NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Intrabeam targeted intraoperative radiotherapy for treatment of early or locally advanced breast cancer

Decision of the panel

Introduction

1. An appeal panel was convened on 8 December 2017 to consider an appeal against NICE's final appraisal determination, to the NHS, on Intrabeam targeted intraoperative radiotherapy for treatment of early or locally advanced breast cancer.

2. The appeal panel consisted of:

• Patrick Storrie	Chair
• Prof Angela Coulter	Non-Executive Director
• Dr Biba Stanton	Health Service Representative
• David Tyas	Industry Representative
• Colin Standfield	Lay Representative

3. None of the members of the appeal panel had any competing interest to declare.

4. The panel considered a joint appeal submitted by the Royal College of Radiologists, Independent Cancer Patients' Voices and the Royal College of Physicians.

5. The joint appellant was represented by:

• Dr Jeanette Dickson	Vice President, Clinical Oncology, Royal College of Radiologists
• Dr Charlotte Coles	Reader in Breast Radiation Oncology at the University of Cambridge and Consultant Clinical Oncologist
• Prof John Yarnold	Professor of Clinical Oncology, The Institute of Cancer Research
• Mairead Mackenzie	Trustee, Independent Cancer Patients' Voices

6. In addition the following individuals involved in the appraisal were present and available to answer questions from the appeal panel:

• Dr Jane Adam	Appraisal Committee Chair
• Meindert Boysen	Programme Director, Centre for Health Technology Evaluation
• Janet Robertson	Associate Director
• Joanna Richardson	Technical Adviser

7. NICE's legal adviser Stephen Hocking was also present.

8. Under NICE's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

9. There are two grounds under which an appeal can be lodged:

   Ground One: In making the assessment that preceded the recommendation, NICE has:
   a) Failed to act fairly
   b) Exceeded its powers.

   Ground Two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

10. The Vice Chair of NICE (Dr Rosie Benneyworth) in preliminary correspondence had confirmed that:

    - The joint appellant had potentially valid grounds of appeal as follows:
      - Ground 1a: NICE has failed to act fairly
      - Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE

11. The appraisal that is the subject of the current appeal provided advice to the NHS on Intrabeam targeted intraoperative radiotherapy for treatment of early or locally advanced breast cancer.

12. Before the appeal panel inquired into the detailed complaints the following made a preliminary statement: Dr John Yarnold, Dr Charlotte Coles and Mairead Mackenzie on behalf of the joint appellant and Dr Jane Adam on behalf of the appraisal committee.

13. The relationship between preventing local recurrence and reducing mortality in the treatment of early or locally advanced breast cancer was raised by the appellants under both Ground 1a and Ground 2. There was therefore some overlap in the points raised during the hearing under these two grounds. However, the appeal panel felt there were distinct appeal points concerning fairness and reasonableness, so these have been presented separately in this decision letter.

Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly. *"There was a failure of procedure by the appraisal committee at the final consultation resulting in a serious factual inaccuracy in the Final Appraisal Determination (FAD) Section 4.2. This states: "A clinical expert confirmed that local recurrence is not related to an increased risk of metastatic disease or mortality". This statement as it stands is inaccurate because it is incomplete. It is correct only in a small, highly selected group of older women (60 years or above) with very low risk breast cancer (small, low grade, oestrogen receptor positive and node negative). The current FAD, if enacted, would allow treatment of patients outside the low risk category with Intrabeam, potentially leading to avoidable excess mortality from breast cancer."*

14. Prof John Yarnold for the joint appellant, stated that two systematic reviews regarded as international gold standards estimate that one breast cancer death can be prevented for every four local recurrences prevented. He went on to estimate that this would translate into somewhere between one excess death per 60 women treated with Intrabeam and one excess death per 400 women treated with Intrabeam.

15. Dr Charlotte Coles for the joint appellant said that the statement in the FAD that "A clinical expert confirmed that local recurrence is not related to an increased risk of metastatic disease or mortality" was incorrect. She confirmed that she had been the clinical expert who had given that advice. However, she had believed that it was implicit in her statement that this applied only to a small subgroup of low risk women. She assumed the notion that one breast cancer death can be prevented for every four local recurrences prevented was so widely accepted that it need not be stated explicitly. She also commented that the meeting of the appraisal committee on 15 November 2016 was running very late and that she felt pressured and unable to expand on her evidence as she would have liked to.

16. Mairead Mackenzie for the joint appellant said that patients want to be informed of significant risks, especially where these concern an increased risk of death.

17. Dr Jane Adam for NICE stated that Dr Charlotte Coles attended four meetings and that the appraisal committee had listened carefully to her evidence. She pointed out that the statement the appellants are concerned about also appeared in the second Appraisal Consultation Document (ACD 2). Dr Coles had an opportunity to comment on the way her evidence was used in ACD 2 in her response to the consultation but she did not do so.

18. Dr Jane Adam, asked by the appeal panel whether evidence that preventing local recurrence may reduce mortality had been heard by the committee, said that it had. She stated that the meta-analysis which suggested that one breast cancer death can be prevented for every four local recurrences prevented was included in the systematic review by the Assessment Group and had also been highlighted by two consultees. She said that a higher risk of metastatic disease and death with Intrabeam was included in the statistical model used by the Assessment Group.

