Early and locally advanced breast cancer: diagnosis and management – radiotherapy dose fractionation (update)

Consultation on draft guideline - Stakeholder comments table
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Association of Breast Surgery	Guideline	General	General	One general comment: We wondered if there ought to be a comment on the role of intra-operative radiotherapy in the document to help guide the patients/clinicians even if it was not being commissioned?	Thank you for your comment. This update has focused on dose fractionation for external beam radiotherapy and intraoperative radiotherapy is outside of the scope for this update. As such, we did not review any evidence on intraoperative radiotherapy and the committee could not make any changes to the existing recommendations on it. The guideline does include information on intraoperative radiotherapy for the management of breast cancer, with a link to the NICE technology appraisal guidance (TA501) which currently does not recommend the routine commissioning of the intraoperative radiotherapy system for adjuvant treatment of early breast cancer.
Breast Cancer Now	Guideline	General	General	Breast Cancer Now welcomes the updated guidelines which bolster criteria for administering each standard regimen dependant on patient circumstance. Noting that the patient must be better informed of the risks to both regimens and encouraging the decision to be reached together is laudable and will bring an essential feeling of control to patients at a particularly vulnerable and stressful time. Recognising that the current evidence on long term outcomes is slightly more favourable for 40Gy in 15 fractions over 3 weeks, but can be more arduous and costly for both the patient and trust, we also welcome the research suggestions that will further solidify the criteria for radiotherapy dosage for breast cancer patients.	Thank you for your comments and support of the recommendations and research recommendations.

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British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	3	21 and 22	The comment (1.10.6 in the Guidelines) is based on 2018 recommendations. This pre-dates the latest and long-term findings of the TARGIT-A trial that show a single dose of intra-operative radiotherapy is as effective as standard radiotherapy regimes in treating patients with early breast cancer, gives patients better quality of life, superior cosmetic outcome. Compared with traditional whole breast external beam radiotherapy, patients treated with TARGIT-IORT given during the lumpectomy procedure experience significantly fewer deaths: from non-breast-cancer causes: deaths from cardiovascular causes, lung problems and other cancers deaths are significantly reduced with TARGIT-IORT compared with extremal beam radiotherapy, because targeted intraoperative radiotherapy is more focussed and avoids scattered irradiation of nearby vital organs such as the lungs and the heart; such irradiation that inevitably accompanies extremal beam radiotherapy has been well documented to have short term and long term deleterious effects on patients. These side effects from external beam radiotherapy are even higher in smokers. With a high survival rate that modern treatments confer on early breast cancer patients, it is a shame that smokers amongst them will have a 23% chance of dying from heart attacks or lung cancer in the 30 year, an increased risk because they had external beam radiotherapy. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5548226/ Please see https://bit.ly/3LOnx5E	Thank you for your comment. This update has focused on dose fractionation for external beam radiotherapy and intraoperative radiotherapy is outside of the scope for this update. As such, we cannot review any of the referenced evidence in the comment or make any changes to the existing recommendations on intraoperative radiotherapy. The guideline does include information on intraoperative radiotherapy for the management of breast cancer, with a link to the NICE technology appraisal guidance (TA501) which currently does not recommend the routine commissioning of the intraoperative radiotherapy system for adjuvant treatment of early breast cancer. However, we will pass your comments onto the surveillance team who monitor guidelines for update.

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British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	3	1	The option of radiotherapy during breast-conserving surgery needs to be at the beginning of this document. Otherwise, patients will be denied this choice and that would contravene the GMC guidance on patient choice. Therefore, Radiotherapy during breast conserving surgery should form the first section before the section on Radiotherapy *after* breast conserving surgery. Figures showing results of TARGIT-A trial https://bit.ly/3ZhseIk	Thank you for your comment. This update has focused on dose fractionation for external beam radiotherapy and intraoperative radiotherapy is outside of the scope for this update. As such, we cannot review any of the referenced evidence in the comment or make any changes to the existing recommendations on intraoperative radiotherapy. The guideline does include information on intraoperative radiotherapy for the management of breast cancer, with a link to the NICE technology appraisal guidance (TA501) which currently does not recommend the routine commissioning of the intraoperative radiotherapy system for adjuvant treatment of early breast cancer. The position of the recommendation doesn't mean that it isn't an option where appropriate and as indicated by TA501.
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	3	18	It is no longer true that local control beyond 5 years is unknown. With partial breast radiotherapy with TARGIT-IORT, the long term local control up to 20 years is now known to be the same as whole breast radiotherapy as per NIHR funded large international randomised TARGIT-A clinical trial – this point should be added here. BMJ https://www.bmj.com/content/bmj/370/bmj.m2836.full.pdf British Journal of Cancer https://www.nature.com/articles/s41416-021-01440-8.pdf	Thank you for your comment. This update focused on external beam radiotherapy. The referenced articles reflect evidence for intraoperative radiotherapy which was out of scope for this update. Therefore, this review did not look at the evidence for intraoperative radiotherapy, and the committee were unable to make recommendations on its use. However, we will pass your comments onto the surveillance team who monitor guidelines for update.
British Association of Cancer	Guideline	3	20	It is not just potential reduction in late side effects – it is proven reduction should be mentioned that with TARGIT-IORT, there are fewer early and late	Thank you for your comment. This update focused on external beam radiotherapy. The referenced articles reflect evidence for intraoperative radiotherapy which

