NICE National Institute for Health and Care Excellence

2022 exceptional surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101)

Surveillance report

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Surveillance decision

We will update the recommendation on dose fractionation in the section on radiotherapy in the NICE guideline on early and locally advanced breast cancer.

Reason for the exceptional review

The purpose of this exceptional review was to examine any impact on the NICE guideline following the publication of Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial (Brunt et al. 2020).

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence that triggered the exceptional review.
- Considering the evidence used to develop the guideline in 2009.
- Considering relevant information from previous surveillance reviews of the guideline.
- Feedback from topic experts.
- Examining related NICE guidance and quality standards (none identified).
- Examining the NICE event tracker for relevant ongoing and published events.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

We decided that full updated literature searches were not needed because the information we had from the original guideline, new evidence and topic experts was enough to establish whether an update to the guideline was needed. However, any update will require a focussed literature search to identify and assess all relevant evidence on the most effective radiotherapy dose fractionation regimen for patients undergoing external beam radiotherapy after surgical excision of breast cancer.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered in this exceptional surveillance review

The FAST-Forward trial is a UK based multicentre, non-blinded, randomised non-inferiority trial assessing whether a 5-fraction schedule of adjuvant radiotherapy given over 1 week (with a total dose of 27 Gy (Gray) or 26 Gy) is non-inferior to standard adjuvant radiotherapy of 40 Gy in 15 fractions given over 3 weeks on local cancer control and safety in adult patients with invasive carcinoma of the breast after breast conservation surgery or mastectomy.

Methods

There were 4,110 participants recruited from 97 UK hospitals (47 radiotherapy centres and 50 referring hospitals) between November 2011 and June 2014. Participants (women and men) were included if they were aged 18 years or over, had early stage breast cancer (eligibility: pT1–3, pN0–1, M0; see TNM staging system for further information) and had received complete microscopic excision of the primary tumour by breast conservation surgery or mastectomy (reconstruction allowed). To increase the overall primary event rate (ipsilateral breast tumour relapse), inclusion criteria were changed in February 2013 to exclude patients considered to be at lowest risk of ipsilateral breast tumour relapse: those aged 65 years or over, with low or intermediate grade stage 1 oestrogen receptor positive, HER2-negative breast cancer.

All patients had axillary surgery. Concurrent endocrine therapy and/or trastuzumab was allowed, but not concurrent chemotherapy. Patients who required nodal radiotherapy were excluded as they were the subject of a sub-study (see topic expert feedback).

Patients were randomised to either the standard 40 Gy 15-fraction schedule (2.67 Gy per fraction; n=1,361 included in the intention-to-treat [ITT] population) or a hypofractionated schedule of 27 Gy 5-fraction schedule (5.4 Gy dose per fraction; n=1,367 ITT population) or 26 Gy 5-fraction schedule (5.2 Gy per fraction; n=1,368 ITT population).

The choice of test dose levels was informed by findings from 2 trials. These were the UK

Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer (see Haviland et al. 2013); and the FAST trial: a prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control. These studies provided information on the dose-effect relationship for late normal tissue effects, described in terms of alpha/beta (α/β) values. This information is used to calculate a biologically effective dose, in this case a dose that is the equivalent to the current standard of 40 Gy in 15 fractions. The Brunt et al. 2020 paper reports that: 'assuming an α/β value of 3 Gy and no effect of overall time on outcomes, 27 Gy in 5 fractions of 5.4 Gy was predicted to match late normal tissue effects of 40 Gy in 15 fractions of 2.7 Gy' and 'allowance for a possible effect of treatment time informed the choice of the slightly lower 26 Gy dose level'. A sequential tumour bed radiotherapy boost to the conserved breast was also allowed, 'with centres required to specify boost intention and dose (10 Gy or 16 Gy in 2-Gy fractions) before randomisation'.

The primary outcome of interest was ipsilateral breast tumour relapse. Secondary outcomes were:

- late normal tissue effects: breast distortion, shrinkage, induration (localised hardening of soft tissue of the body), telangiectasia (small, widened blood vessels on the skin), breast or chest wall oedema, and discomfort
- locoregional relapse (including regional relapse of axilla, supraclavicular fossa, and internal mammary chain)
- distant relapse
- disease-free survival and overall survival.

