

Although DCIS is non-invasive, approximately 15% of women treated with surgery alone will develop ipsilateral invasive recurrence and 6% contralateral breast cancer within 15 years; around 3% will die from breast cancer within that time.

Adjuvant radiotherapy has been shown not only to reduce the risk of local recurrence and progression to invasive carcinoma but also to improve cause-specific survival. Five large

randomised trials, each with more than 12 years of follow-up, demonstrated that radiotherapy in DCIS reduces the 10-year risk of local recurrence by up to 48% and the risk of invasive recurrence by up to 42%, with consistent benefit across all patient subgroups regardless of age, tumour size, histological grade, or margin status. Additionally, a SEER-18 registry analysis of 140,366 patients found that lumpectomy followed by radiotherapy was associated with lower 15-year breast cancer-specific mortality (1.74%) compared with lumpectomy alone (2.33%) or mastectomy (2.26%).

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As with invasive breast cancer, hypofractionated radiotherapy schedules are recommended as standard practice in DCIS, with or without a tumour bed boost, and moderate hypofractionation in 15 fractions is the current norm.

In recent years, ultra-hypofractionated (UHF) regimens have gained popularity for early-stage invasive breast cancer and are considered a viable alternative for both whole-breast irradiation (WBI) and chest wall irradiation. However, DCIS remains under-represented in studies assessing the feasibility and safety of 1-week UHF schedules.

While some prospective UHF trials have included DCIS patients, their numbers have been limited, and major randomised trials comparing moderate and ultra-hypofractionation (e.g., FAST-Forward, HYPORT, MC1635) have explicitly excluded this subgroup. This limits the applicability of current evidence to in situ disease, although retrospective data suggest that UHF may also be safe and effective for selected DCIS patients, paralleling the earlier adoption pattern seen with moderate hypofractionation.

Our aim was to address this evidence gap by evaluating the feasibility and safety of delivering whole-breast UHF in just five fractions, with outcomes comparable to those reported for invasive tumours. Acknowledging the need for long-term follow-up in breast cancer to capture late recurrences and treatment-related complications, we reported only patients with at least 12 months of follow-up to minimise attrition. We hope our results will help support UHF as a valid treatment option for DCIS.

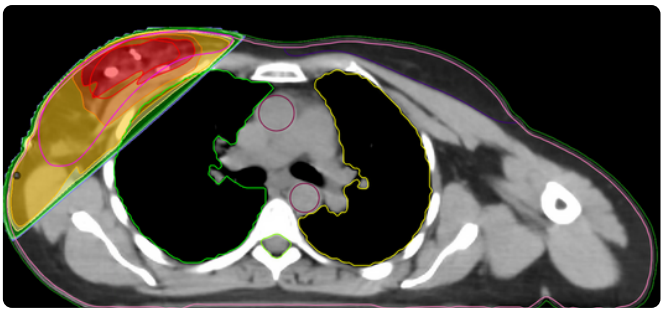
Your study reports almost no locoregional or distant recurrences with a median follow-up exceeding three years. How do these results challenge traditional views on radiotherapy fractionation for DCIS?

The prognosis for DCIS is generally excellent, with 10-year breast cancer-specific survival rates approaching 98%. The primary treatment goal is to prevent local recurrence and potential progression to invasive disease. Options include mastectomy or breast-conserving surgery (BCS), with or without radiotherapy and/or endocrine therapy.

In our updated analysis (median follow-up: 44 months), only one of 100 patients experienced a true local recurrence - new DCIS in the lumpectomy bed - three years post-treatment. This was successfully salvaged with repeat BCS and partial-breast re-irradiation (30 Gy in 5 fractions). The fact that all BCS patients received a tumour bed boost - an approach still under debate - may partly explain the low recurrence rate, though longer follow-up is needed.

The necessity of adjuvant radiotherapy after DCIS surgery remains an area of ongoing debate.

The indolent nature of some DCIS cases has fuelled interest in omitting RT in selected low-risk patients, but results have been mixed. For example, the RTOG 9804 trial, which enrolled small, low/intermediate-grade, clear-margin DCIS, showed sustained local recurrence reduction with RT at both 7 and 12 years (2.8% vs 11.4%, p = 0.0001) with minimal grade ≥ 3 toxicity. Similarly, ECOG-ACRIN E5194 demonstrated that recurrence risk continued to rise for up to 15 years after surgery alone, even in low-risk cases. Pending final results from ongoing de-escalation trials, adjuvant WBI remains the standard for most BCS-treated DCIS.



While omission may be reasonable in carefully selected very-low-risk cases after shared decision-making, accepting a modest but real increase in ipsilateral breast events, UHF offers a compelling compromise—providing short, well-tolerated schedules without compromising outcomes. UHF is now a standard for early-stage invasive breast cancer per ESTRO-ACROP guidelines, and our findings, along with other groups' results, support extending its use to DCIS.

The results indicate that smaller planning target volumes are significantly associated with reduced acute toxicity, while larger breast PTVs correspond to fewer late complications. Could you provide further insight into these observations and their potential clinical implications?

Although early results hinted at differences in acute and late toxicities based on treated volumes (breast and/or boost), we now believe these initial findings were due to chance.

In the final analysis with longer follow-up, no statistically significant differences in toxicity were observed related to PTV size. However, patients who had post-surgical complications before starting RT, particularly seromas, tended to have higher rates of RT-related effects, though this was not statistically significant.

A notable feature of our study is that all BCS patients received a protocol-mandated simultaneous integrated boost (SIB), with the dose adapted to margin status. While the boost's benefit in DCIS is debated, given modern improvements in baseline control and concerns about cosmesis, evidence supports its role in reducing recurrence.