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Surgeons (BASO-ACS) & University College London				adverse effects, statistically fewer and clinically substantially deaths from causes other than breast cancer - BMJ https://www.bmj.com/content/bmj/370/bmj.m2836.full.pdf British Journal of Cancer https://www.nature.com/articles/s41416-021-01440-8.pdf And other papers (over 200 of which nearly 100 are after the 2018 guidelines) are here : https://bit.ly/TARGIT-IORT-Bibliography	was out of scope for this update. Therefore, this review did not look at the evidence for intraoperative radiotherapy, and the committee were unable to make recommendations on its use. However, we will pass your comments onto the surveillance team who monitor guidelines for update.
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	3	20	It is necessary to mention that with TARGIT-IORT there is a substantial overall survival benefit to patients with grade 1 or grade 2 cancers (aged>=45 years, with unifocal invasive ductal carcinoma up to 3.5cm in size, with no other exclusion criteria) – please see https://bit.ly/40j0X9H from reference British Journal of Cancer https://www.nature.com/articles/s41416-021-01440-8.pdf This overall survival benefit from TARGIT-IORT (compared with external beam radiotherapy) is similar in magnitude to that obtained by giving one year of trastuzumab (HERCEPTIN) for such patients. Please see https://bit.ly/40unfVE	Thank you for your comment. This update focused on external beam radiotherapy. The referenced articles reflect evidence for intraoperative radiotherapy which was out of scope for this update. Therefore, this review did not look at the evidence for intraoperative radiotherapy, and the committee were unable to make recommendations on its use. However, we will pass your comments onto the surveillance team who monitor guidelines for update.
British Association of Cancer Surgeons	Guideline	3 and 4	23, 24, 25 1 to 15	This recommendation should be modified to include the need to inform patients that the risk of local recurrence without radiotherapy is 9.8% even in the best prognosis cases and that this risk could be greatly reduced to a much lower level (the same as	Thank you for your comments. This update has focused on dose fractionation of external beam radiotherapy and although the committee were aware of the PRIME-II evidence this study and intraoperative radiotherapy were outside of the scope

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(BASO-ACS) & University College London				external beam radiotherapy), if they are given intraoperative radiotherapy (TARGIT-IORT) during their lumpectomy surgery; thus obviating any further visits to the hospital, and saving NHS resources. This is because the results of PRIME-II trial shows a 9.8% risk of local recurrence at 10 years when radiotherapy is omitted. Omitting radiotherapy even in the best prognosis-cohort of patients has this detriment of 1 in 10 women having to have repeat surgery and the consequences of having a recurrence (eg. Distant spread). Please see https://bit.ly/3nop7B2 In addition, while paying the price of high local recurrence these patients cannot even reap the benefit of avoiding irradiation of nearby vital organs by completely omitting radiotherapy. The benefit is wiped out because of the high local recurrence rates that would lead to higher breast cancer mortality, nullifying the reduction in benefit of fewer deaths from non-breast cancer causes https://www.abstractsonline.com/pp8/#!/9223/presentation/579 If instead these patients receive targeted intraoperative radiotherapy during lumpectomy surgery, there is no scattered irradiation of nearby organs such as the heart and the lung AND the effective radiotherapy leads to local control just the same as whole breast radiotherapy	for this update. Therefore, the committee did not look at this evidence and were unable to make recommendations relating to the use of intraoperative radiotherapy. However, we will pass your comments onto the surveillance team who monitor guidelines for update. The guideline does include information on intraoperative radiotherapy for the management of breast cancer, with a link to the NICE technology appraisal guidance (TA501). This guidance currently, does not recommend the routine commissioning of the intraoperative radiotherapy system for the adjuvant treatment of early breast cancer.

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				This information must be given to patients before they have their cancer operation so that they still can avail of the option to receive TARGIT-IORT during their operation.	
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	5	1 to 8	This table needs to include the data from the comment 8 and explain that despite paying the price of high local recurrence (1 in 10) the patient do not derive any benefit of avoidance of scattered irradiation because it is nullified by the higher breast cancer mortality leading to zero overall survival benefit.	Thank you for your comment. This update focused on dose fractionation of external beam radiotherapy. Data from the referenced articles in your comment above focus on intraoperative radiotherapy which is outside the scope of this update, and the committee were therefore unable to make any changes to the table you refer to, as it was out of the scope of this update. However, we will pass your comments onto the surveillance team who monitor guidelines for update.
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	6	1 to 10	Also mention another point that there is no survival benefit of giving radiotherapy after a mastectomy unless they are heavily node positive.	Thank you for your comment. This update focused on dose fractionation using external beam radiotherapy. The decision about when to give radiotherapy was out of scope for this update.
British Association of Cancer Surgeons (BASO-ACS) &	Guideline	6 And 7	11 to 15 1 to 7	Mention that with the 26 Gy over 5 fractions, there is significantly higher toxicity – 19 times more risk of fibrosis as assessed by physicians, which means that 25% of patients complain of a hardened and firmer breast – this is much higher than the 3 or 5 week regimens. There is also no improvement in survival by giving this 5-day regimen.	Thank you for your comments. The risks and benefits of treatment are discussed in the rationale section of the guideline and the committee discussion section in the evidence review. These sections highlight that the committee were aware that the evidence does not show increased survival for people receiving the 26 Gy in 5 fractions