Outcomes were assessed by clinicians annually, starting at 12 months after trial entry.

There were also 2 additional sub-studies (studies involving patients from the main FAST-Forward trial) which were designed to assess changes to the affected breast after treatment, results of which are reported in the Brunt et al. 2020 paper. Participants were recruited to a patient-reported outcomes sub-study (no additional inclusion criteria from the main FAST trial; n=1,771 questionnaires at baseline and n=1,334 out of 1,771 available at 5 years follow-up) and a photographic sub-study. For the photographic sub-study all patients who had breast conservation surgery were eligible, but they could not participate in further photographic assessments after breast reconstruction surgery (for example, surgery to make a new breast shape after removal of the breast or part of the breast) or

further ipsilateral disease (n=1,634 baseline photographs; photographs available for n=1,309 at 5 years follow-up). While patients who had a mastectomy were also recruited in order to validate the scoring method in patients who had chest wall radiotherapy, due to the small sample size with available photographs (n=76), their results are not reported in the Brunt et al. 2020 paper.

A sample size analysis was undertaken to ensure recruitment of enough patients to show non-inferiority between the control and intervention groups. A non-inferiority margin of 1.6% in 5-year ipsilateral breast tumour relapse incidence between the control and intervention groups was agreed as acceptable and appropriate before the start of the trial by a group including clinicians and patient advocates. This assumed a 2% 5-year incidence of ipsilateral breast tumour relapse in the 40 Gy group, based on data from the START trial and 'allowing for reduced ipsilateral breast tumour relapse due to evolution of surgical techniques and systemic therapy'. This resulted in a total target sample size of 4,000 patients, assuming a balanced allocation between the control and 2 intervention groups, which provided 80% power and allowed for 10% loss to follow-up. Non-inferiority of each 5-fraction schedule compared with the control was also assessed using an *a priori* critical hazard ratio (HR) of 1.81 and a p value <0.025 was required to be considered statistically significant.

For the photographic and patient-reported outcomes sub-studies, a sample size of 2,196 patients (732 per group) was estimated 'to provide 80% power to detect an 8% difference in 5-year prevalence of late normal tissue effects between the 5-fraction schedules (assuming 35% with 5-year mild or marked change in photographic breast appearance from START-B 40 Gy results), allowing for 10% loss to follow-up.' Changes in photographic breast appearance were analysed at 2 and 5 years, with mild and marked changes combined (due to the low level of reported changes); and because of multiple testing, a p value $\leq$0.005 was considered as indicting a significant difference for normal tissue effects between the intervention and control groups.

Survival analysis methods analysed time to first moderate or marked event. Analyses were performed on an ITT basis. There was 99% treatment compliance.

Results

Demographic and clinical characteristics of patients at baseline were similar between groups. The majority of patients had breast conservation surgery (total n=3,832) rather than mastectomy (total n=264). Over 99% of patients were female, with only 12 males

included in the study and 2 people of unknown sex. Approximately 62% of patients were considered as low risk for ipsilateral breast tumour relapse (age 50 years and over and tumour grade 1 or 2), with the remaining 38% considered as high risk (age under 50 years and/or tumour grade 3). The majority had a negative pathological node status (between 81% and 82% depending on allocated radiation schedule group) and had oestrogen receptor (ER) positive, HER2-negative breast cancer (between 80% and 82% depending on allocated radiation schedule group). Approximately 96% of ER positive patients received adjuvant endocrine therapy. Between 24% and 27% (depending on allocated radiation schedule group) received adjuvant chemotherapy. A sequential tumour bed radiotherapy boost to the conserved breast was offered to 25% of patients in the 40 Gy group, 20% in the 27 Gy group and 19% in the 26 Gy group, with the majority receiving 10 Gy in 5 fractions (76%, 81% and 77% respectively) rather than 16 Gy in 8 fractions.