19. In response to a further question from the panel, Dr Adam said that the relationship between local recurrence and mortality was not discussed in detail at the appraisal committee meeting of 15 November 2016 but pointed out that it had not been highlighted by the clinical experts present at that meeting. Furthermore, she believed that it was not relevant at that meeting because the appraisal committee were not minded to favour making a positive recommendation for the routine use of Intrabeam in the NHS.

20. The appeal panel concluded that the appraisal committee had heard the evidence that preventing local recurrence may reduce mortality. This was clear both from the use of different mortality rates in the model and from the responses to ACD 2. They acknowledged Dr Coles' concern that her evidence at the meeting of 15 November 2016 may have been rushed. However, the panel concluded that this did not constitute unfairness because Dr Coles had opportunities to correct any perceived misinterpretation of her advice and because this evidence on the link between local recurrence and mortality had been heard by the appraisal committee elsewhere in the process.

21. The appeal panel therefore dismissed the appeal on this point.

22. The appeal panel would suggest that the wording of the FAD is clarified in response to Dr Coles' factual error submission of 29 August 2017.

Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.

23. There was no appeal under this ground.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE. *"As described under Appeal Ground 1a, the appraisal committee took clinical evidence out of context, with potentially dangerous consequences for patients. This means that in the FAD the risks, including avoidable breast cancer deaths, of implementing Intrabeam technology are significantly underestimated."*

24. As set out in paragraphs 14 and 15, Prof John Yarnold and Dr Charlotte Coles for the joint appellant highlighted the evidence that one breast cancer death can be prevented for every four local recurrences prevented. They stated that there is consensus amongst oncologists on this ratio. They expressed their concern that they believe this could translate into up to one excess death per 60 women treated with Intrabeam.

25. Prof John Yarnold expressed concern that the current information available for patients in some centres using Intrabeam states that there are fewer deaths with Intrabeam than with external beam radiotherapy and implies that many patients (not just the lowest risk group) should be eligible for Intrabeam treatment.

26. Mairead Mackenzie, for the joint appellant argued that patients must be able to make informed choices and can only do this with clear evidence. She said that most patients would not put convenience above evidence of effectiveness.

27. Dr Jane Adam, for NICE, prefaced her comments by saying that the appraisal committee agreed with the appellants' position that Intrabeam should not be recommended for routine commissioning because there was not sufficient evidence of non-inferiority. However, the committee had gone on to consider whether the six existing machines should continue to be used in any circumstance. They had concluded that it was unlikely that there were no patients who would benefit from Intrabeam continuing to be available in these few centres. (For instance, Dr Adam gave examples of patients who do not want external beam radiotherapy for specific reasons such as claustrophobia.) She explained that the appraisal committee concluded that clinical multidisciplinary teams could make appropriate decisions about which patients should be offered Intrabeam in these centres, after consideration of the individual risks and benefits.

28. Meindert Boysen, for NICE highlighted the recommendation in paragraph 1.5 of the FAD that clinicians must ensure that patients understand the uncertainties about the procedure and that clinicians should provide written information from NICE as an aid to shared decision making.

29. Mairead Mackenzie, asked by the panel whether patients should be offered the choice of Intrabeam as long as they had written information that included the potential risk of higher mortality, said that choice should always be on the table.

30. Prof John Yarnold, asked by the panel whether the provision of such information would allay his concerns, said that it would.

31. In response to a question from the panel, Dr Jane Adam for NICE stated that the issue whether or not there is a link between local recurrence and mortality did not have a significant bearing on decision-making at the meeting of 15 November 2016 because the committee was not minded to favour a positive recommendation for the routine commissioning of Intrabeam. For the decision to recommend limited use of Intrabeam with existing machines under specified governance arrangements, she said that this decision was based on the judgement that there may be patients who would benefit from this.

32. The panel asked whether there was a level of possible risk beyond which the appraisal committee would not have recommended Intrabeam in any circumstances. Dr Adam said that if there was evidence that the technology was dangerous they would not recommend it, but that the committee did not think there was any evidence that Intrabeam could be dangerous in properly selected patients. She went on to highlight the low absolute rate of local recurrence with Intrabeam which the appraisal committee believe is within the range generally considered acceptable by oncologists. In response to questions from the panel, Dr Adam also said that the suggestion that one breast cancer death can be prevented for every four local recurrences prevented was not universally

accepted. (She said this ratio was based on a meta-analysis of trials carried out at a time when local recurrence rates were much higher, and that another recent trial showed no difference in rates of metastatic disease with differential recurrence rates of 1 and 4%.)

33. The appeal panel concluded that, whilst there seems to be some debate on the best interpretation of the evidence regarding the link between prevention of local recurrence and reduced mortality, the appraisal committee did hear this evidence (see paragraph 20). The panel further concluded that the appraisal committee took account of this evidence to an extent that their decision was not unreasonable. In response to questioning, it was clear that the committee had considered what degree of concern about harm would have led to a decision not to recommend Intrabeam in any circumstances. The appraisal committee's conclusion that there was not sufficient concern about harm to reach this decision was not unreasonable. For existing Intrabeam machines, the appeal panel judged that the appraisal committee's view that potential risks could be weighed against benefits by multi-disciplinary teams and patients themselves (once provided with adequate information) was not unreasonable.

34. The appeal panel therefore dismissed the appeal on this point.

35. The appeal panel does so on the understanding that the decision aid produced by NICE will inform patients about the benefits and risks of Intrabeam.

Conclusion and effect of the appeal panel's decision

36. The appeal panel dismissed the appeal against this appraisal on all grounds.

37. There is no possibility of further appeal against this decision of the appeal panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.