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University College London				More importantly this guideline is based on a study where the follow up short and is not as complete – with a short median follow up of just 5 years. The Fast Forward paper states that "*5-year visit forms were available for 3681 (96%) patients of 3833 still in follow-up (not died, withdrawn, or lost)*." This could not have been strictly true because at this point in follow up, the number 'at risk' on the published Kaplan-Meier plot of overall survival at the 5-year mark (adding all 3 treatment groups together) was down to just 3213 patients, with 657 patients censored. These 657 censored patients would of course have been seen on or before the 5th anniversary of their day of randomisation. Therefore, unless 468 (3682 minus 3213) of the 657 patients were genuinely seen at the 5th anniversary of their day of randomisation, the completeness of follow up at 5 years would actually be lower than the 96% that they have claimed. If all these patients were seen before the 5th anniversary then the figure would be actually 3213/3833 which is 83.8%, rather than the 96% that the authors have led the readers to believe. https://www.bmj.com/content/370/bmj.m2836/rr-8 This information about short and incomplete follow up should be shared with patients before they have their surgery and they should be given a choice of having radiotherapy during their lumpectomy operation (TARGIT-IORT) which not only is more convenient, it is less expensive, improves breast related quality of	compared with 40 Gy in 15 fractions. However, survival with 26 Gy in 5 fractions was not worse than 40 Gy in 15 fractions and there are some benefits for the 5 fractions regimen, such as the need for fewer attendances. This informed the committee's decision to recommend the 26 Gy in 5 regimen for many people who have external beam radiotherapy. The committee also included a recommendation to discuss the risks and benefits of the 2 regimens with patients. One of the main discussion points for the committee was the limited availability of long-term data. This is highlighted in the committee discussion section of the evidence review. When long-term data, are published we will assess them for impact on our recommendations and may update the relevant sections of the guideline if appropriate. The committee also made recommendations for future research, each of which highlighted the need for studies to provide longer term data. More information on the research recommendations can be found in Appendix K of the evidence review (evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens). Intra-operative radiotherapy was out of scope for this update and therefore wasn't considered as an intervention for this review. The committee therefore could not compare the effectiveness of this intervention in comparison with the other regimens,

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				life, reduces hospital visits, travel times, and other benefits. Most importantly reduces non-breast cancer deaths that leading to substantial improvement in overall survival in the large subgroup of patients with grade 1 and grade 2 cancers. The breast cancer mortality and local control with TARGIT-IORT in every subgroup of patients is the same as whole breast radiotherapy. BMJ https://www.bmj.com/content/bmj/370/bmj.m2836.full.pdf British Journal of Cancer https://www.nature.com/articles/s41416-020-01233-5.pdf British Journal of Cancer https://www.nature.com/articles/s41416-021-01440-8.pdf Environmental and Social impact https://bmjopen.bmj.com/content/6/5/e010703 QOL improvement references: Sperk, E., et al., Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: results from the randomized phase III trial TARGIT A. Breast Cancer Res Treat, 2012. 135(1): p. 253-60. https://link.springer.com/article/10.1007/s10549-012-2168-4 Corica, T., et al., Cosmesis and Breast-Related Quality of Life Outcomes After Intraoperative Radiation Therapy for Early Breast Cancer: A Substudy of the TARGIT-A Trial. Int J Radiat Oncol Biol Phys, 2016. 96(1): p. 55-64. https://www.redjournal.org/article/S0360-	or make recommendations on intra-operative radiotherapy.

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				3016(16)30135-3/fulltext Welzel, G., et al., Health-related quality of life after breast-conserving surgery and intraoperative radiotherapy for breast cancer using low-kilovoltage X-rays. Annals of surgical oncology, 2010. 17 Suppl 3: p. 359-67. https://link.springer.com/article/10.1245/s10434-010-1257-z	
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	6 And 10	13 26	There is absolutely no RCT evidence for safety or efficacy of the 26 Gy in 5 fraction regimen for use as partial breast radiotherapy. The rationale to use this regimen for partial breast radiation needs to be established by randomised trial data. The guideline committee must remember that many 'logically sound' cancer treatments have been repeatedly disproven to be ineffective or toxic (please see the books Ending Medical Reversal and Malignant) – hence the need to change practice based on evidence and not peer-pressure or 'logic' Therefore, the phrase partial must be removed from this sentence. The Fast Forward trial based on which this regimen is being promoted, did not have any patients receiving partial breast regimen. That regimen involved only whole breast radiotherapy and has been found to be efficacious but provides no survival benefit and a much worse quality of life and cosmetic and worse patient related outcomes – e.g., hardened and firm breast in 25% of cases and 19 times higher incidence of fibrosis as per physician assessment.	Thank you for your comments. The committee discussed how the 40 Gy in 15 regimen is comparable to the 26 Gy in 5 fractions regimen for people who had whole breast radiotherapy. The committee agreed that there is no evidence for the effectiveness of this regimen in people having partial breast radiotherapy, but as they are considered a lower risk group than those having whole breast radiotherapy the committee were confident the results could be to extrapolated to this population without the risk of unexpected adverse events. The committee also thought that only offering the 40 Gy in 15 regimen to people who have partial breast radiotherapy may disadvantage a large proportion of the treatment population and would not be in line with current practice. The committee were aware of the role that the COVID-19 pandemic played in the promotion of different hypofractionation regimens, but, based on the evidence and their clinical experience, they were confident that 26 Gy in 5 regimen is comparably effective and safe to the 40 Gy in 15 regimen. For further information on the committee's discussion,