For the primary outcome, a total of 79 patients had ipsilateral breast tumour relapse over the 5 years follow-up (n=31 in the 40 Gy group, n=27 in the 27 Gy group, n=21 in the 26 Gy group). The ITT analysis found that at 5-years follow-up there was no statistical difference in incidence of ipsilateral breast tumour relapse between treatment groups: compared with 40 Gy in 15 fractions, for 27 Gy the HR=0.86 (95% confidence interval [CI] 0.51 to 1.44), for 26 Gy the HR=0.67 (95% CI 0.38 to 1.16). The estimated cumulative 5-year incidence of ipsilateral breast tumour relapse in the control group was within the expected incidence of 2% (it was 2.1%, 95% CI 1.4 to 3.1). For the 27 Gy group, estimated incidence was 1.7% (95% CI 1.2 to 2.6); and for the 26 Gy group it was 1.4% (95% CI 0.9 to 2.2). The estimated absolute difference in ipsilateral breast tumour relapse for 27 Gy compared with 40 Gy was -0.3% (95% CI -1.0 to 0.9), and for 26 Gy compared with 40 Gy it was -0.7% (95% CI -1.3 to 0.3). As the upper 95% CI limits were below 1.6%, both the 27 Gy and 26 Gy schedules can be considered to be non-inferior to the standard 40 Gy schedule.

For secondary outcomes, the ITT analysis found that at 5-years follow-up there was also no statistical difference in incidence of distant relapse, disease-free survival, or overall survival between patients who received a 27 Gy 5-fraction schedule, or 26 Gy 5-fraction schedule compared with the 40 Gy 15-fraction schedule.

For late-onset normal tissue effects in the ipsilateral breast or chest wall, a longitudinal analysis of moderate or marked clinician-assessed late normal tissue effects for patients with at least one annual clinical assessment (n=3,975) found that while there was evidence of no significant differences between the 40 Gy and 26 Gy groups, there was evidence that patients in the 27 Gy group had significantly worse outcomes in comparison

with both the 40 Gy group and 26 Gy group for any adverse event in the breast or chest wall. In comparison with the 40 Gy group, the 27 Gy group had significantly worse (for example at a p value ≤0.005) breast distortion, shrinkage, and induration (tumour bed and outside tumour bed) and breast or chest wall oedema. In comparison with the 26 Gy group, the 27 Gy group had significantly worse breast shrinkage.

Results of the patient-reported assessment and photographic assessment sub-studies also reported significantly higher normal tissue effect risks in the 27 Gy compared with 40 Gy group, but not for the 26 Gy compared with 40 Gy group.

The results overall indicate that a 5-fraction 26 Gy schedule of adjuvant radiotherapy given over 1 week is non-inferior to the standard 40 Gy in 15 fractions over 3 weeks for ipsilateral breast tumour relapse, distant relapse, disease-free survival, overall survival and normal tissue effects up to 5 years in patients given adjuvant local radiotherapy after breast conservation surgery for early and locally advanced breast cancer. The results also indicate that while a 27 Gy schedule is non-inferior to the 40 Gy schedule for local tumour control, it is not as safe as either the 40 Gy or 26 Gy schedule when normal tissue effects are considered.

Discussion

This study was a well-designed randomised control trial (RCT) that is directly relevant to the UK population and health service, the sample size met the requirements set out to ensure adequate power to assess non-inferiority, which was pre-determined using an agreed non-inferiority margin and the study included an ITT analysis.

There are some limitations to the study:

- Patients and clinicians were aware of which procedure patients received, which while it would be clear to a patient whether they received a 1-week or 3-week schedule, it is not obvious why patients would need to know whether they were receiving a 26 Gy or 27 Gy schedule. For clinicians undertaking annual assessments it would be difficult for them to be blinded to the radiation schedule as hospital patient notes must record what radiation treatment was administered.