A large pooled analysis found a 3.6% absolute 15-year reduction in ipsilateral breast tumour recurrence with a boost in DCIS, similar to the 4.4% benefit in the EORTC trial for invasive cancer. This was consistent across ages, tamoxifen use, and other factors, but more pronounced in younger patients.

Likewise, BIG 3-01/TROG 07.01 reported a drop in 5-year IBTR from 7.3% to 2.9% with a boost, and a 4% reduction in salvage mastectomy rates. These gains came at the cost of more grade ≥ 2 toxicity, mainly mild acute dermatitis and moderate late fibrosis/pain, though delivered with older techniques and schedules.

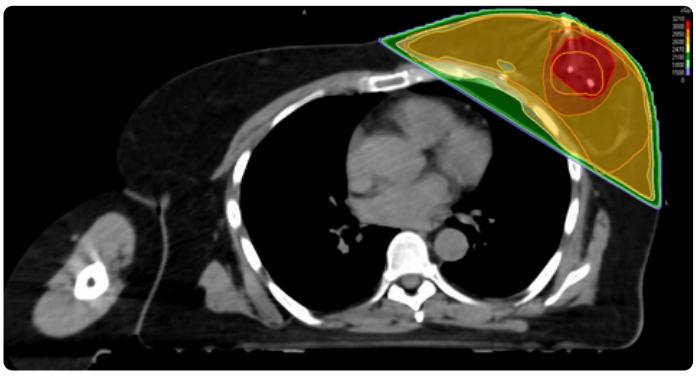
Given the inclusion of post-mastectomy patients in your cohort—a group not commonly treated with radiotherapy for DCIS—could you explain the clinical considerations and decision-making process that led to their inclusion in this study?

The role of post-mastectomy radiotherapy (PMRT) in DCIS is poorly defined, and randomised trials are unlikely. Local recurrence after mastectomy for DCIS is rare (0–7.5%), but when it occurs, it is often invasive and carries a worse prognosis. As several studies suggested administering post-mastectomy radiation therapy (PMRT) to patients with DCIS harbouring "high risk" factors for local recurrence, identifying these risk factors is currently one of the main challenges in optimal DCIS management. The main risk factors for Locoregional failure (LRF) after mastectomy in DCIS, as identified in the various studies, were the presence of close/positive margins, high nuclear grade, and young age at diagnosis. Some authors also correlated the risk of LRF after mastectomy with tumour size or skin-sparing mastectomy. There are not, nor are there likely to be, randomized studies on the role of PMRT in DCIS, but the combined presence of different risk factors, including age under 50 years, the presence of close/positive surgical margins, or a large tumor size, could warrant consideration of PMRT in selected DCIS patients.

In our study, PMRT was offered to selected patients meeting these criteria after multidisciplinary discussion.

"The evolution of modern RT aligns with the principles of Citius, Altius, Fortius-faster, higher, stronger—while embracing the Less is More philosophy"

Looking ahead, how do you envision ultra-hypofractionated radiotherapy evolving over the next decade, and what are the key research questions or challenges that must be addressed to establish this approach as a new standard of care for DCIS?



The evolution of modern radiotherapy aligns seamlessly with the principles of Citius, Altius, Fortius—faster, higher, stronger—while embracing the Less is More philosophy.

In recent years, the 5-fraction radiotherapy regimen has emerged as a transformative approach, offering shorter treatment durations, higher precision, and enhanced therapeutic efficacy, all while optimizing healthcare resources.

The COVID-19 pandemic caused significant hardship but also spurred rapid advancements, including in cancer care. In radiotherapy, it led to broader acceptance of shorter treatment regimens, particularly the 5-fraction schedule, which proved equally effective for breast cancer and many other tumors.

The adoption of the 5-fraction regimen in breast cancer radiotherapy has also been influenced by technological advancements over recent decades.

Developments include the use of advanced imaging techniques for more accurate definition of irradiation target volumes and the implementation of dose delivery systems that improve homogeneity within the target area while reducing exposure to surrounding healthy tissues via steep dose gradients. Imaging advances have also enabled more precise, image-guided treatments and consistent daily reproducibility during therapy. These

improvements have supported the wider use of the 5-fraction regimen in clinical settings.

Embracing 5 fractions for all breast cancer treatments as a standard for 21st-century radiotherapy is no longer the vision of a few pioneering oncologists but a tangible reality that is gaining widespread acceptance. Perhaps it is time to redefine what we consider the "standard fractionation" regimen as 15–16 fractions, while reserving the term "hypofractionation" exclusively for the 5-fraction regimens currently labeled as "extreme hypofractionation."

However, widespread implementation may also depend on other factors, such as evolving clinical evidence and institutional preferences. Adoption is often hindered by reimbursement models still prevalent in many countries, which are based on a fee-for-service system. Under these models, payment per fraction results in decreased financial compensation for physicians and healthcare institutions, creating a disincentive for transitioning to shorter regimens. To overcome this barrier, some experts advocate for the implementation of an Alternate Payment Model (APM) in these countries, which establishes a fixed reimbursement rate regardless of treatment technique, number of fractions, or fraction size. This approach could promote broader adoption of 5-fraction regimens by aligning financial incentives with clinical efficiency. Conversely, in countries with universal healthcare systems and bundled payment structures, such as Spain and several other European Union nations, enthusiasm for 5-fraction regimens has been greater. In these settings, such protocols have already become the standard of care for many indications, offering the advantages of reduced treatment duration, cost savings, and more efficient resource utilization.

Thank you, Professor Montero, for such an engaging and insightful discussion!

Thank you for your interest in our work and for the opportunity your journal offers us to present and elaborate on our study findings.