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				Unfortunately, this regimen was promoted during COVID_19 even before the data were peer-reviewed and published and is not used in most other parts of the world. https://www.bmj.com/content/370/bmj.m2836/rr-8	please refer to the rationale in the guideline and the committee discussion section in evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens.
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	General	General	These guidelines do not properly follow the principle laid out in the first line (page2 section 1.10.1, lines 4 and 5) viz. recommend using radiotherapy technique that minimises the dose to the lung and heart However, as they overlook important new evidence peer reviewed and published randomised trials published in high impact journals, they will be misleading. The best method of radiotherapy that avoids radiation of the lung and the heart is TARGIT-IORT (https://targit.org.uk) for which long term (up to 20 years follow up) of the randomised TARGIT-A trial have been published since the last guidelines were published and show a reduction in mortality by avoiding radiation dose to the lung and heart. Also, the TARGIT-A trial was the first large RCT to propose and test the hypothesis of PBI and it is misleading to omit this information from clinicians and patients whilst including subsequent and less clinically important trials.: In June 2010, the conclusion of the first publication of the TARGIT-A trial was displayed on the front page masthead of the Lancet: stating: "*For selected patient with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be*	Thank you for your comment. Recommendation 1.10.1 refers to whole breast radiotherapy. Both recommendation 1.10.1 and 1.10.2 refer to techniques that will reduce the dose to the heart and lung, such as the breath hold technique, which is standard of care in centres across the UK and can be used for both the 26 Gy in 5 fractions and 40 Gy in 15 fractions regimens. This update focused on external beam radiotherapy. Intraoperative radiotherapy is outside of the scope for this update. As such, we cannot review any of the referenced evidence in the comment or make any changes to the existing recommendations on intraoperative radiotherapy. However, we will pass your comments onto the surveillance team who monitor guidelines for update.

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				considered as an alternative to external beam radiotherapy..". The accompanying independent commentary that was prompted by the TARGIT-A trial results was entitled "*Partial breast irradiation: new standard for selected patients*" https://bit.ly/3ZoXeWB In 2020, the long-term results of the TARGIT-A trial were published in the BMJ which confirmed the early results. These and further analysis also confirmed the reduction in mortality and improvement in overall survival in large subgroups of patients with grade 1 or 2 cancer. This is a substantial improvement – a 28% reduction in overall mortality (improvement in overall survival) is seen with TARGIT-IORT compared with external beam radiotherapy. Furthermore, even though local recurrence is not common with both TARGIT-IORT and external beam radiotherapy, the prognosis of patients *after* local recurrence is poor if the local recurrence occurs after external beam radiotherapy. On the contrary if patients get a local recurrence after TARGIT-IORT, their prognosis remains the same as those without local recurrence. Please see these links to the latest long-term results of the TARGIT-A trial published in 2020 and 2021 BMJ https://www.bmj.com/content/bmj/370/bmj.m2836.full.pdf	

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				British Journal of Cancer https://www.nature.com/articles/s41416-020-01233-5.pdf British Journal of Cancer https://www.nature.com/articles/s41416-021-01440-8.pdf It is not adequate to refer to 2018 guideline of intraoperative radiotherapy because they are outdated These 2023 edition of radiotherapy guidelines which relate to radiotherapy for breast cancer must include TARGIT-IORT as an option for patients, especially when it already includes sections on partial breast irradiation (PBI) – of which TARGIT-IORT is a prime example with the largest amount of data amongst PBI trials for invasive breast cancer, as well as the and most complete follow up : see figure 6 taken from https://www.bmj.com/content/370/bmj.m2836 shows the amount of data: https://bit.ly/3zbHDiO	
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	General	General	Offering only external beam radiotherapy in these guidelines and omitting intraoperative radiotherapy with TARGIT-IORT a) Exacerbates treatment inequalities (examples below) b) Conflicts with NICE and NHS principles of diversity, equality, equity and justice in the population Conflicts with GMC guidance that dictates that patients should be offered a choice for their treatment	Thank you for your comments. This update has focused on external beam radiotherapy and intraoperative radiotherapy is outside of the scope of this update. Therefore, this review did not look at the evidence for intraoperative radiotherapy, and the committee were unable to make recommendations on its use. The guideline does include information on intraoperative radiotherapy for the management of breast cancer with a link to the NICE technology