- While the chosen non-inferiority margin was decided before the trial started and the choice of 1.6% was agreed upon as appropriate by a group of clinicians and patients, an update would need to consider any clinical or methodological limitations of the chosen margin.
- Subgroup analysis by patient demographics and/or breast cancer profile or adjuvant therapies was not possible due to the size of the sample. Of particular relevance, is the small number of breast cancer patients that had a mastectomy, which means it is not possible to make a conclusion concerning whether or not the 26 Gy schedule is a suitable alternative to the 40 Gy schedule for these patients.
- The trial currently only has 5-year follow-up data available. Ideally, we would want the 10-year follow-up data so we can look at longer term efficacy and later side effects and the health economics evaluation; however the authors argue that previous research assessing different radiotherapy schedules in the same patient group on ipsilateral breast tumour relapse and normal tissue effects with 10-years follow-up data found that 'although normal tissue effects continue to accumulate beyond 5 years, there is evidence that relative differences between test and control groups change very little over time'.
- In relation to health economics, the authors note that the 26 Gy schedule 'is convenient and substantially less expensive for patients and for health services', likely due to reduced radiotherapy costs in terms of work hours and fewer fractions, plus fewer visits for a patient to receive radiotherapy at a clinic. There may also be better adherence to treatment as patients frequently have to travel some distance to access radiotherapy treatments in England.

Information considered when developing the guideline

Recommendation 1.10.13 on dose fractionation in the NICE guideline was not revised as part of the 2018 update. The recommendation was made in the 2009 guideline following a literature search for evidence that could answer the review question 'what is the most effective radiotherapy dose fractionation regimen for patients undergoing external beam radiotherapy after surgical excision of breast cancer?'. All study types were initially included in searches from 1973 up to 29 or 31 January 2008 (depending on database searched), with update searches of databases from the end date of previous search dates to April or July 2008 for RCTs or systematic reviews. Details of the search strategy are

available in appendix A of the evidence review – February 2009 (see topic 41, page 2,048).

Two systematic reviews, 8 RCTs (plus results reported in an abstract or ongoing RCT study), 2 cohort studies, 4 non-randomised studies and 2 guidelines were included. These reported on the effects of radiotherapy delivered using fraction sizes greater than 2 Gy (total lower doses than 50 Gy and fewer number of fractionations than 25: 'hypofractionated schedules') compared with the standard at the time of 50 Gy in 25 fractions for whole breast or chest wall radiotherapy in patients with early invasive breast cancer who had undergone breast-conserving surgery or mastectomy. The outcomes of interest were quality of life, overall survival, patient acceptability, local recurrence, late effects of radiotherapy (any delayed reaction to treatment that can happen months or years after treatment such as effects on the heart, lungs, bones and joints), normal tissue effects, adverse effects and cosmesis. The included evidence, evidence summary and evidence tables are provided in the 2009 evidence review, section 6.4 (pages 1,347 to 1,422).

In summary, the systematic review and relevant RCT evidence indicated that hypofractionated schedules achieved comparable 5-year overall survival rates to the conventional schedule of 50 Gy in 25 fractions. Rates of local recurrence were not significantly different between conventional 50 Gy fractions and hypofractionated schedules. Results were mixed for distant recurrence, with RCT evidence indicating that there was either no difference between conventional 50 Gy fractions and hypofractionated schedules (2 RCTs) or a significant reduction in distant recurrences for hypofractionated 40 Gy delivered over 3 weeks in comparison to 50 Gy over 5 weeks (this latter RCT also reported a significant reduction in all-cause mortality in the shorter hypofractionated 40 Gy arm, possibly because of the lower rate of distant recurrences). There were mixed findings from RCTs for cosmetic outcomes, with either no significant differences reported between conventional 50 Gy fractions and hypofractionated schedules or reports of significant improvements in 'no change in breast appearance' for hypofractionated schedules. There were also mixed findings concerning adverse effects, with findings of either no significant difference between conventional 50 Gy fractions and hypofractionated schedules or a significant reduction in adverse effects for hypofractionated schedules (when considering the lowest overall total Gy schedule assessed). Quality of life was only reported in 1 non-randomised study, and this found no difference in quality of life between people receiving 50 Gy compared with 40 Gy.

Information considered in previous surveillance of

this guideline

A surveillance review in 2012 identified no relevant evidence on radiotherapy dose fractionation regimen for patients undergoing external beam radiotherapy after surgical excision of breast cancer following a 'high-level RCT search' and intelligence from topic experts and stakeholders.

A surveillance review in 2016 also identified no relevant evidence from a search for systematic reviews published between 1 October 2011 and 15 January 2015. A topic expert highlighted an RCT reporting on preliminary results of the UK FAST trial of radiotherapy hypofractionation for treatment of early breast cancer (Agrawal et al. 2011). The RCT included women aged 50 years or younger (n=915) with node-negative early breast cancer. The results indicated that after 3 years of median follow-up, 28.5 Gy in 5 fractions was comparable to 50 Gy in 25 fractions, and that 28.5 Gy in 5 fractions was associated with significantly milder adverse effects in the breast than 30 Gy in 5 fractions. The surveillance decision was that while the evidence indicated that hypofractionation may be associated with fewer adverse events than the previous standard-dose radiotherapy, the new evidence was unlikely to impact on the recommendation 1.10.13 to 'use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for women with invasive breast cancer after breast-conserving surgery or mastectomy' as data for outcomes such as recurrence and survival were not yet available.

Other relevant NICE guidance

NICE's technology appraisal guidance on intrabeam radiotherapy system for adjuvant treatment of early breast cancer is a mobile irradiation system designed to deliver a single dose of targeted low-energy radiation (X-rays) directly to the tumour bed, while limiting the exposure of healthy tissue to radiation. Current recommendations are that 'the Intrabeam radiotherapy system is not recommended for routine commissioning for adjuvant treatment of early invasive breast cancer during breast-conserving surgical removal of the tumour' but that 'use of the Intrabeam radiotherapy system is recommended only using machines that are already available and in conjunction with NHS England specified clinical governance, data collection and submission arrangements'. The committee discussion on this technology references the NICE guideline's dose fractionation recommendation and acknowledged that 'clinical practice is evolving and that the delivery and use of external radiotherapy may change in the future, moving towards a more targeted approach in which patients have treatment based on their individual risks'. Any changes to recommendation 1.10.13 in the NICE guideline may have an

impact on the technology appraisal, and the relationship between both pieces of guidance may need to be considered as part of an update.

Topic expert feedback

In this exceptional review we contacted a topic expert in therapeutic radiography who was a member of the guideline development group for the NICE guideline and a member of the NICE Centre for Guidelines Expert Advisers Panel. They were asked for their views on:

- whether the NICE guideline should be updated in response to the new evidence
- whether they had any concerns with the research only having 5 years of follow-up data available, and the use in principle of doses larger than 2 Gy given per fraction in the 26 Gy 5-fraction schedule
- whether patients who are having postoperative radiotherapy for breast cancer are being offered in practice 26 Gy in 5 fractions over 1 week for whole breast radiotherapy and/or chest wall radiotherapy.

The topic expert responded that they thought the NICE guideline should be updated in response to the new evidence, that they had no concerns with the radiation dose of 5.2 Gy per fraction in the 26 Gy 5-fraction schedule; and that while 10-year data would provide more reassurance in terms of tumour control than 5-year data, especially in cancers such as breast cancer that can recur late, 'the NICE guidelines are well placed in suggesting the level of discussion to be shared with patients, such as identifying the limitations that 5-year versus 10-year data may have'. They also noted that the 2009 evidence review that informed recommendation 1.10.13 in the NICE guideline used trials reporting data on 5-year follow-up as the basis for the 40 Gy in 15 fraction recommendation.

The topic expert highlighted that in their own practice the decision on choosing between the 5- or 15-fraction schedule is a shared decision between the consultant and patient, with a discussion of the potential limitations of the FAST-Forward trial data, such as only having 5-year follow-up data and a small proportion of patients with triple negative disease or very young patients in the trial population.

In relation to current practice, the topic expert said that in their radiotherapy department 26 Gy in 5 fractions is discussed and offered to all patients referred for adjuvant radiotherapy to the breast or non-reconstructed chest wall. It is not offered to patients

requiring nodal radiotherapy as data on the outcomes of the FAST-Forward nodal sub-study have not yet been published; nor is it offered to patients that have had a mastectomy and reconstruction (due to small numbers of these patients in the FAST-Forward trial). They said that while they think offering the 5-fraction regimen to people having autologous tissue breast reconstruction 'is probably a reasonable approach', they 'would welcome a national consensus on this before implementing'.