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				(particularly when the choice will improve their convenience, QOL and reduce deaths)	appraisal (TA501) guidance which does not currently recommend the routine commissioning of the intraoperative radiotherapy system for adjuvant treatment of early breast cancer. Information about patient choice has been included in the guideline, with the recommendation for the use of 40 Gy in 15 for some people to allow for adjustments of treatment for people with 'any other factor' that may affect their treatment efficacy and safety. Moreover, the recommendations also highlight the importance of assessing the risks and benefits of each treatment regimen as per the NICE guidelines on patient experiences in adult NHS services (CG138) and the shared decision making (NG197) NICE guideline. This therefore includes a discussion between a clinician and patient to establish which radiotherapy regimen is most appropriate.
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	General	General	An issue of inequality, inequity and loss of dignity: Example 1: Learning Disabilities: Patients with learning difficulties are offered health screening and assessment. These patients must be offered similar treatment options as breast cancer patients who do not have learning difficulties. However, due to the practical and safety aspects of administering traditional post-operative external beam radiotherapy (whether whole breast or partial breast) cannot be offered to them. These patients are then unable to be considered for breast conservation / breast preservation. (It is not safe or possible for carers to remain with patients with moderate or	Thank you for your comment. The committee discussed your comment and how the decision to offer people with severe learning disabilities radiotherapy is made by a multidisciplinary team. In the committee's experience, people with severe learning disabilities may be coached and risk assessed for radiotherapy prior to their treatment. These assessments and opportunities for coaching mean that not everyone with learning difficulties is denied radiotherapy. For people with learning disabilities who are assessed as being suitable for radiotherapy, a shorter treatment duration such as the newly

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				severe learning difficulties whilst radiotherapy is being administered). These disadvantaged patients, are therefore given mastectomy the only viable choice. By not including TARGIT-IORT in the guidelines NICE will promote such inequality and inequity. Therefore, these patients must be offered the option of preserving their breast by the use of intra-operative radiotherapy (TARGIT-IORT) at the time of surgery under the same anaesthetic, thereby removing the need to lie still for external beam radiotherapy and avoiding a mastectomy.	recommended 26 Gy in 5 fractions over 1 week may be more tolerable and practical. More information on the committee's discussion of these issues can be found in the discussion section of the evidence review (review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens) and the equalities and health inequalities assessment (EHIA) for this update. Intraoperative radiotherapy is outside the scope of the current update and as such the committee did not look at any evidence for this topic and were unable to make any changes to the recommendation concerning intra-operative radiotherapy.
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	General	General	An issue of inequality, inequity and loss of dignity: example 2: Deprivation It is well attested that certain groups do not have easy access to health services; the homeless, the travelling communities, prisoners etc. For patients within these groups who might have a diagnosis of breast cancer, the options for breast conservation and the need to access a radiotherapy centre for a number of sessions following surgery are difficult and often impossible. In these patients a mastectomy is thought to be preferable (by proxy) only because of the impractical or even impossibility of attending for radiotherapy. These vulnerable patients are therefore forced into more extensive surgery that they may not require or desire. If a similarly efficacious radiotherapy treatment such as TARGIT-IORT were to be given at the time of the breast conserving	Thank you for your comment. These groups were identified in the equalities and health inequalities assessment (EHIA) and the committee thought that the reduced number of appointments associated with the 5 fraction regimen would help with access. More information on discussions about this can be found in the committee discussion section of the evidence review (evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens) and the EHIA. Intraoperative radiotherapy is outside the scope of the current update and as such the committee did not review evidence for the topic and are unable to make any changes to the recommendation concerning intra-operative radiotherapy.

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				surgery this group of patients could retain their breast, and dignity too.	
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	General	General	An issue of inequality, inequity and loss of dignity: example 3: Zero-hours contracts and Self-Employed patients. Many people are employed on zero-hours contracts meaning that considerations on the impact of travelling time and attendance for treatment will affect decisions. A patient who has a considerable distance to travel to receive radiotherapy, or one in whom this will impact their employment will be more likely to choose a surgical option where no radiotherapy is required, such as a mastectomy. Instead, if TARGIT-IORT were to be offered to this group of patients then the concerns about loss of income and impact of travel time etc would be negated.	Thank you for your comment. These groups were identified in the equalities and health inequalities assessment (EHIA) and the committee thought that the reduced number of appointments associated with the 5 fraction regimen would help with access. More information on discussions about this can be found in the committee discussion section of the evidence review (evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens) and the EHIA. Intraoperative radiotherapy is outside the scope of the current update and as such the committee did not review evidence for the topic and are unable to make any changes to the recommendation concerning intra-operative radiotherapy.
British Association of Cancer Surgeons (BASO-ACS) & University College London	Guideline	General	General	We would like to alert the committee of a potential financial disincentive to use IORT, previously reported to the NICE MTA panel: the activity and fees are considerably higher for external beam radiotherapy than for intraoperative radiotherapy all over the world. For example, in the USA, the radiation oncologist's fees are typically $2330 to $3008 for a usual course of external beam radiotherapy while they are only $871 if they prescribe TARGIT-IORT. These fees would be similar to each other if the payment were by value than by activity; adopting a value-based-payment is promoted by clinicians and policy makers around the world.	Thank you for your comment. This update had focused on external beam radiotherapy and intraoperative radiotherapy is outside of the scope of this update. The committee did not review evidence for the topic and are unable to make any changes to the recommendation concerning intra-operative radiotherapy. As part of our methods for developing guidelines, we take into account the cost effectiveness of interventions when reviewing evidence. This weighs up both of the relative costs and the benefits of a treatment and assesses whether they can be

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				See figure 1, page 258 (https://bit.ly/40hfdj3) , "The TARGIT-A randomised trial -TARGIT-IORT vs whole breast radiotherapy: long term local control and survival: In Reply to Ward et al, 01/01/2023, International Journal of Radiation Oncology Biology Physics, https://pubmed.ncbi.nlm.nih.gov/36526392/ Patients should not be denied an improved quality of life and survival benefit because of financial considerations.	considered value for money. We prioritise economic evidence from UK sources, since evidence from other countries is less likely to be applicable, given the difference in funding systems that you've highlighted. Alongside our guidance we publish a Resource Impact Assessment to allow local teams to estimate the cost impact of implementing a new recommendation. More information on this for the recommendations on dose fractionation can be found in the evidence review (evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens).
British Association of Cancer Surgeons (BASO-ACS) & University College London	Methods, Evidence Review	General	General	The collated evidence is incomplete and omits important data published in 2020, 2021 and 2022 In the papers and studies examined (and subsequently listed as dismissed in Appendix J) there is no mention made of targeted intra-operative radiotherapy (TARGIT-IORT) as a partial breast, single-fraction treatment for early breast cancer. This important and large (n=2298) randomised controlled trial was published in August 2021 in the British Medical Journal and compared a single fraction of radiotherapy (20gy) given at the time of surgery, with standard external beam radiotherapy. This is a serious omission of important high impact publications (led by teams in the UK and regarded by a breakthrough by NIHR). The TARGIT research was hailed by NIHR as one of the 5 major health breakthroughs in the previous 12 months.	Thank you for your comment. This update has focused on dose fractionation for external beam radiotherapy and intraoperative radiotherapy is outside of the scope for this update. As such, we cannot review any of the referenced evidence in the comment or make any changes to the existing recommendations on intraoperative radiotherapy. The guideline does include information on intraoperative radiotherapy for the management of breast cancer, with a link to the NICE technology appraisal guidance (TA501) which currently, does not recommend the routine commissioning of the intraoperative radiotherapy system for adjuvant treatment of early breast cancer. However, we will pass your comments onto the surveillance team who monitor guidelines for update.

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				https://bepartofresearch.nihr.ac.uk/Articles/Health-research-breakthroughs/ We would strongly advice that the guidance reflects what patients regard as important choices rather than their choices being potentially censored by clinicians who may have their own views/ agenda about what is or is not important for patients. Notably, this treatment is now adopted worldwide and is included in several national guidelines. By the beginning of 2020, 260 centres in 38 countries had treated over 45000 patients with TARGIT-IORT and through the COVID-19 pandemic these numbers would have increased considerably. https://www.targit.org.uk/targit-iort-in-guidelines It is still not widely available in the UK. Please see a list of over 200 important references that do not seem to have been considered in this review. These can be accessed online at https://bit.ly/TARGIT-IORT-Bibliography	
NHS England	Guideline	07	01	We strongly suggest this section makes to reference the importance of communication when discussing the risks and benefits of recommendations and the communication of information. Staff should communicate with and try to understand the person they are caring for. Check with the person themselves, their family member or carer or their	Thank you for your comments. The committee discussed the importance of shared decision making, tailoring health care to personal needs and ensuring that information is provided in a clear and suitable format. The committee therefore included a recommendation linking to the sections covering communication in the NICE guideline on patient

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				hospital or communication passport for the best way to achieve this and involve families and carers in conversations regarding their care where requested or stated as a preference. Use simple, clear language, avoiding medical terms and 'jargon' wherever possible. Some people may be non-verbal and unable to tell you how they feel. Pictures may be a useful way of communicating with some people, but not all. Staff should also be aware of and pay attention to healthcare passports: Some people with a learning disability and some autistic people may have a healthcare passport giving information about the person and their health needs, preferred method of communication and other preferences. Ask the person or their accompanying carer if they have one of these.	experience in adult NHS services (CG138) and the shared decision making NICE guideline (NG197). The committee also discussed specific considerations for people with learning disabilities for example, making adjustments to how information is provided and coaching for patients who are having radiotherapy. The committee's discussions of health inequalities are included in the committee discussion section of the evidence review and in the equalities and health inequalities assessment (EHIA) of this update.
NHS England	Guideline	General	General	We strongly suggest making reference to reasonable adjustments throughout the guideline and feel there is room for this to be reflected in the updated content. Reasonable adjustments are a legal requirement as stated in the Equality Act 2010 and is important to help you make the right diagnostic and treatment decisions for an individual. You can ask the person and their carer or family member what reasonable adjustments should be made. Adjustments aim to remove barriers, do things in a different way, or to provide something additional to enable a person to receive the assessment and treatment they need.	Thank you for your comment. As reasonable adjustments are a legal requirement, we expect that these are being implemented and therefore don't include specific mention of them as part of the recommendation on discussing the benefits and risks about treatment decisions. However, we have considered these issues in some detail during the development of this update. In developing the recommendations, the committee took into account the health inequalities issues identified as part of the equalities and health inequalities assessment (EHIA) that accompanies this work. The issues identified included the barriers

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					people with learning disabilities and people from neurodiverse populations may face when accessing treatment and information about treatment options. The committee agreed that it is important that a person's individual circumstances are taken into consideration when planning treatment. This includes providing information about radiotherapy in a format most appropriate for each person, and tailoring treatment choices to the individual. For this reason, a recommendation is included which refers to the sections on communication in the NICE guidelines on patient experience in adult NHS services (CG138) and shared decision making NICE guideline (NG197). In addition, one of the recommendations includes a statement that rather than the 26 Gy in 5 fractions regimen, a 40 Gy in 15 fractions regimen can be considered for people who have 'any other factor' that may affect their treatment efficacy, acceptability and safety. This enables treatment to be tailored to the individual patient's needs. Further information about what the committee considered when making recommendations and more information about their discussions can be found in the rationale of the guideline, the committee discussion section of the evidence review (evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens) and the EHIA document.