System intelligence

NICE is aware that in the UK, since the beginning of the Covid pandemic there has been considerable pressure on radiotherapy machine capacity in the NHS; and the 26 Gy 5-fraction schedule has become widely used. Our understanding is that it is mostly used for people with lymph node-negative breast cancer after wide local excision.

The NICE field team notified the surveillance team of the Royal College of Radiologists (RCR) Postoperative radiotherapy for breast cancer: hypofractionation consensus statements 2021. The consensus statements were based on consideration of the 5-year follow-up results of the FAST-Forward trial in particular, plus other research literature and with regard to the rapid change of breast practice during the COVID-19 pandemic. Agreement (or not) with the consensus statements was voted on by breast radiotherapy leads from 55 of 62 invited UK radiotherapy centres. The 2021 consensus statements include:

- to offer 26 Gy in 5 fractions over 1 week for whole breast radiotherapy, chest wall radiotherapy and partial breast radiotherapy (consensus statements 1, 2 and 4 respectively, which were all very strongly supported: 90% to 99% voted in support)
- to consider 26 Gy in 5 fractions over 1 week for chest wall radiotherapy with reconstruction (consensus statement 3; strongly supported)
- to consider 28.5 Gy in 5 fractions over 5 weeks instead of 26 Gy in 5 fractions over 1 week for patients with significant co-morbidities and/or frailty that make daily radiotherapy difficult (consensus statement 5; very strongly supported)

- that '15 fractions over 3 weeks is the current standard of care for breast nodal radiotherapy. Consider 26 Gy in 5 fractions for nodal radiotherapy (excluding the internal mammary chain [IMC]) only for patients with significant co-morbidities while awaiting the 2-year normal tissue results of the FAST-Forward nodal sub-study' (consensus statement 6; strongly supported). The FAST-Forward nodal sub-study has not published as of May 2022.

The RCR 2021 consensus statements are intended to supplement the RCR's Postoperative radiotherapy for breast cancer: UK consensus statements 2016, which says 'there is no indication to use more than 15 fractions for the breast, chest wall or nodal areas' (consensus statement with strong support: 70% to 89% supported the statement). The RCR note that it is important (as with any treatment) to discuss the benefits, risks and uncertainties of a hypofractionated schedule with the patient to reach a shared decision on treatment; and that 'there may be situations whereby 15 fractions is deemed to be optimal compared to 5 fractions for the individual patient'.

Equalities

A shorter radiotherapy course may be more convenient for patients, improve patient adherence and lead to more efficient use of radiation services, thereby improving equality of access to treatment and outcomes for some people. However, potential unintended consequences of a change to treatment options would need to be considered such as whether those who are on a low income, only able to get statutory sick pay, live in a rural area, etc are more likely to want and/or accept a quicker treatment regime which may have longer term effects that we are not currently aware of as the FAST-Forward trial has not yet reported 10-year follow-up data. In line with practice that has been reported by topic experts, careful consideration of which groups of breast cancer patients would be suitable for a hypofractionated schedule and information needs of patients should be considered in an update.

Overall decision

Based on the 5-year results of the FAST-Forward trial, we are proposing that recommendation 1.10.13 in the NICE guideline is updated to consider evidence on hypofractionated radiotherapy schedules for patients with early and locally advanced breast cancer undergoing external beam radiotherapy after surgical excision of breast cancer. The FAST-Forward trial is a well conducted RCT which reports on the outcomes of interest that were considered in the evidence review for the NICE guideline; and its

findings are directly relevant to the NHS. Current NHS practice has already moved on from offering 40 Gy in 15 fractions as standard practice for people with invasive breast cancer after breast-conserving surgery or mastectomy to offering certain groups of breast cancer patients a 26 Gy in 5 fractions schedule after breast-conserving surgery; and this has been reflected in the RCR's 2021 consensus statements on hypofractionation for postoperative radiotherapy for breast cancer. As such, recommendation 1.10.13 in the NICE guideline is now out of date and an update considering the full body of evidence on hypofractionated radiotherapy schedules for patients with early and locally advanced breast cancer is required.

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