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Royal College of Radiologists	Guideline	General	General	We wish to make the following comments on this draft document: The committee refer to 2 randomised trials (RCT) comparing 40Gy in 15 fractions with 26Gy in 5 fractions. We are only aware of 1 RCT with published primary endpoints using these dose-fractionation regimens – this is FAST-Forward[1]. The FAST study did investigate 5-fraction radiotherapy, but this was over 5 weeks and did not include 26Gy in 5 fractions over 1 week[2]. In addition, the control group in FAST was 50Gy in 25 fractions not 40Gy in 15 fractions. The HYPORT-Adjuvant trial has reported acute toxicity and dosimetry quality assurance but is still recruiting[3]. Please can details of the second RCT be described in the text? References 1. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. 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. Lancet. 2020;395(10237):1613-26. 2. Brunt AM, Haviland JS, Sydenham M, Agrawal RK, Algurafi H, Alhasso A, Barrett-Lee P, Bliss P, Bloomfield D, Bowen J, Donovan E, Goodman A, Harnett A, Hogg M, Kumar S, Passant H, Quigley M, Sherwin L,	Thank you for your comment. The committee reviewed evidence from 2 RCTs that compared 40 Gy in 15 fractions with 26 Gy in 5 fractions. The first study was the FAST-Forward trial. The second study was Ivanov, a Serbia-based study, which was published in 2022. Both studies randomised people with early and or locally advanced breast cancer requiring radiotherapy. References for both of the studies can be found below. Details of each study can be found in the evidence review document which was uploaded alongside the guideline in the consultation period and will also be published with the guideline. The FAST trial was included as part of our review, but this did not inform the recommendations on 26 Gy in 5 fractions because, as you mention, it took place over 5 weeks. The committee focused on the FAST-Forward and Ivanov 2022 studies when discussing the recommendations as they considered these to be most relevant to current practice. More information on the FAST study, and how the committee considered the whole evidence base in addition to the FAST-Forward and Ivanov 2022 studies, can be found in evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens. The evidence review will be uploaded in the evidence tab for the guideline. 1. Brunt, A.M., Haviland, J. S., Wheatley, D. A., Sydenham, M. A., Alhasso, A., Bloomfield, D.

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				Stewart A, Syndikus I, Tremlett J, Tsang Y, Venables K, Wheatley D, Bliss JM, Yarnold JR. Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer. J Clin Oncol. 2020 Oct 1;38(28):3261-3272. doi: 10.1200/JCO.19.02750. Epub 2020 Jul 14. PMID: 32663119; PMCID: PMC7526720. Chakraborty S, Chatterjee S; Hyport Adjuvant Author Group. HYPORT adjuvant acute toxicity and patient dosimetry quality assurance results - Interim analysis. Radiother Oncol. 2022 Sep;174:59-68. doi: 10.1016/j.radonc.2022.07.003. Epub 2022 Jul 9. PMID: 35817323.	J., … Yarnold, J. (2020). 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. The Lancet, 395(10237), 1613–1626. doi:10.1016/s0140-6736(20)30932-6 **2.** Ivanov, O., Milovancev, A., Petrovic, B., Prvulovic Bunovic, N., Licina, J., Bojovic, M., … Lalic, N. (2022). Ultra-Hypofractionated vs. Moderate Fractionated Whole Breast Three Dimensional Conformal Radiotherapy during the COVID-19 Pandemic. Medicina (Kaunas, Lithuania), 58(6). doi:10.3390/medicina58060745
Royal College of Radiologists	Guideline	General	General	The committee state that: "..the evidence did show that there was a higher incidence of outcomes related to adverse events at 5 years (such as normal tissue effects, and quality of life measurement related to swollen breast and harder or firmer breasts) for people who were given 26Gy in 5 fractions compared with 40 Gy in 15 fractions". This is incorrect. The only statistically significant difference with 26Gy compared with 40Gy was clinician-assessed breast induration outside the tumour bed. However, the clinical significance of this is questionable as the absolute treatment effects are tiny: less than 1% moderate/marked at 5 years in 40Gy and 2% in 26Gy. The committee have appeared to have considered p< 0.05 as statistically significant instead	Thank you for your comment. The committee noted that for most outcomes the differences between 5 fractions and 15 fractions were not clinically meaningful. The committee discussed that there were slightly fewer clinician assessed adverse events and that quality of life scores were slightly higher for some outcomes for people receiving 40 Gy in 15 fractions compared to 26 Gy in 5 fractions. However, they did not think this was an indication of potential severe harms and this is why the 5 fraction regimen is recommended for most people. This is further explained in the committee discussion section of evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens. In addition, Appendix L: Methods sets out

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				of following the methodology in the published paper (pre-specified in the statistical analysis plan), which was to take a threshold of p< 0.005 as significant for adverse effect outcomes given the large number of tests performed.	how clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. This is different to the interpretation of statistical significance using p values. We have also edited our explanation in the rationale to reflect this discussion and highlight that the differences between regimens did not show a clinically meaningful difference that would cause concerns about recommending the 5 fraction regimen.
Royal College of Radiologists	Guideline	General	General	Fatigue has not been reported in any publication associated with the FAST-Forward or FAST trials (fatigue data were not collected in FAST). Therefore, we would like to know where the committee obtained the evidence to support their statement: "The committee also noted that some people experienced increased levels of fatigue from the 5-day regimen". Given that the acute effects with 26Gy were reduced and shorter compared with 40Gy, we could hypothesise that fatigue could be less with a 5-fraction regimen. There are no reported results to support this from FAST-Forward[4] but there are published data demonstrating that a 28.5Gy/5#/2 weeks regimen is associated with less fatigue than a 40Gy in 15# over 3 week regimen[5]. References:	Thank you for your comment. NICE recommendations are based on a combination of the evidence base and the committee's clinical knowledge and experience. The example of fatigue was discussed by the committee as one of the reasons why, in their experience, the 40 Gy in 15 fractions regimen may be preferred by some people. Other adverse events that the committee were also aware of included fibromyalgia, breast oedema and pain with the 5 fraction regimen. The committee discussed your comments and acknowledged that concern about fatigue does not mean that a person cannot be offered the 5 fraction regimen. Therefore, fatigue has been removed as a specific example from the recommendation highlighting the use of 40 Gy in 15 for certain people and other examples of factors or people who may be offered 40 Gy in 15 were included. More information about some of the factors that may make the 40 Gy in 15 fractions regimen more suitable for someone are discussed in the

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				3. Brunt AM, Wheatley D, Yarnold J, Somaiah N, Kelly S, Harnett A, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. Radiother Oncol. 2016;120(1):114-8. Van Hulle H, Vakaet V, Monten C, Deseyne P, Schoepen M, Colman C, Paelinck L, Van Greveling A, Post G, Speleers B, Vandecasteele K, Mareel M, De Neve W, Veldeman L. Acute toxicity and health-related quality of life after accelerated whole breast irradiation in 5 fractions with simultaneous integrated boost. Breast. 2021 Feb;55:105-111. doi: 10.1016/j.breast.2020.12.009. Epub 2020 Dec 24. PMID: 33401157; PMCID: PMC7785945.	rationale of the guideline and in the committee's discussion section of the evidence review (evidence review M: on the effectiveness of different external beam hypofractionation radiotherapy regimens).
Royal College of Radiologists	Guideline	General	General	Concomitant chemotherapy is not standard of care for adjuvant breast radiotherapy. We would not recommend this with any dose-fractionation regimen within routine practice outside of a clinical study. Therefore, this recommendation needs to be removed. The Katherine trial[6] investigated the antibody-drug-conjugate TDM-1 and the protocol stated that "When indicated, radiotherapy is to be given concurrently with study therapy" and "Dose fractionation of adjuvant whole breast, chest wall and regional node radiotherapy may be done according to local institutional guidelines". Therefore, there is no evidence to recommend TDM-1 concomitantly with a specific dose-fractionation regimen.	Thank you for your comment. The committee discussed your comments and have removed any reference to concurrent chemotherapy from all the recommendations in this section and the research recommendations.

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				Reference: von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, Jacot W, Conlin AK, Arce-Salinas C, Wapnir IL, Jackisch C, DiGiovanna MP, Fasching PA, Crown JP, Wülfing P, Shao Z, Rota Caremoli E, Wu H, Lam LH, Tesarowski D, Smitt M, Douthwaite H, Singel SM, Geyer CE Jr; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019 Feb 14;380(7):617-628. doi: 10.1056/NEJMoa1814017. Epub 2018 Dec 5. PMID: 30516102.	
Royal College of Radiologists	Guideline	General	General	We do not agree with the current statement recommending 40Gy in 15F fractions in the following situation: '…have any other factor that would mean having radiotherapy over 3 weeks is more acceptable (for example, people who experience high levels of fatigue". The example of fatigue is not evidence-based as far as we are aware and "any factor" is open to anecdotal interpretation.	Thank you for your comment. The section of the recommendation about 'any other factor' was based on a combination of the evidence and the committee's clinical knowledge and experience. Fatigue was discussed by the committee as one of the reasons why, in their experience, the 40 Gy in 15 fractions regimen may be preferred by some people. Other adverse events that the committee were also aware of included fibromyalgia, breast oedema and pain with the 5 fraction regimen. The committee discussed your comments and acknowledged that concerns about fatigue do not mean that a person cannot be offered the 5 fraction regimen. In the committee's experience, there are a range of factors that might mean that someone is more suited to 40 Gy in 15 fractions than 26 Gy in 5 fractions. More information about some of the factors that may

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					make the 40 Gy in 15 fractions regimen more suitable for someone are discussed in the rationale of the guideline and in the committee's discussion section of the evidence review. The committee also removed mention of fatigue in the recommendation but included other examples of factors or people who may be offered 40 Gy in 15.

**None of the stakeholders who commented on this clinical guideline have declared any links to the tobacco industry.*